Prostate disease 48

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Key points

Benign prostatic hyperplasia

- Benign prostatic hyperplasia (BPH) is a common condition which increases in prevalence with age.
- A combination of increased adrenergic tone in the prostatic stroma and bladder neck as well as the anatomical effects of an enlarging prostate lead to lower urinary tract symptoms (LUTSs) and bladder outflow obstruction (BOO).
- Surgical treatments such as transurethral resection of the prostate (TURP) are effective, but less invasive procedures such as laser therapy, and less commonly thermotherapy, are used.
- α-Adrenoceptor blocking drugs are effective in reducing symptoms.
- 5α-Reductase inhibitors reduce prostate size, improve symptoms, increase urinary flow rates and reduce the risk of developing complications such as acute urinary retention (AUR) or the need for prostate surgery.

Prostate cancer

- Prostate cancer (PC) typically progresses slowly but is influenced by factors such as tumour grade, stage of the disease, co-morbidities and life expectancy.
- Aetiology is multi-factorial and includes age, race, family history and dietary habit.
- Early detection is difficult because there are no symptoms specific to PC.
- A combination of digital rectal examination (DRE), serum prostate-specific antigen (PSA) and transrectal ultrasonography (TRUS) is used to confirm diagnosis.
- Curative treatments include radical prostatectomy or radiotherapy.
- Treatment depends on the grade and stage of tumour, life expectancy and patient choice.

Prostatitis

- Prostatitis is classified as acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome and asymptomatic inflammatory prostatitis.
- There is no absolute diagnostic tool for prostatitis. Diagnosis is based on physical examination and clinical history.
- The pathophysiology of prostatitis is poorly understood and the aetiology is unclear in the majority of patients.
- Prostatitis cases associated with infection or inflammation are treated with antibiotics.
- α-Adrenoceptor antagonists are used for the treatment of chronic prostatitis/chronic pelvic pain syndrome.

Benign prostatic hyperplasia

Epidemiology

Benign prostatic hyperplasia (BPH) is the most common benign tumour in men and is responsible for urinary symptoms in the majority of males over the age of 50 years. Autopsy studies have revealed the histological presence of BPH in 50% of males aged 51–60 years, increasing to 90% in those over 85. By the age of 80 years, virtually all men exhibit one or more of the symptoms associated with BPH.

BPH is seen in all races although the overall size of the prostate varies from race to race.

Pathophysiology

The prostate is a part glandular, part fibromuscular structure about the size of a walnut that surrounds the first part of the male urethra at the base of the bladder (Fig. 48.1). In simple terms, the prostate can be divided into a lobular inner zone encapsulated by an external layer. The inner zone is where benign hypertrophic changes are generally found, whereas most malignant changes originate in the peripheral zone.

Prostatic hypertrophy is directly related to the ageing process and to hormone activity. Within the prostate, testosterone is converted by 5α-reductase to dihydrotestosterone (DHT). DHT is five times more potent than testosterone and is responsible for stimulating growth factors that influence cell division leading to prostatic hyperplasia and enlargement.

Histologically, depending on the predominance of the type of prostatic tissue present, prostatic hypertrophy can be stromal, fibromuscular, muscular, fibroadenomatous or fibromyoadenomatous.

As the prostate enlarges, it can compress the urethra (Fig. 48.2) and this, together with increased adrenergic tone, can lead to bladder outflow obstruction (BOO) and lower urinary tract symptoms (LUTSs). Therefore, the term BPH includes benign prostatic enlargement (BPE), the clinical features associated with urinary obstruction and LUTSs.

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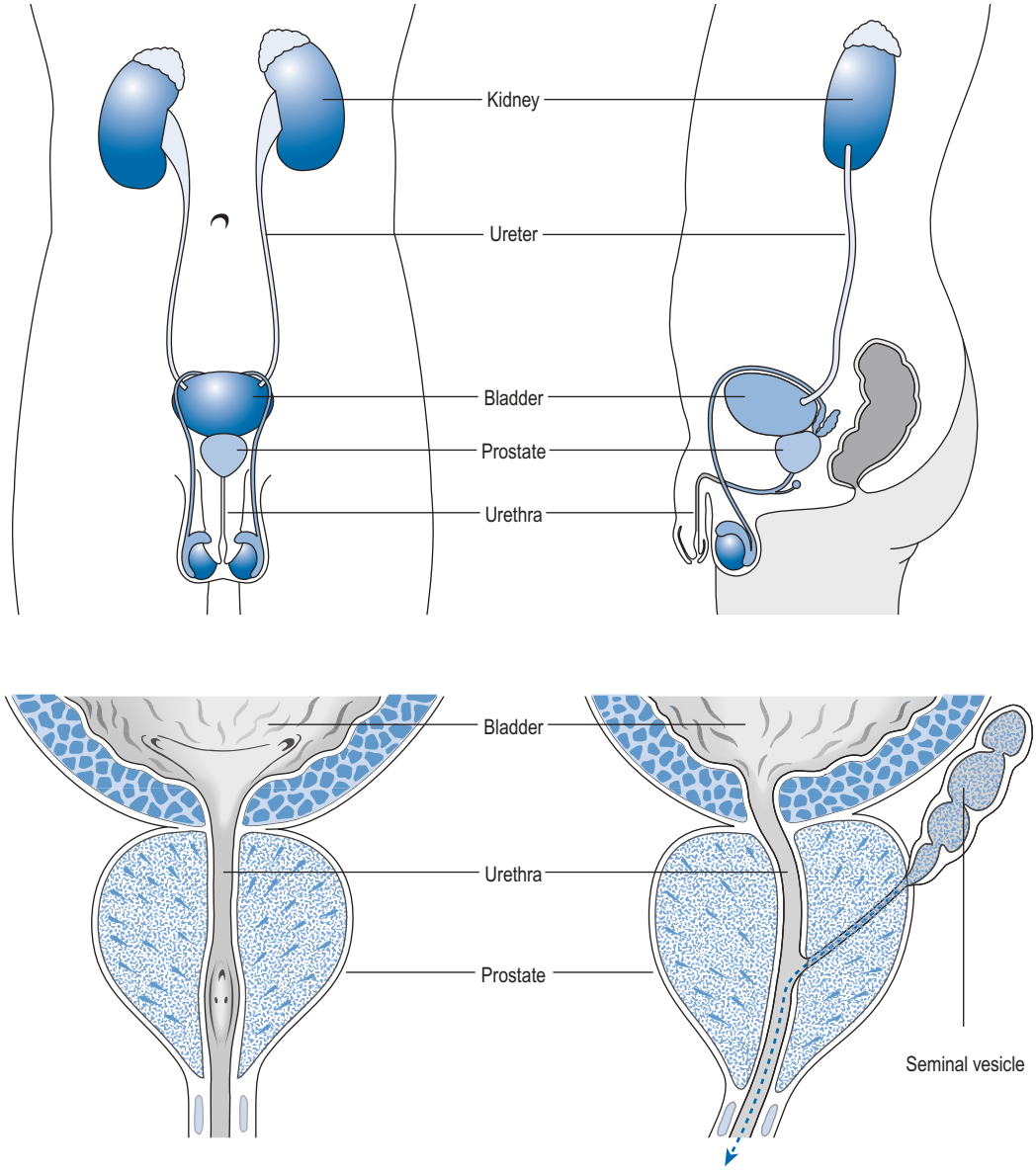


Fig. 48.1 Male urinary system demonstrating the location of the prostate.

Symptoms

Men with BPH can develop bothersome LUTSs that can impact negatively on their quality of life. It is important to emphasise that not all men who experience LUTSs have BPH. LUTSs can have different aetiologies including bladder cancer or stones, urinary tract infection (UTI) or urethral stricture. Furthermore, a histological diagnosis of BPH does not mean the patient will suffer from LUTSs.

LUTSs can be divided into symptoms of failure of urine storage (irritative) and those caused by failure to empty the bladder (obstructive or voiding).

Irritative symptoms

- Frequency
- Nocturia
- Urgency and urge incontinence

Obstructive symptoms

- Poor urinary flow
- Hesitancy in initiation of micturition
- Post-micturition dribble
- Sensation of incomplete emptying
- Occasional acute retention of urine requiring emergency treatment

Examination and investigations

There is a range of investigations and diagnostic tests available for the evaluation of patients with suspected BPH. Some tests are standard during the assessment of all men with LUTSs. Other investigations are optional and are only performed depending on the patient's presentation and the clinician's judgement.

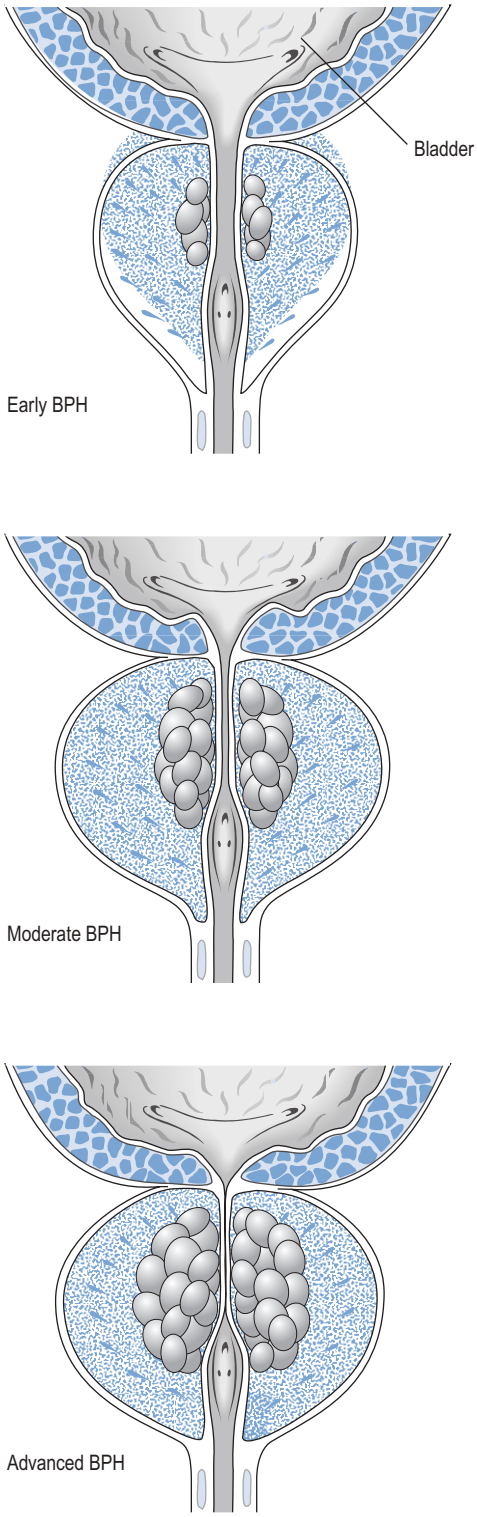


Fig. 48.2 Diagrammatic representation of the impact of prostate hyperplasia on the urethra demonstrating overgrowth of cells in the inner zone of the prostate.

History

A focussed medical history of all men with LUTSs should be taken to elucidate the aetiology of their symptoms. As part of the process, LUTSs should be evaluated using a validated scoring tool such as the international prostate symptom score (IPSS). This can be used to monitor the severity and progression of the disease and assess the impact of therapy on LUTSs.

Physical examination

All patients who present with suspected BPH should undergo a digital rectal examination (DRE) which involves the examiner palpating the prostate with a finger through the rectum wall. A DRE is performed to exclude the presence of prostate cancer (PC) and can also be used to estimate the shape and size of the prostate, although transrectal ultrasonography (TRUS) provides a more accurate measurement of prostate volume.

Urodynamic studies

Simple non-invasive urodynamic studies provide a surrogate measure of BOO. These include maximum flow rate and post-void residual (PVR). Large PVRs of 300 mL, for example, are indicative of bladder dysfunction and predict a poor response to therapy. Definitive proof of BOO requires invasive pressure flow studies.

Imaging

In the past, upper tract imaging involving an ultrasound scan and intravenous urography were used routinely to evaluate LUTSs associated with BPH. These tests are not normally undertaken except in patients with abnormal renal function and LUTSs who should have an ultrasound scan of their kidneys. The following represent the imaging options used for the assessment of men with BPH.

Flexible cystoscopy

Flexible cystoscopy provides an endoscopic image of the bladder for the assessment of prostatic obstruction and informs possible management options. For example, if the prostate has grown and there is intravesical extension, each time the patient tries to void the internal urethral meatus is obstructed. This type of tissue requires surgical removal, whereas simple lateral lobe enlargement may well respond to non-surgical measures.

Prostatic ultrasound scan

Prostatic ultrasound or TRUS uses high-frequency scanners to produce images of the prostate. This imaging is used to obtain an accurate evaluation of the prostate volume and to detect malignant change. TRUS is also used to guide the placement of the needle when obtaining prostatic biopsies.

Other investigations

Other investigations may be carried out to facilitate the diagnostic assessment of patients with LUTSs due to BPH, and these include urinalysis, urine cultures if infection is suspected,

and serum creatinine to assess renal function and establish possible upper urinary tract damage. The measurement of serum prostate-specific antigen (PSA) can be considered after counselling the patient, particularly if DRE reveals a nodular or hard prostate.

Treatment

Most men over the age of 50 years exhibit some of the symptoms of BPH. The range of treatment options for the management of BPH includes watchful waiting, medical therapies and surgical interventions. The key issue, therefore, is deciding who should be treated and when.

The British Association of Urological Surgeons has published guidelines for the management of BPH in primary care (Speakman et al., 2004), focussing on when urological referral is required and when non-invasive treatment can be initiated (Fig. 48.3).

Watchful waiting

Men with mild or moderate and not significantly bothersome LUTSs should be offered a trial of watchful waiting. This management strategy does not include any medical or surgical treatment but involves regular active monitoring. In some cases, symptoms remain unchanged for years and no further interventions are necessary since disease progression is minimal. Patients that adopt this modality should be offered education and lifestyle advice (Box 48.1) to manage their urological symptoms together with a review of their medication, particularly diuretics or other medicines known to affect the urinary system.

Therapeutic management

The principal treatment options are α-adrenoceptor blocking drugs, 5α-reductase inhibitors and combination therapy. Phytotherapy is also used in the management of BPH, although the benefits remain unproven.

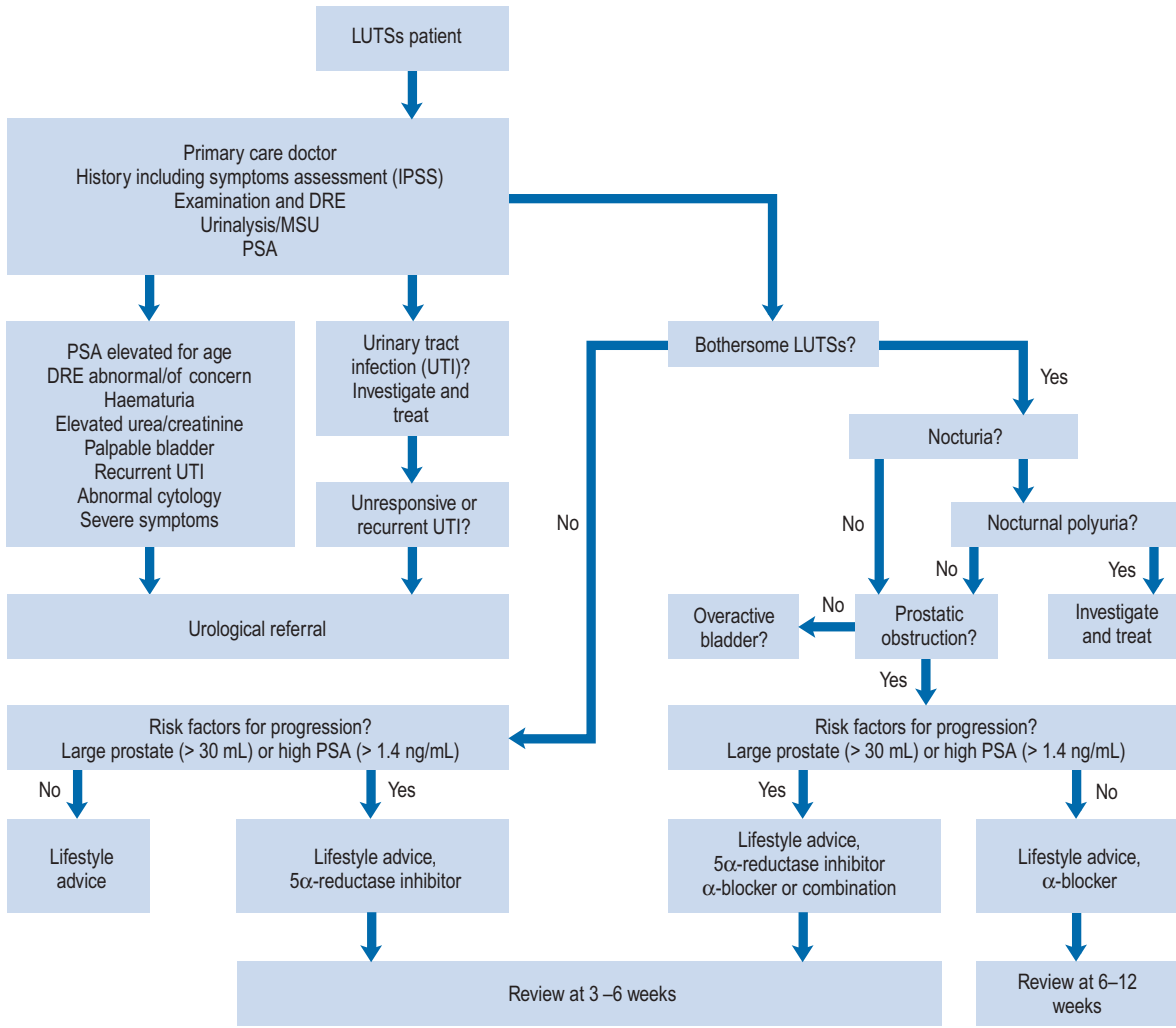


Fig. 48.3 Algorithm for the treatment of lower urinary tract symptoms (LUTSs) in males in primary care (from Speakman et al., 2004) (DRE, digital rectal examination; MSU, mid-stream urine sample; PSA, prostate-specific antigen).

Box 48.1 Advice for the management of lower urinary tract symptoms

Limit fluid consumption before going out and before going to bed (to reduce urinary frequency and nocturia)
Reduce alcohol and caffeine intake
Schedule toilet visits
Manage constipation
Review medication (including diuretics and other medicines that can affect the urinary system)
Bladder training (encourage patient to go longer between voiding and increase the volume voided)
Use distraction techniques (practice breathing exercises and penile squeezing to control symptoms of irritation)

α-Adrenoceptor blocking drugs

The prostate gland is very responsive to adrenergic stimulation. In fact, prostatic outlet obstruction in BPH is partly due to the hypertrophied bulk of the gland, but it also arises from an increase in adrenergic tone. In the prostate, α_1-receptors predominate and mediate the contraction of the gland's smooth muscle. At least three subtypes of this receptor exist (α_{1A}, α_{1B} and α_{1D}). The α_{1A} is thought to be the dominant receptor in the prostate, although its role clinically has still to be confirmed. This increase in sympathetic tone is potentially reversible by α-adrenoceptor antagonists.

In general, all the agents are considered to produce similar clinical improvements of LUTSs and urinary flow. Benefits can be seen usually within the first few days of therapy and can be maintained in the long-term. α-Adrenoceptor antagonists also have a comparable side-effect profile, which includes postural hypotension, dizziness, fatigue, headache, drowsiness, nasal congestion and ejaculatory dysfunction.

Patients with BPH frequently experience erectile and ejaculatory dysfunction. The treatment of BPH should also aim to improve sexual function. However, the effect of α_1-adrenoceptor antagonists on male sexual function is variable and influenced by the choice of agent and patient characteristics (Van Dijk et al., 2006).

Prazosin. Prazosin was the first α_1-blocker used to relieve the symptoms of BPH but it lacks relative selectivity for α_{1A} receptors and has been associated with many adverse affects such as drowsiness, weakness, headache and postural hypotension (especially after the first dose).

Terazosin. Terazosin was the first in the category to appear in controlled trials aimed at evaluating the efficacy and safety profile of long acting α_1-blockers in the management of BPH. Efficacy is dose dependant and dose titration is necessary, as terazosin can cause postural hypotension. Adverse effects, although generally mild, occur more frequently than with other α_1-adrenoceptor antagonists, resulting in up to a four-fold increase in treatment discontinuation.

Indoramin. Indoramin is readily absorbed from the gastro-intestinal tract and undergoes extensive first-pass hepatic metabolism. Its hypotensive effect may be increased by diuretics and other anti-hypertensive agents. Alcohol has been reported to increase the bioavailability and sedative effects of indoramin.

Doxazosin. Doxazosin has a long half-life of about 22 h, which allows for once-daily dosing. When starting treatment, dose titration is recommended to limit postural hypotension. There would appear to be no significant difference in symptom score regardless of whether the standard or controlled-release preparation is used (Kirby et al., 2001).

Tamsulosin. Tamsulosin is a selective inhibitor of the α_{1A}- and α_{1B}-adrenoceptor. It has an elimination half-life of about 13 h and is available as a prolonged release formulation that allows once-daily dosing. There is no requirement to titrate the dose upward when initiating treatment. Although the side-effect profile of tamsulosin is similar to other α_1-adrenoceptor antagonists, it is normally well tolerated (O'Leary, 2001). Intraoperative floppy iris syndrome (IFIS) has been reported during cataract surgery in men treated with tamsulosin, as it is highly selective to iris dilator muscle (Chaim et al., 2009). IFIS can lead to complications and poor outcomes during cataract surgery. As a result, it is essential that patients inform their cataract surgeon that they are taking tamsulosin during the pre-operative assessment. It has been recommended to avoid starting treatment and to discontinue treatment with tamsulosin 1–2 weeks before cataract surgery.

Alfuzosin. Alfuzosin displays a higher selectivity for the prostate compared with tamsulosin or doxazosin. It has a half-life of 5 h, but it is available as a once-daily formulation. It has a rapid onset of action and good tolerability (MacDonald and Wilt, 2005). It reduces the overall clinical progression of BPH and it appears to have a sustained beneficial effect on quality of life (Roehrborn, 2006). Alfuzosin has the least effect on ejaculatory function. Alfuzosin should not be co-administered with potent inhibitors of cytochrome P450 3A4 such as itraconazole, ketoconazole and ritonavir, since this can lead to a several fold increase to exposure in alfuzosin.

5α-Reductase inhibitors

The primary androgen responsible for the development and progression of BPH is DHT. There are two isoenzymes of 5α-reductase: type 1 is found in most 5α-reductase producing tissues such as the liver, skin and hair; type 2 is predominant in genital tissue, including the prostate. 5α-Reductase inhibitors downregulate prostate growth by blocking the conversion of testosterone to the more potent DHT.

The two agents currently available in this group are finasteride and dutasteride. Both have been shown to reduce prostate volume, to improve symptom scores and flow rates, and reduce the incidence of complications such as acute urinary retention (AUR) and the need for surgical intervention to treat BPH (Roehrborn et al., 2000, 2002). Improvements in LUTSs are normally seen after the first 6 months of treatment and are sustained during continuous treatment (Lam et al., 2003).

Finasteride. Finasteride is a type 2, 5α-reductase inhibitor that can reduce prostate size by about 30%, improve symptom scores and increase urinary flow. Those most likely to benefit are men with a prostate larger than 40 mL. Side effects include decreased libido, impotence, reduced ejaculatory volume and, less commonly, gynaecomastia and breast tenderness. Serum

concentrations of PSA may be reduced by 50% in the first year of treatment with finasteride, a fact which must be taken into account when attempting to interpret the PSA concentration in men with suspected PC.

Dutasteride. Dutasteride inhibits both type 1 and type 2 isoenzymes of 5α-reductase. Although the clinical significance of this is unclear, this double inhibition can reduce serum dihydotestosterone levels by about 90%. Dutasteride decreases prostate volume by up to 26% and reduces the risk of progression to serious complications of BPH. LUTSs also improve after 6 months of treatment. Dutasteride is well tolerated although side effects which include erectile and ejaculatory dysfunction and breast enlargement occur with similar frequency to finasteride.

Combination therapy

It is well established that α-adrenoceptor antagonists are best for managing acute symptoms but have no impact on reducing the risk of complications such as AUR or progression to prostate surgery. In contrast, 5α-reducatase inhibitors have little impact on short-term acute symptoms but reduce prostate size, improve urinary flow and obstructive symptoms in the long-term. Furthermore, α-adrenoceptor antagonists are effective regardless of prostate volume, whereas the 5α-reductase inhibitors are more suited for the management of LUTSs in men with large prostates. In terms of long-term benefits, continued treatment with 5α-reductase inhibitors decreases the risk of AUR and BPH-related surgery. Therefore, it appears logical to use a combination of an α-adrenoceptor antagonist and a 5α-reductase inhibitor to manage acute symptoms and reduce progression of BPH.

The benefits of using a combination of doxazosin and finasteride compared to monotherapy have been demonstrated in over 3000 men (McConnell et al., 2003). Similarly, the combAT trial (Roehrborn et al., 2010) involved nearly 5000 men with moderate to severe symptoms of BPH and prostate enlargement treated with a combination of dutasteride and tamsulosin. This study demonstrated a significant improvement in BPH symptoms over a 4-year period when compared to either agent used alone. The combination was also found to reduce AUR and progression to BPH-related surgery and, although superior to tamsulosin with respect to these complications, combination therapy was not better than dutasteride. Overall, the adverse events associated with combination therapy were few and treatment was well tolerated.

Combination therapy with an α-adrenoceptor antagonist and a 5α-reductase inhibitor has now been adopted widely into routine practice for the early management of LUTSs and to reduce progression of BPH.

Phytotherapy

A number of plant extracts are reputed to be effective in the management of symptoms of BPH. They include saw palmetto berry (*Serenoa repens*), African plum tree (*Pygeum africanum*), stinging nettle (*Urtica dioica*) and rye grass pollen. Their mechanism of action remains unclear but may exert an anti-inflammatory effect by inhibition of prostanoid formation and perhaps produce some degree of inhibition of 5α-reductase. Most of the data available to support the use of plant extracts derive from poorly designed studies. As evidence to assess efficacy and safety is lacking, phytotherapy remedies are not currently recommended by international guidelines for the management of BPH.

Surgical treatments

Surgical interventions are commonly performed in men with LUTSs caused by BPH that have failed to respond to medical treatment. Surgery is also indicated in patients who develop complications such as intractable or recurrent urinary retention, renal impairment, persistent haematuria, recurrent UTIs or bladder stones.

Transurethral resection of the prostate. Transurethral resection of the prostate (TURP) is a common and effective procedure which achieves a high level of improvement in symptoms and flow rate. It is the preferred surgical intervention in men with a prostate volume between 30 and 80 mL. Sections of prostate are removed using electrical wire loops attached to a tube-like telescope (resectoscope) inserted into the urethra. The tissue removed is collected for histological assessment. There is a small incidence of perioperative mortality associated with TURP along with complications such as bleeding, UTIs and epididymitis. Long-term complications include stress incontinence, urethral and bladder neck strictures and erectile dysfunction.

Open prostatectomy. Open prostatectomy involves the surgical removal of an enlarged prostate. Typically, an incision is made through the lower abdomen although sometimes the incision is between the rectum and the base of the penis. This procedure is now performed infrequently and restricted to very enlarged prostate glands (larger than 100 mL) and those with large bladder stones or bladder diverticula (Stoevelaar and McDonnell, 2001). Open prostatectomy requires a longer hospital stay than transurethral resection and is associated with a higher incidence of bleeding and other complications.

Minimally invasive techniques

Various treatment modalities have been tried as alternatives to TURP to reduce the risks associated with resection. Thermotherapy and laser technology are the most commonly used. Thermotherapy uses techniques such as electrovaporisation and transurethral microwave heat treatment (TUMT), which heats the prostate to cause vaporisation of the tissue. Various types of laser energy can also be used to destroy prostatic tissue mainly by coagulation or vaporisation.

Patient care

Patients generally seek medical help for BPH because of the impact of symptoms on their quality of life. Most men tolerate a high degree of symptoms and impact on daily activities before they seek help. Table 48.1 lists some common

Table 48.1 Common therapeutic problems and proposed management strategies in benign prostatic hyperplasia

Problem	Solution
Patient taking α-blocker still symptomatic after 2 weeks	Patients should be advised that it may take 2–6 weeks before symptomatic treatment relief is seen
Patient taking an α-adrenoceptor blocker complains of cardiovascular adverse effects such as dizziness, syncope, palpitations, tachycardia or angina	These side effects are more likely in elderly patients. They are most common after the first dose and reflect the hypotensive effects of the drugs. They can be reduced by titrating the dose or using more uroselective drugs such as tamsulosin
Sexual dysfunction	Decreased libido or impotence can occur in patients taking finasteride and dutasteride. Abnormal ejaculation can be caused by α-blockers. Tamsulosin in particular can cause a dry climax (retrograde ejaculation). Patients should be forewarned when discussing treatment options
Patient taking finasteride notices breast enlargement	Unilateral or bilateral gynaecomastia is a frequently reported side effect with finasteride and patients need to be counselled accordingly when discussing treatment options
Patient taking finasteride or dutasteride has a sexual partner who is pregnant	Exposure to semen should be avoided as both drugs can cause abnormalities to genitalia in a male fetus. The patient should be advised to use a condom

therapeutic problems in the management of BPH. Patients should receive information about the management options available, the investigations that they need to undergo and possible treatment outcomes and adverse effects. Patients receiving drug therapy should receive specific information about their treatment, including potential benefits, timeline of expected outcomes and possible side effects.

There are two websites which produce particularly useful educational material on prostatic disease: the Men's Health Forum (http://www.menshealthforum.org.uk/) and the Prostate Research Campaign (http://www.prostateuk.org/index.htm).

Prostate cancer

Epidemiology

PC is the second most common cancer in the world and the most common form of cancer in men. Incidence varies from country to country with the highest rates in America, Canada and Scandinavia and the lowest rates in China and other Asian countries (Quinn and Babb, 2002; Gronberg, 2003). In the UK, nearly a quarter of all new male cancer diagnoses are of the prostate. The lifetime risk of PC is 1 in 10 in males in the UK.

The aetiology of PC is multi-factorial. Testosterone and DHT have an important role in the disease as males who undergo castration before puberty do not develop PC. Other factors which can influence the risk of developing PC include the following:

Age. PC is rare before 50 years in Caucasians and before 40 years in Africans, but after this age, the incidence and mortality increase exponentially with every passing decade. Most cases are detected around the age of 70.

Race. Incidence and mortality is high among Caucasians and African Americans and lowest in Chinese males. Environmental factors may play a role in this variation as studies have found an increased incidence in East Asian men who relocate to western countries.

Family history. Presence of PC in a first-degree relative or in multiple family members who need not be first-degree relatives increase risk. Inheritance of a susceptible gene or polymorphism of gene may be responsible for this.

Diet. Although there is no compelling evidence to prove the direct influence of diet, high intake of fat, red meat and dairy produce, typically the main sources of dietary fatty acids in a Western diet, have individually been linked with PC. The low incidence of PC in China and Japan may be due to their use of soya bean products which contain isoflavones and inhibit protein tyrosine kinases responsible for cell proliferation.

Other factors. These include exposure to cadmium (found in cigarette smoke), pesticides, alkaline batteries, radionuclides and heavy metals.

Pathophysiology

The growth and differentiation of cells in the prostate is under androgen control. In the prostate, free testosterone diffuses into the epithelial cells where it is converted to DHT. Various growth factors are present in stromal cells, and the interaction of these with epithelial cells can play a role in cell proliferation and growth. The development of PC is generally a slow, gradual process where cellular structure changes from normal through dysplastic to cancer. High-grade prostatic intra-epithelial neoplasia (HGPIN) represents the precancerous stage of cellular proliferation in prostate cells and can be detected by biopsy. It can predate carcinoma by 10 years or more. There is no link between PC and BPH but they can coexist.

Screening

Population-based screening based on PSA levels is prevalent in the USA, and the annual incidence here has doubled due to this. In the UK, screening is not advocated as the prevailing view is that there is a lack of evidence to support it. Due to the aetiology and nature of PC, most patients will not be symptomatic in their lifetime and screening may increase the risk of overtreatment.

Symptoms

Clinical symptoms of PC are similar to those for BPH, and there are no symptoms which correlate specifically to early PC. As more than 50% of men above the age of 50 years have prostate-related symptoms, it is difficult to detect early PC. Advanced PC typically presents with symptoms of urethral and bladder outlet obstruction, anaemia, weight loss, haematuria or bone pain.

Examination and investigation

Physical examination

A DRE is an important diagnostic tool for PC with an estimated sensitivity of more than 60%. A palpable tumour will have a distinctive texture, but the accuracy of detection may depend on the experience of the clinician. False-positive results can occur in the presence of BPH or cysts.

Imaging

TRUS of the prostate is commonly used to aid the diagnosis of PC. Sensitivity ranges from 48% to 100%. Cancer in the anterior and central region of the prostate can, however, be missed. Computerised tomography, MRI scan of the pelvis and isotope bone scan are also useful to stage PC, but they are not effective as screening methods.

Prostate-specific antigen

Measurement of PSA is an accurate and clinically useful biochemical marker because it is specific to prostate tissue and produced by the columnar epithelial cells in the prostate gland. Unfortunately, PSA is not cancer specific as any damage to the internal architecture of the prostate can result in release. As a consequence, it is not a useful tool for diagnosing cancer on its own, but it is useful in monitoring the effect of treatment or tumour progression in untreated patients. Generally, PSA is high in PC, but it can sometimes be low in high-grade malignancy. The standard assay for PSA measures total prostate-specific antigen (tPSA) and includes all molecular forms. Age-specific ranges are available (Table 48.2) and help make it a better predictor, but this is only a rough guide as variations occur due to racial difference. There is no threshold for PSA below which PC cannot be found.

Table 48.2 Age-specific levels of prostate-specific antigen

Age	Prostate-specific antigen (ng/mL)
40–49	≤2.5
50–59	≤3.5
60–69	≤4.5
>70	≤6.5

Prostate biopsy

This is a definitive method to detect PC. TRUS guided biopsy will help obtain samples from the peripheral and transitional zones of the prostate and other suspicious areas. The peripheral zone of the prostate is the location where the majority of the PC occurs and the most common location for HGPIN. It is difficult to identify PC from trans-urethral resection of the prostate specimens as not much of it occurs in the transitional zone. In the UK, USA and Europe, the most widely accepted histological grading system, which corresponds to biological malignancy, is based on the Gleason scale (Gleason and Mellinger, 1974). Histological examination of biopsy tissue is undertaken to identify cancer cells and these are scored from 1 to 5 depending on the different pattern of glandular tissue (Fig. 48.4). A score of 1 corresponds to well-differentiated cells, while a score of 5 corresponds to poorly differentiated cells. The higher the score, the more aggressive the cancer. The number for the two most common types of cell in the sample are added together to get a Gleason score. The score ranges from 2 to 10. This is an important prognostic factor as it can help predict the future behaviour of the tumour and determine the treatment required.

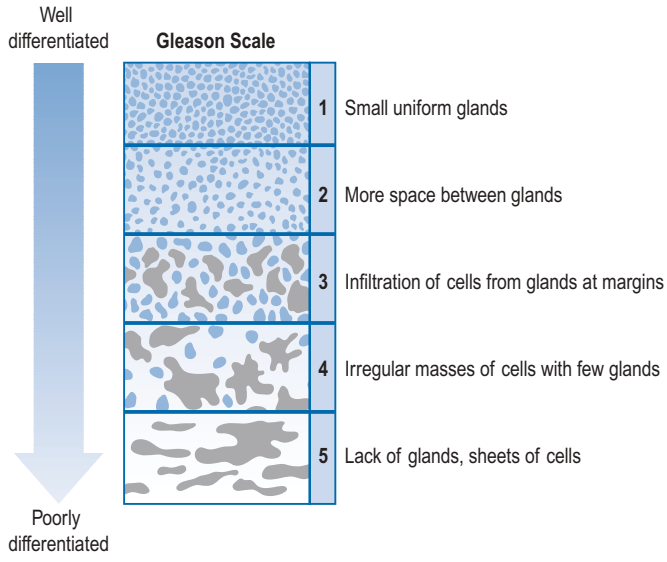


Fig. 48.4 Gleason scale.

Cancer staging

Results from a DRE, biopsy and scan are used to identify the extent of the cancer. The tumour volume, whether there is invasion into or through the capsule, and spread to lymph nodes or bone are all taken into consideration for staging. Staging based on the tumour, node, metastasis (TNM) system is a classification accepted worldwide (Epstein et al., 2005). Based on the TNM classification, PC can be classified into localised disease, locally advanced disease and advanced/metastased disease.

Treatment

The factors that must be considered to aid the treatment decision relate to the tumour and the patient:
Tumour: Staging result, histology, Gleason score and the PSA concentration.
Patient: Age at diagnosis, life expectancy and the presence of co-morbidities such as cardiovascular disease, chronic obstructive pulmonary disease and diabetes (Fig. 48.5).

Localised prostate cancer

Established treatments with curative intent

Active surveillance. It is difficult to distinguish PC which may not cause any problems to that which may grow and spread aggressively. Curative treatment can improve longevity but has side effects which include impotence and incontinence and can affect the quality of life of the individual. Patients on active surveillance are monitored closely by repeated testing of PSA levels, DRE and biopsy with the intention to make a radical intervention to treat if there is disease progression. A 20-year outcome study following conservative management of localised PC found that the annual mortality rates did not support aggressive treatment (Albertsen et al., 2005). Although active surveillance can spare side effects of treatment without compromising survival, regular biopsies used to monitor the disease can also be uncomfortable and carry a risk of infection. The optimal schedule for measuring PSA and repeating biopsies is unclear.

Radical prostatectomy. This is the treatment of choice and the procedure involves the total removal of a prostate, seminal vesicle, distal vasa, ejaculatory ducts and prostatic urethra. In the open procedure, it is performed by the retro pubic or perineal approach based on the surgeon's choice. Laparoscopic prostatectomy, and more recently robotic-assisted laparoscopy, has been developed. The most common complications of prostatectomy are blood loss, post-operative thromboembolism, urinary incontinence, impotence and rectal injury. Systemic review and meta-analysis have shown that the laparoscopic and robotic methods are associated with less blood loss and transfusion, but oncological outcomes, incontinence and erectile dysfunction rates are similar with all three types of prostatectomy.

Radical external-beam radiotherapy. Radiotherapy is used for locally confined disease and more recently for locally advanced disease state as well. In this treatment, high-energy photons produced by a linear accelerator are targeted at the prostate. Sometimes, special particles such as protons and heavy ions are used and have advantages over photons in terms of dose distribution. The side effects of radiotherapy include impotence, genitourinary stricture, rectal bleeding, haematuria and incontinence.

Interstitial brachytherapy. With interstitial brachytherapy radioactive isotope seeds are placed in the prostate under ultrasound or fluoroscopic control. These implants can emit radiation of low energy over several weeks and can be temporary or permanent. This treatment has the potential advantage of less erectile dysfunction than other treatment.

Minimal invasive procedures

The minimal invasive procedures are in the development stage and, although they may be used in some centres, there are no medium- or long-term follow-up data to prove efficacy. The various procedures include:

Cryosurgical ablation of prostate (CSAP). Cryosurgical ablation involves freezing the prostate which results in cell death by protein denaturation, direct rupture of cellular membranes and apoptosis. Freezing is achieved by placing 12–15 cryoneedles into the prostate guided by a transrectal ultrasonograph and using the cryoneedles to create freeze thaw cycles using temperatures of −40 °C.

High-intensity focussed ultrasound (HIFU). In this technique, ultrasound waves from a transducer are focussed on the prostate tissue to cause damage to the cells by mechanical and thermal effects. The malignant tissue is subjected to temperatures above 65 °C and hence is destroyed by coagulative necrosis.

Radio-frequency interstitial tumour ablation (RITA). A needle electrode is placed inside the prostate and radio-frequency waves are delivered through it to heat the tissue up to 100 °C thereby causing necrosis.

Watchful waiting

This approach implies that the patient is observed for symptomatic progression and will only receive palliative treatment when clinical symptoms develop. Since the disease often progresses slowly, watchful waiting is an option for patients with early disease as it maintains their quality of life and avoids complications related to surgery or radiation therapy. On the downside, it is not a curative option, the cancer can metastasise and be a source of pain and reduce life expectancy.

Locally advanced prostate cancer

Hormonal therapy/androgen deprivation therapy

In locally advanced disease involving areas outside the capsule, there is an increased risk of relapse and lymph node metastasis after prostatectomy.

Androgens are produced both in the testes (95%) under the stimulation of luteinising hormone (LH) and luteinising hormone-releasing hormone (LHRH) from the pituitary

gland, and in the adrenal glands (5%) under the stimulation of adrenocorticotropic hormone (ACTH). The androgens produced by the adrenal gland are hormone precursors that are enzymatically converted to testosterone and DHT in prostatic and peripheral tissue. Since testosterone is a well-known etiologic factor associated with PC, it follows that testosterone deprivation can be utilised as part of treatment. In practice, this can be achieved by either surgical or medical castration with the response time varying from a few months to years.

Surgical castration. This is further discussed under metastatic disease.

Medical castration. A number of drugs can be used to reduce the levels of testosterone to those achieved by castration.

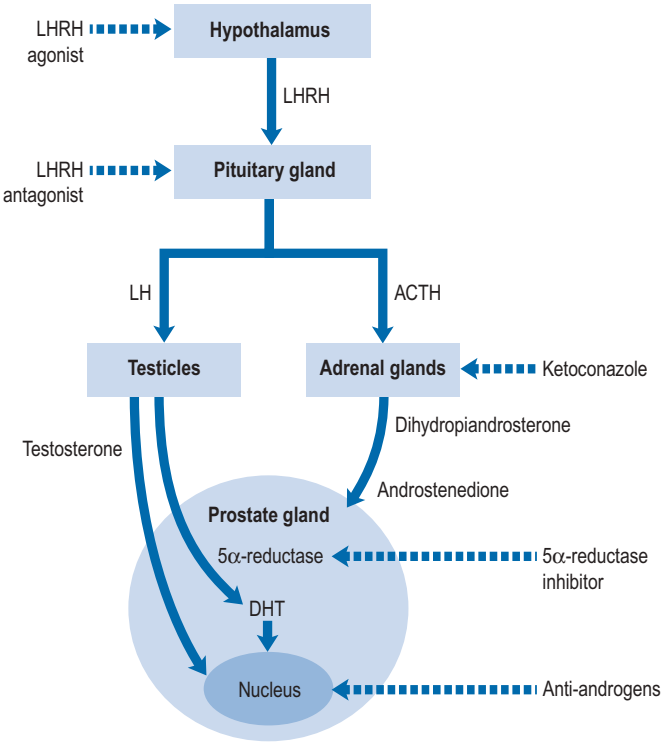


Fig. 48.5 Diagrammatic representation of the site of action of some treatments used in prostate cancer.

LHRH agonists. LHRH is released in the hypothalamus and stimulates the secretion of LH by binding to the LHRH receptors in the pituitary. This LHRH receptor complex is normally broken down by enzymes which lead to the release of lutenising hormone and frees the receptors for further binding with LHRH. LHRH agonists are synthetic analogues that bind to the LHRH receptor and the complex formed is resistant to enzymatic action. Thus, they maintain a continuous presence on the receptor and render the pituitary gland refractory to hypothalamic regulation compared to the pulsatile release in normal individuals. Continuous administration of LHRH agonists exhibits a biphasic response. There is an initial increase in LH, and testosterone release referred to as 'tumour flare up' followed by a fall over the following 1–2 weeks due to the down regulation and decrease in LHRH release as the receptors are continuously occupied. 'Tumour flare up' is prevented by first initiating treatment with an anti-androgen before the use of LHRH agonist. The anti-androgen is then continued for a further 3–4 weeks. Currently available LHRH analogues include buserelin (nasal spray), goserelin, triptorelin and leuprorelin. Goserelin is administered subcutaneously at monthly or 3 monthly intervals, whereas triptorelin and leuprorelin are administered intramuscularly at monthly or 3 monthly intervals.

In advanced PC, therapy with an LHRH agonist is comparable in efficacy to surgical orchiectomy or diethylstilboestrol but with reduced physical and psychological discomfort of the former or the cardiovascular risks of the latter. There would appear to be little difference between the various formulations of LHRH agonists. UK, U.S. and European guidelines support the use of LHRH agonists as first-line agents in the treatment of advanced PC.

More recently, a novel agonist called histrelin was introduced. This is a 1-year subcutaneous preparation which is surgically implanted.

Anti-androgens. Anti-androgens competitively inhibit the effect of androgens peripherally by competing with testosterone and DHT for binding sites in the prostate. This results in inhibition of cell growth and apoptosis. Based on their chemical structure, the anti-androgens can be further divided into steroidal agents, which include cyproterone acetate, megesterol acetate and medroxyprogesterone, and non-steroidal agents such as nilutamide, flutamide and bicalutamide.

The steroidal agents also possess progestational activity and inhibit leutinising hormone secretion by acting centrally on the pituitary thereby reducing serum testosterone levels. The non-steroidal agents do not possess this additional property. Cyproterone is the most widely used steroidal agent normally administered in two or three daily doses of 100 mg despite having a half-life of 30–40 h. It can be used to treat the hot flushes associated with LHRH agonists or orchiectomy. Side effects include hepatoxicity, loss of libido and potency, fatigue and depression. Use of medroxy progesterone and megestrol is limited because of less favourable outcomes in clinical trials compared to cyproterone.

Non-steroidal anti-androgens are used in patients who wish to preserve their quality of life as they do not suppress testosterone and hence preserve libido, physical performance and bone mineral density. The disadvantage of nilutamide, flutamide and bicalutamide is a reduced survival when used as monotherapy because of a gradual rise in testosterone. All three agents have side effects of gynaecomastia, gastrointestinal upsets, idiopathic hepato-cellular toxicity and haematuria. Bicalutamide has a better safety and tolerability profile compared to nilutamide and flutamide (Inverson, 2002). Some trials show that non-steroidal anti-androgens used in combination with surgical castration or LHRH agonists bring about complete or total androgen blockade by also reducing the production of androgens from the adrenal glands, which normally accounts for 5% of the body's production, thereby conferring a small survival advantage.

LHRH agonists and the non-steroidal anti-androgen flutamide have been used as neoadjuvant (treatment to reduce tumour size before further surgery or other treatment) or

adjuvant (treatment given in addition to primary/initial treatment to reach a treatment goal) with radiotherapy to improve disease-free and overall survival in patients with locally advanced disease.

Metastatic prostate cancer

LHRH agonists

Patients with metastatic cancer of the prostate usually respond to treatment with LHRH agonists and use is as described above for locally advanced disease.

Surgical castration

Surgical castration by bilateral orchiectomy is the treatment of choice for metastatic disease. Advantages include its low cost and morbidity with testosterone levels falling to castration levels within 5–12 h of surgery. The disadvantages include psychological trauma, its irreversible nature and the fact that nearly half experience side effects including loss of libido and potency, hot flushes and bone and muscle loss.

Other palliative treatments

LHRH antagonists. LHRH antagonists, which include abarelix and degarelix, work by competitively binding to LHRH receptors in the pituitary thereby suppressing LH release and creating a rapid and sustained decrease in testosterone levels. They do not cause an initial surge in testosterone levels and hence there is no 'tumour flare up' or need for short-term treatment with anti-androgens unlike the LHRH agonists. Abarelix requires an induction regimen followed by monthly injections and use is associated with anaphylactic reactions. Degarelix is given as a monthly depot injection; the most common side effect is a local reaction at the injection site such as swelling and erythema. Degarelix has a place in high-risk PC where the patient is acutely symptomatic with impending spinal cord compression, ureteric obstruction and urinary retention. Degarelix reduces testosterone, LH and PSA levels faster than LHRH agonists and reduces microsurges of testosterone.

The European Association of Urology (EAU) guidelines on PC recommend the use of LHRH antagonists in patients with metastasis and impending spinal cord compression (Heidenreich et al., 2009).

Bisphosphonates. Skeletal involvement in PC can be disease related or due to androgen depletion therapy. Bisphosphonates are pyrophosphates that inhibit osteoclast activity in bones and hence prevent and treat bone lesions. Pamidronate prevents bone loss but zolendronate not only increases bone mass while on androgen depletion therapy but also reduces skeletal complications in patients with bone metastasis secondary to PC (Saad and Schulman, 2004). Bisphosphonates are also recommended for pain relief when analgesics and palliative radiotherapy to bone have failed. Dental examination needs to be carried out before commencing treatment with a bisphosphonate due to the risk of osteonecrosis of the jaw in those with a history of dental trauma, infection or surgery.

Ketoconazole. This broad-spectrum, imidazole, anti-fungal can be used at a higher dose than is normal for its anti-fungal effect to inhibit the testicular and adrenal cytochrome P-450 enzyme synthesis of sex sterols. It has a rapid onset of action and is usually prescribed at a dose of 400 mg three times daily. As it causes adrenal suppression, hydrocortisone supplementation is necessary. Side effects of ketoconazole include drug-induced toxicity, adrenal suppression and hepatotoxicity.

Dexamethasone. Dexamethasone is used if spinal cord compression is suspected.

Castrate resistant prostate cancer

Androgen deprivation therapy can fail to control disease progression. The reasons for this are unclear but include the clonal selection hypothesis or adaption hypothesis. In the clonal selection hypothesis, the premise is that the basal cells are the stem cells of the prostate and generate secretory epithelial cells. Whilst the secretory epithelial cells undergo apoptosis upon androgen withdrawal, this is not the case with basal or stromal cells. As a consequence, there is selective survival of these androgen independent cells within the tumour. With the adaption hypothesis, there is the assumption that androgen independence may be an intrinsic, but dormant property of some prostate cells that is activated by androgen deprivation. Whatever the explanation, when there is failure of first-line therapy, quality of life can be improved by using single or combination therapy that includes a second-line hormone treatment (oestrogens), corticosteroids, ketoconazole, chemotherapy and bisphosphonates for short-term palliative response.

Oestrogen

Diethylstilboestrol (DES) is a synthetic oestrogen which acts by producing negative feedback on the hypothalamus and anterior pituitary, thereby down regulating the secretion of LHRH and hence the production of testosterone. Diethylstilboestrol is the least expensive of the synthetic oestrogens and causes fewer hot flushes and psychological trauma compared to the surgical option. Side effects include gynecomastia, loss of libido and potency, oedema, nausea and vomiting, and increased risk of thromboembolism. It is usually used in a dose of 1 mg once daily to reduce the risk of cardiovascular side effects as it is associated with increased cardiovascular mortality.

Corticosteroids

Both prednisolone and hydrocortisone are anti-inflammatory and can alter the body's immune response to various stimuli and are used in combination with other treatments.

Chemotherapy

Chemotherapy inhibits cell growth and proliferation; it has a variable response rate and is used as a last resort. In the USA, a regimen using mitoxantrone and prednisolone is approved

for use in palliation of advanced PC. In the UK, it is recommended that docetaxel is used within its licensed indication to treat men with hormone refractory metastatic disease. Repeat courses of treatment are not recommended if the disease reoccurs when the planned course is complete.

Chemoprevention

Chemoprevention is defined as the administration of micronutrients, dietary products or drugs to prevent or delay the progression of PC.

Diet

There has been interest in a variety of products and numerous studies have been conducted. Currently in favour are soya-containing foods, green tea, pomegranates and omega-3 fatty acids. Selenium and vitamin E are no longer considered favourable. Similarly, vitamin D and lycopene found in tomatoes are also out of favour due to the lack of positive outcomes.

Drugs

5α-Reductase inhibitors which are currently used in BPH to reduce prostate size due to their inhibitory effect on the production of DHT are thought to have potential for chemoprevention.

Studies with dutasteride have shown it can reduce the risk of PC and improve outcomes in BPH by reducing AUR. On the down side, it appears to increase the risk of cardiac failure and consequently is not routinely used in chemoprevention.

Patient care

Treatment is decided after discussing the various options and side effects with the individual. Urinary and sexual function related problems are common side effects of most treatments in PC and need to be discussed in detail with the patient. Emotional factors like depression may also need to be addressed as they can adversely affect the quality of life of the individual. Some of the common problems associated with PC are listed in Table 48.3. Patients can also be referred to http://www.nhs.uk/prostatecancer for facts, information and details of choices available in the diagnosis and treatment of PC. Information on how to cope with the disease and live with PC together with details of various support organisations are available from http://www.cancerhelp.org.uk, whilst http://www.prostatelink.org.uk describes various patient experiences.

Prostatitis

Epidemiology

The term prostatitis comprises a range of disorders that have been defined and classified (Table 48.4) by the International Prostatitis Collaborative Network (IPCN) into four categories (Krieger et al., 1999).

Prostatitis has been estimated to affect up to 16% of adult men. Unlike BPH and PC, which are more prevalent in older men, prostatitis affects men of all ages.

In most instances (between 90% and 95%), the aetiology of prostatitis is unknown with bacteria isolated in only 5–10% of men presenting with prostatitis.

Table 48.3 Common problems associated with prostate cancer

Problem	Solution
Loss of erectile function after prostatectomy	Phosphodiesterase 5 inhibitors such as sildenafil have shown efficacy in prevention and help improve chance of spontaneous erection. If medication fails or is contraindicated a vacuum device, intraurethral inserts or penile prosthesis may be used
Advanced disease with impending spinal cord compression	Treat with oral dexamethasone and either cyproterone or ketoconazole with external-beam radiotherapy. LHRH agonist treatment is not advisable as the tumour flare up in the initial stage can stimulate tumour growth and exacerbate the condition
Bleeding and coagulation disorder	Prostate cancer can cause disseminated intravascular coagulation as a pathological response to the disease. This is a rare condition where small blood clots are formed in the body, disrupt the normal coagulation process and cause bleeding. This can be further complicated if the patient has co-morbidities which require treatment with anti-coagulants. Prompt treatment of the cancer with hormones and in some cases replacement of blood, platelets and clotting factors may be required
Hot flushes during androgen deprivation therapy	The hypothalamus is the centre for thermoregulation. Orchiectomy and LHRH agonists inhibit some of the peptides involved in thermoregulation. This increases central adrenergic activity and inappropriate stimulation of thermoregulatory centres, causing peripheral body vasodilatation and hot flushes. Low dose cyproterone acetate (100 mg a day) has been used to suppress hot flushes

Table 48.4 International Prostatitis Collaborative Network (IPCN) classification of prostatitis

IPCN classification	Comment
I. Acute bacterial prostatitis	Acute infection of the prostate
II. Chronic bacterial prostatitis	Chronic infection of the prostate
III. Chronic prostatitis/chronic pelvic pain syndrome	No evidence of infection
A. Inflammatory	Leucocytes in prostatic secretions, post prostate massage urine, or semen
B. Non-inflammatory	No evidence of inflammation
IV. Asymptomatic inflammatory prostatitis	Lack of genitourinary symptoms

Pathophysiology

Acute bacterial prostatitis (ABP) is caused by bacterial infection. The most common isolated uropathogen is *Escherichia coli*. Other causative agents include *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp. and, less commonly, enterococci, *Bacteroides and Staphylococcus* spp. Chronic bacterial prostatitis (CBP) usually involves recurrent bacterial urinary infections caused by the same organism involved in acute bacterial prostatitis. Both syndromes are of infective origin and represent the minority of cases of prostatitis.

In contrast, the aetiology of chronic prostatitis/chronic pelvic pain syndrome is poorly understood. Several possible mechanisms have been proposed including autoimmune disorders, infection, neurogenic inflammation and voiding dysfunction.

Symptoms

In prostatitis, the clinical presentation and symptoms are a strong diagnostic determinant. A validated, nine-point questionnaire, the Chronic Prostatitis Symptom Index (CPSI) quantifies the severity, frequency and location of pain and discomfort. It is also used to assess urinary symptoms and to establish the impact of symptoms on the patient's quality of life.

Patients with acute bacterial prostatitis usually present with symptoms of a UTI which may include dysuria, urinary frequency or urgency, whilst some may present with pain of penile, lower back or perineal origin. Signs and symptoms of systemic infection can be present in some cases and include pyrexia, rigors, malaise and myalgia. Acute bacterial prostatitis can sometimes precipitate AUR due to prostatic inflammation.

In chronic bacterial prostatitis, symptoms of UTI and pain can also be present. Typically, men with chronic bacterial prostatitis remain asymptomatic between infective episodes.

The main feature in chronic prostatitis/chronic pelvic pain syndrome is urological pain (perineum, lower abdomen and back, rectum, penis and testicles). These symptoms are usually present for at least 3 months before a diagnosis can be made. LUTSs and ejaculatory dysfunction can also affect men with chronic prostatitis/chronic pelvic pain syndrome.

Patients with asymptomatic inflammatory prostatitis have no symptoms. The condition is usually diagnosed when patients undergo investigation to assess other genitourinary complaints. For example, prostatitis may be found in biopsies taken from patients investigated for elevated PSA or when leucocytes are found in semen samples from men being investigated for infertility.

Examination and investigations

If acute bacterial prostatitis is suspected, a urine dipstick and culture are performed to reveal the presence of pathogens and leucocytes. Depending on the clinical picture, a blood culture may be indicated to diagnose concomitant bacteraemia. An ultrasound scan of the bladder can be conducted to evaluate the residual volume of urine and problems with voiding and urinary retention.

Chronic bacterial prostatitis is diagnosed in men with a history of recurrent or relapsing UTIs. A positive urine dipstick and culture is a common finding during acute episodes. Microscopy and culture of lower tract urinary secretions (urine and prostatic) between symptomatic periods can be performed and will help identify the prostate as the main focus of infection. Imaging of the urinary tract can be conducted to rule out any structural abnormalities.

Chronic prostatitis/chronic pelvic pain syndrome is a diagnosis of exclusion. Typical disorders which must be excluded include the presence of active urethritis, urogenital cancer, urinary tract disease, functionally significant urethral stricture or neurological disease affecting the bladder (Krieger et al., 1999). The main component of this syndrome is the presence of genitourinary pain. After taking a detailed medical history, the evaluation of symptoms can be done using the Chronic Prostatitis Symptom Index. Other investigations include a DRE, urinalysis, urine culture and cytology, screening for sexually transmitted diseases, urodynamic studies, prostatic TRUS and serum PSA.

Treatment

Acute bacterial prostatitis can present as a serious infection and therapy normally includes empirical treatment with parenteral antibiotics. Commonly used agents include broad-spectrum penicillins, fluoroquinolones or third-generation cephalosporins usually in combination with aminoglycosides. Urine culture and sensitivities will inform the choice of future antibiotic treatment, which is recommended to be continued for 2–4 weeks. General supportive measures such as maintenance of appropriate hydration and pain relief are important. Suprapubic catheterisation may be required if AUR is present.

The treatment of chronic bacterial prostatitis involves long courses (at least 4 weeks) of antibiotics. Fluoroquinolones are used as first-choice agents because of good prostatic penetration, their spectrum of anti-bacterial activity and favourable safety profile. If infective episodes are frequent, patients can be offered prophylactic antibiotics for several months with periodic follow-up to monitor progress (McNaughton-Collins et al., 2007).

Since the aetiology of most cases of chronic prostatitis/chronic pelvic pain syndrome is unknown, management often involves empirical treatment. Despite not being considered to have an infective nature, up to 50% of patients with chronic prostatitis/chronic pelvic pain syndrome respond to long courses of fluoroquinolones (Nickel et al., 2001), especially men with symptoms of relatively recent onset (a few weeks). Patients with longstanding symptoms refractory to treatment are less likely to benefit from fluoroquinolones. α-Adrenoceptor antagonists are also used alone or in combination with antibiotics in the management of chronic prostatitis/chronic pelvic pain syndrome. The evidence for efficacy is conflicting but remains an option for patients with persistent symptoms. There are also limited data describing the use of other therapies in chronic prostatitis/chronic pelvic pain syndrome such as fluoxetine, pollen extract, quercertin, finasteride, mepartricin and pelvic electromagnetic therapy.

No treatment is necessary for patients with asymptomatic inflammatory prostatitis since the condition is characterised by the lack of symptoms.

Patient care

Patients need to be made aware that prostatitis is common and affects between 1 and 2 out of every 10 men. The cause is generally poorly understood and it is difficult to diagnose. In chronic cases of prostatitis, symptoms may persist for long periods, although the severity can vary over time. Treatment may involve several therapies. Patients treated with antibiotics must be informed of the importance of completing the prolonged courses necessary to eradicate infection.

The British Prostatitis Support Association has a website (http://www.bps-assoc.org.uk) that offers patients information and support.

Case studies

Case 48.1

A 64-year-old man presents with complaints of poor urinary flow and having to visit the toilet at least twice during the night to pass urine. There is no family history of prostate disease and he is taking no medication.

Question

What investigations are appropriate and how should this patient be managed?

Answer

This patient should be asked to present a frequency volume chart of voided urine and undergo a full clinical examination, including measurement of PSA. The PVR volume of urine within the bladder should be measured after micturition.

If the PSA is within the normal range and the residual volume is less than 100 mL, the patient can be reassured about his condition and a 'watch and wait' policy adopted. If the patient finds this unacceptable, then he should be offered treatment with an α-adrenoceptor antagonist. If he is not hypertensive, a uroselective drug such as tamsulosin can be considered. This should have few systemic side effects and requires no initial titration of dose. If he is hypertensive, a less specific α-blocker may be more appropriate which will serve the dual purpose of an anti-hypertensive agent as well as treating his urinary symptoms. Careful dose titration may be necessary initially to counter any potential postural hypotension. The combination of an α-adrenoceptor antagonist and 5α-reductase inhibitor may be considered the treatment of choice for this patient.

Case 48.2

A 50-year-old man requests treatment from his primary care doctor for a 'bladder infection'. On questioning, he describes symptoms of urinary frequency, urgency and urge incontinence, but fever is absent.

Question

How should this patient be treated?

Answer

The lay person may interpret the symptoms of frequency and urgency as representing a UTI, but in the absence of dysuria this is unlikely. The patient should be referred for a full clinical assessment which should include urodynamic studies, filling and voiding cystometry, an ultrasound scan of the upper urinary tract, measurement of PSA and assessment of renal function. It is likely the patient has an outflow obstruction which has given rise to secondary instability of the detrusor muscle in the bladder, causing involuntary contractions of the bladder and resulting in incontinence. The obstruction may be due either to prostate enlargement or a dysfunctional bladder neck. In either case, treatment with an α-adrenoceptor antagonist is appropriate to reduce the outflow resistance. Should the flow be adequate but symptoms of incontinence persist, then concurrent treatment with an anti-muscarinic drug such as oxybutynin or tolterodine may be necessary to inhibit the cholinergic-mediated contractions of the detrusor.

There is emerging evidence that phosphodiesterase-5 inhibitors may also be useful in the management of LUTSs. It is known there is an abundance of the phosphodiesterase-5 isoenzyme in the prostate, and it is thought this is involved in the regulation of smooth muscle tone. A number of small-scale studies have shown the benefit of agents such as sildenafil and tadalafil, although both are currently licensed only for the treatment of erectile dysfunction. It may be appropriate to prescribe one of these agents for the patient in question.

Case 48.3

A 75-year-old male presents with AUR and a history of nocturia for the past 2–3 months. His medical history includes a heart valve replacement. He denies any haematuria or dysuria and

has good flow while passing urine. On DRE, the prostate is found to be hard and nodular on one side and the PSA was 662 ng/mL

Questions

1. What investigations are recommended and how should this patient be managed?
2. What treatment choice is available for this patient?
3. What are the most likely future complications expected in this patient?

Answers

1. Since AUR is painful and can cause renal damage, he needs to be catheterised to relieve his bladder. A hard and nodular prostate on DRE together with elevated PSA suggests PC. The patient needs to have a range of baseline investigations including a TRUS biopsy, MRI of the pelvis and isotope bone scan. Although the DRE is suggestive of PC, the TRUS biopsy helps to grade the cancer using the Gleason scale and helps in making the decision about treatment. The bone scan helps identify bone metastasis which along with the results from MRI is used to stage the cancer based on the TNM score.

   The MRI pelvis revealed an enlarged and irregular prostate with intra-vesicle extension of the medial lobe into the bladder neck. The patient was confirmed to have adenocarcinoma of the prostate with a Gleason score of 8 and with bone metastasis.
2. Surgical castration can bring down the testosterone levels immediately and is relatively inexpensive but may have a psychological impact on the patient in addition to impotence and hot flushes. Medical castration with LHRH analogues would be effective treatment as well. LHRH agonists can be used to treat systemically as it produces response in more than 70% men, but the concern with this group of drugs is the flare up of the disease due to the initial surge in testosterone levels in addition to the other side effects of decreased libido, hot flush and impotence. Flare can precipitate life-threatening symptoms of the disease if the cancer is close to the spinal cord where it may cause spinal cord compression and paralysis. If lymph nodes near the ureter are involved the flare can increase the node size and compress the ureter causing renal impairment. It can also increase bone disease causing severe bone pain. Although initiation of anti-androgens can reduce symptoms of hot flushes associated with flare up to some extent, the preferred option for patients with increased risk of spinal cord compression would be LHRH antagonist as it can reduce testosterone levels much more quickly with no flare up.

   Hormonal treatment was commenced with an LHRH agonist injection together with a 1-month course of cyproterone acetate to protect against tumour flare. His PSA fell from 662 to 130 ng/mL in 5 months and continued to fall to 3.2 ng/mL after 9 months indicating a good response to hormonal treatment. Although the patient wanted to be catheter free, he failed several trials without a catheter and was offered radical radiotherapy and TURP to control local obstructive symptoms.
3. As the disease progresses, the patient can develop hormone resistance and non-hormonal treatment such as chemotherapy with docetaxel and ketoconazole may need to be considered. Osteoporosis is an important potential complication of long-term androgen deprivation therapy and metastatic bone disease and consequently the patient may experience severe bone pain. Palliative radiotherapy to metastatic bone areas and NSAIDs are recommended to control the symptoms initially, but if pain persists use of bisphosphonates may be necessary as they are known to inhibit osteoclast activity and relieve bone pain.

Case 48.4

A 35-year-old man presents with a 3-month history of dysuria, frequency and hesitancy. He also complains of pain in the perineum and discomfort while ejaculating. A DRE reveals the size and shape of his prostate seems to be normal although it is tender on examination.

Question

What are the various conditions that need to be considered and what medication will help confirm the diagnosis?

Answer

A urine dipstick and culture is recommended to rule out UTI. PSA can be measured but is raised in BPH, PC and prostatitis and hence is not a definitive test. The symptoms and physical examination are suggestive of chronic prostatitis. A swab should be taken to rule out chlamydia and other sexually transmitted diseases. Prostatitis needs to be confirmed after ruling out other possibilities like epididymitis, epididymo-orchitis, urethral stricture, renal calculus, PC, bladder and colorectal cancer.

The available evidence suggests a cure or an improvement in symptoms will occur if a quinolone antibiotic is prescribed for 4 weeks. NSAIDs and paracetamol can be used to relieve any associated pain whilst faecal softeners may be required to reduce discomfort and pain when opening bowels.

Case 48.5

A 43-year-old male seeks advice from a community pharmacist regarding his difficulty, over the past 3–4 months, when attempting to start urinating and then urinating for a long time. On questioning, he does not have any other significant medical history and he has no symptoms of a UTI, pain or haematuria.

Questions

1. Is it appropriate to sell over-the-counter tamsulosin to this patient?
2. Does the pharmacist need to maintain a record of the sale?

Answers

1. LUTSs, like hesitancy and weak stream, indicate BPH which is prevalent in one in four men above the age of 40 years. Since it is a very sensitive topic for most males, the patient needs to be consulted in a private area to assess the severity of his symptoms by using the IPSS. This is a sum of seven urinary symptoms which include incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia. If these symptoms severely affect the quality of life and there are no contraindications, a supply of tamsulosin 400 µcg to be taken once daily for 2 weeks initially and then for a further 4 weeks can be made while simultaneously referring the patient to his primary care doctor to confirm diagnosis and to assess his suitability for long-term treatment. If the symptoms do not improve within 14 days or the symptoms worsen, the patient should be asked to discontinue treatment and seek medical advice.
2. Record keeping is necessary to confirm that the doctor has assessed the patient within 6 weeks of initiating treatment and thereby permit further supply. It is important that the patient's consent is obtained to keep this record.

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49 Anaemia

C. Acomb and R. Sanderson

Key points

- Anaemia is a common condition which is caused by a number of pathologies and can be subdivided into microcytic, megaloblastic and haemolytic types.
- Iron deficiency is the commonest form of microcytic anaemia worldwide. Once the primary cause has been corrected, ferrous salts are the standard treatment.
- Folate deficiency results in a macrocytic anaemia and is treated with replacement therapy.
- Lack of intrinsic factor prevents absorption of vitamin B_{12} leading to a macrocytic anaemia. Treatment with parenteral B_{12} reverses the blood picture but does not always alleviate the accompanying neuropathy.
- Haemolytic anaemias include the generic disorders of sickle cell anaemia, thalassaemia and glucose-6-phosphate dehydrogenase deficiency. In these diseases, abnormal forms of haemoglobin lead to haemolysis.
- Sideroblastic anaemia is a rare anaemia caused by impaired haem synthesis where the body has adequate iron stores but is unable to incorporate them into haemoglobin.

Anaemia is not one disease, but a condition that results from a number of different pathologies. It can be defined as a reduction from normal of the quantity of haemoglobin in the blood. The World Health Organisation defines anaemia in adults as haemoglobin levels less than 13 g/dL for males and less than 12 g/dL for females. However, there are apparently normal individuals with levels less than this. The low haemoglobin level results in a corresponding decrease in the oxygen-carrying capacity of the blood.

Epidemiology

Anaemia is possibly one of the most common conditions in the world and results in significant morbidity and mortality, particularly in the developing world. Worldwide, over 50% of pregnant women and over 40% of infants are anaemic. In the UK, 14% of women aged 55–64 and 3% of men aged 35–64 have been found to be anaemic.

Aetiology

The low haemoglobin level that defines anaemia results from two different mechanisms:

- Increased haemoglobin loss due to either:
  - haemorrhage (red cell loss) or
  - haemolysis (red cell destruction).
- Reduced haemoglobin synthesis due to either:
  - lack of nutrient or
  - bone marrow failure.

Reduced haemoglobin synthesis leads to either reduced proliferation of precursors or defective maturation of precursors or both (see Table 49.1). It is not unusual to find more than one cause in a single patient.

This chapter will cover some of the more common anaemias that involve drug therapy:

Microcytic anaemias	iron deficiency anaemia anaemia of chronic disease sideroblastic anaemia
Megaloblastic anaemias	folate deficiency vitamin B_{12} deficiency
Haemolytic anaemias	autoimmune haemolytic anaemia sickle cell disease thalassaemia glucose-6-phosphate dehydrogenase deficiency

Table 49.1 Examples of conditions that cause reduced haemoglobin synthesis

Reduced proliferation of precursors	Defective maturation of precursors
Iron deficiency	Vitamin B_{12} deficiency
Anaemia of chronic disease	Folate deficiency
Anaemia of renal failure	Iron deficiency
Aplastic anaemia (primary)	Disorders of
Aplastic anaemia (secondary to drugs, etc.)	– globin synthesis (thalassaemias)
Infiltration of the bone marrow:	– iron metabolism (e.g. sideroblastic)
– leukaemia or lymphoma	Myelodysplastic syndrome
– myelofibrosis	
– metastases	

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Normal erythropoiesis

It is thought that white cells, red cells and platelets are all derived from a common cell known as the pluripotent stem cell found in the bone marrow. As these cells mature, they become committed to a specific cell line (Fig. 49.1). The red cells mature through the various stages, during which time they synthesise haemoglobin, DNA and RNA. Reticulocytes are found in the peripheral circulation for 24 h before maturing into erythrocytes. Reticulocytes are released into the peripheral circulation prematurely during times of increased erythropoiesis.

Erythropoietin is a hormone produced by the cells of the renal cortex. The kidney responds to hypoxia and anaemia by increasing the production of erythropoietin. The red cell progenitors BFU-E and CFU-E have receptors on their surface. When erythropoietin binds to these receptors, it promotes differentiation and division, and consequently increased erythropoiesis. Patients with end-stage renal disease fail to produce appropriate amounts of erthropoietin and so develop anaemia. Erythropoietin production is also impaired in other conditions such as rheumatoid arthritis, cancer and sickle cell disease, though the impairment is not as great as in renal disease. Also of interest is the fact that theophylline decreases erythropoietin production, though the clinical relevance of this is uncertain.

Each day approximately 2×10^{11} erythrocytes enter the circulation. Normal erythrocytes survive in the peripheral circulation for about 120 days. Abnormal erythrocytes have a shortened lifespan. At the end of their life, the red cells are destroyed by the cells of the reticuloendothelial system found in the spleen and bone marrow. Iron is removed from the haem component of haemoglobin and transported back to the bone marrow for reuse. The pyrole ring from globin is excreted as conjugated bilirubin by the liver, and the polypeptide portion enters the body's protein pool.

Clinical manifestations

In its mildest form anaemia results in tiredness and lethargy; at its most severe it results in death unless treated. There is some suggestion that even mild anaemia may inhibit physical exercise and result in reduced mental performance. The reduced oxygen-carrying capacity of the blood leads to reduced tissue oxygenation and widespread organ dysfunction (Box 49.1).

A rapid blood loss, for example, haemorrhage, produces shock, with collapse, dyspnoea and tachycardia. Anaemia that develops over a period of time allows the body to partially compensate. As the anaemia becomes worse, more and more signs and symptoms may develop.

Even though in anaemia the amount of haemoglobin is reduced, all the blood that passes through the lungs is fully oxygenated. Increasing the respiratory rate or increasing the FiO_2 (fraction of inspired oxygen) will not improve tissue oxygenation. When the haemoglobin falls below 7 or 8 g/dL, there is almost always a compensatory increase in cardiac output.

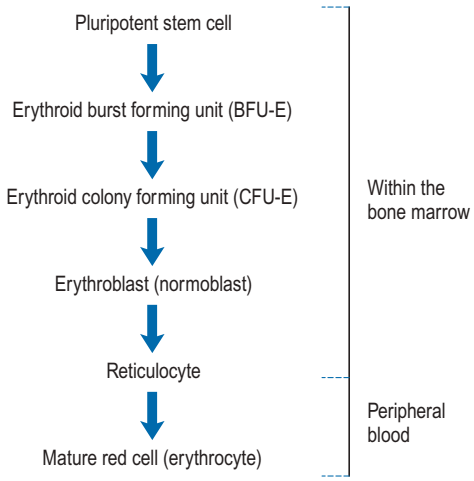


Fig. 49.1 Simplified diagram of some of the stages within erythropoiesis.

Investigations

It is essential to find the cause of the anaemia; there is no place for 'blind' treatment. In most patients, the anaemia is a consequence of a reduced concentration of haemoglobin in each red cell and/or a reduced number of red cells in the peripheral circulation. Blood volumes may be increased in pregnancy and heart failure and haemoglobin concentration appear falsely low. Splenomegaly and signs of heart failure are sure signs of an increased blood volume. A blood transfusion in such a patient would precipitate left ventricular failure.

The most important parameter to assess anaemia is the haemoglobin concentration of the blood. It is also usual to count the number of red cells. In addition the size, shape and colour all contribute to the investigation (Box 49.2). The mean corpuscular volume (MCV) is a useful parameter that helps determine the type of the anaemia. However, care must be

Box 49.1 Non-specific signs and symptoms associated with anaemia

- Tiredness
- Pallor
- Fainting
- Exertional dyspnoea
- Tachycardia
- Palpitations
- Worsening angina
- Worsening cardiac failure
- Exacerbation of intermittent claudication

Box 49.2 Anaemia classified by size and colour of red cells

Hypochromic–microcytic
- Iron deficiency
- Sideroblastic
- Anaemia of chronic disease

Normochromic macrocytic
- Folate deficiency
- Vitamin B_{12} deficiency

Polychromatophilic macrocytic
- Haemolysis

taken since the MCV indicates the average size of the cells. If there are two pathologies, where one causes large cells and other causes small cells, the MCV may appear normal or be misleading. Following on from this baseline other investigations may be required. Bone marrow examination by either aspiration or trephine may be needed to make a diagnosis.

Iron deficiency anaemia

Epidemiology

Iron deficiency anaemia is the commonest form of anaemia worldwide and may be present in up to 20% of the world's population. A diet deficient in iron, parasitic infestations, for example, hookworm (causing blood loss), and multiple pregnancies contribute to its high prevalence in underdeveloped countries. Even in Western societies, it has been reported that as many as 20% of menstruating females show a rise in haemoglobin levels on iron therapy.

Aetiology

In Western societies, the commonest cause of iron deficiency is due to blood loss. In women of childbearing age, this is most commonly due to menstrual loss. Amongst adult males, the most likely cause is gastro-intestinal bleeding. Other causes of blood loss associated with iron deficiency anaemia include haemorrhoids, nosebleeds or postpartum haemorrhage. A loss of 100 mL of blood represents the amount of iron normally absorbed from a Western diet over 40 days. The major causes of iron deficiency are listed in Box 49.3.

Pathophysiology

The elimination of iron is not controlled physiologically, so the homeostasis is maintained by controlling iron absorption. Iron is absorbed mainly from the duodenum and jejunum. Absorption itself is inefficient; iron bound to haem (found in red meat) is better absorbed than iron found in green vegetables. The presence of phosphates and phytates in some vegetables leads to the formation of unabsorbable iron complexes, whilst ascorbic acid increases the absorption of iron. In a healthy adult, approximately 10% of the dietary iron intake will be absorbed. Iron is transported around the body bound to a serum protein called transferrin. Normally, this protein is only one-third saturated with iron.

Anaemia may result from a mismatch between the body's iron requirements and iron absorption. The demand for iron varies with age (Table 49.2). Diets deficient in animal protein or ascorbic acid may not provide sufficient available iron to meet the demand. Poor nutrition in children in inner cities in the UK frequently leads to anaemia. Milk fortified with iron given to inner city infants up to the age of 18 months has been shown to increase haemoglobin levels and improve developmental performance compared to unmodified cow's milk (Williams et al., 1999). A systematic review showed that iron supplementation in children over seven improved intelligence tests scores in those who were initially anaemic (Sachdev et al., 2005). However, universal iron supplementation may not be appropriate because there is a theoretic increased risk of susceptibility to infectious diseases, although this has only been demonstrated for diarrhoea (Gera and Sachdev, 2002) and malaria in endemic areas (Prentice et al., 2007). Targeting supplementation only to children with anaemia and withholding iron supplementation during malaria treatment is sensible as iron may inhibit treatment, and absorption of oral iron is blocked by the inflammatory response.

Malabsorption of iron has been reported in patients with coeliac disease and in 50% of patients following partial gastrectomy. Tetracyclines, penicillamine and fluoroquinolines bind iron in the gastro-intestinal tract and reduce the absorption of iron from supplements. They probably do not affect the absorption of dietary iron.

During pregnancy, there is an increase in red cell mass but there is also a proportionally bigger increase in plasma volume, which results in a physiological dilutional anaemia. It is thought that the gut increases its ability to absorb iron during pregnancy to meet the additional demands of fetal red cell production. Some of the increased demand is met by the stopping of menstruation. If, however, there is inadequate iron absorption, then anaemia may result.

Table 49.2 Typical daily requirements of iron

Infant (0–4 months)	0.5 mg
Adolescent male	1.8 mg
Adolescent female	2.4 mg
Adult male	0.9 mg
Menstruating female	2.0 mg
In pregnancy	3–5 mg
Postmenopausal female	0.9 mg

Box 49.3 Major causes of iron deficiency anaemia

- Inadequate iron absorption
  - Dietary deficiency
  - Malabsorption
- Increased physiological demand
- Loss through bleeding

Clinical manifestations

In addition to the general symptoms of anaemia, various other features may be present (Box 49.4). The colour of the skin is very subjective and often unreliable. Patients at risk of heart failure may present with breathlessness when anaemic. Koilonychia, dysphagia and pica are found only after chronic iron deficiency and are relatively rare.

A full blood count is an essential screening test. The cells of the peripheral blood are microcytic and hypochromic with poikilocytes (often pencil shaped) and occasional target cells

Box 49.4 Features of iron deficiency anaemia

Pale skin and mucous membranes
Painless glossitis
Angular stomatitis
Koilonychia (spoon shaped nails)
Dysphagia (due to pharyngeal web)
Pica (unusual cravings)
Atrophic gastritis

(abnormal thin erythrocytes which when stained show a dark centre and peripheral ring).

The main parameter used to help establish the iron status of the patient is the serum ferritin. The serum ferritin level is low in iron deficiency anaemia and markedly raised in iron overload. It is a good measure of the iron stores in the body. Care needs to be used in interpreting raised ferritin levels as these are sometimes found in cancer, inflammatory conditions and liver disease. Serum iron is a less useful parameter and exhibits diurnal variation, being higher in the morning.

Investigations

The aim of treatment is to correct the anaemia and replenish iron stores. Although the treatment of iron deficiency anaemia is relatively simple, it should not be embarked upon lightly. It is important to resolve the underlying cause as far as possible. Since gastro-intestinal blood loss is the most common cause in men and postmenopausal women, examination of the upper and lower tract is an important investigation. If necessary, this may need to include upper gastro-intestinal tract endoscopy, colonoscopy, barium enema and small bowel biopsy.

Over-the-counter sales of iron should be discouraged except in those patients who have been fully investigated. It is not unknown for patients to be given iron unnecessarily, resulting in iron overload. Also, giving iron therapy to a patient who is continuing to bleed from their gastro-intestinal tract will not help resolve the underlying problem.

Treatment

Prophylaxis of iron deficiency anaemia was widely used in pregnancy (together with folic acid); however, it is now only used for women who have additional risk factors for iron deficiency, for example poor diet. Prophylaxis may also be used in menorrhagia, after partial gastrectomy and in some low birth weight infants, for example, premature twins.

If gastro-intestinal investigation has been performed and any underlying cause treated, all patients should receive iron supplementation to correct their anaemia and replenish stores. Oral iron in the ferrous form is cheap, safe and effective in most patients. Depending on the state of the body's iron stores, it may be necessary to continue treatment for up to 6 months to both correct the anaemia and replenish body stores. The standard treatment is ferrous sulphate 200 mg two to three times a day. It typically takes between 1 and 2 weeks for the haemoglobin level to rise 1 g/dL. An earlier indication of the patient's response can be seen by looking at the reticulocyte count, which should start to rise 2–3 days after starting effective treatment. Nausea or abdominal pains trouble some patients and this tends to be related to the dose of elemental iron. Giving the iron with food makes it better tolerated but tends to reduce the amount absorbed. Alternative salts of iron are sometimes tried; these tend to have fewer side effects simply because they contain less elemental iron (Table 49.3). Taking fewer ferrous sulphate tablets each day would have the same effect. A change in bowel habit (either constipation or diarrhoea) is sometimes reported, and this is probably not dose related. During the early stages of treatment, the body absorbs oral doses of iron better. Absorption is commonly around 15% of intake for the first 2–3 weeks but falls off to an average of 5% thereafter. It has been shown that for some patients eradication of *Helicobacter pylori* aids recovery from iron deficiency anaemia (Annibale et al., 1999).

There are a number of modified-release oral preparations available. They have no clear therapeutic advantage over ferrous sulphate and are not recommended. Indeed, the modified-release characteristic may cause the oral iron to be carried into the lower gut, which is much poorer at absorbing iron than the duodenum. Modified-release preparations may be more likely to exacerbate diarrhoea in patients with inflammatory bowel disease or diverticulae.

There is a limited place for parenteral iron in iron deficiency anaemia; it should be reserved for patients who fail on oral therapy, usually because of poor adherence or intolerable gastro-intestinal side effects. For most patients when equivalent doses of oral and parenteral iron are used, there is no difference in the rate of at which the haemoglobin level rises. Patients who have lost blood acutely may require blood transfusions. The need for a rapid rise in haemoglobin is not an indication for parenteral iron. Intravenous iron has been shown to have some benefit during the perioperative management of anaemia in selected patients undergoing orthopaedic surgery, but not been observed in other types of surgery (Beris et al., 2008).

There is a risk of anaphylactoid reactions with intravenous iron but the incidence appears to be lower with the newer products than with the older preparations which have now been discontinued. Patients given the newer licensed

Table 49.3 Elemental iron content of common oral preparations

Preparation	Approximate iron content (mg)
Tablets	
Ferrous sulphate 210 mg	68
Ferrous gluconate 300 mg	35
Ferrous fumarate 322 mg	100
Ferrous fumarate 210 mg	68
Oral liquids	
Ferrous fumarate 140 mg in 5 mL	45
Ferrous sulphate 125 mg in 1 mL	25
Sodium feredetate 190 mg in 5 mL	27.5

products, iron dextran (CosmoFer®), iron sucrose (Venofer®), iron III isomaltoside (Monofer®) and ferric carboxymaltose (Ferinject®) should have a test dose, and there should be facilities for cardiopulmonary resuscitation available. The dose for all products is calculated from the body weight and iron deficit. The manufacturer's product information provides details on administration. Some products can be given as a bolus injection (small doses) or by a short intravenous infusion or by a total dose infusion method. There seems to be a higher incidence of adverse reactions with the total dose infusions. Iron dextran may also be given by deep intramuscular injection. Intravenous iron should not be given during acute bacterial infections, since it may stimulate bacterial growth. As intravenous iron significantly reduces the oral absorption of iron, there is no rationale for giving oral iron for several days after administering intravenous iron.

Patient care

It is usual practice to advise patients to take iron products with or after meals as this probably reduces the incidence of nausea. Patients should be told that their faeces may become darker and that this is nothing to worry about. This is important in patients who have had malaena since they may associate their dark stools with the bleed and worry that they are still bleeding from the gastro-intestinal tract. The length of treatment, and adherence should be discussed and an explanation given that iron stores need to be replenished and that this takes time.

Anaemia of chronic disease

Epidemiology

This is the second most common form of anaemia (after iron deficiency). It is associated with a wide variety of inflammatory diseases including arthritis, malignancies, inflammatory bowel disease, HIV and other infections. It is increasingly being referred to as ‘anaemia of inflammation’. Related to anaemia of inflammation are the anaemias associated with chronic kidney disease and chronic heart failure.

Aetiology

In anaemia of inflammation, there appears to be impaired response to erythropoietin and the inflammatory cytokines lead to a reduction in the availability of circulating iron. This cytokine-mediated shift of iron from the circulation into reticuloendothelial system leads to iron restricted erythropoiesis, despite normal iron stores. In malignancies, in addition to the anaemia of inflammation, the cytotoxic treatments themselves decrease erythrocyte production through their anti-proliferative effects on the bone marrow. Certain cytotoxic agents, such as platinum-based therapies, are more likely to cause anaemia.

In chronic kidney disease and chronic heart failure, the reduced renal blood flow leads to a decreased production of erythropoietin.

Pathophysiology

During infections, inflammation and cancer, the inflammatory cytokines, in particular interleukin-6 released from macrophages, lead to an increased production of hepcidin. Hepcidin, a peptide produced by hepatocytes, plays a key role in iron availability. The hepcidin causes

- increased uptake of iron by hepatocytes;
- reduced iron absorption;
- reduced release of iron from macrophages.

The reduction of circulating iron is thought to limit this essential nutrient's availability to invading microbes and tumour cells, blocking their proliferation.

In addition, the inflammatory cytokines increase the production of white blood cells which potentially lead to fewer stem cells being available for red cell production.

Clinical manifestations

Patients have the general symptoms of anaemia in addition to their symptoms of the chronic inflammatory condition. The anaemia frequently leads to a reduced quality of life for these patients.

Investigation

Patients have a hypochromic microcytic anaemia similar to iron deficiency anaemia, but the two conditions can be differentiated by reviewing other serum factors (see Table 49.4).

Treatment

Treating the underlying chronic condition is important. Blood transfusions are rarely needed in anaemia of inflammation. Oral iron therapy is not usually indicated despite the apparent reduced iron availability since these patients have a functional iron deficiency rather than an actual iron deficiency; also, the raised hepcidin levels reduce the oral absorption of iron.

A number of patients with chronic renal failure appear to have a functional iron deficiency that responds to intravenous iron. These patients, despite receiving oral iron and erythropoietin analogues, do respond with a rise in haemoglobin when given regular intravenous iron together with an erythropoietin

Table 49.4 Differentiation between iron deficiency anaemia and anaemia of chronic disease

Test	Iron deficiency anaemia	Anaemia of chronic disease
Serum iron	Low	Low
Serum ferritin	Low	Normal or high
Serum transferrin	High	Normal or low
Total iron binding capacity	High	Low

analogue (Silverberg et al., 1996). Intravenous iron in combination with erythropoietin analogues is widely used in chronic kidney disease. The patient's serum ferritin is monitored to check for iron overload. Concerns have been expressed about the possible long-term complications of intravenous iron, for example, atherosclerosis or increased risk of infection (Cavill, 2003). There appears to be a slightly increased risk of infections, but the improvement in anaemia leads to an improved quality of life.

Patients with anaemia-associated inflammatory bowel disease or with rheumatoid arthritis respond to intravenous iron; however, the use of intravenous iron in chronic inflammatory conditions is not generally recommended because of an increased risk of infections and also possible increased risk of acute cardiovascular events. Some small studies have shown intravenous iron to be beneficial in patients with heart failure, but currently this should be reserved for patients with proven iron deficiency and failure on oral iron (Dec, 2009).

Some patients with chronic disorders respond to erythropoietin analogues, none are licensed for use in chronic disease states other than anaemia associated with chronic renal failure or cancer. Elevated endogenous erythropoietin levels in patients with heart failure are associated with adverse outcomes (Felker, 2010). Some clinical trial data show a higher mortality and increased risk of tumour progression in patients with anaemia associated with cancer who have been treated with erythropoietins. It is not recommended that erythropoietin analogues are routinely used in the management of cancer treatment-induced anaemia (NICE, 2008). However, they may be considered, in combination with intravenous iron, for:

- women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin concentration of 8 g/100 mL or lower. The use of erythropoietin analogues does not preclude the use of existing approaches to the management of anaemia, including blood transfusion when necessary;
- patients who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

Tocilizumab, the interleukin-6 antagonist monoclonal antibody licensed for use in rheumatoid arthritis, has been shown to improve haemoglobin levels (Raj, 2009). It has also been suggested that drugs which downregulate interleukin-6 may have some effect (Altschuler and Kast, 2005). Olanzepine and quetiapine (potent H_1 antagonists) are known to be regulators of interleukin-6 but are not used clinically for this purpose. Furthermore, it is not known what the other effects of modifying interleukin-6 or hepcidin would have on the chronic inflammatory condition.

Patient care

Some patients hearing they have anaemia may be tempted to go and purchase iron or other supplements. Careful explanation will help them make an informed decision.

Sideroblastic anaemias

Epidemiology

Sideroblastic anaemias are a group of conditions that are diagnosed by finding ring sideroblasts in the bone marrow. There are both hereditary and acquired forms. The hereditary forms are rare, whilst some of the acquired forms are relatively common with as many as 30% of alcoholics admitted to hospital having sideroblastic anaemia.

Aetiology

In the majority of hereditary forms, there is an X chromosome-linked pattern of inheritance. Both autosomal dominant and autosomal recessive families have been described. The main defect is a reduced activity of the enzyme 5-aminolevulinate synthase (ALAS) which is involved in haem synthesis.

The acquired forms include idiopathic forms, forms associated with myeloproliferative disorders and forms secondary to the ingestion of drugs (Box 49.5). Regardless of the cause, there is impaired haem synthesis, where the body has adequate iron stores but is unable to incorporate it into haemoglobin.

Pathophysiology

An examination of the bone marrow typically shows a number of erythroblasts that have iron granules surrounding the cell nucleus. These cells are known as ring sideroblasts. In the hereditary forms, there are low levels of ALAS. This mitochondrial enzyme is involved in the first step in the synthesis of haem and requires pyridoxal phosphate as a co-factor. Pyridoxine is a precursor for pyridoxal.

Drugs and toxins

Alcohol can lead to the formation of ring sideroblasts. Ethanol is metabolised to acetaldehyde. It is the acetaldehyde that lowers the levels of ALAS and pyridoxal. Isoniazid is a known cause of sideroblasts. In slow acetylators of

Box 49.5 Acquired sideroblastic anaemia

Associated with other disorders
Myelodysplastic syndromes
Myeloid leukaemia
Myeloma
Collagen diseases

Associated with drugs and toxins
Alcohol
Isoniazid
Chloramphenicol
Penicillamine
Pyrazinamide
Cycloserine
Progesterone (single case report)
Copper deficiency (associated with penicillamine, triethylene tetramine and tetrathiomolybdate)

isoniazid, the drug reacts with pyridoxal and the resulting product is then rapidly excreted. Pyridoxine prophylaxis is usually given to all patients on isoniazid. Doses of chloramphenicol over 2 g a day invariably lead to sideroblasts. This is thought to be due to the inhibition of mitochondrial protein synthesis. Sideroblastic anaemia is also associated with copper deficiency which can be caused by an overdose of the chelators: penicillamine, trientine and the experimental tetrathiomolybdate. These are all used in the treatment of Wilson's disease.

Clinical manifestations

The hereditary forms typically develop in infancy or childhood. The anaemia can be severe or mild (haemoglobin typically 4–10 g/dL). There may be splenomegaly, which can lead to mild thrombocytopenia. The idiopathic acquired forms tend to develop insidiously usually in middle age or later. Many patients may be asymptomatic for long periods. In the forms associated with other disorders, the clinical picture tends to be dominated by the underlying diseases.

Investigations

The common finding in all forms is the presence of sideroblasts in the bone marrow. In the hereditary form, the red cells in the peripheral blood are hypochromic and microcytic. Despite this, there are frequently increased iron stores in the bone marrow. The serum iron and ferritin may also be high. In the acquired forms, the peripheral blood has hypochromic cells, which may be either normocytic or macrocytic.

Treatment

In patients with the hereditary forms, large doses of pyridoxine (typically 100–200 mg daily or even up to 400 mg) may reduce the severity of the anaemia. Long-term high-dose pyridoxine has been associated with peripheral neuropathy and so lower maintenance doses are sometimes tried. There have been case reports of patients responding to parenteral pyridoxal-5-phosphate after failing to respond to pyridoxine. Patients with an acquired form occasionally respond to high-dose pyridoxine, and a 2- to 3- month trial may be helpful in symptomatic patients. The response tends to be slow and only partial. Haem arginate (licensed for use in porphyria) has been shown to increase the red cell count and decrease the number of ring sideroblasts in some patients with acquired sideroblastic anaemia, in common with other conditions where an increased turnover of cells in the bone marrow and folate supplements are often necessary.

Although the peripheral blood cells are frequently hypochromic and microcytic, the condition is associated with increased iron stores; therefore, iron supplements should be avoided. The drugs and toxins (Box 49.5) tend to cause a reversible anaemia. Removing the offending agent usually resolves the anaemia.

Iron overload

Inevitably, some patients fail to respond to these treatments and frequent blood transfusions are required. This leads to the complications of iron overload and sensitisation and the risk of blood-borne virus transmission. The chelating agent desferrioxamine is given either by intravenous or by subcutaneous infusion. It binds free iron and iron bound to ferritin. Therapy should be considered when the serum ferritin level reaches 1000 µcg/L. Patients with very high ferritin levels may need daily infusions. Daily subcutaneous infusions using a disposable infusor or small infusion pump are suitable for home use. In the UK, a number of commercial healthcare companies provide a desferioxamine home care service. Published evidence suggests that for an equivalent dose, a longer infusion time results in increased iron excretion. Intravenous infusions can be given whenever the patient comes into hospital for a blood transfusion. Small doses (<200 mg) of vitamin C increase the effectiveness of desferrioxamine probably by facilitating iron release from the reticuloendothelial system. Higher doses of vitamin C are reported to increase the cardiotoxicity of iron overload. Patients with cardiac failure should not be given vitamin C with desferrioxamine. Desferrioxamine should not be given concurrently with prochlorperazine as prolonged unconsciousness may result.

There are two oral agents (desferiprone and deferasirox) licensed for iron overload. Deferiprone unfortunately causes reversible neutropenia in some patients and weekly neutrophil counts are required. It is licensed for patients intolerant of desferrioxamine. Deferasirox has been more recently introduced and comes as a dispersible tablet that needs to be taken at least 30 min before food. It is associated with a high incidence of gastro-intestinal ulcers and renal impairment. Decreased hearing and lens opacities have been reported. Auditory and ophthalmic testing is recommended before the start of treatment and at regular intervals thereafter (every 12 months).

Patient care

Few patients with hereditary or the idiopathic acquired forms have completely reversible anaemia. Patients need to be aware that treatment with pyridoxine may take several months before any signs of improvement are seen. They should be advised not to purchase over-the-counter iron or vitamin supplements, particularly ascorbic acid or pyridoxine, without discussing it with their consultant.

Megaloblastic anaemias

The megaloblastic anaemias are macrocytic anaemias (raised MCV). There is an abnormality in the maturation of haematopoietic cells in the bone marrow. In addition to abnormal red cells, the white cells and platelets may be affected. The two major causes are folate deficiency and vitamin B_{12} deficiency. Pernicious anaemia is a specific autoimmune disease that causes malabsorption of vitamin B_{12} due to a lack of intrinsic factor.

Epidemiology

Folate deficiency anaemia

Much of the world's population has a marginal dietary intake of folate. Body stores are low, and as soon as there is a decrease in dietary intake or there is increased folate demand, deficiency readily occurs.

Vitamin B_{12} deficiency anaemia

Strict vegans (e.g. Hindus) commonly have low vitamin B_{12} levels due to their dietary deficiency though actual anaemia is rarer. All patients who have had a total gastrectomy and up to 15% of those with a partial gastrectomy will develop vitamin B_{12} deficiency anaemia.

Pernicious anaemia

Pernicious anaemia is found most commonly in people of northern European descent. In Britain, the incidence is about 120 per 100,000 being higher in Scotland than in the south of England. Pernicious anaemia is usually a disease of the elderly, the average patient presenting at 60 years of age.

Non-megaloblastic macrocytic anaemia caused by alcohol abuse, hypothyroidism or paroxysmal nocturnal haemoglobinuria will not be discussed in this chapter.

Aetiology

Folate deficiency anaemia

Folate is readily available in a normal diet. Fruit, green vegetables and yeast all contain relatively large amounts of folate. Despite this relative abundance of folate in many foods, dietary deficiency is common, either as the sole cause of the folic acid deficiency anaemia or in conjunction with increased folate utilisation.

Vitamin B_{12} deficiency anaemia

Deficiency occurs from inadequate intake or malabsorption. The only dietary source of vitamin B_{12} (cyanocobalamin) is from food of animal origin. It is present in meat, fish, eggs, cheese and milk. Cooking does not usually destroy vitamin B_{12}. Daily requirements are between 1 and 3 µcg. Deficiency arises either from inadequate intake over a prolonged period or more commonly, in the West, from impaired absorption due to lack of intrinsic factor.

Malabsorption occurs if the distal ileum is removed; it may also occur with certain intestinal pathologies, particularly stagnant loop syndrome, tropical sprue and fish tapeworm infestation. Passive absorption does take place in the jejunum, but this is very inefficient and usually accounts for less than 1% of an oral dose.

Pathophysiology

The common biochemical defect in all megaloblastic anaemias is the inhibition of DNA synthesis in maturing cells.

Folate deficiency anaemia

The folate found in food is mainly conjugated to polyglutamic acid. Enzymes found in the gut convert the polyglutamate form to monoglutamate, which is readily absorbed. During absorption, the folate is methylated and reduced to methyltetrahydrofolate monoglutamate. This travels through the plasma and is transported into cells via a carrier specific for the tetrahydrofolate form. Within the cell, the methyl group is removed (in a reaction requiring vitamin B_{12}) and the folate is reconverted back to a polyglutamate form (Fig. 49.2). It has been suggested that the polyglutamate form prevents the folate leaking out of cells. The folate eventually acts as a coenzyme involved in a number of reactions including DNA and RNA synthesis. Defective DNA synthesis mainly affects cells with a rapid turnover, for example, gastro-intestinal cells and red blood cells, hence the sore tongue and anaemia seen in folate deficiency. During DNA synthesis, the folate coenzyme is oxidised to the dihydrofolate form, which is inactive and has to be reactivated by the enzyme dihydrofolate reductase. This is the enzyme inhibited by methotrexate and to a lesser extent by trimethoprim and pyrimethamine. Co-trimoxazole has been shown to increase the severity of megaloblastic anaemia.

Vitamin B_{12} deficiency

Absorption of vitamin B_{12} is mainly by an active process. Enzymes in the stomach release vitamin B_{12} from protein complexes. One molecule of vitamin B_{12} then combines with one molecule of a glycoprotein called intrinsic factor. The intrinsic factor protects the vitamin B_{12} from breakdown by microorganisms. There are specific receptors in the distal ileum for the intrinsic factor-vitamin B_{12} complex. The vitamin B_{12} enters the ileal cell and is then transported through the blood attached to transport proteins. Intrinsic factor does not appear in the blood.

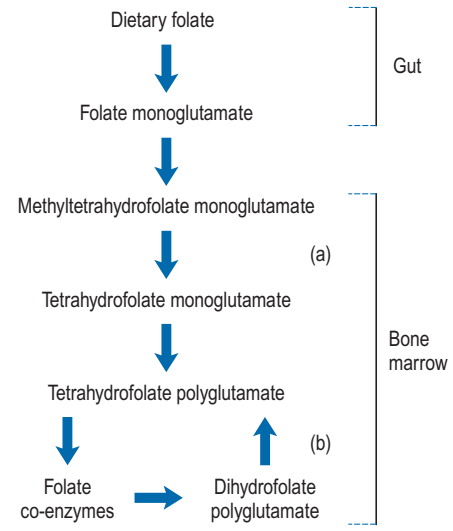


Fig. 49.2 Simplified pathway of folate metabolism: (a) vitamin B_{12} is required as a coenzyme for this reaction: (b) the enzyme dihydrofolate reductase converts inactive dihydrofolate back to the active tetrahydrofolate.

Since intrinsic factor is only produced by the gastric parietal cells, a total gastrectomy always leads to vitamin B_{12} deficiency. Approximately 10–15% of patients who have had a partial gastrectomy also develop deficiency. The onset of anaemia is usually delayed because the body typically has stores of 2–3 mg, which is sufficient for 2–3 years. Vitamin B_{12} is a coenzyme for the removal of a methyl group from methyltetrahydrofolate. Lack of vitamin B_{12} traps the folate as methyltetrahydrofolate and prevents DNA synthesis (Fig. 49.2). The exact mechanism by which vitamin B_{12} deficiency causes neuropathy is not clear but may be due to a defect in the methylation reactions needed for myelin formation.

Pernicious anaemia

Pernicious anaemia is probably autoimmune in origin. Patients typically have a gastric atrophy and no (or virtually no) intrinsic factor secretion. Although not present in all patients, two different antibodies have been found in the serum of some patients with pernicious anaemia.

Clinical manifestations

In addition to the general features of anaemia, megaloblastic anaemia, of which folic acid deficiency and B_{12} deficiency anaemia are the two most common examples, has certain characteristics described in Box 49.6.

Folate deficiency anaemia

Alcoholics and the elderly are particularly prone to nutritional deficiency. Elderly people living alone on tea and toast are typical examples of patients at risk. Many alcoholics develop deficiency due to their poor diet; although some beers contain small amounts of folate, spirits contain none. A number of drugs have been implicated in causing folate deficiency (Box 49.7). Actual megaloblastic anaemia from drug therapy is uncommon, and the exact mechanism(s) has not always been established. Serious malabsorption can occur in tropical sprue and coeliac disease. Reduced absorption is seen in Crohn's disease and following partial gastrectomy or jejunal resection.

There is a physiological increase in folate utilisation during pregnancy. There may be an increased utilisation in various pathological conditions, in association with inflammation or in a number of chronic haemolytic anaemias, particularly thalassaemia major, sickle cell disease and autoimmune haemolytic anaemia. Chronic folate deficiency probably predisposes patient to thrombosis, depression and neoplasia (Green and Miller, 1999).

Box 49.6 Features of megaloblastic anaemia

- Glossitis (sore, pale, smooth tongue)
- Angular stomatitis
- Altered bowel habit (diarrhoea or constipation)
- Anorexia
- Mild jaundice
- Insidious onset
- Sterility
- Bilateral peripheral neuropathy (mainly vitamin B_{12} deficiency)
- Melanin skin pigmentation (rare)
- Fever (mainly vitamin B_{12} deficiency)

Box 49.7 Drugs implicated in causing folate deficiency

Malabsorption
- Phenytoin
- Barbiturates
- Sulphasalazine
- Colestyramine
- Oral contraceptives

Impaired metabolism
- Methotrexate
- Pyrimethamine
- Triamterene
- Pentamidine
- Trimethoprim

Vitamin B_{12} deficiency anaemia

The megaloblastic anaemia caused by vitamin B_{12} deficiency has similar features to folate deficiency (Box 49.6). In addition to the macrocytosis, anisocytosis and poikilocytosis, there is often mild thrombocytopenia. The spleen may be slightly enlarged and there may be a slight fever. Mild jaundice may be present due to the increased breakdown of haemoglobin found in the abnormal red cells. The onset is slow and insidious, so patients often present late or are diagnosed during other investigations. The feature that separates vitamin B_{12} deficiency from the other megaloblastic anaemias is progressive neuropathy. It is symmetrical and affects the legs rather than the arms. Patients notice a tingling in their feet and a loss of vibration sense. Occasionally, patients have muscle weakness, difficulty in walking or experience frequent falls.

Investigations

Folic acid deficiency anaemia

Many patients are symptomless initially, and the diagnosis is made following a full blood count carried out for another reason. The peripheral blood reveals large oval red cells. Anisocytosis and poikilocytosis are common. Some of the neutrophils are hypersegmented, and thrombocytopenia may be present. The red cell folate concentration accurately reflects folate stores and is a more preferable parameter than the serum folate concentration, which is subject to changes in diet and does not correlate as closely with anaemia.

Vitamin B_{12} deficiency anaemia

Following the detection of macrocytes in the full blood count, one of the first investigations will be the determination of the serum vitamin B_{12} level. The serum vitamin B_{12} level is

low in mild anaemia and may be very low if there is marked megaloblastic anaemia or neuropathy. If there is no concurrent folate deficiency, the serum folate level tends to be raised whilst the red cell folate level falls, possibly due to a failure of folate polyglutamate synthesis in cells. False positives (low vitamin B_{12} level without true deficiency) may be seen in multiple myeloma, excessive ascorbic acid intake and pregnancy. In contrast, liver disease, lymphoma, autoimmune disease and myeloproliferative disorders may lead to a false-negative result (normal levels in the presence of true deficiency).

The detection of autoantibodies is helpful to distinguish pernicious anaemia from other forms. The presence of intrinsic factor antibodies is virtually diagnostic of pernicious anaemia being rarely found in any other condition. However, it is not a very sensitive test since only half the patients with pernicious anaemia have these antibodies. Gastric parietal cell antibodies are found in 85% of patients with pernicious anaemia (a more sensitive test) but unfortunately also found in up to 10% of people without pernicious anaemia (less specific) (see Table 49.5).

Oral vitamin B_{12} absorption can be measured using the Schilling test though this is now rarely used in practice as most vitamin B_{12} deficiencies are treated in the same way. The test measures the absorption of radiolabelled oral dose of vitamin B_{12}.

Treatment

It is necessary to establish whether the patient with megaloblastic anaemia has vitamin B_{12} deficiency or folic acid deficiency or both. Treatment of vitamin B_{12} deficiency with folic acid may lead to the resolution of the haematological abnormalities but does not correct the neuropathy, which continues to deteriorate. If it is not possible to delay until a definitive diagnosis is made, both folic acid and vitamin B_{12} may be given.

Folate deficiency anaemia

Folate deficiency is usually managed by replacement therapy. The duration of the treatment depends on the cause of the deficiency. Changes in dietary habits or removal of any precipitating factor should also be considered.

The normal daily requirement of folic acid is approximately 100 µcg a day; despite this, the usual treatment doses given are 5–15 mg a day. Even in malabsorption states, because of these large doses, sufficient folate is usually absorbed. Therefore, parenteral folic acid treatment is not normally required. Treatment for 4 months will normally be sufficient to ensure that folate deficient red cells are replaced.

Large doses of folic acid can produce a partial haematological response in patients with vitamin B_{12} deficiency. The blood picture appears nearly normal but the neurological damage due to the vitamin B_{12} deficiency continues. Folic acid therapy should not be started until vitamin B_{12} deficiency has been excluded. It has also been suggested that patients on long-term folic acid therapy should have their vitamin B_{12} levels checked at regular intervals (e.g. yearly).

Pregnancy. The folate requirement increases in pregnancy and is higher in twin pregnancies. Folate deficiency regularly occurs in patients with a poor diet who do not take supplements. Prophylaxis with folate (350–500 µcg daily) is now frequently given in pregnancy, often in combination with iron, starting before conception and during the first 12 weeks of pregnancy. It is important that these products with low doses of folate are not used to treat megaloblastic anaemia. Although this low-dose folate should be started before conception to prevent a first occurrence of neural tube defect, higher doses (5 mg daily) are required in women with a history of neural tube defects and again continued until week 12 (DH, 1992).

Table 49.5 Autoantibodies in pernicious anaemia

	Intrinsic factor antibodies	Parietal cell antibodies
Patients *with* pernicious anaemia	Detected in 50% of patients	Detected in 85% of patients
People who do not have pernicious anaemia	Rarely detected	Detected in up to 10%

Vitamin B_{12} deficiency anaemia

The majority of patients with vitamin B_{12} deficiency require lifelong replacement therapy. Occasionally, specific therapy related to the underlying disorder may be all that is necessary, for example, treatment of fish tapeworm.

Since the anaemia has developed slowly, the cardiovascular system does not tolerate blood transfusions very well and is easily overloaded. Transfusions should not normally be given. In severe cases where emergency transfusion is deemed necessary, packed cells may be given slowly whilst blood (mainly plasma) is removed from the other arm. Diuretics may also need to be given, especially if the patient has congestive heart failure and poorly tolerates fluid overload.

For most patients, a definite diagnosis is made before treatment is started. The standard treatment is hydroxocobalamin 1 mg intramuscularly three times a week for 2 weeks then 1 mg every 3 months. Where there is neurological involvement, a slightly higher dose regimen is recommended, 1 mg on alternate days, until no further improvement then 1 mg every 2 months. There is no evidence that larger doses than those recommended provide any additional benefit in neuropathy. In the UK, hydroxocobalamin is the treatment of choice. It is retained in the body longer than cyanocobalamin, and reactions to it are very rare. US texts recommend cyanocobalamin rather than hydroxocobalamin because of the fear that some patients appear to develop antibodies to the vitamin B_{12} transport protein complex in the serum. The haematological response to both is probably identical. A small amount of passive absorption of vitamin B_{12} does take place from the gastro-intestinal tract. High (1 mg) daily oral and sublingual doses of cyanocobalamin are absorbed in sufficient quantities to manage pernicious anaemia. There have been calls for this oral regimen

to replace regular injections as used in other countries. This is potentially cheaper than injections, but this indication is currently unlicensed. It may be worth considering in patients who are unable to have injections. In the UK, cyanocobalamin tablets are not available on the NHS except to treat or prevent vitamin B_{12} deficiency in a patient who is a vegan or who has proven vitamin B_{12} deficiency of dietary origin.

Hypokalaemia develops in some patients during the initial haematological response because potassium is an intracellular ion used in the production of new cells. Potassium supplements may be needed in the elderly and patients receiving diuretics or digoxin. The serum iron level also falls as it is incorporated into haemoglobin. The more severe the anaemia, the more likely it is to see a fall in the serum potassium or iron level.

Not only is it very gratifying to follow the response to treatment, but it is also important to monitor the response to ensure that the patient returns to normal without any attendant problems. There is often a subjective improvement before an objective one. Typically, the patient feels better within 24–48 h, and yet there may be no discernible haematological response. The first haematological change in the peripheral blood is a rise in the reticulocyte count starting around day 3 or 4 and peaking after 7–8 days. The more severe the anaemia, the higher the peak reticulocyte count. The reticulocyte count should remain raised whilst the haematocrit is less than 35%. Failure to remain raised during this time indicates the need for further evaluation. The arrest or slowing down of erythropoiesis may be due to inadequate stores of other essential factors, for example, iron, or may be due to coexisting disease such as hypothyroidism or infection.

The red cells return to normal and the platelet count rises to normal (or even higher) after 7–10 days. The haemoglobin takes much longer to return to normal. It should rise by approximately 2–3 g/dL each fortnight. Neurological damage may be irreversible. Peripheral neuropathy of recent onset often partially improves, but any spinal cord damage is irreversible even with optimum therapy.

Patient care

Folic acid deficiency anaemia

In patients who have a dietary component to their deficiency, appropriate nutritional advice should go alongside their folic acid therapy. If the cause of the deficiency has been eliminated, patients can expect to receive folic acid for approximately 4–6 months. In patients with a continuing requirement, for example, haemolytic anaemia patients can expect lifelong treatment. Those commencing folic acid therapy can anticipate feeling better after a few days but should be informed that their blood count will take much longer to return to normal.

Vitamin B_{12} deficiency anaemia. Patients feel subjectively better very shortly after their first hydroxocobalamin injection. They can be told that their sore tongue will start to improve within 2 days and return to normal after 2–4 weeks. Patients need to be informed that they need regular injections, usually every 3 months. Surprisingly, some patients say that they feel they are ready for this injection as they approach their appointment time and feel better after their injection.

Haemolytic anaemias

In the haemolytic anaemias, there is a reduced life span of the erythrocytes. Anaemia occurs when the rate of destruction of the erythrocytes exceeds their rate of production. There are a wide range of haemolytic anaemias with both genetic and acquired disorders (Table 49.6). Only autoimmune haemolytic anaemia, sickle cell anaemia, thalassaemia and glucose-6-phosphate dehydrogenase deficiency will be briefly discussed. Haemolytic anaemias account for approximately 5% of all anaemias.

General clinical manifestations

Patients with acute haemolytic anaemia commonly complain of malaise, fever, abdominal pain, dark urine and jaundice. They have haemoglobulinaemia, hyperbilirubinaemia, reticulocytosis and increased urobilinogen levels in the urine. Patients with chronic haemolytic anaemia also usually have splenomegaly. Their anaemia is usually normochromic and normocytic.

General treatment

Many patients with chronic haemolytic anaemia will have an over active bone marrow to compensate for the chronic haemolysis. This increases demand for folate and therefore folic acid supplements are often required, particularly for patients with a poor diet. Patients who require frequent transfusions are at risk of iron overload and require chelation therapy with desferioxamine, desferiprone or deferasirox (as previously discussed under sideroblastic anaemia).

Autoimmune haemolytic anaemia

Epidemiology

This is a range of conditions consisting of warm autoimmune haemolytic anaemia (WAIHA) and cold autoimmune haemolytic anaemia also known as cold agglutinin disease (CAD).

Table 49.6 Some examples of haemolytic anaemias

Genetic disorders of	Examples
Haemoglobin	Sickle cell anaemias Thalassaemias
Energy pathways	Glucose-6-phosphate deficiency
Membrane	Hereditary spherocytosis Hereditary ovalcytosis
Acquired disorders	
Immune	Autoimmune Rh or ABO incompatibility
Non-immune	Infections (parasitic, bacterial) Drugs and chemicals Hypersplenism

Both forms can be subdivided into idiopathic and acquired forms, and the condition is found in all races. The most common form being idiopathic WAIHA occurring in approximately 40% of all cases with an incidence of between 1 in 4000 and 1 in 80,000. Idiopathic CAD tends to present in middle age.

Aetiology

WAIHA is frequently associated with other diseases with an immunological component, for example, chronic lymphocytic leukaemia, systemic lupus erythematosus and hepatitis B. Acquired CAD is sometimes associated with viral or bacterial infections: cold agglutinins develop in more than 60% of patients following infectious mononucleosis but haemolytic anaemia is rare. A number of drugs have been implicated as leading to immune haemolysis (Box 49.8).

Pathophysiology

The anaemia results from the presence of autoantibodies which agglutinate or lyse the patient's own erythrocytes. In WAIHA, the haemolysis is usually extravascular and mediated by IgG. These antibodies react best at body temperature. CAD is usually mediated by IgM and is capable of fixing complement. The IgM antibody attaches to the erythrocytes and causes them to agglutinate at temperatures below 37 °C resulting in impaired blood flow to fingers, toes, nose and ears when exposed to cold.

Clinical manifestations

The symptoms in WAIHA depend on the severity of the haemolysis. In CAD, there is a range in severity of the clinical manifestations from an inconsequential laboratory finding of a benign variety to serious manifestations, such as acute haemolytic crises and Raynaud-type phenomena. A common complaint is painful fingers and toes with purplish discolouration associated with cold exposure. In chronic CAD, the patient is more symptomatic during the colder months.

Investigations

A positive direct Coomb's test indicates the presence of antibodies to red blood cells. Further laboratory serological testing helps determine the exact nature of the reaction.

Box 49.8 Drugs associated with autoimmune haemolytic anaemia

- Ciclosporin
- Fludarabin
- Interferon A
- Levodopa
- Mefenamic acid
- Methyldopa
- Penicillin
- Quinine
- Quinidine

Drug-induced haemolytic anaemia may be difficult to distinguish from other forms of autoimmune haemolytic anaemia, and a clear medication history will help. The antibodies produced may react with the red cells only in the presence of the drug (or one of its metabolites) or may also react without the drug being present.

Treatment

Treatment is dependent on the specific cause (Pruss et al., 2003). In WAIHA, the standard treatment is high-dose corticosteroids. Patients who do not respond can be managed with azathioprine or cyclophosphamide. Blood transfusions are necessary in severe cases, although providing blood free from underlying alloantibodies is difficult. Rituximab, the anti CD-20 monoclonal antibody, has been shown to be beneficial in some patients who fail to respond to the forementioned conventional anti-inflammatory therapy. However, this is an unlicensed indication. (D'Arena et al., 2007) Patients with CAD need to be kept warm with supportive measures as well as treated for any underlying disorder.

Patient care

Patients requiring rituximab will require careful explanation of its unlicensed use and the necessary pretreatment with paracetamol and chlorphenamine.

Sickle cell anaemia

Epidemiology

Sickle cell disease is a hereditary condition. Several different variants of sickle cell disease exist. It is found in a number of ethnic groups, mainly in populations that originate from tropical regions. In the UK, approximately 5000 people, largely from the Afro-Caribbean population, have sickle cell disease.

Aetiology

Patients with sickle cell disease have a different form of haemoglobin. Patients with the most common variant of sickle cell disease have haemoglobin S (Hb S). Normal haemoglobin is usually designated Hb A. Haemoglobin S has valine substituted for glutamic acid as the sixth amino acid in the β-polypeptide compared with normal haemoglobin. Patients with homozygous haemoglobin S develop many problems including anaemia.

Sickle cell trait is where a person is a carrier of the gene (heterozygous for the sickle cell gene). These people are usually asymptomatic. Sickle cell trait provides some protection from malaria and is more common in those ethnic groups originating from geographical areas that are endemic for malaria. The offspring from a father with the trait and a mother with the trait has a one in four chance of having sickle cell disease (Fig. 49.3).

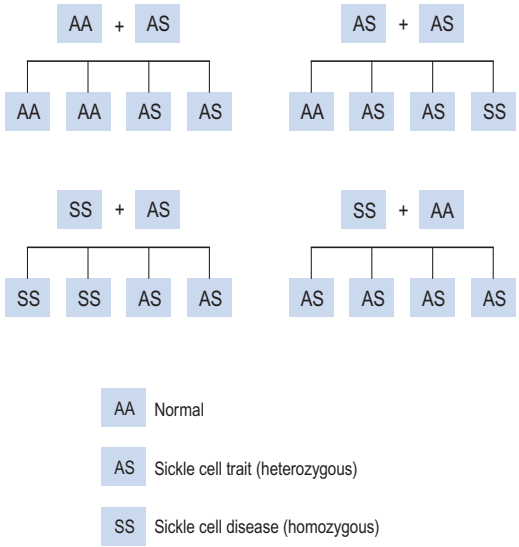


Fig. 49.3 Inheritance patterns in sickle cell trait and sickle cell disease.

Pathophysiology

The membrane of red cells containing haemoglobin S is damaged, which leads to intracellular dehydration. In addition, when the patient's blood is deoxygenated, polymerisation of haemoglobin S occurs, forming a semisolid gel. These two processes lead to the formation of crescent-shaped cells known as sickle cells. Sickle cells are less flexible than normal cells (flexibility allows normal cells to pass through the microcirculation). The inflexibility leads to impaired blood flow through the microcirculation, resulting in local tissue hypoxia. Anaemia results from an increased destruction (haemolysis) of red cells in the spleen. Some red cells in patients with sickle cell disease contain fetal haemoglobin (Hb F). These cells do not become sickle cells.

Clinical manifestations

Patients with severe variants of the disease have chronic anaemia, arthralgia, anorexia, fatigue and splenomegaly. They have crises more frequently than patients with other variants of the disease. A crisis can be precipitated by infection and fever, dehydration, hypoxia or acidosis. A combination of these factors is sometimes present. The clinical manifestation of a crisis can vary with the most common being an infarct crisis. Infarction of the long bones and larger joints or an infarction of a large organ, for example, the liver, lungs or brain, may all occur. Severe pain is a common feature, depending on the site of the infarction. Destructive bone and joint problems are frequently seen.

Investigations

The common form usually presents in the first year of life. From then on, the patients have a chronic haemolytic anaemia interspersed with crises. Abnormal haemoglobin can be detected using electrophoresis. The proportion of haemoglobin S is a useful monitoring parameter. Regular serum ferritin determinations identify the need for desferrioxamine therapy and are used to monitor progress.

Treatment

Patients with sickle cell disease have a high incidence of pneumococcal infections. A number of studies have shown the benefit of prophylactic antibiotics. Penicillin V 250 mg twice a day is usual for adults with erythromycin prescribed for patients allergic to penicillin. Administration of pneumococcal vaccine and *Haemophilus influenzae* vaccine is now common. Folic acid is commonly used because of the high turn over of red cells.

Attempts have been made to increase the proportion of haemoglobin F and reduce the proportion of haemoglobin S in the circulation. Several drugs (Box 49.9) have been shown (some only in animal models) to stimulate fetal haemoglobin production (Charache et al., 1995).

Hydroxycarbamide is effective and may reduce the frequency of crises but is limited by its cytotoxicity. Erythropoietin has been shown to increase haemoglobin F in some animal models, but this has yet to be fully demonstrated in humans. Transfusions and exchange transfusions have also been used to decrease the proportion of haemoglobin S. This is limited by the usual complications of chronic infusions: iron overload, the risk of blood-borne virus transmission and sensitisation.

Sickle cell crises require prompt and effective treatment. Removal of the trigger factor, hydration and effective pain relief are the mainstays of treatment. Appropriate antibiotic therapy should be started at the first signs of infection. Strong opioids are required for pain relief. Traditionally, many patients have been given frequent intramuscular injections of pethidine. Pethidine is not ideal since it is short acting, not very potent and repeated injections lead to the accumulation of metabolites that have been associated with seizures. Morphine is a more logical choice of opioid and has been successfully used in patient-controlled analgesia systems.

Patient care

Patients need to be encouraged to take their prophylactic penicillin and folic acid therapy regularly between crises. During a crisis, some health professionals worry about the patient developing opioid addiction. While this may happen, it is also important to recognise that crises are extremely painful and the patient requires effective analgesia.

Box 49.9 Drugs that may increase fetal haemoglobin production

5-Azacytidine
Cytarabine
Vinblastine
Hydroxycarbamide
Erythropoietin
Short chain fatty acids (butyrates, valproate)

Thalassaemias

Epidemiology

The thalassaemias are a group of inherited autosomal recessive diseases. The β thalassaemias occur mainly in populations from around the Mediterranean, North and West Africa, Middle East and Indian subcontinent. More than 100 β thalassaemia mutations have been identified, and they tend to produce severe anaemia. The α thalassaemias are more common, of which the milder variants do not cause severe anaemia, whilst the severe homozygotes lead to death *in utero* or infancy.

Aetiology

In α thalassaemia, there is either no α chain production (α^0 thalassaemia) or reduced production of a chain (α^+ thalassaemia). Similarly for β thalassaemia. Heterozygotes are usually symptomless, whilst homozygotes are more severely affected, as are compound heterozygotes in which there is a thalassaemia gene and a gene from another haemoglobin variant, for example, haemoglobin S.

Pathophysiology

In β thalassaemias, there is a reduced or absent production of the globin β chain. This leads to a relative excess of α chain which when unpaired become unstable and precipitates in the red cell precursors. There is ineffective erythropoiesis and those mature cells that reach the circulation have a shortened life span.

In α thalassaemias, the pathology is slightly different. The deficiency of α chains leads to an excess of γ or β chains. This time erythropoiesis is less affected, but the haemoglobin produced (haemoglobin Bart's or Haemoglobin H) is unstable when the cells are in the circulation and precipitates as the cells grow older. This leads to a shortened life span with the spleen trapping many of the cells. Haemoglobin Bart's or haemoglobin H is also physiologically useless.

Clinical manifestations

The anaemia causes erythropoietin production to increase and results in expansion of the bone marrow. In severe disease, this causes bone deformity and growth retardation. The spleen is actively involved in removing the abnormal mature cells from the circulation and becomes enlarged.

Investigations

For β thalassaemia, the diagnosis is relatively straightforward: haemolytic anaemia from infancy and racial background. Haemoglobin electrophoresis is used to determine the amounts of abnormal haemoglobin.

Treatment

There is currently no effective treatment. Patients with thalassaemia minor (those who carry the thalassaemia gene, but still make enough normal haemoglobin) usually do not require treatment. Many patients with severe forms are dependent on blood transfusions from an early age. This inevitably leads to iron overload. Desferrioxamine, deferiprone and deferasirox are routinely needed for such patients (see sideroblastic anaemia for additional information). Splenectomy helps some patients, and allogeneic stem cell transplant is used in severe cases. Prevention is actively explored with genetic counselling programmes in Italy and Greece, and antenatal screening in a number of countries.

As in sickle cell disease, much attention is being placed on the idea of switching the bone marrow to the production of fetal haemoglobin rather than the defective adult haemoglobin of β thalassaemia. It is likely that a combination of drugs (hydroxycarbamide and erythropoietin) will provide some clinical improvement.

Patient care

Drug therapy does not currently play a large part in treatment. If hydroxycarbamide becomes standard treatment, pharmacists will become involved in educating the patient particularly with regard to its cytotoxic nature.

Glucose-6-phosphate dehydrogenase deficiency

Epidemiology

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a recessive hereditary disease and affects approximately 400 million people worldwide. There are more than 300 different forms of G6PD deficiency, only some of which cause anaemia. The most common form of G6PD deficiency is found in 15% of black Americans. It causes anaemia when the individual is exposed to a trigger factor. A more severe form is the Mediterranean variant of G6PD deficiency. Some of these individuals may have chronic haemolytic anaemia even in the apparent absence of exposure to a precipitating factor.

Aetiology

There are a large number of variants of G6PD activity found in different populations and ethnic groups. G6PD is an erythrocyte enzyme that is indirectly involved in the production of reduced glutathione. Glutathione is produced in response to, and protects red cells from, oxidising reagents.

Pathophysiology

G6PD is essential for the production of (NADPH) in erythrocytes. If there is a deficiency in G6PD, this decreases the production of NADPH which is needed to keep glutathione in a reduced form. Reduced glutathione helps erythrocytes deal with oxidative stress. Hence, in G6PD deficiency, if the erythrocytes are exposed to an oxidising agent, the cell membrane becomes damaged, the haemoglobin becomes oxidised and forms what are known as Heinz bodies. Some of the red cells haemolyse and others have their Heinz bodies removed by the spleen to form 'bite cells'.

Clinical manifestation

Clinically, the two most important types of G6PD deficiency occur in the black population and in people originating from the Mediterranean. The black population has a milder form that results in an acute self-limiting haemolytic anaemia following exposure to an oxidising agent, for example, infection, acute illness, broad beans (fava) beans or drugs (Box 49.10). The haemolytic anaemia is self-limiting because the young cells produced by the bone marrow have higher levels of G6PD activity than old cells. Following exposure to the oxidising agent, the old cells are haemolysed but the new cells produced in response are more capable of tolerating the insult until they grow old. In the Mediterranean form of the disorder, the enzyme activity is very low, haemolysis is not usually self-limiting and, indeed, some patients have a chronic haemolytic anaemia despite the absence of an obvious causative factor.

Investigations

The history and the clinical findings steer the diagnosis, which is then confirmed by measuring G6PD activity. Care must be taken during the acute phase since there are increased numbers of young cells with higher levels of activity that may be misleading. The increased numbers of young cells result from the selective destruction of older cells and the increased production of reticulocytes.

Treatment

Prevention of haemolysis by avoiding trigger factors (drugs or food) is important. Vaccination against hepatitis A and hepatitis B may reduce attacks. In cases of acute haemolytic anaemia, the causative oxidising agent should be stopped and general supportive measures adopted. In chronic haemolytic anaemia, most patients become reasonably well adjusted to their anaemia. They need to avoid known precipitating factors to prevent acute episodes occurring on top of their chronic haemolytic anaemia.

Box 49.10 Common drugs implicated in causing haemolysis in G6PD deficiency

Drugs to be avoided in all variants
Ciprofloxacin (and probably other quinolones)
Dapsone
Methylene blue
Primaquine (reduced dose may be used in milder variants)
Nalidixic acid
Sulphonamides (including co-trimoxazole)

Drugs to be avoided in more severe variants
Aspirin (low dose used under supervision)
Chloramphenicol
Chloroquine (may be acceptable in acute malaria)
Menadione
Probenecid
Quinidine
Quinine (acceptable in acute malaria)

There is no specific drug treatment. During acute episodes, the patient should be kept well hydrated to ensure good urine output to prevent haemoglobin damaging the kidney. Blood transfusions may be necessary. Vitamin E (an antioxidant) appears to have little clinical benefit in preventing haemolysis.

Patient care

Since drug therapy does not play a large part in the management of these patients, pharmacists do not often become involved in patient education. Patients can be given a list of drugs to avoid, but since most of these drugs are prescription only medicines, it is important that patients remind health care professionals of their condition.

Case studies

Case 49.1

Mr HA, a 60-year-old single unemployed man, was admitted to hospital for investigation of anaemia. He presented with a 6-month history of lethargy, chest pain, dizziness and falls and a past history of having a gastrectomy 26 years ago. The drug history on admission showed that Mr HA was taking diazepam and GTN spray.

Review of systems revealed no vomiting and no melaena. He complained of some indigestion after meals and reported his appetite was fine if someone else cooked. On examination he was pale, with a blood pressure of 140/80, pulse 90 and haematoglobin level of 2.5 g/dL (normal range: 13.5–18.0 g/dL). A gastroscopy was normal and a biopsy showed no evidence of coeliac disease. A barium enema was normal and faecal occult bloods (FOBs) negative.

Over the first 2 days, he was transfused with 8 units of blood and given furosemide 40 mg with alternate bags. On day 7 he was started on ferrous sulphate 300 mg three times a day, folic acid 5 mg twice daily and ascorbic acid 200 mg three times a day.

Questions

1. What additional questions should Mr HA have been asked at admission?
2. Comment on the use of vitamin C in Mr HA.
3. How long should Mr HA remain on ferrous sulphate?

Answers

1. Although Mr HA's prescribed drugs were documented, it is possible that he was taking purchased medication. On admission, he complained of indigestion over the last 3 months, and on questioning revealed that he was self-medicating with aluminium hydroxide mixture. From a theoretical point of view, antacids may reduce the amount of iron absorbed by increasing the pH of the stomach and by reducing the solubility of ferrous salts. It is unlikely that this contributed significantly to the development of his anaemia, but if he intends to continue using an antacid after discharge, which he should be discouraged from doing, it would be better not to take a dose of the antacid within 1–2 h of his ferrous sulphate. It would also be worth checking to see if he has been self-medicating with a purchased

aspirin or ibuprofen-based product, both drugs have been implicated in causing gastro-intestinal blood loss, though in this case his gastroscopy was normal and FOBs negative.
2. Ascorbic acid increases the absorption of iron in some patients, it probably keeps iron in solution either in the ferrous form or by being a soluble chelat with the ferric form. In most patients, this has little clinical benefit. It may be an advantage in Mr HA since he may also benefit from a short course of multivitamins.
3. Mr HA needs to continue iron therapy until he has at least replenished his iron stores. This may take up to 6 months after which time he should be reassessed, taking into account whether he is now having a suitable diet. In practice, since his iron was dangerously low on admission, it may be quite reasonable to leave him on iron for the rest of his life.

Case 49.2

Mr WK, a 46-year-old mechanic, is referred to hospital by his primary care doctor. He gave a history of diarrhoea and vomiting a week ago and now was complaining of headaches and feeling 'lousy'. His doctor had given him metoclopramide and ferrous sulphate. Mr WK did not appear jaundiced although he said he had noticed his urine was unusually dark a few weeks ago. On examination, he was obese with a blood pressure of 120/80 mmHg and had a pulse of 80. Rectal examination revealed black stools. He had a normal gastroscopy with three negative FOBs. His serum biochemistry showed a normal level of alanine transaminase and a slightly raised total bilirubin level. Mr WK's reticulocyte count was 13.5% (normal range: 0.5–1.5%). He was diagnosed with having G6PD deficiency, probably triggered by an infection.

Questions

1. How do you explain Mr WK's dark urine and dark stools?
2. Would Mr WK benefit from any medication following admission?
3. Why is it necessary to repeat his red cell G6PD levels after 2 months?

Answers

1. Mr WK's dark urine was a consequence of his haemolytic anaemia. Bilirubin is a breakdown product of haemoglobin that is transported to the liver and conjugated before being excreted in the bile. Bacteria in the intestine converts this to urobilinogen, most of which is excreted in the stools. Small amounts of urobilinogen are reabsorbed and some of this appears in the urine. Urobilinogen is oxidised to urobilin, which is coloured. During episodes of haemolysis, erythrocytes are destroyed faster than normal, and hence there is an increase in the formation of bilirubin and increased excretion of urobilinogen in the urine. Also during haemolysis, free haemoglobin may be released into the blood. If the haemolysis is severe enough, the normal mechanism for removing haemoglobin from the circulation is overcome and haemoglobin may appear in the urine. Dark stools may indicate melaenia and upper gastro-intestinal bleeding. In Mr WK's case, his gastroscopy was normal and he had three negative FOBs. His dark stools were due to the ferrous sulphate prescribed by the primary care doctor prior to admission.
2. His raised reticulocyte count indicates he is rapidly replacing his lost red cells. Erythropoiesis consumes folate and iron and since his folate is towards the lower end of the reference range, it may be worth giving him a short course of folate supplements.
3. Young red cells tend to have higher levels of enzyme activity than more mature cells. Determining G6PD levels during the acute phase may be misleading since there is a relatively high proportion of young cells. Mr WK's result 2 months later would more accurately represent his normal state.

Case 49.3

Ms PR, a 58-year-old lady, was admitted to the emergency department. She had fallen over and bruised herself but had not broken any bones. On examination, it was noted that she appeared pale with possibly a lemon-yellow tinge to her skin, she was slightly confused and had paraesthesiae of the feet and fingers. She has a past history of heart failure and was taking furosemide and enalapril. She was admitted for investigation and discovered to have a macrocytic anaemia. Pernicious anaemia was suspected. Folate level, vitamin B_{12} levels and Schilling test were carried out before commencing treatment.

Questions

1. What are the features that may lead you to consider a diagnosis of pernicious anaemia?
2. Can Miss PR have a blood transfusion after samples have been taken for folate and vitamin B_{12}?
3. The red cell folate is reported as 150 mg/L (reference range: 160–640 mg/L). Would Ms PR benefit from folate therapy?

Answers

1. Macrocytic anaemia and paraesthesia are typical features, though not diagnostic of pernicious anaemia. Patients may be mildly jaundiced which is often described as lemon-yellow in colour. Interestingly, pernicious anaemia is more common in women than men and is associated with blue eyes and early greying of the hair. Miss PR may have other features of pernicious anaemia which include glossitis, angular stomatitis and altered bowel habit.
2. Patients with pernicious anaemia develop their anaemia over a long period of time and tend not to tolerate increases in blood volume very well. A transfusion may result in fluid overload and precipitate heart failure. Miss PR already has heart failure, so unless she becomes severely compromised by anaemia, a transfusion should not be given. In patients who have such pronounced anaemia that an urgent transfusion is required, an exchange transfusion of a small volume of packed cells may be appropriate.
3. In vitamin B_{12} deficiency folate tends to leak from cells and the red cell folate is often low (serum folate is sometimes raised). Many patients initially require both folate and vitamin B_{12} although folate can usually be stopped after a short course. Folate therapy must never be given to patients who have not been fully investigated for vitamin B_{12} deficiency. If vitamin B_{12}-deficient patients are given large doses of folate without hydroxocobalami, the full blood count may appear to improve but the peripheral neuropathy from the vitamin B_{12} deficiency progresses.

Case 49.4

Mrs GN, a 76-year-old retired factory worker, was seen by her primary care doctor, complaining of tiredness. She had been seen 2 months earlier and started on ferrous sulphate for microcytic anaemia. Initially, she had felt better but the tiredness soon returned. A bone marrow aspiration revealed increased erythropoiesis, iron stores and red cell precursors.

A diagnosis of sideroblastic anaemia was made and it was decided to give her monthly transfusions. She was started on pyridoxine 50 mg three times a day in addition to ferrous sulphate.

Questions

1. What are the potential problems with Mrs GN's treatment?
2. After 3 months there appeared to be little benefit to show from pyridoxine. How might management be improved?

Answers

1. Mrs GN's bone marrow aspiration and serum ferritin level showed that she has high levels of stored iron. Repeated monthly transfusions will also have contributed to further iron accumulation. In sideroblastic anaemia, the bone marrow appears to be inefficient at incorporating the iron into haem. The administration of iron leads to iron overload which may result in damage to the heart, liver and endocrine organs. The ferrous sulphate must be stopped. If iron accumulation remains a problem, desferrioxamine therapy must be tried.
2. Pyridoxine does not always improve the blood picture in patients with sideroblastic anaemia. In sideroblastic anaemia, the dose of pyridoxine required is usually 400 mg daily. So, in the case of Mrs GN, an increase in dose should be tried. In addition, patients with sideroblastic anaemia often do not realise that pyridoxine is not just a simple vitamin but a specific treatment for anaemia. Therefore, counselling the patient may improve adherence.

Case 49.5

Mrs RO, a 70-year-old retired teacher, presented with a history of increased tiredness over the last 6 weeks. She has a past history of a partial gastrectomy 4 years ago. On questioning, her relevant symptoms included 'pins and needles' in her toes and loose bowels. She said that she had never been a good eater but ate red meat twice a week.

Questions

1. Why was it 4 years after her gastrectomy before Mrs RO developed vitamin B_{12} deficiency?
2. How long will it take for Mrs RO to respond to treatment?
3. What therapy will Mrs RO require?

Answers

1. Vitamin B_{12} requires intrinsic factor produced by the stomach for absorption. Patients with a total gastrectomy and some with a partial gastrectomy malabsorb vitamin B_{12}. Most patients have good body stores and even if no new vitamin B_{12} enters the body (e.g. following a total gastrectomy) it will take at least 2 years to deplete the stores.
2. Many patients will feel better within days of starting treatment with hydroxocobalamin and before a change in their haemoglobin concentration can be detected. Mrs RO's blood picture may take a number of weeks to return to normal. However, her 'pins and needles' may be a sign of peripheral neuropathy which can be irreversible and may not respond to the hydroxocobalamin treatment.
3. Mrs RO will require lifelong replacement therapy. The standard treatment for vitamin B_{12} deficiency is hydroxocobalamin 1 mg intramuscularly three times a week for 2 weeks, then 1 mg every 3 months. If neurological involvement is identified, as in the case of Mrs RO, then a slightly higher dose regimen is recommended of 1 mg on alternate days until no further improvement, followed by 1 mg every 2 months thereafter.

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50 Leukaemia

G. Jackson and G. Jones

Key points

- Leukaemias are uncommon malignancies.
- Acute lymphoblastic leukaemia (ALL) is the most common malignancy in childhood.
- With the exception of ALL, leukaemias are more common in the elderly.
- Age is one of the most important prognostic factors in the treatment of leukaemia. With the exception of neonates, older patients are less likely to be cured than younger patients.
- The treatment of leukaemia is continually improving with the introduction of more focused therapy and improvements in supportive care.
- The use of bone marrow transplantation in the treatment of all forms of leukaemia is increasing. Some of the results are exciting, but the short- and long-term problems of this type of intensive treatment need to be considered.

Leukaemias and lymphomas are the commonest forms of haematological malignancy. Although rare, they are of particular interest in that dramatic improvements in the prognosis of patients with these cancers have been achieved through the use of chemotherapy, and cure is now a possibility for many patients.

Many forms of leukaemia exist, but they are all characterised by the production of excessive numbers of abnormal white blood cells. The leukaemias can be broadly divided into four groups:

- acute myeloblastic leukaemia (AML)
- acute lymphoblastic leukaemia (ALL)
- chronic myelocytic leukaemia (CML)
- chronic lymphocytic leukaemia (CLL)

The adjectives 'myeloid' and 'lymphoid' refer to the predominant cell involved, and the suffix-cytic and -blastic to mature and immature cells, respectively. These characteristics can be determined by a combination of cellular appearances, surface antigen expression and cytogenetic features. The international standard for leukaemia classification is the WHO system (Swerdlow et al., 2008).

Epidemiology

Haematological malignancies account for only 5% of all cancers; of these, CLL is the most common form of leukaemia. UK incidence data are presented in Table 50.1. CLL mainly affects an older age group: 90% of patients are over the age of 50 and nearly two-thirds are over 60 years old at diagnosis. It rarely occurs in young people and is twice as common in men as in women. CML is primarily a disease of middle age with the median onset in the 40–50 year old age group, but it can occur in younger people.

Table 50.1 Incidence of leukaemia in the UK (Leukaemia and Lymphoma Research, 2010)

	New cases/year	Incidence per 100,000 of the population
CLL	2750	4.58
CML	750	1.5
ALL	650	1.00
AML	1950	3.25

Acute leukaemia is rare, with a total annual incidence of approximately 4 per 100,000 population. The more common form of the disease is AML, which accounts for 75% of cases. The incidence of AML rises steadily with age, occurring only rarely in young children. In contrast, ALL is predominantly a childhood disease, with the peak incidence in the 3–5 year age group, and is the most common childhood cancer.

Aetiology

In common with other cancers, the aetiology of leukaemia is not fully understood. Leukaemia is thought to result from a combination of factors that induce genetic mutations which allow mutated cells to proliferate faster than normal cells and/or to fail to die in response to normal apoptotic signals. Epidemiological studies have, however, identified a number of specific risk factors for the development of leukaemia, which are described as follows.

Radiation

The association between the ionising radiation and the development of leukaemia is evident from nuclear disasters such as Hiroshima and more recently Chernobyl. Long-term

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follow-up of survivors of Nagasaki and Hiroshima has shown an increase in all forms of leukaemia other than CLL. The link is also apparent for patients who received radiotherapy for the treatment of malignant and non-malignant conditions such as Hodgkin's disease or ankylosing spondylitis. The effect of chronic low-level exposure to radiation is less certain.

Exposure to chemicals and cytotoxic drugs

There is a small but definite risk of acute leukaemia occurring in patients successfully treated for other malignancies with cytotoxic and immunosuppressive agents. The combination of chemotherapy, especially alkylating agents such as cyclophosphamide and radiotherapy, presents the highest risk. This has practical implications as an increasing number of patients achieve a 'cure' as a result of combination therapy, while occupational exposure of health professionals to these agents is also an area of concern. Occupational exposures to paint, insecticides and solvents, in particular, the aromatic solvent benzene, have all been associated with the development of leukaemia, but it is difficult to be certain whether such exposures genuinely cause the disease.

Viruses

Human T-cell lymphotrophic virus, an RNA retrovirus endemic in Japan and the West Indies, has been linked to a rare T-cell leukaemia/lymphoma.

Genetic factors

Down's syndrome, constitutional trisomy of chromosome 21, is associated with an increased risk of leukaemia. Disorders that predispose to chromosomal breaks such as Fanconi's anaemia and ataxia telangectasia are also associated with an increased risk of developing acute leukaemia. These alterations may permit the expression of oncogenes, which promote malignant transformation.

Haematological disorders

Many patients with other haematological disorders have a greatly increased risk of developing leukaemia, particularly AML. These disorders include the myelodysplastic syndromes, the non-leukaemic myeloproliferative disorders, aplastic anaemia and paroxysmal nocturnal haemoglobinuria.

Pathophysiology

In leukaemia, the normal process of haemopoiesis is altered (Fig. 50.1). Transformation to malignancy appears to occur in a single cell, usually at the pluripotential stem cell level, but it may occur in a committed stem cell with capacity for more limited differentiation. Accumulation of malignant cells leads to progressive impairment of the normal bone marrow function.

Acute leukaemias

In acute leukaemia, the normal bone marrow is replaced by a malignant clone of immature blast cells derived from the myeloid (in AML) or lymphoid (in ALL) series. More than 20% of the cellular elements of the bone marrow are replaced with blasts. This is usually associated with the appearance of blasts in the peripheral circulation accompanied by worsening pancytopenia as a result of the marrow's reduced ability to produce normal blood cells as the proportion of malignant cells increases. In ALL, the blasts may infiltrate lymph nodes and other tissues such as liver, spleen, testis and the meninges, in particular. In AML, blasts tend to infiltrate skin, gums, liver and spleen.

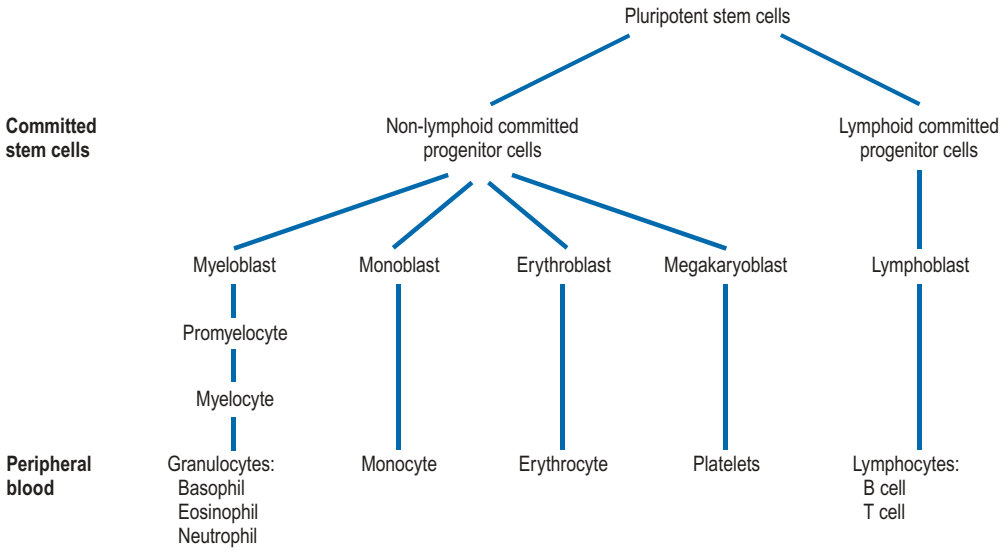


Fig. 50.1 Haemopoiesis.

Classification of acute myeloblastic leukaemia

AML has traditionally been classified on the basis of morphological features of the disease. Subtypes displaying granulocytic, monocytic, erythroid and megakaryocytic differentiation can be demonstrated. Recently, the World Health Organization (WHO) has updated this system (Table 50.2). AML is now classified using a combination of morphological, genetic and immunological cell marker features (surface antigen expression) in an attempt to define disease groups of greater prognostic significance (Swerdlow et al., 2008).

Classification of acute lymphoblastic leukaemia

As with AML, the WHO classification system takes account of morphological, genetic and immunological features. The disease is, however, mainly classified immunologically, based on the presence or absence of B- or T-cell markers (Table 50.3). Each subtype displays different clinical presentations, response to treatment and, ultimately, prognosis, with pre-B having the best prognosis and B-ALL the worst. It is worth noting that B-ALL (Burkitt's type), which is associated with translocations of the myc gene normally located on chromosome 8, seems to be a morphologically and biologically distinct form of leukaemia.

Table 50.2 WHO classification of AML

Subgroup	Examples
AML with recurrent genetic abnormalities	Inversion chromosome 16 (inv 16) t(15;17) t(8;21)
AML with multilineage dysplasia	
Therapy-related AML	
AML not otherwise classified	AML without maturation AML with granulocytic maturation AML with granulocytic and monocytic differentiation AML with monocytic differentiation AML with erythroid differentiation AML with megakaryocytic differentiation

Table 50.3 Classification of ALL

Pre-B ALL	Possessing the common ALL antigen CD 10
B cell type	B-ALL of Burkitt's type
T cell type	T-ALL
Null	Non-B, non-T and lacking the common ALL antigen CD 10

Chronic leukaemias

In chronic leukaemia, the normal bone marrow is replaced by a malignant clone of maturing haemopoietic cells.

Chronic lymphocytic leukaemia

CLL is characterised by a clonal expansion of morphologically mature lymphocytes of B-cell origin. These cells accumulate in the peripheral blood and give rise to a lymphocytosis that may be very marked. Lymphocytes accumulate in lymph nodes and spread to the liver and spleen, which become enlarged. The bone marrow is progressively infiltrated. Although the malignant lymphocytes appear morphologically normal, they are functionally deficient.

Chronic myelocytic leukaemia

The characteristic feature of CML is the predominance of maturing myeloid cells in blood, bone marrow, liver, spleen and other organs. CML was the first cancer to be associated with a specific chromosomal abnormality: the Philadelphia chromosome translocation (Ph) seen in over 90% of cases. This is a translocation of genetic material between the long arms of chromosome 22 and chromosome 9. This results in the apposition of the BCR gene (chromosome 22) and the ABL gene (chromosome 9). This novel BCR-ABL gene encodes a fusion protein which has tyrosine kinase activity. This genetic event is believed to be crucial in the pathogenesis, or perhaps even to initiate the development, of CML since overactivity of the tyrosine kinase results in the uncontrolled growth characteristic of leukaemic cells (Cilloni and Saglio, 2009).

Clinical manifestations

Acute leukaemia

Most of the clinical manifestations of acute leukaemia are related to bone marrow failure. The disease commonly presents with a short history, and left untreated, it is rapidly fatal. Symptoms of infection, anaemia and bleeding are common and life-threatening presenting problems. Bleeding may be particularly severe in one subtype of AML, acute promyelocytic leukaemia (APL). This condition is associated with a translocation of genetic material between chromosomes 15 and 17, t(15;17). Disseminated intravascular coagulation (DIC) is commonly the presenting feature of this disease. Some patients with AML develop symptoms and signs due to infiltration of major organs by leukaemic cells.

The involvement of other tissues such as spleen, liver, lymph nodes and meninges is more common in ALL than AML. Involvement of the central nervous system (CNS) may give rise to headaches, vomiting and irritable behaviour. CNS disease is rare at presentation, but develops in up to 75% of children with ALL unless specific prophylactic treatment is given. Less commonly, patients present with features of hypermetabolism, hyperuricaemia or generalised aches and pains.

Chronic leukaemia

Chronic myelocytic leukaemia

Patients with CML commonly present with non-specific symptoms, such as malaise, weight loss and night sweats. The main physical sign is an enlarged spleen that may give rise to abdominal discomfort. Hepatomegaly is also detected in approximately 40% of newly diagnosed patients. Neutropenia and thrombocytopenia are uncommon at presentation. Thus, unlike the acute leukaemias, patients with CML rarely present with symptoms of infection or haemorrhage. In up to 30% of cases, patients are asymptomatic and the disease is detected as a result of a routine blood test performed for other reasons.

CML is a triphasic disease. The initial chronic phase may last from several months to 20 years; the median is around 5 years. During this time, treatment can alleviate symptoms and reduce the white blood count (WBC) and spleen size, allowing patients to lead near normal lives. An accelerated phase eventually occurs where the disease becomes more aggressive with progressively worsening symptoms: unexplained fevers, bone pain, anaemia, thrombocytopenia or thrombocytosis. Finally, after a period of weeks or months, a blast crisis occurs, resembling fulminating acute leukaemia. In a small percentage of patients, this occurs abruptly with no prior accelerated phase.

Chronic lymphocytic leukaemia

An increasing number of patients are diagnosed as having CLL by chance, when a full blood count is performed for an unrelated reason. Symptomatic patients often suffer B symptoms: night sweats, unexplained fever and weight loss. At diagnosis, findings may include generalised lymphadenopathy and some enlargement of the liver and spleen. The course of CLL is variable; in some patients, the disease may remain indolent for many years, while others experience a steady deterioration in their health. Survival typically varies from 2 to 20 years depending on the extent of disease. Patients are immunocompromised with a reduction in serum gammaglobulin and are at increased risk of bacterial and viral infections. There is an increased susceptibility to autoimmune disease, particularly immune haemolytic anaemias and thrombocytopenia. With progressive disease, bone marrow failure becomes apparent, resulting in fatigue, infection and bleeding, and the disease becomes less responsive to treatment. Patients with CLL also have an increased risk of developing a more aggressive malignancy such as high-grade non-Hodgkin's lymphoma (known as Richter's transformation) or prolymphocytic leukaemia (PLL).

Investigations

Examinations of peripheral blood and bone marrow are the key laboratory investigations carried out in cases of suspected leukaemia. However, some additional investigations can help in the diagnosis and classification of this group of diseases. Some of the main findings at diagnosis are presented in Table 50.4.

Table 50.4 Findings at diagnosis in leukaemia

	AML	ALL	CML	CLL
WBC	↑ in 60%, may be N or ↓	↑ in 50%, may be N or ↓↓	↑↑ commonly 100×10^9–250×10^9 L^{-1}	Commonly ↑
Differential WBC	Mainly myeloblasts	Mainly lymphoblasts	Granulocytes ↑↑, especially neutrophils, myelocytes, basophils and eosinophils <10% blasts present	>5×10^9 L^{-1} monoclonal lymphocytes
RBC	Severe anaemia	Severe anaemia	Anaemia common	Anaemia in 50% of patients, generally mild
Platelets	↓↓	↓↓	Usually ↑, may be N or ↓	↓ in 20–30%
Bone marrow aspiration and trephine	Predominantly blasts	Predominantly blasts	Hypercellular blasts < 10%	Lymphocytic infiltration
Cytogenetic analysis	Important abnormalities detected	Important abnormalities detected	Presence of Ph chromosome	
Lymphadenopathy	Rare	Common	Rare	Common
Splenomegaly	50%	60%	Usual and severe	Usual and moderate
Other features	DIC, high urate	High urate, CNS involvement	↑ Serum uric acid	Immune paresis

N, normal; ↓, reduced; ↑, increased; WBC, white blood cells; DIC, disseminated intravascular coagulation; Ph, Philadelphia; RBC, red blood cells.

In acute leukaemia, leukaemic blast cells are usually seen on the peripheral blood film. The blasts of ALL and AML are distinguished using morphology, cytochemical stains, cytogenetics and cell surface antigen analysis. In CML, the principal feature is a leucocytosis with WBC usually ranging from 10×10^9 L^{-1} to 250×10^9 L^{-1} and comprising the complete spectrum of myeloid cells. In CLL, it is lymphocytes, in particular, which are increased, with clonal lymphocyte counts exceeding 5×10^9 L^{-1}. Non-random chromosome abnormalities are increasingly being identified in patients with leukaemia. The information obtained from cytogenetic analysis of bone marrow or peripheral blood cells can be used to confirm the diagnosis and classification of leukaemia and may provide a guide to the likely response to treatment and prognosis.

Treatment

Although significant progress has been made in the treatment of leukaemia, work continues to further improve prognosis. As leukaemias are rare malignancies, the most important studies are undertaken on a national or international basis. In addition to the specific anti-leukaemia treatment, general supportive therapy is vital to manage both the disease and the complications of therapy.

Acute leukaemia

At the outset, intensive combination chemotherapy is given in the hope of achieving a complete remission (CR). This initial phase of treatment is termed induction or remission induction chemotherapy. A CR can only be achieved by virtual ablation of the bone marrow, followed by recovery of normal haemopoiesis. If two cycles of therapy fail to induce CR, an alternative drug regimen can be used. If this is unsuccessful, it is unlikely that CR will be achieved. The subsequent duration of the first remission is closely linked to survival.

Remission is defined as the absence of all clinical and microscopic signs of leukaemia, less than 5% blast forms in the bone marrow and return of normal cellularity and haemopoietic elements. Despite achieving CR, occult residual disease (also termed minimal residual disease or MRD) will persist, and further intensive therapy is given in an attempt to sustain the remission. This post-remission consolidation therapy may comprise chemotherapy or a combination of chemotherapy and bone marrow transplantation.

Acute lymphoblastic leukaemia

Treatment of ALL in childhood has been one of the success stories of the past 3 decades. Over 80% of children will achieve a remission lasting more than 5 years, and current studies are often focused on trying to identify the 20% of children with poor risk disease and treating them more aggressively (Vrooman and Silverman, 2009). Unfortunately, the results in adults are not so impressive. The combination of vincristine, prednisolone, anthracyclines and asparaginase induces CR in about 90% of children with ALL and 80% of adults, although sadly relapse is far more common in adults (Table 50.5). Other active drugs in the treatment of ALL include methotrexate, 6-mercaptopurine, cyclophosphamide and mitoxantrone.

Table 50.5 Treatment of ALL (adapted from MRC protocol UKALL 12-2005)

	Dose	Route	Regimen
Induction (4 weeks)			
Vincristine	1.5 mg/m^2	i.v.	Weekly for 4 weeks
Prednisolone	40 mg/m^2	oral	Daily for 4 weeks
L-Asparaginase	6000 u/m^2	i.m.	3 × weekly for 3 weeks
Daunorubicin	45 mg/m^2	i.v.	Daily for 2 days
Intensification (1 week)			
Vincristine	1.5 mg/m^2	i.v.	1 dose
Daunorubicin	45 mg/m^2	i.v.	Daily for 2 days
Prednisolone	40 mg/m^2	oral	Daily for 5 days
Etoposide	100 mg/m^2	i.v.	Daily for 5 days
Cytarabine	100 mg/m^2	i.v.	2 × daily for 5 days
Thioguanine	80 mg/m^2	oral	Daily for 5 days
CNS prophylaxis (3 weeks)			
Cranial irradiation	24 Gy		
Methotrexate	i.t. weekly for 3 weeks also given during induction and intensification		
Maintenance therapy (2 years)			
Methotrexate	20 mg/m^2	oral	Weekly
6-Mercaptopurine	75 mg/m^2	oral	Daily
Prednisolone	40 mg/m^2	oral	5 days/month
Vincristine	1.5 mg/m^2	i.v.	Monthly

i.m., intramuscular; i.v., intravenous; i.t., intrathecal; MRC, Medical Research Council; ALL, acute lymphoblastic leukaemia.

Patients with ALL are at a high risk of developing CNS infiltration. Cytotoxic drugs penetrate poorly into the CNS which thus acts as a sanctuary site for leukaemic cells. For this reason, all patients with ALL receive CNS prophylaxis. Cranial irradiation plus intrathecal methotrexate or high-dose systemic methotrexate can be used.

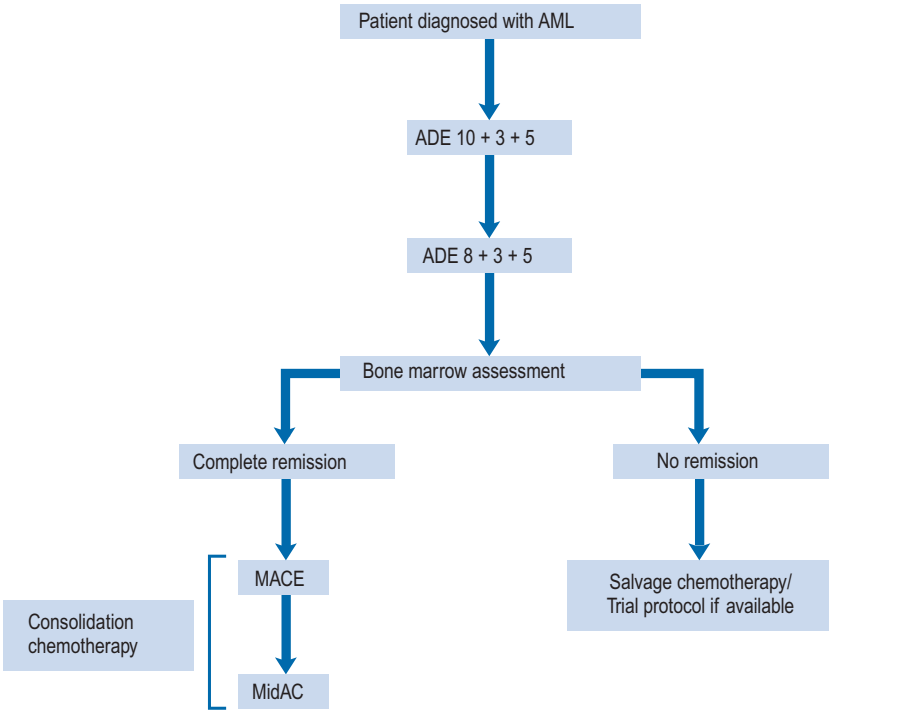
Maintenance treatment is important to sustain a CR. It is usually milder than induction or consolidation chemotherapy, but is carried on for at least 18 months. Treatment usually consists of weekly methotrexate and daily 6-mercaptopurine with intermittent vincristine and prednisolone.

The treatment of relapsed disease varies with the site of relapse. Isolated CNS or testicular relapse may be successfully treated with radiation and reinduction therapy. Cure can still be achieved for some patients. Bone marrow relapse is much more difficult to cure, especially if it occurs early.

A small proportion of paediatric patients and a larger proportion of adult patients have the Philadelphia chromosome translocation within their ALL blasts. Such patients have a relatively poor prognosis and therefore require more intensive therapy. There is some evidence that drug combinations including imatinib may enhance the response of these leukaemias to therapy.

Acute myeloblastic leukaemia (non-acute promyelocytic leukaemia)

As for ALL, the treatment of AML involves induction and consolidation chemotherapy. In AML therapy, however, the chemotherapy regimens used to achieve remission are much more myelotoxic, and patients require intensive supportive care to survive periods of bone marrow aplasia (Fig. 50.2). The pyrimidine analogue cytarabine has formed



List of abbreviations

ADE 10+3+5	Cytosine arabinoside 100mg/m^2 i.v. twice daily days 1 to 10 Daunorubium 50mg/m^2 i.v. once daily days 1,3,5 Etoposide 100mg/m^2 i.v. once daily days 1 to 5
ADE 8+3+5	Cytosine arabinside 100mg/m^2 i.v. twice daily days 1 to 8 Daunorubium 50mg/m^2 i.v. once daily days 1,3,5 Etoposide 100mg/m^2 i.v. once daily days 1 to 5
MACE	Amsacrine 100mg/m^2 i.v. once daily days 1 to 5 Cytosine arabinoside 200mg/m^2 i.v. by continuous infusion days 1 to 5 Etoposide 100mg/m^2 once daily days 1 to 5
MidAC	Mitoxantrone 10mg/m^2 i.v. once daily days 1 to 5 Cytosine arabinside 1g/m^2 i.v. once daily days 1 to 3

Fig. 50.2 One example of a possible treatment regimen for AML. The figure demonstrates that patients are treated with initial induction therapy, then remission is consolidated with at least two courses of chemotherapy. This figure provides a summary only and should not be used as a guide to prescribing or dispensing therapy.

the basis of treatment for AML for 20 years. The addition of daunorubicin and oral thioguanine has achieved a CR rate of 75% in patients under the age of 60 years and about 50% in those over 60 years (Dohner et al., 2010). The precise dose and scheduling of these agents is continually being refined in order to improve the response rates. Despite the numbers of patients who achieve CR following induction therapy, the majority relapse, with only about 25% becoming long-term disease-free survivors (Stone et al., 2004). Thus, in common with ALL, additional post-remission therapy is required. Intensive consolidation chemotherapy with high-dose cytarabine and daunorubicin or amsacrine appears to improve survival rates to approximately 50% after 3 years, with even more encouraging results being obtained in patients under 25 years of age (Dohner et al., 2010; Robak and Wierzbowska, 2009). There is generally no role for maintenance therapy in AML. Similarly, CNS prophylaxis is not routinely indicated though patients thought to be at particularly high risk of CNS disease, such as those with testicular or sinus involvement, should receive prophylactic therapy.

An alternative approach to post-remission therapy is stem cell transplantation. In patients under 40 years of age, allogeneic bone marrow transplantation has resulted in disease-free survival of 45–65% at 5 years post-transplant. These patients are considered cured of their disease. Only about 10% of patients are suitable for allogeneic bone marrow transplants, and there is little evidence to suggest that autologous stem cell transplantation improves the outcome for patients with AML in first CR. It is always worth remembering that AML is most common in the elderly, and intensive intravenous chemotherapy regimens are not always appropriate for this population of patients.

Treatment of AML in relapse is difficult and the prognosis is generally poor. Encouraging results have been seen using a combination of fludarabine, cytosine arabinoside and granulocyte colony-stimulating factor (G-CSF). Novel approaches in AML therapy are often piloted in this group of poor-risk patients. A combination of anti-CD33 antibody, which targets myeloid blasts, with calicheamicin, an anthracycline antibiotic, is a promising and effective approach (Stone et al., 2004), but appears most effective when given in combination with conventional chemotherapy. A newly developed purine analogue, clofarabine, has also been shown to have activity against AML. This drug is a promising agent, particularly in the treatment of older patients, as pilot studies suggest that its toxic effects may be less severe than those associated with other chemotherapy regimens (Robak and Wierzbowska, 2009). 5-Azacytidine is also of interest, especially in older patients and those whose disease has evolved from myelodysplastic syndrome MDS. This agent inhibits DNA methyltransferase resulting in DNA hypomethylation. This process is thought to increase activity of some tumour suppressor genes resulting in antitumour effects. The agent has been shown to slow the rate of progression to AML in patients with high-risk myelodysplastic syndrome and is currently the subject of clinical trials in AML.

Acute Promyelocytic Leukaemia

This subtype of AML deserves special consideration as the treatment is quite different from that of other AML variants. APL is associated with the t(15;17) translocation which involves a genetic translocation of material between chromosomes 15 and 17. The disease is clinically characterised by the presence of disseminated intravascular coagulopathy (DIC) at presentation. Since these patients are so prone to life-threatening haemorrhage at diagnosis, the management of a new case of APL is considered a medical emergency. The leukaemic cells are exquisitely sensitive to all-trans retinoic acid (ATRA), which induces blast maturation and can induce remission when used as a single agent (Sanz et al., 2009; Soignet and Maslak, 2004). Using a combination of ATRA and anthracycline chemotherapy, it is now possible to achieve long-term cure in >80% patients. There are some data to suggest that the ongoing use of ATRA in consolidation and maintenance treatment improves outcome further. A number of studies have been published demonstrating the efficacy of arsenic trioxide (ATO) in treating relapsed or refractory APL. Comparison of ATRA and anthracyclines against ATO and ATRA is now the subject of a large UK study of newly diagnosed patients (AML 17). The latter regimen has the potential advantage of avoiding significant myelosuppression.

Chronic leukaemia

Chronic myelocytic leukaemia

Until recently, the treatment of CML has been essentially palliative, producing modest increases in survival, but with the main aim of keeping patients asymptomatic by normalising the WBC. Hydroxycarbamide was the most widely used drug in the management of CML in chronic phase. Treatment with hydroxycarbamide is initiated at a dose of 1.5–2 g/day and usually brings the WBC under control within 1–2 weeks. The dose can then be reduced to a maintenance dose of 0.5–2 g/day. Withdrawing or reducing the dose abruptly can cause a rebound increase in WBC. The side effects of hydroxycarbamide are generally mild but include rashes and gut disturbances.

Interferon can control symptoms of CML but was also the first agent shown to modify the disease process. It promotes the expression of suppressed normal haemopoiesis at the expense of the malignant clone. Studies have shown that interferon-α therapy prolongs the chronic phase and improves the median survival of patients with CML, and its effects seem to be enhanced by the addition of low-dose cytarabine (Sawyers, 1999).

Therapeutic options for patients with CML have changed dramatically in the past 10 years due to the development of imatinib mesylate. This drug was specifically designed to target the abnormal tyrosine kinase product of the BCR-ABL fusion gene (Fig. 50.3). In a large randomised controlled trial, patients were randomised to receive imatinib or a combination of interferon-α and cytarabine. Many patients were intolerant of the interferon and cytarabine combination and crossed over to receive imatinib after trial commencement.

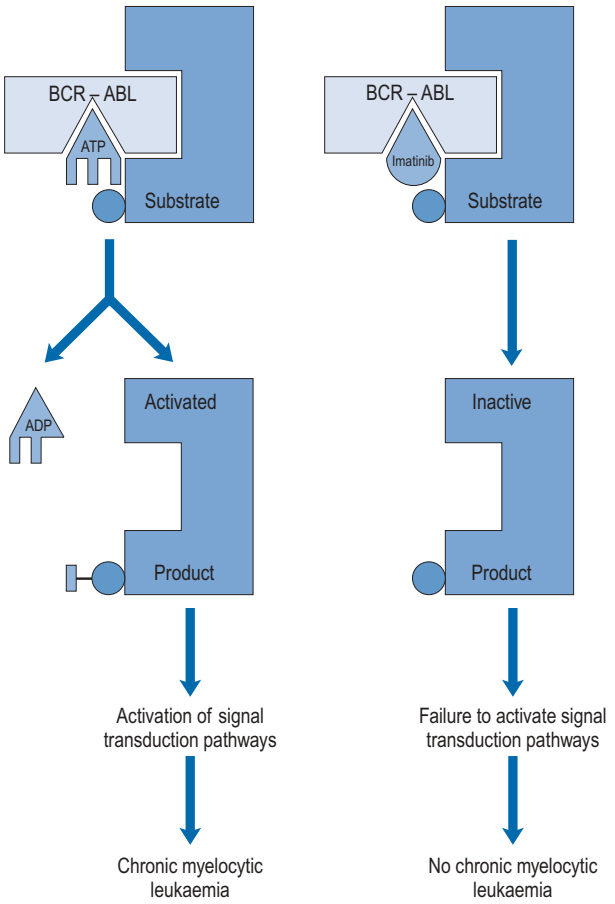


Fig. 50.3 Inhibition of BCR-ABL protein by imatinib. The protein product of the BCR-ABL fusion gene (BCR-ABL protein) acts as a constitutively active tyrosine kinase and uses ATP, bound within a kinase pocket in the molecule, to phosphorylate tyrosine (o) in a variety of substrates. In doing so, ATP (adenosine triphosphate) is reduced to ADP (adenosine diphosphate) which falls out of the kinase pocket to be replaced by further ATP. Imatinib prevents the action of the BCR-ABL protein by blocking ATP entry into the kinase pocket.

Despite this problem, progression-free survival at 1 year was 97% in the imatinib arm and 80% in the interferon and cytarabine arm in an intention-to-treat analysis (O'Brien et al., 2003). The Philadelphia chromosome became undetectable in 68% of imatinib recipients compared to 7% of those in the alternative arm (Hughes et al., 2003). However, more sensitive testing methods, such as real-time polymerase chain reaction (PCR), have now shown that many patients who are Philadelphia chromosome negative still possess very low levels of the abnormal BCR-ABL gene produced by the Philadelphia translocation.

Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors (TKIs) designed to overcome resistance to imatinib caused by mutations in the kinase domain of BCR-ABL. Both agents work well as second-line therapies, producing complete cytogenetic responses in about 50% of patients. The use of dasatinib and nilotinib in newly diagnosed patients is currently being evaluated in ongoing clinical trials. Due to the effectiveness of imatinib therapy and the development of second-generation agents, allogeneic stem cell transplantation is now rarely used to treat CML, but it does represent a potentially curative option for patients with resistant disease.

Transformation of CML into acute leukaemia can be treated in the same manner as *de novo* acute leukaemia, in an effort to achieve a second chronic phase. Treatment is slightly more successful if transformation is lymphoid rather than myeloid. Imatinib, typically at higher doses than are used in chronic phase disease, can also be used to attempt to return patients to chronic phase disease. In general, remissions are rare and the median survival is less than 6 months.

Chronic lymphocytic leukaemia

Currently, there is no cure for CLL. All treatment is, therefore, considered palliative. There is no evidence that early treatment of asymptomatic patients improves outcome. Indications for treatment are:

- rapidly increasing WBC
- increasing or troublesome lymphadenopathy
- systemic symptoms
- marrow failure
- autoimmune complications.

Formerly, the alkylating agent chlorambucil was the most common agent used in the treatment of CLL. Corticosteroids can reduce the lymphocyte count without contributing to myelosuppression and are used to treat autoimmune phenomena such as haemolytic anaemia and immune thrombocytopenia. The use of purine analogues, particularly fludarabine, marked the beginning of an exciting phase in the treatment of CLL. Although CRs were unusual, good responses were seen even in patients whose leukaemia was resistant to alkylating agents. With regard to initial therapy of CLL, fludarabine-treated patients show a higher response rate than patients treated with chlorambucil. However, no survival advantage for the use of fludarabine has been demonstrated (Rai et al., 2000). More recently, a large randomised study comparing fludarabine and cyclophosphamide with and without the anti-CD20 antibody, rituximab, has been published (Hallek et al., 2009). This study demonstrated an overall response rate of 86% and 73%, respectively. The median progression-free survival with rituximab is the best published in a large randomised controlled trial to date, at 40 months. This combination of fludarabine, cyclophosphamide and rituximab has been adopted, in the UK, as the regimen of choice for first-line treatment of CLL as long as patients are considered fit enough. Chlorambucil remains an excellent choice for patients with significant co-morbidities as the treatment is less immunosuppressive.

Splenic complications may necessitate splenectomy or splenic irradiation. Radiotherapy can also be used to control localised painful lymphadenopathy. Combination chemotherapy, such as CHOP (see Chapter 51) used in lymphoma, may be beneficial in advanced disease. Campath-1H is a humanised monoclonal anti-CD52 antibody. CD52 is present on most lymphocytes including malignant lymphocytes in CLL. Binding of this antibody induces both antibody-mediated

and complement-mediated T-cell cytotoxicity against malignant B cells. In relapsed patients, the duration of response to Campath-1H is relatively short. However, the agent is currently being studied, both in combination with other drugs and as a possible means of purging the bone marrow of residual cells prior to autologous stem cell harvest and transplantation.

Patients with CLL are very susceptible to infection. Herpes viruses, in particular herpes zoster, can cause significant problems. This susceptibility is increased because many treatments, such as campath-1H and fludarabine, have generalised anti-lymphocyte action and are not absolutely specific for malignant lymphocytes.

Stem cell transplantation

The potential role of stem cell transplantation is increasingly being explored in the management of all types of leukaemia.

The basic principle

This technique provides a means of rescuing the patient from the potentially lethal effects on the bone marrow of ablative therapy given in an attempt to eradicate all traces of disease (Fig. 50.4). The conditioning regimen most commonly used is a combination of high-dose cyclophosphamide and total body irradiation. Other conditioning regimens include high-dose melphalan, etoposide, busulphan or cytarabine.

Following administration of conditioning therapy, 2–3 days elapse to allow its elimination from the body, and then previously harvested stem cells are reinfused peripherally. The stem cells will return to and repopulate the marrow, restoring normal haemopoiesis. Peripheral blood counts recover in 2–4 weeks. Throughout this time, patients require intensive supportive care and the procedure, particularly allogeneic stem cell transplantation, causes significant morbidity and has a mortality rate of 5–30%.

The source of stem cells

During allogeneic stem cell transplantation (allograft), stem cells are obtained from a human leucocyte antigen (HLA)-matched donor. These stem cells can be removed directly from the bone marrow, under general anaesthetic, or harvested from the peripheral blood. Under certain circumstances, in the absence of a matched donor, an autologous bone marrow or peripheral blood stem cell transplant (autograft) can be performed. Following conditioning, the patients receive their own cryopreserved marrow or peripheral blood stem cells, previously harvested from them while in CR. There is a potential risk, however, that stem cells obtained in this way may contain undetected, residual disease. Attempts have been made to purge the bone marrow of disease *in vitro*, but these have generally been unsuccessful.

Peripheral blood stem cell transplantation

This technique for rescuing bone marrow following ablative conditioning therapy is used to restore haemopoiesis (Russell, 1998). Patients receive the haematopoetic growth factor G-CSF, either alone or following an infusion of high-dose chemotherapy such as high-dose cyclophosphamide. Patients receive G-CSF for a period of about 7 days. This stimulates the release of stem cells into the peripheral circulation. Stem cells are then harvested from the peripheral circulation by a process of cell pheresis. The harvested cells can then be reinfused, fresh, into the patient following conditioning therapy or frozen and stored for later use.

Peripheral stem cell transplantation offers some advantages over conventional bone marrow transplant techniques; collection of peripheral stem cells negates the need for general anaesthesia and it has been found that the haemopoietic recovery period following transplantation is shortened by 5–10 days. This technique can also be used to harvest stem cells from allogeneic donors. In this case, G-CSF is used alone to stimulate stem cell release into the peripheral circulation. It is sometimes impossible to harvest enough stem

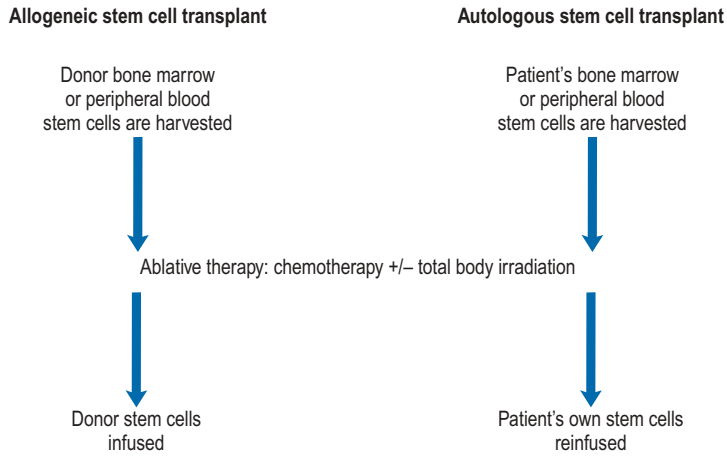


Fig. 50.4 Stem cell transplantation.

cells from patients to allow an autologous transplant to be performed. The commonest reason for this is that the patient has been heavily pretreated with chemotherapy or radiotherapy. A new CXCR4 chemokine antagonist, plerixafor, is now available. This agent is thought to reduce adhesion of stem cells within the bone marrow milieu. It can be given along with G-CSF and allows a proportion of patients who have failed to mobilise stem cells using G-CSF alone to mobilise cells for an autograft.

Complications

Infection is almost inevitable in patients undergoing bone marrow transplantation. Other significant complications of allografts include interstitial pneumonitis and hepatic veno-occlusive disease, but the major life-threatening complication is acute graft-versus-host disease (GVHD). The likelihood of graft-versus-host disease occurring increases with age, and for this reason, myeloblative allografts are largely restricted to patients under 45 years of age. Graft-versus-host disease is caused by T-lymphocytes in the donated marrow reacting to host tissues. The severity of the reaction ranges from a mild maculopapular rash to multisystem organ failure with a high mortality rate. Acute graft-versus-host disease typically occurs within 100 days of the bone marrow transplantation and typically presents with fever, rash, diarrhoea and liver dysfunction. Prophylactic therapy is routinely given with methotrexate or ciclosporin, alone or in combination, for 6–12 months post-transplant. Should acute graft-versus-host disease develop, high-dose methylprednisolone, ciclosporin, antithymocyte globulin and, more recently, anti-cytokine monoclonal antibodies, for example, anti-TNF (tumour necrosis factor) antibodies, have been used to treat the condition.

Chronic graft-versus-host disease can occur after 3 months following bone marrow transplantation. It is a multisystem disorder associated with chronic hepatitis, severe skin inflammation and profound immunosuppression. Treatment is successful in approximately 50% of patients and consists of immunosuppression with azathioprine and prednisolone together with prophylactic antibiotics. Ciclosporin and thalidomide have also been used successfully in the treatment of chronic steroid-refractory graft-versus-host disease. The main cause of death amongst patients with chronic graft-versus-host disease is infection.

Reduced intensity allografting

Myeloablative allogeneic transplantation, as described earlier, is a very intensive procedure associated with significant morbidity and mortality, hence its restriction to younger patients. Attempts have been made to reduce the intensity of transplant conditioning regimens whilst using increased immunosuppression to facilitate marrow engraftment. Although such an approach reduces the intensity of therapy delivered to any residual tumour, the possible downside of this reduction is offset by an immunological graft-versus-tumour effect and by reduced early post-transplant mortality. This form of transplant is often offered to older patients who are considered unfit to receive a standard allograft. However, the long-term outcomes of this approach are under continual review. Several trials now suggest that the overall survival after myeloablative and reduced intensity transplants may be similar though the causes of death in the two groups are different. More patients die of disease relapse after reduced intensity transplants, and more die of transplant-related complications in the myeloablative group (Pollack et al., 2009).

Table 50.6 Indications for allogeneic stem cell transplantation in leukaemia

AML	First remission with the exception of patients with good risk genetic abnormalities: t(15;17), t(8;21) and inversion of chromosome 16
CML	Chronic phase but only if patient fails to respond to first- and second-line tyrosine kinase inhibitors
ALL	First remission in adults Second remission in children
CLL	Not generally appropriate as part of standard therapy but under investigation within several clinical studies

The place of stem cell transplantation

The place of stem cell transplantation in the management of a particular form of leukaemia depends very much on the prognosis of patients treated with conventional chemotherapy (Table 50.6). For example, the results of intensive chemotherapy in children with ALL are good, and bone marrow transplantation is generally only considered for children who have relapsed and in whom a second remission can be achieved. However, conventional treatment of adults is less successful, and allogeneic bone marrow transplantation may be offered to adults in first remission.

Patient care

Supportive care

The treatment of CLL and CML is largely carried out on a hospital outpatient basis, with patients taking oral medication at home or attending outpatient clinics on a weekly or monthly basis for injections of chemotherapy. Patients are routinely monitored to follow the progress of disease and to observe treatment-related side effects. Supportive therapy such as blood transfusions can also be given on an outpatient basis. In contrast, the intensity of induction and consolidation regimens used in the management of patients with acute leukaemia renders them severely pancytopenic. Therapy is usually given as a hospital inpatient with patients often remaining in hospital following treatment for 3–4 weeks until

their bone marrow recovers sufficiently. This is in contrast to therapy for most solid tumours where, following administration of treatment, patients are often well enough to remain at home until their next cycle of chemotherapy is due.

Advanced leukaemia, bone marrow transplantation and aggressive chemotherapy for acute leukaemia all result in pancytopenia. Red cell transfusions are given to patients to maintain their haemoglobin above 9–10 g/dL. Evidence of bleeding includes petechial haemorrhages in skin and mucous membranes, and patients receiving aggressive treatment must be examined daily for any of the above signs. Platelet concentrates are given to thrombocytopenic patients who have signs of bleeding and are given prophylactically should platelets fall below 10×10^9 L^{-1}. The probability of infection developing rises as the WBC, specifically the neutrophil count, falls. With an absolute neutrophil count of below 0.5×10^9 L^{-1}, patients are at high risk of infection, with the risks being even greater if the period of neutropenia is prolonged.

Chapters 51 and 52 examine many of the non-haematological toxicities which result from the use of cytotoxic drugs, and these are clearly pertinent to haematology patients. The major contributors to morbidity and mortality in patients with leukaemia are relapsed disease and infection.

Infection in the immunocompromised patient

A number of intrinsic and extrinsic factors all contribute to the risk of infection in this vulnerable group of patients (Fig. 50.5).

While cross-infection can occur via staff, other patients or contaminated objects, the main sources of infection in this group of patients are endogenous, arising from commensal gut and skin organisms. The normal host defences to infection are broken down; damage to mucous membranes, particularly in the gastro-intestinal tract, occurs with chemotherapy and radiotherapy, allowing infecting organisms to enter the bloodstream. Most infections in neutropenic patients arise from three main sites: the gastro-intestinal and respiratory tracts, and the skin. Table 50.7 lists the main pathogens responsible for infection in this group of patients.

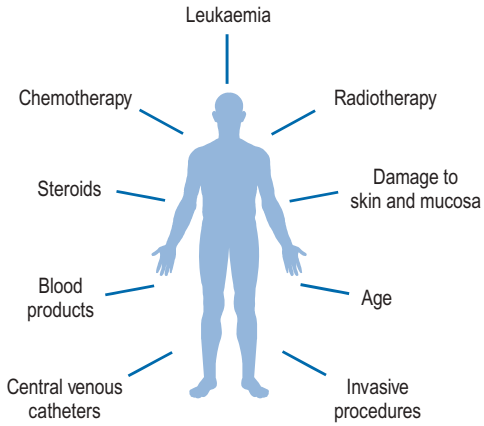


Fig. 50.5 Infection risk in immunocompromised patients.

Table 50.7 Pathogens commonly causing infection in neutropenic patients

Gram-negative bacteria	*Pseudomonas* spp. *Escherichia coli* *Klebsiella* spp. *Enterobacter* spp. *Proteus* spp. *Serratia* spp. *Legionella pneumophilia*
Gram-positive bacteria	*Streptococcus* spp. *Staphylococcus epidermidis* *Staphylococcus aureus*
Anaerobes	*Clostridium difficile* *Clostridium perfringens* *Bacteroides* spp.
Fungi	*Candida* spp. *Aspergillus* spp.
Viruses	Herpes simplex Herpes zoster Cytomegalovirus Hepatitis
Protozoa	*Pneumocystis carinii*

Preventive measures

Oral hygiene. Mouth care is important in all patients receiving chemotherapy but particularly neutropenic patients. Patients are generally asked to use mouthwashes regularly, and prophylactic antifungal therapy may also be given. Although it is important to avoid any sort of trauma to the oral mucosa, teeth should be cleaned regularly using a soft toothbrush. Attention must also be paid to the care of dentures. Patients require careful counselling on mouth care, stressing the importance of oral hygiene.

Prophylactic anti-infectives. In general, prophylactic antibiotics are avoided because of the possible development of resistant organisms, but they may have a place in the management of periods of prolonged myelosuppression following chemotherapy and bone marrow transplantation. Prophylactic antifungal agents are often given and patients undergoing bone marrow transplantation and therapy for ALL require prophylaxis against herpes virus and *Pneumocystis carinii* (Table 50.8).

Gut decontamination. Gut decontamination using a combination of non-absorbable oral antibiotics and antifungal agents reduces the burden of potentially pathogenic organisms in the intestine. One such combination includes neomycin sulphate, colistin sulphate, nystatin and amphotericin. However, opinions are divided over this practice, as gut decontamination can lead to the overgrowth of resistant organisms.

Growth factors. An exciting development in the care of patients with leukaemia has been the production of haemopoietic growth factors using recombinant DNA technology. The first of these, G-CSF, given daily by subcutaneous

Table 50.8 Prophylactic anti-infectives	
Gram-negative bacteria	Ciprofloxacin
Candidiasis	Nystatin Fluconazole Itraconazole
Herpes simplex	Aciclovir
Pneumocystis carinii	Co-trimoxazole

injection or intravenous infusion after completion of chemotherapy, stimulates neutrophil production and may reduce the duration of neutropenia by up to 7 days. The cost of these compounds is a major issue and results of studies investigating the effects of G-CSF on morbidity and mortality, following chemotherapy, have been disappointing (Smith et al., 2006). Newer pegylated growth factors have been introduced. These have a longer half-life than standard agents, and thus fewer injections are required. The impact of these agents on morbidity and mortality post-chemotherapy, however, remains controversial.

Aseptic technique. Careful attention should be paid to the care of intravenous cannulae, particularly central venous catheters. The increased incidence of staphylococcal infection in immunocompromised patients can largely be attributed to their use. Invasive procedures, such as venepuncture, must be carried out using strict aseptic technique. Similarly, urinary catheters are a major source of infection and their use should be avoided if at all possible.

Protective isolation. Reverse barrier isolation during periods of neutropenia, nursing in strict sterile environments and high-efficiency particulate air (HEPA) filtration have been used in an attempt to reduce infection rates. This is extremely demanding for staff and patients alike and is generally only appropriate following bone marrow transplantation.

Treatment of infection

Commonly, neutropenic patients show no signs of focal infection; they are unable to form pus. The only clinical manifestations of septicaemia might be general malaise, fever or hypotension. A patient's condition can deteriorate very rapidly, with collapse occurring within hours of the first signs of infection. Treatment should be instigated as soon as infection is suspected. Following a clinically serious febrile episode (temperature: 37.5 °C for more than 1 h or 38 °C or more on a single reading), samples are taken for culture; these may include blood, urine, sputum and stool cultures along with line and throat swabs. Intravenous antibiotics must be started empirically without delay (Sipsas et al., 2005). Standard empirical therapy varies from unit to unit but may involve the combination of an aminoglycoside with an antipseudomonal penicillin such as piperacillin to provide broad-spectrum bactericidal cover. In penicillin-allergic patients, ceftazidime or cefotaxime may be substituted, but local resistance patterns are of paramount importance. Antibiotics with a broad spectrum of activity, such as ciprofloxacin, have been used as single agents.

Vancomycin or teicoplanin are often prescribed if an infected central venous catheter is suspected, to provide additional cover against Gram-positive organisms. Microbiological advice should be sought in cases of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. Metronidazole may be added to the antibiotic regimen to cover anaerobes if the clinical presentation suggests that the source of the infection may be oral, perineal or gut. Anti-infective therapy should subsequently be modified on the basis of cultures, but in the majority of neutropenic patients, a causative organism is never identified.

If the pyrexia persists for more than 4 days in spite of broad-spectrum antibiotics, or if the patient's condition is deteriorating, systemic fungal infection should be suspected. Empirical antifungal therapy for neutropenic patients with antibiotic-resistant fever reduces mortality and is considered a standard of care. A number of broad-spectrum agents are now available for use in this setting, including standard amphotericin, lipid formulation of amphotericin, caspofungin and voriconazole. Intravenous amphotericin is often the first choice to ensure that *Aspergillus* and *Candida* are covered. The main limitation of amphotericin is its toxicity, in particular, nephrotoxicity. Lipid formulation of amphotericin may be appropriate in patients with pre-existing renal impairment or in cases where conventional amphotericin has induced nephrotoxicity. Voriconazole is a useful agent with a similarly broad spectrum of activity. Hepatotoxicity, visual disturbances and prolonged QT interval are the most common side effects of voriconazole. This agent has the advantage of being available as both intravenous and oral preparations, so the conversion from parenteral to oral therapy is straightforward.

Although the antifungal activity of the echinocandin, caspofungin, is more limited than that of amphoteracin or voriconazole, it has been shown to be effective for empirical therapy as it has good efficacy against *Candida* and *Aspergillus* spp. It has the advantage of reduced toxicity in comparison with other available agents. The most common side effect is hepatotoxicity. Since this agent has a relatively limited spectrum of activity, it is probably best avoided in the setting of presumed fungal sinus or CNS infection, which are often caused by fungi other than *Aspergillus* or *Candida* spp. Table 50.9 lists some of the common problems encountered in the treatment of the leukaemias.

The following practice points should be used to control infection in immunocompromised patients.

- Measures to prevent infection are important.
- Particular attention should be paid to scrupulous hand washing, mouth care and the use of antifungal, antiviral and antipneumocystis prophylaxis for patients at high risk.
- Preventive measures do not eliminate the risk of infection.
- Treatment of fever in a neutropenic patient is a medical emergency.
- Empirical antifungal therapy should be used to treat neutropenic patients with antibiotic resistant fever, at high risk of fungal infection.

Table 50.9 Common therapeutic problems in the leukaemias

Problem	Cause	Solutions
Mucositis and oral ulceration	Chemotherapeutic agents directly toxic to mucosal epithelium Radiotherapy is directly toxic to the mucosa and also reduces saliva production by salivary glands Vulnerable mucosa is likely to be attacked by infective agents, for example, herpes simplex, *candida*	Regular mouth toilet including the use of antibacterial mouthwash Prophylactic use of antiviral and antifungal agents for patients in whom myelosuppression is likely to be prolonged
Fever in neutropenic patients	Infection predominantly caused by bacteria and/or fungi	Broad-spectrum antibiotics must be commenced as soon as blood cultures have been taken A strategy of planned progressive therapy including use of an antifungal agent in non-responsive fever is appropriate
Graft-versus-host disease (GVHD)	T lymphocytes from the donor react against host tissues	Use a sibling donor if possible Use the donor most closely HLA matched to the patient Consider T-cell depletion of graft (though this may increase the risk of disease relapse) Prophylactic therapy with methotrexate and ciclosporin Treat GVHD with corticosteroids, ciclosporin, anti-thymocyte, globulin, FK 506, anticytokine monoclonal antibodies Irradiate all blood products
Late complications of treatment	Risks of haemopoietic malignancy and non-haemopoietic malignancy are increased post-chemotherapy Late cardiotoxicity secondary to anthracyclines	Aim to tailor therapy to the underlying disease, that is, do not overtreat and do not undertreat Do not exceed maximum cumulative doses of anthracyclines Liposomal anthracyclines may be useful in the future

Case studies

Case 50.1

A 30-year-old woman recently diagnosed with CML attends the haematology clinic to discuss the options for treatment.

Questions

1. Which treatment options are available?
2. Which treatment is likely to be the best choice for this patient?

Answers

1. There are clearly a number of potential treatment options which need to be explored with the patient.
   The various treatment options are:
   - palliative therapy with hydroxycarbamide to control cell counts
   - interferon-α
   - interferon-α and cytosine
   - imatinib
   - allogeneic matched sibling transplant
   - matched unrelated donor (MUD) transplantation if a matched sibling is not available
   - treatment as part of a clinical trial which is likely to involve imatinib in varying doses or in combination with other effective agent.
2. A purely palliative approach is unlikely to be acceptable to a young patient, but hydroxycarbamide can still be used acutely to control high cell counts. There is no doubt that use of interferon-α alone results in cytogenetic remission in a small percentage of patients, and this effect is enhanced by the addition of cytosine. The side effects of interferon-α include flu-like and affective symptoms. The addition of cytosine increases myelosuppression and risk of mucositis. Although these treatments can induce cytogenetic remission, the duration of such responses is unclear and only a minority of patients respond completely. The high risk of side effects and the low chance of complete cytogenetic response to interferon-α, with or without cytosine, are likely to make these therapeutic modalities unattractive to this patient.

   It remains true that allogeneic stem cell transplantation is the only proven curative therapy for patients with CML. The difficulty with this approach is that the mortality rate for transplant recipients remains high. The 1-year mortality rate for a 30-year-old patient transplanted using a sibling donor is approximately 15–20%, and this may rise to 25–30% if a MUD

has to be used. The major causes of death in this group are GVHD and infection. In addition to this high risk of mortality in the short-term, there is also a risk of long-term morbidity post-allograft. Chronic graft-versus-host disease can have a significant impact on quality of life for many patients and requires long-term medical follow-up. Ironically, patients with a degree of chronic graft-versus-host disease are at reduced risk of disease relapse since a graft-versus-host response is also associated with a graft-versus-leukaemia effect; some disparity between the immune systems of the transplant donor and recipient is helpful. In addition to these problems, all transplanted patients are at increased risk of a second malignancy developing later in life as a consequence of the conditioning therapy received as part of the transplant and probably also as a consequence of deficiencies within the transplanted immune system.

Given the problems associated with the various therapeutic strategies discussed earlier, it is not surprising that there was great excitement surrounding the development of a targeted tyrosine kinase inhibitor, imatinib. Results with this agent, particularly for patients with newly diagnosed chronic phase disease, are excellent. Complete cytogenetic responses have been seen, although very sensitive quantitative PCR techniques can still detect the abnormal BCR-ABL gene in the vast majority of CML patients in whom the Philadelphia chromosome itself is undetectable. In addition, the drug has been shown to delay progression to accelerated phase disease or blast crisis. It is still not possible, however, to say that imatinib cures patients with CML.

Although no randomised study has been undertaken, it is clear from historical data that, in the short-term, the mortality associated with allogeneic stem cell transplantation far exceeds that associated with imatinib. In addition to these very encouraging data which pertain to the effect of the drug on the disease, the side effects of imatinib are generally mild and patients report this agent far easier to tolerate than interferon-α. The main side effects are rash, cytopenias, fluid retention and abnormalities of liver function tests.

Given the efficacy of imatinib and the fact that the drug is generally very well tolerated, imatinib is regarded as the initial treatment of choice for the vast majority of patients with CML. Ongoing management involves haematological and molecular monitoring of the patient to determine whether they have a good response to imatinib. In the event of a good response, the patient continues to take the drug. If at a later stage the molecular response to the agent begins to diminish, then transplantation is reconsidered. Amongst patients who fail to respond or respond poorly to imatinib, transplantation options are likely to be considered at an earlier stage.

Case 50.2

A patient with AML is currently in first CR and has a fully HLA-matched brother who is medically fit. You have been asked to counsel the potential transplant donor about stem cell collection.

Questions

1. What methods are available for the collection of stem cells for haemopoietic stem cell transplantation?
2. What are the advantages and disadvantages of each of these stem cell collection methods for the transplant donor?
3. What are the advantages and disadvantages of each of these stem cell collection methods for the transplant recipient?

Answers

1. There are two main methods of collection of haemopoietic stem cells from a sibling donor. These are:
   - direct harvesting of cells from the bone marrow in the pelvis;
   - collection of circulating peripheral blood stem cells using an apheresis technique after stimulation of the stem cell compartment using (G-CSF).
2. Direct harvesting of marrow stem cell from the bone marrow is an operative procedure and is performed under general anaesthetic. Clearly, there are risks associated with the use of general anaesthesia, but the risk of death associated with this approach is less than 1 in 10,000 procedures. Marrow harvesting involves a hospital stay, usually for one night post-operatively, but some units also require donors to be admitted the night before surgery. Donors are likely to experience pain around the pelvis, and there is a risk of mechanical back pain in the short to medium term due to pressure applied to the pelvis during repeated needle insertions. This risk is increased in those with a history of back problems prior to the procedure. Indeed, such potential donors may prefer a peripheral blood stem cell harvesting approach. Donors must be warned about bruising and potential infection at the site of their wounds.

   One of the other potential problems associated with marrow harvesting is that it is impossible to select the type of blood cell harvested and a large component of the volume of fluid collected comprises red blood cells. This can lead to a degree of anaemia in the donor who may take several weeks to normalise their haemoglobin. It is usually possible to avoid blood transfusion in this situation as it is unusual for donors to be significantly symptomatic. Nonetheless, donors must be warned that the need for allogeneic blood transfusion is a possibility with this procedure.

   Peripheral blood stem cell harvesting has several advantages over direct marrow harvesting from the iliac crests. The procedure can be undertaken during hospital outpatient visits and does not require the use of a general anaesthetic. As the stem cell-harvesting procedure allows selective collection of mononuclear cells, significant anaemia is very unlikely after this procedure. Clearly, red cells do circulate within the apheresis circuit, and if the circuit clots off and has to be disconnected from the donor, then red cells will be lost. This is unlikely to be of clinical significance unless the donor is a child and hence has a relatively low blood volume.

   Disadvantages of this approach include the need for stimulation of donor haemopoiesis by the G-CSF.

   Marrow stimulation can result in significant pain especially around the shoulders, back and pelvic girdle. Most donors can manage this pain at home with simple analgesia, but very occasionally hospital admission is required for pain control. Very occasionally patients develop splenic pain, and there have been a couple of reports of splenic rupture in normal donors after G-CSF stimulation, but this is very rare. One difficulty with the use of G-CSF is that it has only been in routine use for the past 15 years. This makes it impossible to categorically reassure potential stem cell donors that use of G-CSF in this way is absolutely safe in the long-term. There is, however, currently no evidence that acting as a peripheral blood stem cell donor increases one's risk of leukaemia development later in life. Some potential donors find this element of uncertainty difficult and prefer to undertake a marrow harvest in which the risks, although present, are better quantified.

   The apheresis procedure itself involves the donor lying relatively still with a needle in one or both arms (depending upon the type of apheresis kit used) for approximately 4–5 h. Some collections can be done in one procedure, but some donors will need to be harvested in two procedures, over 2 days.

One prerequisite for peripheral blood stem cell donation is that the potential donor has good enough peripheral veins to allow reliable venous access. If this is not the case and the donor prefers to donate using this method, a temporary central venous line has to be inserted.

Most donors tolerate the apheresis procedure with few problems. One of the most common complications of the procedure is hypocalcaemia which results from calcium binding by the citrate anticoagulant used to prevent clotting within the apheresis circuit. Donors may notice perioral tingling or paraesthesia in other areas and are asked to report this immediately. The problem is easily treated by reducing the concentration of anticoagulant in the circuit and by asking the donor to drink a small amount of milk. If this problem is not picked up early, the consequences can be more severe, with the development of tetany which would require intravenous calcium replacement.

In summary, peripheral blood stem cell donation is generally a less invasive and better-tolerated procedure than direct stem cell harvest from the marrow space. However, the associated procedural risks are more easily quantifiable for the latter procedure.

3. There are some potential advantages, to the transplant recipient, in the use of peripheral blood stem cells as opposed to bone marrow stem cells. Engraftment is quicker, so the recipient spends less time in the neutropenic phase, and hence the risk of infection is reduced. Similarly, there is evidence that duration of hospital stay is reduced when peripheral blood stem cells are used. One potential disadvantage of this approach is that the graft includes a larger dose of T-lymphocytes than a graft of stem cells derived directly from the marrow (approximately a 10-fold increase). There is some evidence that rates of chronic graft-versus-host disease are increased amongst recipients of peripheral blood stem cells, but this observation has not been borne out in all studies. This potential disadvantage of peripheral blood stem cells is negated if a T-cell-depleted approach is used, as is the case for most matched unrelated procedures.

Case 50.3

A 25-year-old woman is admitted with newly diagnosed AML. Once her condition is stabilised, the consultant seeks her consent to start intensive chemotherapy.

Questions

1. How should the consultant ensure the consent process is performed as well as possible?
2. What side effects should the consultant discuss?

Answers

1. It is vital that consent is taken only after very careful discussions. Consent for such intensive chemotherapy usually requires several conversations. The final consent conversation should be done in a quiet private room if possible, and interruptions should be kept to a minimum. The patient should be allowed to have a friend, partner or relative present if they wish, and ideally a clinical nurse specialist should be present too. If possible, the patient should be given some written material on chemotherapy before consent even if it is important the treatment is started promptly. The patient should be given a clear explanation of their potential treatment options and should be informed of any clinical trials that may be available to them. It is vitally important to fully inform patients regarding their condition and its prognosis, and about treatment options and their potential advantages and disadvantages. Only if the patient has all the necessary information can they decide on the treatment option that is most appropriate/acceptable to their individual circumstances.
2. The consent discussion should include a discussion of all common side effects and less common but severe side effects of treatment. Common side effects of AML chemotherapy would include nausea, vomiting, mucositis, tiredness, malaise, infections, hair loss, bleeding and anaemia. Patients should be warned that they will require transfusions of blood and platelets. They will always need good venous access and usually a Hickman or other long-term in-dwelling central line. They will need to be warned they will have to spend at least 3–4 weeks in hospital. Severe side effects may include infertility and a premature menopause in young women. Options for the prevention and treatment of infertility must be discussed before treatments commences. Anthracyclines can be associated with cardiac problems, infections and bleeding can be life threatening and patients must be warned that they may not respond to therapy or may relapse after treatment. They should also be warned that a cure cannot be guaranteed. There is a risk of treatment-related mortality of around 1–2%. Longer-term risks include a greater lifetime risk of cancers including skin cancer and lung cancer, particularly in smokers.

Case 50.4

A 24-year-old patient with ALL is undergoing chemotherapy and needs intrathecal chemotherapy to prevent relapse in the meninges. Giving drugs by this route is EXTREMELY DANGEROUS. Several patients have died as a result of the inadvertent administration of vinca alkaloids into the CSF.

Question

What steps have been taken nationally to try to prevent the inadvertent intrathecal injection of vincristine and other agents not suitable for intrathecal use?

Answer

In the UK, there are now strict guidelines for administration of intrathecal chemotherapy. It can only be performed in hospital units which have passed a rigorous peer review process. The procedure must be undertaken in a specially designated area. Intravenous drugs must not be given in this area. The intrathecal drugs must only be prescribed by a consultant or specialist registrar who has been trained to prescribe or give intrathecal chemotherapy and whose name appears on a locally held register. Drugs for intrathecal administration must only be prescribed on a specially designated prescription sheet. Once the prescription has arrived in pharmacy, the drugs must be manufactured and checked by pharmacists trained in the manufacture and checking of intrathecal prescriptions. The drugs must be positively labelled 'for intrathecal use only' and must be dispensed by a trained pharmacist. They can only be dispensed once the patient has been given any intravenous drugs that are due that day. The doctor collecting the drugs must sign to confirm that the i.v. drugs, if due, have been given before the drugs are dispensed. The drugs must only be dispensed to a doctor trained and on the register for giving intrathecal drugs. The intrathecal drugs must be transported in a specially designated container, and if they need to be stored, then it must be in a separate, specially designated fridge, that is separate from any intravenous chemotherapy. Once the procedure is under way, the intrathecal drugs must be checked by the registered doctor and by a nurse who has been trained and appears on a register of nurses trained to check intrathecal drugs. The drugs should

also be checked by the patient or a patient's representative. Intrathecal drugs must not be given in hospitals not approved for the procedure, in non-designated areas, outside office hours or at the weekend unless there are exceptional circumstances. All staff working on oncology or haematology units should be taught about the rules for giving intrathecal therapy.

In addition, in order to prevent inadvertent vincristine administration into the intrathecal space, hospitals giving intrathecal chemotherapy should follow special rules for labelling vinca alkaloid prescriptions and vinca alkaloids should be made up in a minimum volume of 20 mL in order to prevent intrathecal administration.

Case 50.5

A 37-year-old dental technician presented with acute promyelocytic leukaemia (APL). He had a number of bleeding problems at presentation. He was randomised on an APL trial to be commenced on oral all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).

Questions

1. Why is ATRA used in this circumstance and what are its side effects?
2. Why is ATO used in this circumstance and what are its side effects?

Answers

1. APL is a variant of AML which presents with coagulation defects, low platelet counts and severe bleeding. Patients are at risk of severe haemorrhage at presentation but have a relatively good prognosis with chemotherapy. ATRA can rapidly correct the coagulopathy found at presentation. This agent also increases the likelihood of the patient entering remission, when combined with standard high-dose chemotherapy. It is also used as a maintenance agent and when used with 6-mercaptopurine and methotrexate, it increases the number of patients who remain in long-term remission. The side effects of ATRA include dry eyes and a dry mouth. In addition, ATRA can cause a severe and life-threatening sterile pneumonitis. It is important to recognise this syndrome quickly as it often responds to high-dose dexamethasone and if left untreated leads to respiratory failure and death.
2. ATO has been shown to bring about remission in patients who have APL in association with the 15;17 chromosomal translocation and the PML:RARA genetic abnormality. It is not considered a conventional chemotherapeutic agent and seems to work in a synergistic fashion with ATRA. There is a lot of interest in combining these agents in an attempt to reduce the exposure of these patients to chemotherapy. Side effects include the APL differentiation syndrome, similar to the ATRA differentiation syndrome.

   ATO can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-wasting diuretics or other conditions that result in hypokalemia or hypomagnesemia. Prior to initiating therapy with ATO, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 ms, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using ATO.

Case 50.6

A 57-year-old man with a 6-year history of CLL presented with a rising white cell count, worsening lymphadenopathy and hepatosplenomegaly. Treatment was commenced with oral fludarabine 40 mg/m² and oral cyclophosphamide 250 mg/m² daily for 3 days with rituximab given on day 1 (FC-R).

Question

What additional precautions would you advise the physician to take and why?

Answer

Fludarabine, cyclophosphamide and rituximab are a very powerful combination available for the initial treatment of CLL. It has been used as a second-line therapy, although recent data support its use as a first-line therapy. It has been associated with more frequent and deeper remissions which are longer than single-agent therapy. It is a very immunosuppressive combination with activity against both T- and B-cells, and patients treated with this regime are at high risk of developing *Pneumocystis* pneumonia. It is important that patients are given prophylaxis against this severe infection. Herpes virus infections including herpes simplex and herpes zoster are also common, and most patients are given acyclovir prophylaxis.

As patients are immunosuppressed, they are also at risk of developing transfusion related graft-versus-host disease. This is a complication of blood product transfusion, caused by engraftment of lymphocytes from the transfused product, which is frequently fatal. This complication can be prevented by irradiation of blood products prior to transfusion. Rituximab is an antibody-based therapy and can be associated with significant reactions which can occasionally be severe and life threatening (see Chapter 51).

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Lymphomas 51

L. Cameron and C. Loughran

Key points

- Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) are aggressive diseases that are fatal if untreated.
- Early-stage HL patients are treated with combined modality treatment usually consisting of two to four cycles of ABVD (Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine) and involved field radiotherapy (IFRT) (20–30 Gy); a relapse-free survival rate of 85–90% at 5–10 years is achieved.
- ABVD chemotherapy is the current gold standard regimen for advanced HL, and overall survival at 5 years is 75–80%.
- Low-grade NHL may be treated using R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone) or chlorambucil chemotherapy or by adopting a 'watch and wait' policy.
- R-CHOP (cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), prednisolone, rituximab) chemotherapy is the standard for the treatment of aggressive (intermediate and high grade) NHL, curing 60% of patients.
- Relapsed HL and NHL may be treated with further chemotherapy followed by high-dose chemotherapy with bone marrow or peripheral stem cell transplantation.
- Patients receiving chemotherapy for HL and NHL should have full blood count (FBC) and blood biochemistry monitored at frequent intervals.
- Complications such as nausea and vomiting, tumour lysis syndrome (TLS), mucositis and bone marrow suppression may occur as a result of chemotherapy and are significant factors in morbidity.
- Supportive care of the patient undergoing chemotherapy includes appropriate drug therapy to minimise the adverse effects of the treatment.

Lymphoma is cancer of the lymphatic system and accounts for approximately 3% of new cases of cancer reported in the UK each year. The primary cancerous cell of origin is the lymphocyte; as a result, there is often considerable overlap between lymphomas and lymphoid leukaemias. Lymphomas are subdivided into two main categories: Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Both HL and NHL can be further classified based on histology.

The site of malignancy is usually a lymph node. Extranodal disease, most frequently of the stomach, skin, oral cavity and pharynx, small intestine and CNS, can occur and is more common in NHL than HL.

Hodgkin's lymphoma

Hodgkin's disease, now known as HL, was first described by Thomas Hodgkin in 1832. HL accounts for 30% of all lymphomas and has an incidence in the UK of 2.2 per 100,000 for women and 3.3 per 100,000 for men. It is predominantly a disease of young adults, having a peak incidence between the ages of 15 and 35 years.

Aetiology

The cause of HL is unknown, but a number of risk factors have been identified. Epstein–Barr (glandular fever) virus has been identified in 50% of HL cases and is likely to be associated with an increase in risk of developing HL. Certain associations have been identified which suggest a genetic link with HL; for example, same-sex siblings of patients with HL have a 10 times higher risk of developing the disease. Patients with reduced immunity, for example, AIDS or those taking immunosuppressants, may have an increased risk of developing HL.

Pathology

The diagnosis is made by histological examination of an excised lymph node biopsy. The characteristic pathological finding in HL is the identification of a large, abnormal binucleate lymphocyte called a Reed-Sternberg cell. HL as classified by the World Health Organization (WHO) has two distinct entities: classic HL and nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL). Classic Hodgkin's is further subdivided into four histological types:

- *nodular sclerosis*: this is the most common type in the UK, predominant in young adults and females, and has an excellent prognosis
- *mixed cellularity*: this is second most common type of classic HL and more common in males (70% male)
- *lymphocyte depleted*: this carries a poor prognosis and is more common in HIV-positive individuals
- *lymphocyte rich*: this is a rare type of classic HL

NLPHL accounts for 5% of HL cases and is more common in men.

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Signs and symptoms

HL usually presents with painless enlargement of lymph nodes, often in the neck. About 40% of patients will present with fever, night sweats and/or weight loss. These have prognostic significance and are designated B symptoms; others include malaise, itching (25%) or pain at the site of enlarged nodes after drinking alcohol. Bone pain may result from skeletal involvement. Primary involvement of the gut, central nervous system or bone marrow is rare.

If lymph nodes in the chest are involved, patients may present with breathlessness. There is often a disturbance of immune function due to a progressive loss of immunologically competent T-lymphocytes, with patients becoming particularly prone to viral and fungal infections.

Laboratory findings

Laboratory findings include normochromic, normocytic anaemia, a raised erythrocyte sedimentation rate and eosinophilia. One-third of patients have a leucocytosis due to an increase in neutrophils. Advanced disease is associated with lymphopenia (lymphocytes $<0.6 \times 10^9$ L^{-1}). Plasma lactate dehydrogenase (LDH) is raised in 30–40% of patients at diagnosis and has been associated with a poor prognosis.

Investigations and staging

Once the diagnosis has been made on biopsy, further investigations are needed to assess disease activity and the extent of its spread through the lymphoid system or other body sites. This is called staging and is essential for assessing prognosis, with cure rates for localised tumours (stage I or II) being much higher than those for widespread disease (stage IV). The staging of HL is assessed by the Cotswolds modification of the Ann Arbor classification system (Box 51.1). Information about prognostic factors such as mediastinal mass and bulky disease is included in the classification system. The tests required to establish the stage include a complete history, physical examination, FBC, urea and electrolytes (U and Es), chest X-ray and computed tomography (CT). Other useful tests include erythrocyte sedimentation rate (ESR), serum LDH and liver function tests (LFTs). Positron emission tomography (PET) can be used to detect active residual disease.

Management

HL is potentially curable and, in general, sensitive to both chemotherapy and radiotherapy; therefore, the two main goals of treatment are to maximise the likelihood of cure whilst minimising the risk of late toxicity such as infertility. Stage of disease is the biggest factor in treatment choice and outcome. The management of classic HL is determined by the stage of the disease, and this is summarised in Fig. 51.1. Localised NLPHL frequently involves one isolated lymph node and tends to be indolent (slow growing). If there are no risk factors, it can be treated with IFRT alone (30 Gy); all other types are treated as advanced (stage III or IV) classic HL.

Box 51.1 Cotswolds modification of the Ann Arbor classification system for Hodgkin's lymphoma

Clinical stage	Defining features
I	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions or structures on both sides of the diaphragm: III_1 – with or without involvement of splenic, hilar, coeliac or portal nodes III_2 – with involvement of para-aortic, iliac or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated E
Modifying characteristics	A: no symptoms B: fever, drenching sweats, weight loss X: bulky disease >one-third width of the mediastinum >10 cm maximal dimension of nodal mass E: involvement of a single extranodal site, contiguous or proximal to known nodal site CS: clinical stage PS: pathological stage

In Europe, the treatment of classic HL is determined by whether the disease is staged as early favourable disease, early unfavourable disease, advanced disease or relapsed (see Box 51.2).

Early-stage (favourable) disease

The cure rate for patients with stages I and IIA disease is greater than 90%. Patients with stages I and IIA disease may be cured with radiotherapy alone (wide or extended field irradiation). However, due to radiation-related late effects, cardiac toxicity and secondary malignancy and the incidence of relapse (25–30%), most receive combined modality treatment (chemotherapy and radiotherapy). This usually consists of two to four cycles of ABVD (Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine) chemotherapy followed by IFRT of 20–30 Gy (Diehl et al., 2004). The aim of chemotherapy is to destroy subclinical disease outside the field of radiotherapy.

Where disease is confined to above the diaphragm, the mantle field is used (Fig. 51.2). The inverted Y is employed when the disease is confined below the diaphragm. This group of patients have a relapse-free survival rate of 80% at 5–10 years. Patients should be considered for entry into the National Cancer Research Institute (NCRI) 18–30 study or NCRI Lymphoma Groups PET in Hodgkin's Disease Study.

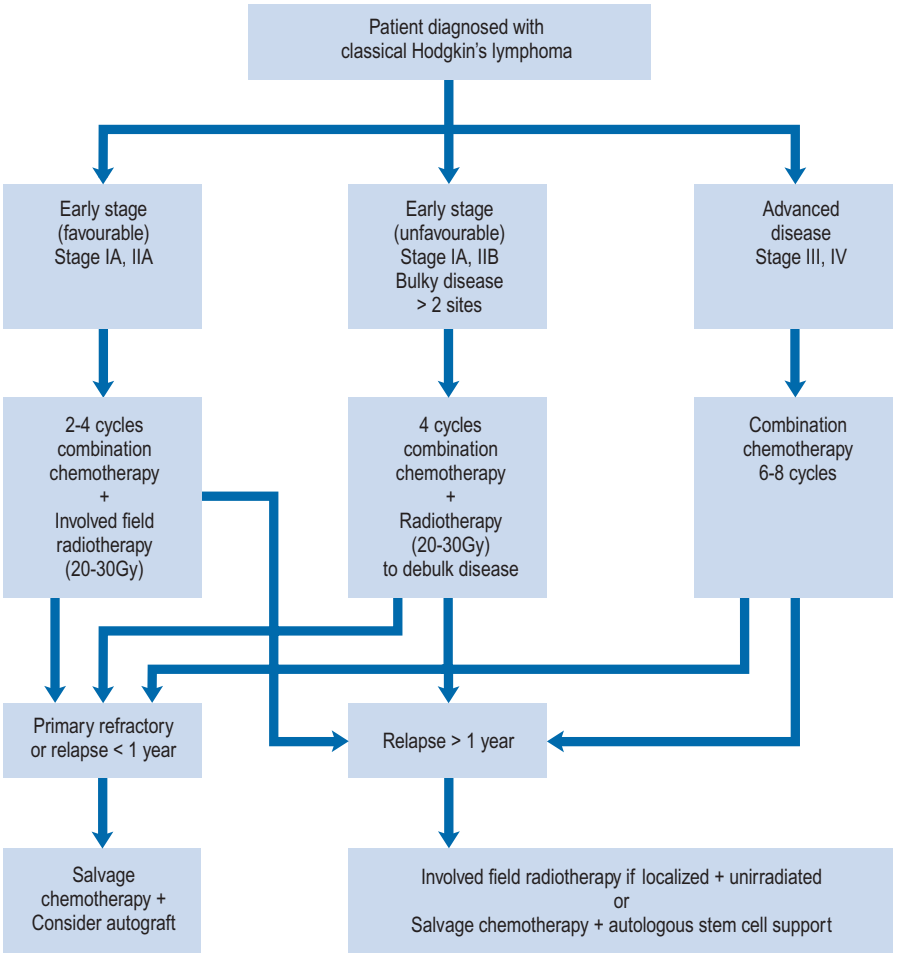


Fig. 51.1 Treatment algorithm for classic Hodgkin's lymphoma.

Early-stage (unfavourable) disease

Patients with stage I or II presenting with bulky disease, B symptoms or with more than two sites of disease are considered to be poor risk if treated with radiotherapy alone. B symptoms are any of the following symptoms: unexplained loss of weight, unexplained fever, drenching night sweats. These patients are treated with four to six cycles of combination chemotherapy, for example, ABVD, and radiotherapy (20–30 Gy) to sites of bulky disease. Patients should be considered for entry into the NCRI 18–30 study.

Advanced disease

Patients with advanced disease (stages III and IV) are treated with combination chemotherapy. The first widely used combination chemotherapy regimen was MOPP (mechlorethamine, vincristine (Oncovin), procarbazine and prednisolone) which produced a response rate of 80% and long-term disease-free survival of approximately 50%. ABVD has replaced MOPP chemotherapy as the regimen of choice as it is as effective but less toxic in terms of fertility, haematological toxicity, and the development of acute leukaemia and myelodysplasia. Six to eight cycles of ABVD is considered the current standard treatment for advanced disease.

Despite advances in HL, 30–40% of patients progress or relapse and respond poorly to salvage chemotherapy. A number of regimens have been investigated to both increase dose intensity and density of treatment, for example, BEACOPP (bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, vincristine, procarbazine, prednisolone) and escalated BEACOPP (Table 51.1). In a trial comparing escalated BEACOPP, standard BEACOPP and COPP-ABVD, escalated BEACOPP demonstrated increased overall survival compared with the other two treatment arms but at the cost of significant toxicity (Engert et al., 2009). First-line escalated BEACOPP can only be recommended currently as part of a clinical trial. A study to investigate the role of BEACOPP and PET imaging in patients with advanced HL is under way and will close in 2012 (UK Clinical Research Network Study Portfolio, 2010).

Other options for patients unlikely to tolerate ABVD include ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone) and CHOP (cyclophosphamide, doxorubicin (hydroxydaonorubicin), vincristine (Oncovin), prednisolone, rituximab.

Box 51.2 Disease staging for Hodgkin's lymphoma (West of Scotland Blood Cancer Network, 2009)

Early stage
European Organisation for Research and Treatment of Cancer (EORTC) risk factors in localised disease

A. Favourable (patients must have all features)
1. Clinical stage 1 or 2
2. Maximum of three nodal areas involved
3. Age less than 50 years of age
4. ESR< 50 mm/h
5. Mediastinal/thoracic mass ratio < 0.33 at D5/6

B. Unfavourable
1. Clinical stage 2 with 4 or more nodal areas involved
2. Age >50 years of age
3. ESR >50 mm/h without B symptoms or >30 mm/h with B symptoms (fever, night sweats, weight loss)
4. Mediastinal/thoracic ratio >0.33 at D5/6[a]

Advanced stage
Hasenclever score
1. Age >45 years of age
2. Male gender
3. Serum albumin <40 g/L
4. Hb <10.5 g/dL
5. Stage 4 disease
6. Leucocytosis, that is, WCC >15 × 10^9 L^{-1}
7. Lymphopenia, that is, <0.6 × 10^9 L^{-1} or <8% of total WCC

[a]Mediastinal/thoracic ratio >0.33 at D5/6 – thoracic ratio of maximum transverse mass diameter greater than or equal to one-third (0.33) of the internal transverse thoracic diameter measured at the T5/6 intervertebral disc level.

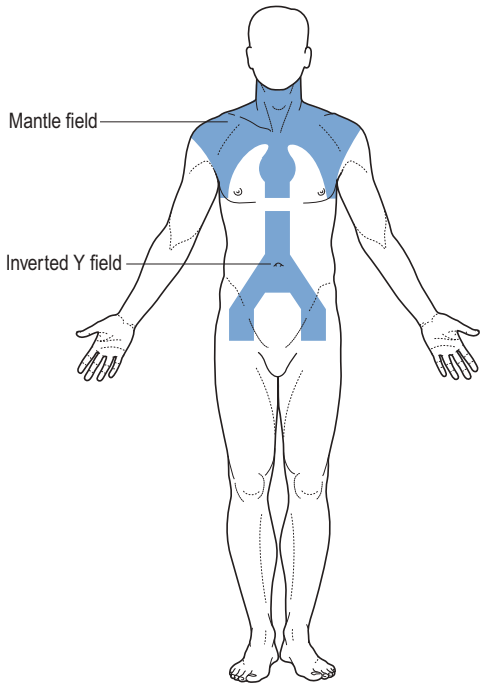


Fig. 51.2 The mantle and inverted Y fields commonly employed in the treatment of Hodgkin's lymphoma with radiotherapy (from Souhami and Tobias, 1998, p. 437, with permission from Blackwell Science).

Salvage therapy for relapsed disease

Relapsed disease refers to disease progression after completion of primary treatment which resulted in a complete remission. Depending on previous treatment, options include salvage radiotherapy, salvage chemotherapy or high-dose chemotherapy with autologous stem cell support. In this procedure, stem cells are collected from the patient and returned following high-dose chemotherapy. Patients who relapse after initial radiotherapy alone have a good chance of cure with combination chemotherapy, at least equal to that of patients initially treated with chemotherapy for advanced disease. Occasionally, radiotherapy is used if the disease is localised and previously non-irradiated. Those who relapse after combination chemotherapy have a worse prognosis, although durable remissions can be obtained with further conventional therapy.

Length of remission following first-line chemotherapy influences the success of subsequent salvage therapy and so failure of chemotherapy can be used to classify disease and determine appropriate therapy. If the duration of remission was greater than 12 months (late relapse), then the patient can be re-treated with their initial chemotherapy, salvage regimen or considered for high-dose chemotherapy with autologous transplantation.

Commonly used chemotherapy salvage regimens are listed in Table 51.2. If relapse occurs less than a year after treatment (early relapse), then high-dose chemotherapy with autologous stem cell support should be considered. A patient who has never achieved complete remission (primary refractory disease) should receive high-dose chemotherapy with autologous stem cell support.

High-dose chemotherapy plus autologous stem cell support is associated with a 40–50% 5-year survival rate. However, the significant toxicity of autologous stem cell transplantation means that it should be reserved for patients in whom there is a clear increase in chance of cure. Allogeneic transplant is an option in patients relapsing after autologous transplant (Brusamolino et al., 2009).

New agents

The anti-CD20 antibody rituximab has shown remission in 80% of cases of NLPHL, but due to short follow-up, its use is still considered experimental. Other monoclonal antibodies targeting CD30, which is expressed in the majority of classic HL cases, are being investigated. The most promising of these is a novel immunotoxin conjugate SGN-35 (Younes, 2009).

Panobinostat, a histone deacetylases (HDAC) inhibitor, has been granted orphan drug designation for the treatment of HL.

Gemcitabine has shown activity in relapsed classic HL with response rates up to 79% in a small series of heavily pretreated patients (Ng et al., 2005). Bortezomib and lenalidomide licensed for myeloma are also being investigated in those who have relapsed HL.

Non-Hodgkin's lymphoma

The NHLs are a heterogeneous group of lymphoid malignancies ranging from indolent, slow-growing tumours to aggressive, rapidly fatal disease. Paradoxically, the

Table 51.1 Combination chemotherapy regimens effective in the treatment of Hodgkin's lymphoma

Regimen	Dose and route	Frequency
ABVD (28-day cycle)		
Doxorubicin	25 mg/m² i.v.	Days 1 and 15
Bleomycin	10,000 iu/m² i.v.	Days 1 and 15
Vinblastine	6 mg/m² i.v.	Days 1 and 15
Dacarbazine	375 mg/m² i.v.	Days 1 and 15
BEACOPP escalated (21-day cycle)[a]		
Bleomycin	10,000 iu/m² i.v.	Day 8
Etoposide	200 mg/m² i.v.	Days 1–3
Adriamycin (doxorubicin)	35 mg/m² i.v.	Day 1
Cyclophosphamide	1250 mg/m² i.v.	Day 1
Vincristine	1.4 mg/m² i.v. (max. 2 mg)	Day 8
Procarbazine	100 mg/m² orally	Days 1–7
Prednisolone	40 mg/m² orally	Days 1–14
BEACOPP standard dose (21-day cycle)[a]		
Bleomycin	10,000 iu/m² i.v.	Day 8
Etoposide	100 mg/m² i.v.	Days 1–3
Adriamycin (doxorubicin)	25 mg/m² i.v.	Day 1
Cyclophosphamide	650 mg/m² i.v.	Day 1
Vincristine	1.4 mg/m² i.v. (max. 2 mg)	Day 8
Procarbazine	100 mg/m² orally	Days 1–7
Prednisolone	40 mg/m² orally	Days 1–14
ChlVPP		
Chlorambucil	6 mg/m² orally	Days 1–14
Vinblastine	6 mg/m² i.v.	Days 1 and 8
Procarbazine	100 mg/m² orally	Days 1–14
Prednisolone	40 mg/m² orally (max 60 mg)	Days 1–14

[a]Escalated BEACOPP and standard BEACOPP have shown activity in Hodgkin's lymphoma, but their usage is not standard in the UK.

Table 51.2 Salvage chemotherapy regimens effective in the treatment of lymphoma

Regimen	Dose and route	Frequency
DHAP		
Cisplatin	100 mg/m² i.v.	Days 1
Cytarabine	2000 mg/m² i.v. 12 hourly	Day 2
Dexamethasone	40 mg orally	Days 1–4
ESHAP		
Etoposide	40 mg/m² i.v.	Days 1–4
Methylprednisolone	500 mg/m² i.v.	Days 1–5
Cytarabine	2000 mg/m² i.v.	Day 1
Cisplatin	25 mg/m² i.v.	Days 1–4
ICE		
Ifosfamide	5000 mg/m² i.v.	Day 2
Carboplatin*a*	AUC 5 i.v.	Day 2
Etoposide	100 mg/m² i.v.	Days 1–3
IVE		
Epirubicin	50 mg/m² i.v.	Days 1
Etoposide	200 mg/m² i.v.	Days 1–3
Ifosfamide	3000 mg/m² i.v.	Days 1–3

AUC, area under the curve; GFR, glomerular filtration rate.
[a]Carboplatin dose (mg) = target AUC (mg/mL × min) × (GFR (mL/min) + 25).

more aggressive NHLs are more susceptible to anticancer therapy. The overall incidence of NHL in the UK is 11 per 100,000 per year and accounts for approximately 3% of all cancers in the UK. The disease is rare in subjects under 30 years of age and the incidence steadily increases with increasing age; the median age at presentation is about 60. NHL is slightly more common in men than in women (1.5:1).

Aetiology

The aetiology is unclear although immunosuppression, for example, following organ transplantation, may predispose to the development of lymphoma. Viruses have been implicated in the pathogenesis of NHL; for example, Burkitt's lymphoma is one of the most common neoplasms to develop in HIV-related immunosuppressed patients, human T-lymphotrophic virus type 1 (HTLV-1) is associated with a rare type of T-cell lymphoma, the adult T-cell leukaemia/lymphoma (ATLL) and Epstein–Barr Virus (EBV) is associated with post-transplant lymphoproliferative disorder (PTLD). Exposure to certain chemicals such as pesticides and solvents can increase the risk of developing NHL. There is an increased incidence of gastro-intestinal lymphomas in patients with Crohn's disease.

Signs and symptoms

The most common presentation of NHL is painless lymphadenopathy, frequently in the neck area in the supraclavicular and cervical regions. Spread of disease is haematogenously (via the blood), and so extranodal sites may be involved. Signs and symptoms of infection, anaemia or thrombocytopenia may be present in patients with bone marrow involvement. Hepatosplenomegaly may also be present. Patients may also present with any of the following symptoms: unexplained loss of weight, unexplained fever, drenching night sweats. These symptoms are described as B symptoms and patients without these symptoms are classified as category A. B symptoms are more commonly seen in advanced or aggressive NHL but may be present in all stages and histological subtypes.

Laboratory findings

Laboratory examinations may reveal anaemia, a raised erythrocyte sedimentation rate and a raised serum LDH level. There may be a reduction in circulating immunoglobulins, and a monoclonal paraprotein may be seen in a small number of cases. The immune disruption caused by the disease may also result in an increased susceptibility to viral infection or autoimmune haemolytic anaemia or thrombocytopenia.

Histopathology and classification

There have been many attempts to classify the NHLs into histological categories that have clinical significance. Despite this, many problems and areas of confusion remain. Approximately 85% of NHLs are of B-cell origin, while 15% are of T-cell origin or are unclassifiable.

There are two classification systems in common use. The Working formulation, developed in 1982, divides the lymphomas into low, intermediate and high grade. More recently, the revised European–American lymphoma (REAL) classification system has been developed (Table 51.3) and adopted by the World Health Organization (Box 51.3) to classify the grade of lymphoma. The REAL/WHO classification incorporates some diagnoses not included in the Working formulation and is a list of lymphomas using morphology, immunophenotype, genotype and clinical behaviour. It recognises the three major categories of lymphoid malignancies: B-cell neoplasms, T-cell/natural killer cell neoplasms and HL. However, in practice, the clinical behaviour of lymphomas informs the treatment strategies employed as these are based on the initial classification into indolent (low grade) or aggressive (intermediate and high grade) NHL. A more biologically relevant classification of lymphoma using the REAL/WHO classification and immunological and molecular characteristics increases the diagnostic specificity and improves selection and targeting of therapy.

Diagnosis

Diagnosis is based on a thorough history, physical examination and investigation of a lymph node. A definitive diagnosis of NHL can only be made by biopsy of pathological lymph nodes or tumour tissue. An expert histopathologist may need to utilise sophisticated techniques such as immunocytochemistry (e.g. CD20) or genotyping to obtain an accurate subclassification.

Table 51.3 Clinical grade and frequency of lymphomas in the REAL classification

Diagnosis	% of all cases
Indolent lymphomas	
Follicular lymphoma	22
Marginal zone B-cell, mucosa-associated lymphoid tissue	8
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	7
Marginal zone B-cell nodal	2
Lymphoplasmacytic lymphoma	1
Aggressive lymphoma	
Diffuse large B-cell lymphoma	31
Mature (peripheral) T-cell lymphomas	8
Mantle cell lymphoma	7
Mediastinal large B-cell lymphoma	2
Anaplastic large cell lymphoma	2
Very aggressive lymphomas	
Burkitt's lymphoma	2
Precursor T-lymphoblastic	2
Other lymphomas	7

Chromosomal abnormalities are of diagnostic importance. Most translocations involve genes associated with either proliferation (e.g. c-MYC) or apoptosis (e.g. BCL-2).

Additional investigations should also be performed to accurately stage the disease and exclude other disease. FBC from peripheral blood and routine biochemistry and uric acid should be performed. Peripheral blood lymphocytosis (increased lymphocytes) with circulating malignant cells is common in low grade and mantle cell lymphomas. A bone marrow aspirate and trephine are required to exclude leukaemia and will detect bone marrow involvement, which is more common than in HL. CT scans of the chest, abdomen and pelvis are required to assess the extent of the disease. The use of PET scans, capable of locating sites not thought to be affected from CT scan images, is increasing. Lumbar punctures should be performed for patients at high risk of CNS involvement, for example, Burkitt's lymphoma. Erythrocyte sedimentation rate, LDH and serum β_2-microglobulin levels may indicate disease activity and can be of prognostic importance.

Staging

Determining the extent of disease in patients with NHL provides prognostic information and is useful in treatment planning. Patients with extensive disease usually require different therapy from those with limited disease. The NHLs can be staged according to the Ann Arbor classification (see Box 51.1). In this system, NHL is defined as stage I, II, III or IV, stage I being disease limited to a single lymph node

Box 51.3 Revised European–American lymphoma classification as adopted by the WHO (REAL/WHO classification)

Precursor B-cell neoplasm
Precursor B-cell acute lymphoblastic leukaemia or lymphoma

Mature (peripheral) B-cell neoplasm
- B-cell chronic lymphocytic leukaemia or small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Lymphoplasmacytoid lymphoma
- Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes)
- Hairy cell leukaemia
- Plasma cell myeloma or plasmacytoma
- Extranodal marginal zone B-cell lymphoma (with or without monocytoid B-cells)
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt's lymphoma or Burkitt's cell leukaemia

Precursor T-cell neoplasm
- Prescursor T-cell acute lymphoblastic leukaemia or lymphoma

Mature (peripheral) T-cell and natural killer neoplasms
- T-cell prolymphocytic leukaemia
- T-cell granular lymphocytic leukaemia
- Aggressive natural killer cell leukaemia
- Adult T-cell lymphoma or leukaemia
- Extranodal natural killer/T-cell lymphoma
- Enteropathy type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/Sezary syndrome
- Primary cutaneous anaplastic large cell lymphoma
- Peripheral T-cell lymphoma
- Angio-immunoblastic T-cell lymphoma
- Primary systemic anaplastic large cell lymphoma

and stage IV being advanced disease, with involvement of extralymphatic sites. The International Prognostic Index (Table 51.4) uses the following factors as predictors of poor prognosis: elevated LDH, stage III or IV disease, greater than 60 years of age, the higher the number of extranodal sites involved and the Eastern Co-operative Oncology Group (ECOG) performance status of two or higher. Other prognostic factors include bulky disease, presence of B symptoms and transformation from low- to high-grade disease. Prognostic indicators are important because they inform the treatment plan to avoid overtreating those with good prognosis and undertreating those with poor prognosis.

Treatment

When designing a treatment plan for an individual patient, various factors must be taken into account. These include the patient's age and general health, the extent or stage of the lymphoma and the particular histological subtype. Indolent (low-grade) lymphoma tends to run a slow course and although it is not curable, patients survive for prolonged periods with minimal symptoms. Aggressive (high-grade) lymphomas result in death within weeks or months if untreated. These lymphomas, however, are very responsive to chemotherapy and up to 50–60% may be cured with combination chemotherapy (Fig. 51.3).

Table 51.4 International prognostic index

Factor	Adverse prognosis
Age	≥60 years
Ann Arbor stage	III or IV
Plasma lactate dehydrogenase level	Above normal
Number of extranodal sites of involvement	≥2
Performance status	≥ECOG 2 or equivalent

ECOG, Eastern Co-operative Oncology Group.

CD20 is essential for cell cycle regulation and cell differentiation. It is expressed on normal B-cells and the majority of malignant B-cell lymphomas. The introduction of rituximab, a monoclonal antibody with specificity for CD20, has changed the way patients with NHL are treated and is now incorporated into most chemotherapy regimens. The mechanism of action of rituximab is not fully understood but is thought to involve complement-mediated lysis of B-cells and antibody-dependent cellular cytotoxicity. Other potential mechanisms include induction of apoptosis and inhibition of cell cycle progression.

Indolent non-Hodgkin's lymphoma

The median age at which patients present with indolent NHLs is 50–60 years, and generally patients have a good performance status. If left untreated, indolent NHL has a comparatively long survival (median: 9 years). Follicular lymphoma is the most common of the indolent lymphomas. For the minority of patients presenting with limited-stage disease (stage I), radiotherapy to the involved field is generally used. However, the majority (80%) of patients present with advanced disease (stages II–IV) where the aim of treatment is to reduce disease bulk and offer symptom relief. Rituximab, cyclophosphamide, vincristine, prednisolone (R-CVP) is used as the first-line treatment for advanced (stage III or IV) follicular lymphoma following the results of a study comparing R-CVP with CVP (cyclophosphamide, vincristine, prednisolone) (Marcus et al., 2005). This approach has been incorporated into national guidance (NICE, 2006). R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) can also be used as first-line treatment for young patients with aggressive disease and is an option in relapsed disease (Table 51.5).

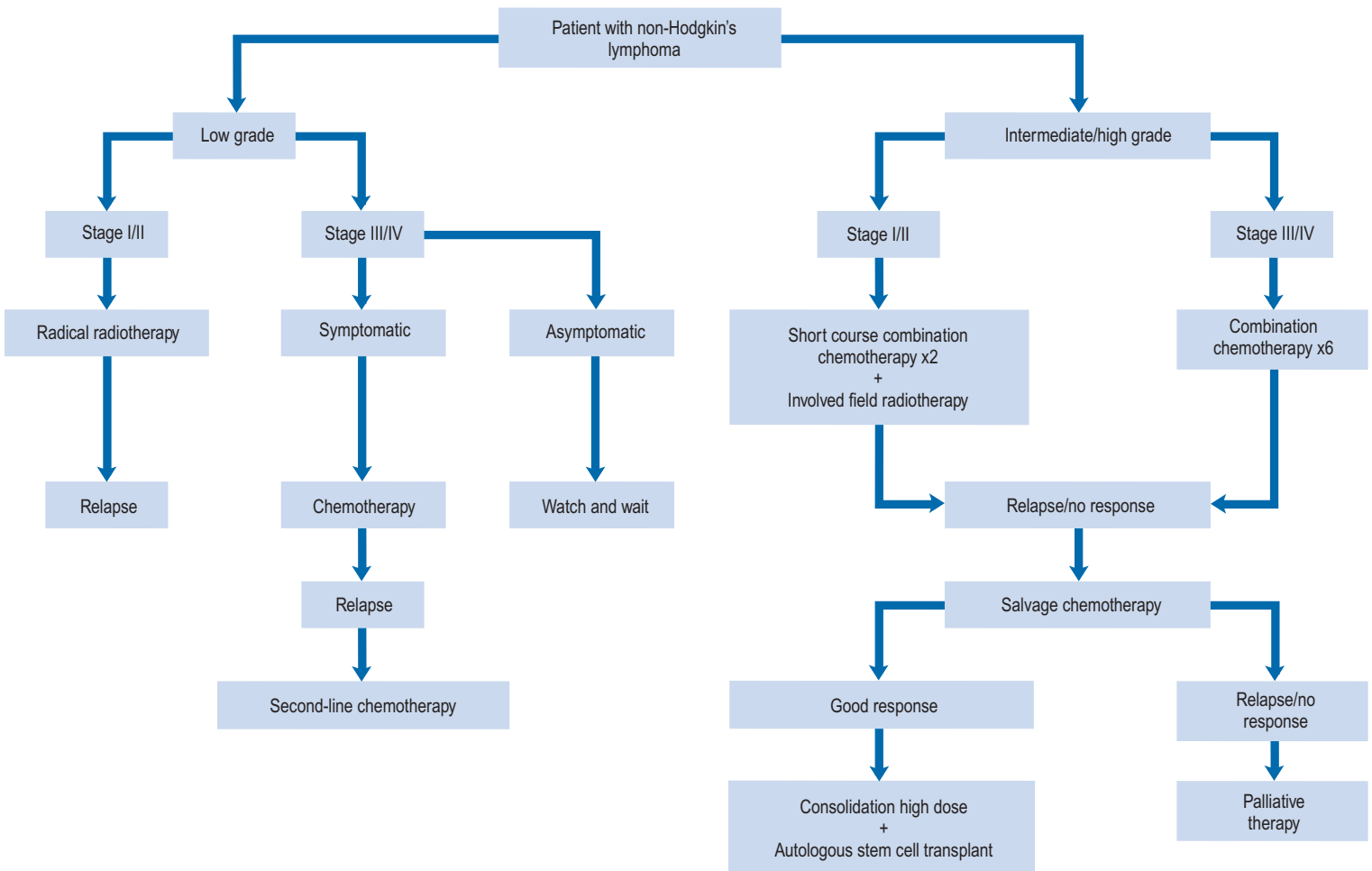


Fig. 51.3 Typical treatment algorithm for non-Hodgkin's lymphoma.

Table 51.5 Chemotherapy regimens effective in the treatment of non-Hodgkin's lymphoma

Drug	Dose and route	Day of administration
R-CHOP (21-day cycle)		
Cyclophosphamide	750 mg/m² i.v.	Day 1
Doxorubicin (hydroxydaunorubicin)	50 mg/m² i.v.	Day 1
Vincristine (Oncovin)	1.4 mg/m² (max 2 mg) i.v.	Day 1
Prednisolone	100 mg orally	Days 1–5
Rituximab	375 mg/m² i.v.	Day 1
R-CVP (21-day cycle)		
Cyclophosphamide	750 mg/m² i.v.	Day 1
Vincristine (Oncovin)	1.4 mg/m² (max 2 mg) i.v.	Day 1
Prednisolone	100 mg orally	Days 1–5
Rituximab	375 mg/m² i.v.	Day 1
FC (28-day cycle)		
Fludarabine	40 mg/m² orally	Days 1–3
Cyclophosphamide	250 mg/m² daily orally	Days 1–3
CHOP (21-day cycle)		
Cyclophosphamide	750 mg/m² i.v.	Day 1
Doxorubicin (hydroxydaunorubicin)	50 mg/m² i.v.	Day 1
Vincristine (Oncovin)	1.4 mg/m² (max 2 mg) i.v.	Day 1
Prednisolone	100 mg orally	Days 1–5

For patients who are asymptomatic at diagnosis, adopting a 'watch and wait' policy with active monitoring and initiating treatment when symptomatic is an option. Patients could be considered for recruitment to clinical trials; there are ongoing studies comparing R-CVP with R-FC (rituximab, fludarabine, cyclosphosphamide) followed by rituximab maintenance and investigating the benefit of bendamustine compared to R-CVP. If patients fail to tolerate the standard treatment options, an oral alkylating agent, for example, chlorambucil, with or without a steroid can be used. Repeated courses may be given.

Relapsed indolent non-Hodgkin's lymphoma

Relapsed patients may be re-treated with rituximab if the time to relapse post-rituximab is greater than 6 months (NICE, 2008). If the time to relapse is less than 6 months, Yttrium-90 labelled ibritumomab tiuxetan (Zevalin®) may be considered. Zevalin® is a new therapeutic development that utilises monoclonal antibodies as tumour-specific vehicles to deliver systemic radiation therapy concurrent with immunotherapy to the targeted tumour. However, for some resistant or relapsing patients, particularly if their condition is too poor to merit further radical chemotherapy, palliation will be appropriate. Radiotherapy may be an option in this situation and this is being evaluated through an ongoing clinical trial.

Aggressive non-Hodgkin's lymphoma

The median age of presentation of aggressive NHL is 60–70 years when 50–60% of patients will present with an advanced stage of the disease. The most common presentation is diffuse large B-cell lymphoma (DLBCL), and therefore the treatment strategies described later refer to this alone. Other aggressive lymphomas, for example, mantle cell, are managed differently. The most important strategy when treating this group of patients is to maintain the dose intensity of chemotherapy and minimise any delay in chemotherapy administration. Treatment is given with curative intent.

The treatment for advanced-stage aggressive NHL is six cycles of the combination of R-CHOP chemotherapy (NICE, 2003). Doxorubicin can cause cardiotoxicity and patients with a reduced cardiac ejection fraction or co-morbidities may not tolerate R-CHOP. The use of gemcitabine (R-GCVP) is currently being investigated for this patient group as part of a clinical trial. The addition of bortezomib to R-CHOP in DLBCL is also being investigated as a clinical trial for patients with high-risk disease.

Relapsed aggressive non-Hodgkin's lymphoma

Combination chemotherapy with R-CHOP probably cures 40–60%. This, therefore, implies that over half of all patients have refractory disease or relapse after first treatment.

In younger patients with aggressive NHL, the aim will be to introduce remission with further chemotherapy, using an alternative, salvage regimen, and then to consolidate remission with high-dose therapy (HDT). HDT is usually supported by mobilised peripheral blood stem cells (PBSCs) and an autologous PBSC transplantation (auto-PBSCT). Lymphoma is the most frequent indication for auto PBSCT in Europe. The European Group for Blood and Marrow Transplantation (EBMT) suggests that the upper age limit for autologous transplantation is 65 years. HDT, with autologous stem cell support, is also used as part of primary treatment for younger patients with indolent lymphoma. Patients who receive HDT after their initial treatment can have progression-free survival rates of around 50% at 5 years.

To induce a remission in patients with aggressive lymphoma and relapsed disease, it may be reasonable to use the same or similar regimen used for front-line chemotherapy. However, in most cases, the regimen chosen introduces new agents that are potentially not cross-resistant with those used in the initial treatment regimen. There are several salvage regimens in use and they generally have response rates of between 40% and 70%. Examples of salvage regimens are ICE (ifosfamide, carboplatin, etoposide), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) and DHAP (cisplatin, cytarabine, dexamethasone) (see Table 51.2). Gemcitabine, a pyrimidine analogue, may be of benefit for patients with relapsed or refractory disease after two lines of treatment. Gemcitabine is used in combination with other agents, such as cisplatin and methylprednisolone. Rituximab can also be added to these salvage regimens. PBSCs are usually

harvested after the second course of the salvage regimen. Patients then receive a high-dose regimen such as BEAM (carmustine, etoposide, cytarabine, melphalan) (Table 51.6) conditioning prior to stem cell infusion (autograft). Patients should only undergo an autograft if they have demonstrated a response to salvage chemotherapy.

CNS prophylaxis for diffuse large B-cell lymphoma. Approximately 5% of patients with DLBCL develop CNS disease. The optimum approach to CNS prophylaxis is uncertain, and it usually involves a course of intrathecal chemotherapy.

The updated national guidance for the safe administration of intrathecal chemotherapy (DH, 2008) sets out the minimum requirements of a hospital providing an intrathecal chemotherapy service.

Very aggressive lymphoma

Burkitt's lymphoma is a rare form of B-cell NHL which occurs most commonly in children and young adults. The median age of adult patients is 30 years. Untreated, survival is measurable in days or weeks, and it is widely accepted that combination chemotherapy should be urgently commenced. Intensive chemotherapy is necessary, together with CNS prophylaxis, and cure is possible in a high proportion of cases.

Multi-agent chemotherapy regimens including high-dose methotrexate, high-dose cytarabine, etoposide and ifosfamide are used and a schedule such as CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate)/IVAC (ifosfamide, etoposide, high-dose cytarabine) is common.

There is an on-going debate about the value of adding rituximab to the CODOX-M/IVAC regimen.

Lymphoblastic lymphomas/leukaemia

Lymphoblastic lymphomas comprise about 2% of adult NHLs. Patients are often treated with the same regimens used in acute lymphoblastic leukaemia (ALL). Despite a very high rate of complete responders, long-term survival remains poor. Patients who fail after first-line chemotherapy have a long-term disease-free survival of less than 10%. These cases are subsequently treated as leukaemias (see Chapter 50).

Table 51.6 Conditioning chemotherapy for autologous transplantation

Drug	Dose and route	Day of administration
BEAM		
Carmustine	300 mg/m² i.v.	6 days before reinfusion
Etoposide	200 mg/m² i.v.	5–2 days before reinfusion
Cytarabine	200 mg/m² 12 h i.v.	5–2 days before reinfusion
Melphalan	140 mg/m² i.v.	1 day before reinfusion
Reinfusion of stem cells		Day 0
LACE		
Lomustine	200 mg/m² orally	7 days before reinfusion
Etoposide	1000 mg/m² i.v.	7 days before reinfusion
Cytarabine	2000 mg/m²	6–5 days before reinfusion
Cyclophosphamide	1800 mg/m² i.v.	4–2 days before reinfusion
Reinfusion of stem cells		Day 0

Patient care

The chemotherapy regimens used to treat HL and NHL (see Tables 51.1 and 51.5) are usually administered on a hospital outpatient basis with the patient visiting the clinic regularly for assessment and treatment. The patient is monitored by FBCs carried out before each cycle of chemotherapy and at the 'nadir' between cycles. The nadir is when the blood count is at its lowest point, usually 10–14 days after the first day of chemotherapy. The interval between each cycle of chemotherapy enables normal body cells to recover before the patient receives further treatment. Disease response to treatment is monitored by repeating some of the diagnostic investigations, such as CT, at suitable intervals and the use of PET. If there is little or no response to treatment, a different chemotherapy regimen will be used or a decision made to withdraw from active therapy and provide optimum supportive care.

Counselling and support

Counselling is an essential part of the care of the cancer patient and involves not only the explanation of drug therapy and investigations but also the provision of psychological support for the patient and family. Prior to treatment with chemotherapy, the patient will be counselled by the doctor, chemotherapy nurse and, increasingly, by oncology pharmacists. It is necessary to explain how the chemotherapy is to be given and discuss both potential and inevitable side effects. The probability of successful treatment must be weighed against the prospect of serious and life-threatening adverse effects. Patients must be made aware of the long-term complications of chemotherapy and radiotherapy, such as secondary malignancy.

The support available to the cancer patient, to help cope with both the illness and its treatment, has improved dramatically in recent years. Multidisciplinary teams working within specialised units have become skilled in anticipating the problems of lymphomas and their treatment. In addition, many charities provide care, support and advice such as Macmillan Cancer Support (www.macmillan.org.uk) and the Lymphoma Association (www.lymphoma.org.uk).

Patient-specific treatment modifications

The selection of appropriate therapy must also take into consideration the individual patient. Factors include the patient's age, renal and hepatic function and underlying medical conditions, such as heart disease, diabetes or chronic pulmonary disease. The patient's tolerance of side effects and complications of therapy may then be predicted. The decision is based on an understanding of the pharmacodynamics and pharmacokinetics of the drugs being used as well as the clinical condition of the patient.

Supportive care

During a course of chemotherapy, the patient requires supportive care to minimise the adverse effects of treatment. The common adverse effects of the chemotherapy regimens discussed in this chapter are outlined in Table 51.7. These will occur to varying degrees depending on the combination of drugs and the doses used as well as individual patient factors.

Nausea and vomiting

Nausea and vomiting is the most distressing and most feared adverse effect of chemotherapy. Its effect on the patient should not be underestimated, and its treatment is an important part of supportive care. The severity will depend on the combination of drugs used. For example, oral chlorambucil is generally well tolerated by almost all patients and requires no antiemetic cover. Regimens such as ABVD, which is highly emetic, will make most patients vomit if no antiemetics are given. Aprepitant, an NK1 receptor antagonist, is licensed for cisplatin chemotherapy regimens and may be useful for managing emesis with DHAP, ESHAP, etc. The patient should be counselled on the appropriate use of prescribed antiemetics (see Table 51.7).

Tumour lysis syndrome

The lymphomas are, in general, highly sensitive to chemotherapy. The resulting lysis of cells which occurs following initiation of chemotherapy may lead to hyperuricaemia,

Table 51.7 Adverse effects associated with chemotherapy regimens used in the lymphomas with supportive measures and counselling points

Adverse effect	Cytotoxics implicated	Supportive measures	Counselling points
Bone marrow suppression	Chlorambucil Cyclophosphamide Dacarbazine Etoposide Vinblastine Prednisolone	Blood transfusion Platelet transfusions Mouth care Antibiotic therapy for febrile episodes Granulocyte-colony stimulating factor (GCSF)	Expect tiredness Report bleeding or unusual bruises Importance of good personal hygiene Adhere to mouth care regimen Avoid people with infections Monitor temperature Report febrile episodes or signs of infection immediately
Nausea and vomiting Mucositis	Cyclophosphamide Doxorubicin Procarbazine Dacarbazine Doxorubicin	Antiemetic therapy Mouth care regimen	Emphasise regular use. A short course is more effective than 'as required' treatment Take tablets before meals Report episodes of vomiting (especially if taking oral cytotoxics). For dexamethasone, emphasise short course not to be continued to ensure the patient does not receive repeat prescriptions from primary care doctor Importance of good oral hygiene, instruct how mouthwashes are used, stress importance of regular use
Tumour lysis syndrome	High tumour load sensitive to chemotherapy	Hydration, allopurinol Rasburicase	Stress importance of regular allopurinol until appropriate to stop Drink plenty of fluids
Alopecia	Cyclophosphamide Doxorubicin, etoposide	Provision of wig if wanted	Hair usually regrows on completion of therapy
Impaired gonadal function	Alkylating agents Procarbazine, doxorubicin (to a lesser degree)	Sperm storage	Refer to doctor, depends on regimen, reversible in some cases
Neuropathy	Vincristine	Discontinue use or substitute vinblastine	Report tingling sensations or difficulty with buttons, jaw pain or stiffness
Constipation			Do not self-treat but refer to doctor
Cardiomyopathy	Doxorubicin		Report breathlessness, tiredness
Lung fibrosis	Bleomycin		Report breathlessness

hyperkalaemia and hypocalcaemia in patients with bulky disease, and result in urate nephropathy. There is a high incidence of tumour lysis syndrome (TLS) in tumours with high proliferation rates and tumour burden such as Burkitt's lymphoma and T-lymphoblastic lymphoma. The mainstay of TLS prevention is hydration with the patient encouraged to maintain a high fluid intake. Hyperuricaemia is controlled with allopurinol and close monitoring of renal function, serum urate levels and electrolytes. Allopurinol must be commenced before chemotherapy and continued until the tumour load has reduced and serum urate levels are normal. In aggressive forms of NHL, rasburicase, a recombinant urate oxidase, may be indicated as prophylaxis. Allopurinol should not be prescribed concurrently with rasburicase because it will inhibit the production of uric acid, the substrate for rasburicase.

Rasburicase can also be used to treat TLS but will only correct hyperuricaemia. Treatment of TLS should include vigorous hydration and diuresis. Historically alkaline diuresis has been recommended, but overzealous alkalinisation can lead to problems such as metabolic acidosis (Cairo and Bishop, 2004). Hypocalcaemia should be corrected if the patient is symptomatic, but this may increase calcium phosphate deposition. Hyperkalaemia and hyperphosphataemia should be corrected; patients may require haemofiltration or dialysis.

Mucositis

Chemotherapy may cause mucositis, which is inflammation of or damage to the surface of the gastro-intestinal tract. In the mouth, this may lead to painful ulceration, local infection and difficulty in swallowing. Dependent on the severity of mucositis, patients may require analgesia from benzydamine mouthwash to systemic opiates. Disruption of the mucosal barrier will give bacteria and fungi easier systemic access. A mouth care regimen should therefore be instituted with myelosuppressive therapy. This involves good oral hygiene, for example, gentle brushing with a toothbrush to remove plaque or rinsing with saline to remove debris. An antiseptic mouthwash such as chlorhexidine 0.2% should also be used regularly to prevent infection. Palifermin, keratinocyte growth factor (KGF), may have a role in autologous haemopoietic stem cell support.

Bone marrow suppression

Myelosuppression is usually the dose-limiting factor with these regimens, and it is necessary to carry out FBCs before treatment to confirm that recovery has occurred. Each chemotherapy protocol should be referred to so as to ensure appropriate management. Generally, if the platelet count is below 100×10^9 L^{-1} and/or the absolute neutrophil count (ANC) is less than 1×10^9 L^{-1}, the subsequent dose may be reduced or treatment delayed by a week.

Anaemia is treated with blood transfusions and thrombocytopenia with platelet transfusions as necessary. Erythropoietin administration reduces blood transfusion requirements and can improve quality of life. However, the evidence suggesting improvement in patient survival is inconclusive.

Neutropenia is the most life-threatening acute toxicity; the neutropenic patient is at constant risk from infections. Seemingly minor infections such as cold sores can spread rapidly, and infections not seen in the normal population, such as systemic fungal infections, can occur. Supportive measures involve reducing the risks and the aggressive treatment of any infectious episodes. The patient is counselled to avoid contact with people with infection or those who may be carriers. Most infections, however, are from an endogenous source such as the gut or skin. The patient is educated on the importance of good personal hygiene, mouth care, how to monitor body temperature and to report any febrile episodes immediately. Co-trimoxazole 960 mg may be prescribed as prophylaxis against *Pneumocystis* pneumonia in patients receiving chemotherapy for lymphomas, particularly in those receiving a regimen containing fludarabine. Thorough and frequent hand washing helps to prevent the transmission of opportunistic infection to the neutropenic patient.

Febrile neutropenia

A febrile episode in the neutropenic patient is an indication for immediate treatment with broad-spectrum intravenous antibiotics. Susceptibility to infection is likely when the neutrophil count is less than 1×10^9 L^{-1} with increasing risk at levels less than 0.5×10^9 L^{-1} and 0.01×10^9 L^{-1}. Fever, usually defined as a temperature above 38 °C maintained for 1 h or 38.3 °C on one occasion, may be the only sign of infection. The patient should be assessed to determine the site of infection, if possible. Blood cultures from all venous access ports and any other appropriate cultures, for example, midstream urine sample and stool sample, are taken and then antibiotic therapy commenced. Blood cultures are taken prior to starting antibiotics to increase the likelihood of obtaining a positive culture. Infection with Gram-negative bacilli, for example, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa,* and Gram-positive cocci, for example, coagulase-negative staphylococci, β-haemolytic streptococci, enterococci, and *Staphylococcus aureus* is probable in this situation. First-line therapy should cover these common pathogens. Options include carbapenems, a third-generation cephalosporin or antipseudomonal penicillin with or without an aminoglycoside. If the patient does not respond to this combination within 24–48 h, then second-line therapy, which may include a glycopeptide for Gram-positive cover, is commenced.

Gram-positive infections are becoming more common with the use of indwelling intravenous catheters. If positive microbiological cultures are found, the appropriate antibiotic can be prescribed on the basis of sensitivities; however, if the patient is responding to empiric therapy, the antibiotics should not be changed. Only one-third of suspected infections are ever confirmed, and the pathogen may not be isolated. The febrile episode may not be due to infection; non-infectious causes include blood transfusion and underlying disease.

Growth factor support

Patients with persistent neutropenia or those who have repeated admissions for neutropenic sepsis may be supported with granulocyte-colony-stimulating factor (GCSF). There is evidence that patients with lymphomas receiving a reduced dose of chemotherapy as a consequence of myelosuppression have a worse prognosis when compared with patients who receive full doses. GCSF is indicated as primary prophylaxis, before any episode of febrile neutropenia, for regimens where there is a high (>40%) incidence of febrile neutropenia. GCSF has been investigated as a prophylactic measure to increase the dose intensity of chemotherapy in regimens such as CHOP-14 (cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), prednisolone at 14-day intervals) and BEACOPP-14 (bleomycin, etoposide, Adriamycin (doxorubicin) cyclophosphamide, vincristine, procarbazine, prednisolone at 14-day intervals).

Case studies

Case 51.1

Mr RB is a 50-year-old man receiving a course of fludarabine and cyclophosphamide (see Table 51.5) for mantle cell lymphoma. He has no other medical problems and has normal renal and hepatic function.

Questions

1. What are the key counselling points for the oral chemotherapy drug fludarabine?
2. What antibacterial agent would you expect to see prescribed with fludarabine?
3. What antiemetic regimen would you recommend with the fludarabine and cyclophosphamide?

Answers

1. Immunocompromised patients, for example, those receiving purine analogues, fludarabine, cladribine and pentostatin, are at risk of developing transfusion-associated graft versus host disease (TAGVHD), a rare but usually fatal complication of transfusion.

   Viable T-lymphocytes in donated blood can recognise the recipient as 'foreign', leading to fever, skin rash, hepatitis and bone marrow involvement. Death occurs in 90% of cases, predominantly due to infection.

   γ-Irradiation of cellular blood components is the mainstay of TAGVHD prevention. Patients should be given an appropriate patient information leaflet and an alert card. The risk of TAGVHD is minimised by informing transfusion staff and the patient of their need for irradiated blood products.
2. Mr RB should be prescribed co-trimoxazole prophylactically to prevent *Pneumocystis jiroveci* infection.
3. Chemotherapy drugs are grouped by how likely they are to cause emesis if antiemetics are not given, called emetogenic potential. Antiemetic regimens are then prescribed to prevent the degree of vomiting expected for each group.

   Fludarabine is rarely emetogenic and oral cyclophosphamide is moderately emetogenic. Therefore, the regimen should be classified and treated as moderately emetogenic.

   Dexamethasone, granisetron and metoclopramide are frequently employed for moderately emetogenic regimens. Guidelines for antiemetic use in oncology are available (American Society of Clinical Oncology, 2006). As corticosteroids are associated with immunosuppression, some clinicians prefer not to use them for emesis prevention with FC chemotherapy.

Case 51.2

Mrs BC is a 72-year-old widow who has been newly diagnosed with low-grade NHL. She has been seen in the hospital outpatient haematology clinic and has brought a prescription to the pharmacy for chlorambucil 10 mg daily for 14 days. When she hands in her prescription, she expresses concern about the side effects of the tablets. The doctor who saw her had spent a lot of time talking to her about her treatment, but she feels confused with all the information given.

Questions

1. What are the side effects of chlorambucil?
2. How would you counsel this patient?

Answers

1. Chlorambucil, an alkylating agent, is generally well tolerated. The major side effect is bone marrow suppression. Other side effects are uncommon and include nausea and vomiting, rash, mucositis and diarrhoea. Hepatotoxicity and jaundice have been reported. Mrs BC is an elderly patient and is thus more likely to experience toxicity because of deteriorating renal and hepatic function and underlying medical conditions.
2. Mrs BC may be distressed by her diagnosis and may not have been able to absorb all the information she was given in the clinic. She may also be seeking confirmation of information.

   Mrs BC should be counselled to complete the course of tablets as prescribed. She should be told that she will probably feel tired and be more prone to infection because the tablets lower the blood count and resistance to infection. She should be advised to inform the haematologist if she feels unwell. Chlorambucil is unlikely to make her feel nauseous, but if this occurs she should inform the doctor, who will be able to prescribe an antiemetic.

Case 51.3

Mr F is 56 years old and was diagnosed with stage III high-grade NHL (DLBCL) over 10 weeks ago. Since then, he has received three cycles of R-CHOP and has come to the hospital for his nadir blood count. He complains of painful mouth ulcers and a sore throat. On examination, he has mucositis and oropharyngeal candidiasis. He has a white blood cell count (WCC) of 3.2 (normal range: 3.5–11 × 10^9 L^{-1}) with ANC of 0.8 × 10^9 L^{-1}.

Questions

1. How would you treat Mr F's *Candida* infection?
2. How would you counsel this patient?

Answers

1. Mr F has an ANC of 0.8 × 10^9 L^{-1} and is therefore neutropenic (ANC <1.0 × 10^9 L^{-1}). Localised candidal infections can spread rapidly in the immunosuppressed patient, so local therapy with

an antifungal mouthwash will be inadequate therapy. A course of fluconazole, 100 mg daily for at least 7 days, should be prescribed. Therapy should continue for a further 7 days if Mr F is still neutropenic or if the thrush has not completely resolved.

An antibacterial mouthwash, such as chlorhexidine 0.2% 10 mL four times daily, should be used. As Mr F is complaining of pain, an analgesic should be added. Benzydamine mouthwash, a locally acting analgesic, could be prescribed initially. If this does not give adequate pain relief, then systemic analgesics such as dihydrocodeine should be given.

2. Regular mouth care reduces the risk of infection but does not entirely remove it. It is not necessarily a reflection of how well the patient has adhered to his mouth care regimen. Chlorhexidine mouthwash should be used first, held in the mouth as long as possible, ensuring the entire mucosa is covered before spitting out. The mouthwash should be used after meals and at bedtime. He should not eat or drink for at least half an hour after using the mouthwash.

   The benzydamine mouthwash should be used before meals as Mr F will probably find eating painful. He should be advised to use a soft toothbrush, to eat soft foods and to avoid hot and spicy dishes. He may be reassured that once his blood count recovers, his mouth ulcers should resolve and that the fluconazole should relieve his sore throat.

Case 51.4

Mr D, 38 years old with advanced HL, is admitted to the haematology ward at the local hospital as an emergency. He had a temperature of 39 °C on the morning of admission, feels generally unwell but has no specific symptoms. It is 12 days since he started his third cycle of ABVD. On admission, he is taking the following medication:

- **co-trimoxazole 960 mg twice daily on 3 days a week**
- **chlorhexidine 0.2% mouthwash 10 mL four times daily**

Blood cultures are taken and piperacillin + tazobactam 4.5 g i.v. three times daily and gentamicin 480 mg i.v. once daily are prescribed, to be commenced immediately. Blood biochemistry results are normal; his FBC was Hb 10.8 (normal range: 13.5–18.0 g/dL for men), WCC 2.5 (normal range: 3.5–11 × 10^9 L^{-1}), neutrophil count 0.6 (normal range: 1.5–7.5 × 10^9 L^{-1}) and platelets 150 (normal range 150–400 × 10^9 L^{-1}). Mr D weighs 86 kg and is 186 cm tall.

Questions

1. Comment on the rationale for the antibiotic therapy prescribed.
2. How would you monitor this patient?
3. What would be an appropriate second-line regimen if he remains pyrexial?
4. What modifications would need to be made to subsequent cycles of chemotherapy?

Answers

1. Mr D's FBC is probably at its nadir following his last course of chemotherapy. He is neutropenic and febrile; fever is often the only sign of infection in neutropenic patients. Immunosuppression is also a feature of HL and contributes to susceptibility to infection. Treatment should commence immediately after cultures have been taken, as infection can be rapidly fatal in these patients. The antibiotics selected should provide broad-spectrum cover and follow local policy as there are institutional variations in predominant pathogens and antimicrobial sensitivities. The organisms responsible for infectious episodes are constantly changing: in the 1970s, Gram-negative infections predominated but now Gram-positive organisms account for 65% of positive cultures. As Gram-negative infections are more rapidly fatal, first-line therapy should be biased towards these infections. Piperacillin, an antipseudomonal penicillin, and gentamicin therefore form an appropriate combination to use in this patient. Piperacillin + tazobactam monotherapy may be sufficient in cases of uncomplicated neutropenic sepsis.

   The dose of piperacillin + tazobactam is appropriate. Infection is considered to be severe in these patients as signs and symptoms are often muted. Single daily dose gentamicin is at least as effective as multiple dosing and less nephrotoxic; it is more convenient and cost effective and overcomes deficiencies of the traditional method such as subtherapeutic dosing and inadequate monitoring. The dose is 5–7 mg/kg and has been calculated correctly for Mr D. He has normal renal function, so no dose modifications are necessary.

2. Monitor temperature, pulse and blood pressure and any patient symptoms for signs of improvement or deterioration. Blood biochemistry should be checked daily to detect any deterioration in renal function. Microbiology reports should be checked and antibiotics reviewed if any micro-organisms have been cultured. However, no change should be made to antibiotics if the patient is showing signs of improvement. The administration of gentamicin should be monitored, checking both administration and sampling time for drug levels. The results should be checked and recommendations for dose modification made where appropriate, using a method such as the Hartford monogram.
3. If the patient remains pyrexial 24–48 h after the first-line antibiotics have been commenced, consideration should be given to broadening cover, for example, adding vancomycin if the patient has mucositis or line infection. If blood cultures show growth, found in only 30–40% of neutropenic patients, the choice of antibiotics should be on the basis of sensitivities. It is important to note that febrile episodes lasting several days may involve more than one infecting organism.

   The patient's FBC should start to recover from day 14 but may be delayed by this infection. It is unusual for patients on conventional chemotherapy for HL to require more than one change to antibiotic therapy, and clinical improvement is often seen with recovery of neutrophil count. If Mr D is still pyrexial at 96 h, then the likelihood of fungal infection must be considered and an intravenous amphotericin-based product or caspofungin commenced if appropriate. The incidence of fungal infection is increasing in patients with prolonged neutropenia. As Mr D's neutropenia is short lived, he is more likely to have a bacterial infection.
4. A dose reduction for subsequent cycles of chemotherapy may be considered. However, as this patient is being treated with curative intent, it may be more appropriate to give GCSF and maintain the dose intensity.

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52 Solid tumours

N. Wood and A. Lamont

Key points

- Cancer involves a group of relatively normal cells dividing without the controls that usually prevent the cells from growing beyond their usual size, site and nutritional base.
- Cancer is now considered a long-term illness with many subgroups.
- Cancer is a collective term for several diseases each with its own characteristics and natural history according to where it has started. Even for a single site of origin, such as breast cancer, major biological and histological differences can be shown.
- Before treatment, patients must be carefully 'staged' to establish the type and extent of disease.
- Depending on the stage of disease, the aim of treatment may be cure, prolongation of survival or symptom control.
- Cytotoxic chemotherapy is the main treatment for disseminated disease.
- Treatment options depend not only on the 'gold standard' of treatment but also patient factors and preferences.
- Targeted medical therapies are becoming more common, generally have fewer side effects and are given over a longer term than conventional chemotherapy.

The term 'cancer' is used to describe more than 200 different diseases, including those affecting discrete organs (solid tumours) and haematological malignancies (which are not localised in the same way). Whereas some tumours are benign and may be harmless, this chapter will focus on the management of patients with solid malignancies which require some form of treatment. Treatment is generally carried out in specialised cancer centres, cancer units or for some agents, in the patient's home. Therapy may include surgery, radiotherapy, chemotherapy and biological or targeted therapy as single modalities or in combination. Care of the cancer patient demands a broad range of services involving a multidisciplinary team working across the hospital, community and hospice network.

Epidemiology

Cancer is a common disease, and more than one in three people will develop some form of cancer in their lifetime. Although more than a quarter of a million people develop cancer each year in the UK, it is predominantly a disease of the elderly, with 74% of new cases diagnosed in people aged over 60 years. Of all deaths in the UK, one in four is due to cancer. The most common single cause of death (22%) is lung cancer, which is potentially preventable by a reduction in tobacco smoking.

Prostate cancer is now the most common cancer in men (24%) followed by lung (15%) and bowel (14%) cancer. In women, breast cancer is the most common (31%) followed by bowel (12%) then lung (12%). However, there are regional variations. From 1979 to 2008, mortality rates from cancer fell by 20% (Cancer Research UK, 2010).

Aetiology

The causes of cancer may be categorised as either environmental or genetic, although these may be interrelated and the causes of some cancers may be multifactorial.

Environmental factors

Increasingly, lifestyle factors play a large part in the development of many cancers. Cigarette smoking has been identified as the single most important cause of preventable disease and premature death in the UK. The beneficial effect of stopping smoking on the cumulative risk of death from lung cancer reduces with increasing age (Doll et al., 2004). Smoking causes about 90% of lung cancer deaths, and the link between tobacco and cancer was established more than 50 years ago.

The most important lifestyle factor for bowel cancer is diet, while cervical cancer is primarily linked to sexual behaviour through the transmissible agent human papilloma virus (HPV) and secondarily to smoking.

Table 52.1 lists a number of other factors which have been associated with cancer development.

Genetic factors

A number of rare tumours are known to be associated with an inherited predisposition, where an individual is born with a marked susceptibility to cancer. This is due to the inheritance of a single genetic mutation which may be sufficient to greatly increase the risk of one or more types of cancer. Examples include the paediatric malignancies, Wilms' tumour of the kidney and bilateral retinoblastoma, a rare cancer of the eye. Some common cancers such as breast, ovarian and colorectal

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Table 52.1 A–K of factors associated with specific cancer sites: An empirical basis for recommending lifestyle changes (Jankowski and Boulton, 2005)

Factor	Associated cancer
*A*lcohol consumption >3 units a day	Most squamous cancers, especially bladder and oesophagus
*B*ody mass index >25 and certainly >30	All solid cancers
*C*igarette smoking at any level (even passive smoking)	Bladder, lung, head and neck, oesophagus and oropharyngeal cancers
*D*iet, especially one that is high in fat	All solid cancers
*E*xercising <30 min a day	All solid cancers
*F*amily history of cancer (in at least one first-degree relative and at least three people in two or more generations)	Inherited cancer syndromes, including breast, colorectal, diffuse gastric, ovarian, prostate and uterine cancers
*G*enital and sexual health (sexually transmitted infections)	Cervical cancer
*H*ealth-promoting drugs that may decrease global cancer risks (but need a careful risk/benefit analysis)	Colonic adenomas can be treated with low-dose aspirin but can have serious side effects Hormone replacement therapy linked with breast cancer
*I*ntense sunburn	Melanoma
*J*ob-related factors	Lung cancer (exposure to asbestos and particulates), skin cancer (contact with arsenic)
*K*nown disease associations	Colorectal cancer has predisposing mucosal pathology – adenomas, coeliac disease, ulcerative colitis

cancer may also show a tendency to occur in families, but these represent a small proportion of the overall presentation of common cancers where identifiable risk factors are relevant in only 5–10% of cases, although when the genetic factor is present the cancers tend to have their onset at a younger age (Garber and Offit, 2005).

Screening and prevention

Screening

Screening programmes aim to detect pre-malignant changes or early-stage cancer in asymptomatic individuals in the general population to provide earlier and thus more effective treatment. Any screening test must be simple, reliable, highly specific (to exclude healthy individuals) and highly sensitive (detection: 90–95%). For a screening programme to be effective in reducing morbidity and mortality, there must also be an available, effective, safe and economically viable treatment that can be applied to the abnormalities detected by the screening test. Screening is well established for cancers of the breast, cervix and, more recently, bowel. Population screening for prostate cancer using the prostate-specific antigen (PSA) blood test remains more controversial due to the lack of specificity and sensitivity of the test, and to the limited evidence on the viability and effectiveness of the treatment options in early-stage disease. It is currently not recommended for use in screening programmes in the UK but is used in the USA. The evidence base for ovarian cancer screening using the blood test CA125 and pelvic ultrasound is evolving through clinical trials.

Prevention

The strong association between cancer risk and lifestyle factors means there is great potential for the primary prevention of cancer through:

- Avoiding tobacco use, especially exposure to cigarette smoke
- Moderate alcohol consumption
- Healthier eating
- Limiting exposure to sunlight and artificial tanning UV exposure
- Encouraging physical exercise
- Maintaining a healthy body weight
- Maintaining adequate protection from asbestos fibres, radon and other occupational and environmental risk factors.

Chemoprevention

Chemoprevention is the prevention of cancer by using medication. The most common example is tamoxifen (pre-menopausal women) or an aromatase inhibitor (post-menopausal women) prescribed daily for 5 years to reduce the risk of developing breast cancer in high-risk women. However, these treatments are not without their side effects, such as menopausal symptoms and increased risk of thromboembolic events. Therefore, the risk-benefit ratio to each patient needs to be carefully assessed.

Another potential future development is the effect of aspirin as a chemopreventive agent for colorectal cancer. Maximal effect requires long-term use of high-dose aspirin that may increase the risk of gastro-intestinal bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors may also be candidates for chemoprevention. However, the regular use of these drugs may also cause gastro-intestinal bleeding and increase the risk of cardiovascular events (Herszényi et al., 2008)

Cancer at the cellular level

Cancer arises from the changes in genes that regulate cell growth. For a normal cell to transform into a cancer cell, genetic changes must occur to the genes that regulate cell growth and differentiation. The nature of the genetic change may be a single point change to a DNA nucleotide, or the complete loss/gain of an entire chromosome. However, the most important factor is that a gene which regulates cell growth and/or differentiation must be altered to allow the cell to grow in an uncontrolled manner. Most cancers require a series of genetic mutations in a cell before an invasive tumour results.

Oncogenes

Oncogenes are where the normal gene, called a proto-oncogene, mutates and is then expressed at inappropriately high levels, therefore increasing the function of that gene. Examples of proto-oncogenes are genes that encode growth factors, signal transducers and transcription factors.

Tumour suppressor genes

Tumour suppressor genes are normal genes which have a protective effect against oncogenes, and are also known as 'anti-oncogenes'. The tumour suppressor gene's normal function is usually to control the cell cycle or act as a check point in division. When this function becomes lost due to mutations affecting both copies of the gene in a potentially malignant cell, other genetic mutations have a greater likelihood of progressing to cancer. An example is the *TP53* gene which codes for the suppressor protein product p53.

The p53 protein acts as a regulator of cell growth and proliferation and controls passage from G1 to S phase in cell division (see Fig. 52.1). Agents which damage DNA cause p53 to accumulate. This accumulation of p53 switches off replication in the cell, arresting the cell cycle and allowing time to repair. If repair fails, p53 may trigger cell suicide by apoptosis. Thus, p53 controls and halts the proliferation of abnormal cell growth.

The cancer cell

Cancer cells differ from normal cells in that they function differently. Inherently unstable, they may display different protein or enzyme content and chromosomal abnormalities (such as translocations or deletions) which may be associated with differences in their susceptibility to chemotherapy or radiotherapy. The changes in internal structure and function lead to changes in their appearance which are visible under light microscopy, for example, larger and more varied appearance of the cell nuclei, and loss of the appearances of specialised cell function such as gland formation. This allows them to be easily detected, particularly when these lead to changes in the way clusters of cells form structures as a group and relate to normal cells in a tissue or organ.

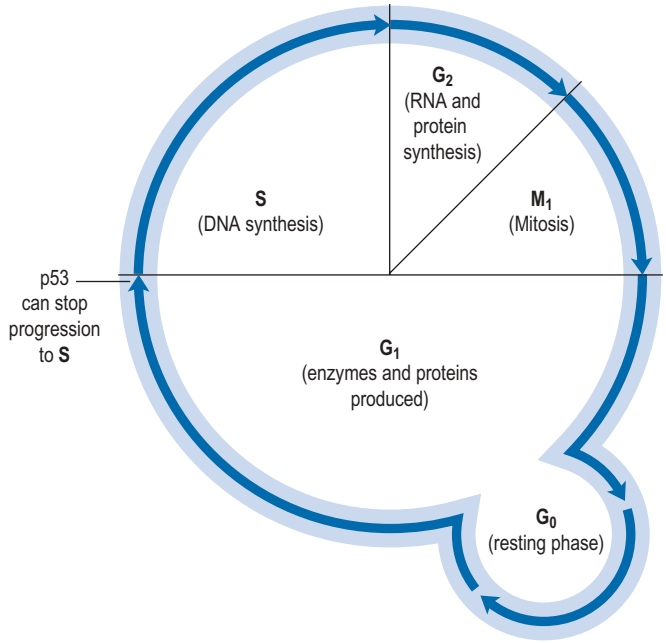


Fig. 52.1 Normal cell cycle.

Tumour growth

A solid tumour represents a population of dividing and non-dividing cells. The time it takes for a tumour mass to double is known as the doubling time. The latter will vary depending on the type of tumour but for most solid tumours it is about 2–3 months. In most solid tumours, the growth rate is very rapid initially (exponential growth) and then slows as the tumour increases in size and age, a pattern described as Gompertzian growth (see Fig. 52.2). The growth fraction is the percentage of actively dividing cells in the tumour, and this decreases with increasing tumour size.

This pattern of tumour growth kinetics has implications for chemotherapy treatment. Generally, chemotherapy is most successful when the number of tumour cells is low and the growth fraction high, which is the situation in the very early stages of cancer.

Tumour spread

As a primary tumour grows, it both pushes the normal surrounding cells aside and invades between them into normal tissue. It is this property of invasion that characterises a

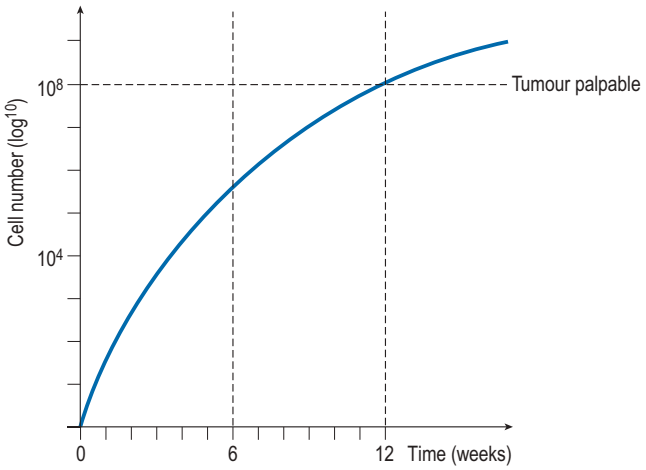


Fig. 52.2 Example of Gompertzian growth of cancer cells.

malignant tumour and leads to distant spread of the disease, since the abnormal cells often infiltrate through the walls of blood vessels and the lymphatic system. Malignant cells are then released from the infiltrating cluster of tumour cells and are transported by the blood or lymphatic fluid to other organs of the body where they can subsequently form secondary cancers or metastases. The pattern of spread tends to be predictable for different tumour types, influenced by the anatomy of the primary site and by differences in the local factors affecting the viability of malignant calls when they become deposited elsewhere. For example, breast cancer usually metastasises to the lymph nodes under the arm, lungs and central nervous system, while prostate cancer tends to metastasise to bone. Generally, when the primary is first detected, the larger the tumour mass the more likely that it has metastasised to other sites.

Patient management

Clinical assessment

Presentation

The clinical features of cancer vary with tumour type. Generally, patients most commonly present with non-specific complaints which include weight loss, unexplained anaemia, malaise, lethargy or pain, or they may have a specific localising symptom such as bleeding from an identifiable site, a non-healing ulcer, a minor symptom such as a cough or hoarseness not resolving in the usual way or the presence of a painful or painless lump. In general, solid tumours are first clinically detectable when there are approximately 10^8–10^9 tumour cells present in a tumour mass in the range of 1–10 g. The patient is usually in the terminal stages of the disease when there are 10^{12} cells present and a tumour burden of around 1 kg. A tumour may be detected by chance during a routine physical examination or by screening or through identification of early symptoms. However, if this does not occur or these symptoms are not present or not recognised, then the disease at presentation is commonly at a stage where there is a high risk that metastatic spread has already occurred at a microscopic level even if that is not clinically detectable.

Before treatment, each patient must undergo a thorough assessment to establish diagnosis, stage of disease and general fitness level. These factors will influence the choice of treatment and give a guide to prognosis.

Diagnosis

An accurate diagnosis is usually made from a tissue sample taken from a suspected primary or secondary tumour, according to the initial clinical investigations. This sampling procedure, biopsy, may be obtained by an open operation, or less invasively by endoscopy. Such samples may be obtained, for example, during bronchoscopy when lung cancer is suspected or, as in the case of a patient presenting with a breast lump, aspiration through a fine needle.

Malignant tumours vary in their sensitivity to chemotherapy. For example, there are two major groups of lung cancer: small-cell and non-small-cell lung cancer. Each of these groups is treated with different combinations of surgery, radiotherapy and chemotherapy drugs. Therefore, precise histopathology is important.

Tumour markers

Tumour markers are usually proteins associated with a malignancy and are clinically useful to:

- Diagnose a specific tumour
- Monitor response to treatment
- Estimate prognosis
- Detect recurrent disease
- Screen a healthy population or a high risk population for the presence of cancer.

They may be detected in a solid tumour, in circulating tumour cells in peripheral blood, in lymph nodes, in bone marrow or in other body fluids. A number of the tumour markers are presented in Table 52.2.

Staging investigations

Since the cancer is often disseminated at the time of presentation, it is vital that patients undergo thorough staging investigations to establish the extent and nature of disease. This will determine the most appropriate treatment offered to the patient. Baseline investigations range from clinical examination, blood tests, liver function tests, diagnostic imaging such as chest and skeletal X-rays, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), depending on the disease type and likely pattern of spread. Clinical guidelines for staging and management of malignancies of the various body systems have been produced at local and national level in most developed countries, with relatively minor variations according to local custom and practice (e.g. NICE in UK, see http://www.nice.org.uk/ for guidance and NCI in USA, see http://www.cancer.gov/ for guidance).

Table 52.2 Examples of tumour markers used in detection, diagnosis and monitoring

Tumour marker	Indicative cancer
CA125	Ovarian cancer, although non-specific
α-Fetoprotein (AFP) β-Human chorionic gonadotrophin (β-HCG)	Testicular tumour
5-Hydroxyindole acetic acid (5HIAA)	Carcinoid tumours
Thyroglobulin	Thyroid cancer
α-Fetoprotein	Hepatocellular carcinoma
Prostate-specific antigen	Prostate cancer
Human chorionic gonadotropin	Gestational trophoblastic tumours

Staging classification

Staging is essentially a measure of how far a tumour has progressed in its development at the time of diagnosis, while grading is a measure of how aggressive its behaviour is likely to be in future based on the microscopic appearance of the cells of the tumour. Both measures are relevant to the patient and clinical team in planning the management.

Most tumours are classified according to the TNM (tumour–nodes–metastases) system where T (0–4) indicates the size of the primary tumour, N (0–3) the extent of lymph node involvement and M (0–1) the presence or absence of distant metastases. Each solid tumour site has a specific grading and staging classification such as Dukes staging in colorectal cancer (Cancer Research UK, 2009) and Gleason scoring for grading prostate cancer (Berney, 2007).

Performance status

The patient's general level of fitness (performance status) at the time of diagnosis is often a surprisingly reliable indicator of prognosis independent of disease-related factors, and will help determine if they are likely to withstand intensive chemotherapy; this therefore influences the choice of treatment. A number of physical rating scales have been devised to assess performance status, including the Karnofsky performance index (Karnofsky and Burchenal, 1949) and the World Health Organization (WHO) performance scale (Box 52.1).

Prognostic factors

These are factors that can predict how the disease is likely to behave and determine an outcome in individual patients. For example, Table 52.3 lists prognostic factors in patients with colorectal cancer.

Box 52.1 Performance status scales

Karnofsky performance index

100 Normal, no complaints, no evidence of disease
90 Able to carry on normal activity, minor signs or symptoms of disease
80 Normal activity with effort, some signs or symptoms of disease
70 Cares for self, unable to carry on normal activity or do active work
60 Requires occasional assistance but is able to care for most of own needs
50 Requires considerable assistance and frequent medical care
40 Disabled, requires special care and assistance
30 Severely disabled, hospitalisation is indicated, although death is not imminent
20 Very sick, hospitalisation necessary, active supportive treatment is necessary
10 Moribund, fatal processes progressing rapidly

WHO performance scale

0. Able to carry out all normal activity without restriction
1. Restricted in physically strenuous activity but ambulatory and able to carry out light work
2. Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3. Capable of only limited self-care; confined to bed more than 50% of waking hours
4. Completely disabled; cannot carry on any self-care; totally confined to bed or chair

Table 52.3 Prognostic factors in patients with colorectal cancer

Favourable	Unfavourable
Good performance status	Presence of nodal involvement
No penetration of the tumour through the bowel wall	Presence of distant metastases
Absence of nodal involvement	Bowel obstruction and bowel perforation
Absence of distant metastases	

Treatment

Treatment goals

After the diagnosis of cancer has been confirmed and the extent of disease fully investigated, the goals of treatment have to be considered. Depending on stage of disease, the goal can be the following (and may change throughout treatment):

- Cure – Patients are said to be 'cured' of cancer when they are completely disease free and have a normal life expectancy. The smaller the tumour bulk when treatment is given, the greater the potential of achieving cure. A common measure of 'cure' is the 5-year disease-free survival rate
- Prolong survival while maintaining patient quality of life
- Provide palliative care with relief of symptoms such as pain.

Childhood malignancies, choriocarcinoma and testicular tumours in adults are most responsive to chemotherapy and these patients are frequently cured, even with advanced disease. However, for most patients treated with chemotherapy, cure is less likely and treatment will be given to maximise the probability of cure, prolong survival or be purely palliative. The decision is influenced by factors such as the extent of the disease as well as co-existing symptoms and concurrent medical conditions, performance status and, importantly, the patient's wishes. The possibility of medium-to long-term survival justifies aggressive treatment but with palliative therapy it is particularly important that the toxicity of treatment is carefully weighed against the potential benefits.

Treatment guidelines

Consensus on the best approach to managing each particular type of cancer is continually evolving, based on the evidence from clinical research most reliably in the form of randomised controlled trials. National guidelines aim to promote equity for patients and ensure a consistent treatment approach taking account of the boundaries of affordability for the healthcare system. In the absence of clinical consensus, patients should be encouraged to participate in clinical trials.

Treatment methods

Three main options are available for the treatment of patients with solid tumours: surgery, radiotherapy and chemotherapy. Targeted and biological therapies are at present minor modalities, and it is hoped that these will be employed more as their effectiveness improves. Each treatment may play a number of roles, either alone or in combination, depending on the disease, stage and grade.

Role of surgery

Surgery can be curative when solid tumours are confined to one primary anatomical site or region as in localised disease. It can also be used to remove isolated metastatic masses with curative intent in rare circumstances or to deal with anatomical consequences of a tumour as a palliative procedure, such as relief of bowel obstruction by defunctioning colostomy. Surgical techniques may be used to support chemotherapy administration when given by continuous infusion or by the intraperitoneal route. Surgery may also play a role in diagnosis through tissue biopsy or in staging to ascertain the extent of tumour involvement such as in ovarian cancer. In the latter, it may also be used to debulk or reduce the size of the tumour to effect pain relief or to improve the effectiveness of subsequent radiation or chemotherapy. However, with more widespread disease, systemic treatment becomes necessary, with chemotherapy playing a major role

Role of radiotherapy

Radiotherapy can be used to cure cancer, reduce the symptoms of the tumour, reduce the size of the tumour ready for surgery or to prevent re-occurrence of the tumour after surgical removal. It can be used alone or in combination with surgery and/or chemotherapy. A full exposition of the role of radiotherapy is beyond the scope of this chapter, which concentrates on the role of systemic agents. However, the combination of radiotherapy and systemic treatment is becoming increasingly employed as research shows the benefit to disease control and long-term survival, for example, in carcinoma of the uterine cervix (Green et al., 2009).

Systemic therapy

This encompasses cytotoxic chemotherapy, hormonal, biological and targeted therapies, but the term does not usually encompass the modalities of nutritional, complementary, alternative, or other 'holistic' interventions, even if employed within a conventional medical environment.

Cytotoxic chemotherapy

Chemotherapy regimen

Although chemotherapy is sometimes administered as a single agent, it is more usual to combine two or more drugs to achieve additive or synergistic effects. Generally, drugs used in combination should have established efficacy as single agents, different mechanisms of action and differing toxicity profiles to allow their use at optimal doses.

Chemotherapy scheduling

As chemotherapy does not specifically target malignant cells, any actively proliferating normal cell will be at potential risk of damage, in particular the cells of the bone marrow. This causes a fall in the white blood cell count and with many cytotoxic drugs, the white blood count is at its lowest level (nadir) around 10 days after treatment. Recovery generally occurs by day 20 post-treatment, and therefore chemotherapy treatment is usually repeated every 3–4 weeks. With agents such as mitomycin and lomustine, haematological recovery may be delayed for 42–50 days following treatment, in which case the interval between treatment cycles needs to be increased. In most cases, a course of treatment will comprise a maximum of six cycles of chemotherapy, although in some less common cancers such as sarcomas and in paediatrics, the regime may continue with a much longer period of adjuvant or consolidation therapy.

Figure 52.3 demonstrates the tumour cell kill for each cycle of chemotherapy together with the healthy normal cell kill. Chemotherapy works in situations where the healthy normal cells recover faster or more completely from the effects of chemotherapy compared to the tumour cells. This allows the tumour cells to be progressively killed off, whilst not having a detrimental effect on the patient.

Chemotherapy dose

The dose of most chemotherapy agents is calculated using the patient's body surface area (BSA) and is usually given in the form of milligrams per square meter. Body surface area may

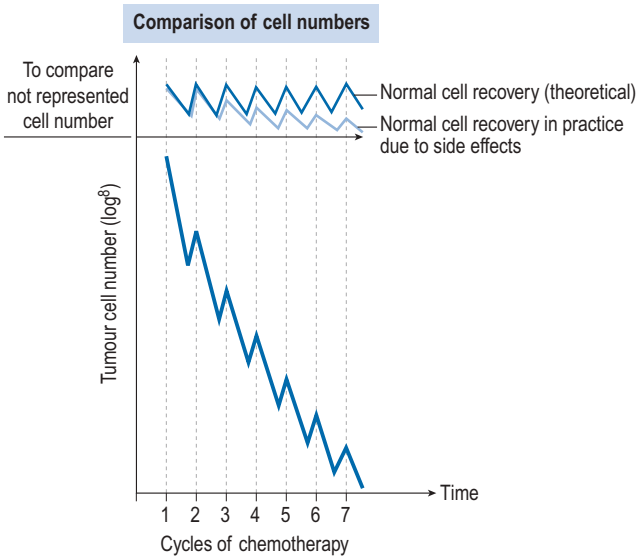


Fig. 52.3 The effect of chemotherapy on tumour mass and healthy cells.

be calculated from the height and weight of the patient using a nomogram and may need to be recalculated for subsequent cycles of chemotherapy if the patient experiences significant weight changes. Table 52.4 gives an example of a chemotherapy regimen used in breast cancer. The reliability of body surface area as a predictor of the effective safe dose is diminished for patients who are either very thin (cachectic) or grossly overweight (morbidly obese) since it does not then reflect a reasonable estimate of lean body mass.

Adjuvant chemotherapy

Adjuvant chemotherapy means literally 'additional treatment' and is usually given after surgery or radiotherapy when all detectable disease has been removed, but where there remains a statistical risk of relapse due to undetectable disease. Adjuvant therapy is, therefore, used to increase the likelihood of cure. Only patients whose cancers have a high or intermediate risk of recurrence tend to be selected for adjuvant chemotherapy since it is not desirable to expose patients whose disease may already have been cured by surgery or radiotherapy to the toxicity of chemotherapy treatment.

In colorectal cancer, for example, adjuvant chemotherapy provides significant disease-free survival benefit by reducing the recurrence rate and also increases overall survival. This indicates the curative role of chemotherapy in the adjuvant setting (Sargent et al., 2009). Similarly, in breast cancer, adjuvant treatment has been shown to increase recurrence-free survival (Levine and Whelan, 2006), and trials are underway to determine which agents and in what combination further improvements in overall survival will be obtained. A recent trial has shown that three-weekly AC/T (doxorubicin, cyclophosphamide, docetaxel [Taxotere®]) is significantly inferior to CEF (cyclophosphamide, epirubicin, 5-flourouricil) or EC/T (epirubicin, cyclophosphamide, docetaxel [Taxotere®]) in terms of recurrence-free survival (Burnell et al., 2010). This is important, as standard treatment choices should move to the superior regimen.

Table 52.4 Example of a chemotherapy regimen FEC–T (Fluorouracil, epirubicin, cyclophosphamide, docetaxel (Taxotere®)) for breast cancer

Indication	Adjuvant Breast Cancer	
Length of cycle	21 days	
No. of cycles	3 cycles of FEC followed by 3 cycles of Taxotere® (Docetaxel)	
FEC		
Fluorouracil	IVB	500 mg/m² day 1
Epirubicin	IVB	100 mg/m² day 1
Cyclophosphamide	IVB	500 mg/m² day 1
T		
Docetaxel	IVI over 1 h	100 mg/m² day 1

IVB, i.v. bolus; IVI, i.v. infusion.

Neo-adjuvant chemotherapy

In neo-adjuvant chemotherapy, chemotherapy is given before local therapy, often preoperatively, to reduce tumour size and facilitate surgical removal. Neo-adjuvant chemotherapy has been of particular value in cases of breast cancer, non-small-cell lung cancer, advanced head and neck cancer, and bone tumours. In Ewings sarcoma, it allows limb-sparing surgery as an alternative to amputation. It also improves survival with reduced morbidity in osteosarcoma.

Synchronous chemoradiation

In several cancers, chemotherapy alongside radical radiotherapy is now established. Agents such as cisplatin are commonly used as a 'radiosensitiser' in head and neck, oesophageal and cervical cancers. The use of cetuximab in combination with radiotherapy for a certain type of head and neck cancer is also recommended (National Institute for Health and Clinical Excellence, 2008). Although common, the use of the term 'radiosensitiser' in this context is somewhat inaccurate and is distinct from the 'true' radiosensitising drugs such as nimorazole, which interact at a chemical level with very short-lived radiation-induced free radicals, and the effect is better termed 'combined modality therapy'.

Adverse effects of cytotoxic drugs

Most cytotoxic drugs have been developed because of their effect on dividing cells. Consequently and as previously mentioned under chemotherapy scheduling, proliferating normal tissue such as bone marrow is at risk. Myelosuppression is frequently the dose-limiting toxicity with these compounds. Neutropenia and thrombocytopenia place patients at risk of life-threatening infection and bleeding, respectively.

The other acute adverse effects occurring most frequently include nausea and vomiting, mucositis, anorexia and alopecia. Individual drugs will also give rise to specific adverse effects, some of which may not be reversible on stopping treatment. Cardiotoxicity, nephrotoxicity and pulmonary toxicity, which are specific to the chemotherapeutic agent or class, may depend on cumulative drug exposure, the schedule of administration and previous therapy. Long-term side effects include infertility due to suppression of ovarian and testicular function and occasionally the induction of a second malignancy.

Chemotherapy-related toxicity is an important issue. Not only can it result in prolonged hospitalisation and a reduction in patients' quality of life, but also successful treatment can be compromised. A reduction in dose intensity, that is the dose of cytotoxic delivered for unit time, because of dose reductions or treatment delays can result in reduced response rates and survival. Recently, the use of granulocyte-colony-stimulating factors (G-CSF) to prevent dose-limiting toxicity of myelosuppression has started to become standard practice. This is often used in adjuvant treatments where the dose intensity given is paramount, and the goal of treatment is cure.

Chemotherapy-specific adjunctive treatments

Both ifosfamide and cyclophosphamide are metabolised to the inactive acrolein which is responsible for bladder toxicity. The co-administration of mesna, a sulphydryl-containing compound which binds to acrolein, has reduced the incidence of haemorrhagic cystitis associated with intravenous regimens of ifosfamide and high-dose cyclophosphamide.

Calcium leucovorin or folinic acid is a reduced form of folic acid and is in effect an 'antidote' to the cytotoxic methotrexate. Folinic acid is effectively used as a form of 'rescue' when high doses of intravenous methotrexate are used to limit the exposure to methotrexate to a defined period of time.

Targeted therapies

In recent years, there has been an increased understanding of biochemical signalling pathways involved in the growth and progression of tumours. This has allowed the development of therapies targeted specifically at the cell receptors involved. A number of these are described. As they are targeted at tumour cells, they suppress disease without inflicting the non-selective toxic effects of cytotoxic chemotherapy on the patient.

Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is a transmembrane protein with an intracellular tyrosine kinase domain. Extracellular binding of the epidermal growth factor receptor induces tyrosine phosphorylation which activates signal cascade pathways. These ultimately lead to cellular proliferation and metastasis. Epidermal growth factor receptor expression is low in normal tissues, and overexpression is associated with a variety of tumours including non-small-cell lung cancer, colon, and head and neck.

Inhibitors of epidermal growth factor receptor (also known as human epidermal growth factor receptor type 1 [HER1]) include:

- Small molecules such as the orally administered erlotinib used in the treatment of non-small-cell lung cancer and imatinib used in the treatment of gastro-intestinal stromal tumours (GIST) which specifically inhibit tyrosine kinase.
- Monoclonal antibodies such as cetuximab which binds to the epidermal growth factor receptor. Cetuximab has demonstrated synergy when given in combination with irinotecan chemotherapy, offering prolonged survival in selected patients with metastatic colorectal cancer.

Vascular endothelial growth factor receptor

Angiogenesis is the formation of new blood vessels on which tumour growth depends. Vascular endothelial growth factor (VEGF) is key in angiogenesis and its overexpression has been associated with increased vasculature, aggressive disease and poor prognosis. The monoclonal antibody bevacizumab inhibits VEGF, thereby reducing new blood vessel growth and interstitial pressure within the tumour, allowing improved chemotherapy access. Studies have demonstrated meaningful survival benefits when bevacizumab is administered in conjunction with chemotherapy in patients with advanced or metastatic colorectal cancer (Hurwitz et al., 2004).

Human epidermal growth factor receptor type 2

Overexpression of human epidermal growth factor receptor 2 (HER2) is associated with a particularly aggressive form of breast cancer (about 20% cases are HER2 positive) linked with a poor prognosis. Trastuzumab, a humanised monoclonal antibody, specifically targets human epidermal growth factor receptor 2 and is only effective in patients with elevated levels. It is used widely in metastatic and early breast cancer (National Institute for Health and Clinical Excellence, 2002, 2006a). The use of trastuzumab in other cancers that express human epidermal growth factor receptor 2 is also under investigation. Trastuzumab has also been licensed for use in human epidermal growth factor receptor 2 positive gastric cancer.

Capecitabine

Although capecitabine does not target a particular receptor, it is mentioned in this section, as it preferentially targets tumour cells.

Capecitabine is a fluoropyrimidine carbamate precursor of 5-fluorouracil (5FU). Given orally, it is converted via enzyme pathways to 5-fluorouracil. As these enzymes are found in higher concentrations in tumour cells, treatment is effectively targeted. Capecitabine has been shown to be at least as effective as intravenous 5-fluorouracil (Twelves et al., 2008), and it is widely used in practice. This is of a particular benefit where the total regimen can then be given orally rather than intravenously.

Management of patients receiving cytotoxic chemotherapy

Prescription verification

Over recent years, there has been considerable effort to improve the quality and safety of chemotherapy services for adult patients (National Chemotherapy Advisory Group, 2009). In particular, the importance of all chemotherapy prescriptions being checked by appropriately trained and competent pharmacists is now recognised. A checklist of key points an authorised pharmacist must undertake to verify any prescription for systemic anti-cancer therapy prior to preparation and release has been determined (British Oncology Pharmacy Association, 2010) and is presented in Box 52.2.

Box 52.2 Standards for chemotherapy prescription verification (British Oncology Pharmacy Association, 2010)

1. Check prescriber's details and signature are present and confirm they are authorised to prescribe SACT
2. Ensure regimen has been through local approval processes, for example, clinical governance and financial approval and/or is included on a list of locally approved regimens
3. On the first cycle, check the regimen is the intended treatment as documented in a treatment plan, in the clinical notes or in the electronic record
4. Check regimen is appropriate for patient's diagnosis, medical history, performance status and chemotherapy history (using the treatment plan, clinical notes or electronic record)
5. Check there are no known drug interactions (including with food) or conflicts with patient allergies and other medication(s)
6. Check that the timing of administration is appropriate, that is the interval since last treatment
7. Check patient demographics (age, height and weight) have been correctly recorded on prescription
8. Check body surface area (BSA) is correctly calculated, taking into account recent weight. Note there should be local agreement for frequency of monitoring and checking patient's weight
9. Check all dose calculations and dose units are correct and have been calculated correctly according to the protocol and any other relevant local guidance, for example, dose rounding/banding
10. Check cumulative dose and maximum individual dose as appropriate
11. Check reason for and consistency of any dose adjustments, for example, reduction(s) or escalations and ensure reason is documented
12. Check method of administration is appropriate
13. Check laboratory values, FBC, U&Es and LFTs are within accepted limits if appropriate
14. Check doses are appropriate with respect to renal and hepatic function and any experienced toxicities
15. Check other essential tests have been undertaken if appropriate
16. Check supportive care is prescribed and it is appropriate for the patient and regimen
17. Sign and date prescription as a record of verification

SAT, Systemic anticancer therapy

Cumulative dosing

The use of doxorubicin is limited by a dose-dependent cardiomyopathy. A number of other factors have been implicated, including treatment schedule, patient age and pre-existing cardiac disease, but dose is the most important. The maximum recommended cumulative dose is 550 or 400 mg/m^2 for patients who have received radiotherapy to the mediastinum. Therefore treatment should be monitored closely to make sure the cumulative dose is not exceeded throughout the patient's lifetime. All other anthracycline antibiotics also have a lifetime cumulative dose limit.

Dose modification or delay

Appropriate investigations must be carried out before each treatment to ensure that patients are fit for chemotherapy. In particular, the patient's haematological, renal and hepatic function should be investigated. For some cytotoxic drugs, it may be necessary to adjust the dose, or even stop treatment, in the presence of renal or hepatic impairment to ensure that delayed excretion or reduced metabolism does not result in excess toxicity. Therefore, the individual summary of product characteristics (SPC) for the chemotherapy agent should be consulted and can be found at http://www.medicines.org.uk.

If the bone marrow does not recover sufficiently between cycles of treatment, then a dose reduction or a delay in treatment may be necessary. In general, patients with a neurophil below 1×10^9/L or a platelet count below 100×10^9/L should not be given myelosuppressive cytotoxics at full doses.

Drug interactions

Prescriptions for cancer chemotherapy are often complex, sometimes involving combinations of both parenteral and oral cytotoxic drugs, intravenous fluids and other supportive therapies. The potential for drug interactions to arise is considerable. However, care is required when assessing the clinical significance of potential drug interactions. A documented interaction does not necessarily imply that drugs should not be used together but can necessitate close monitoring of the patient.

Patient information and counselling

All patients must be provided with information about their treatment, including any anticipated side effects. Patients should be encouraged by health professionals to ask questions about their treatment.

Patients must understand the different medication, the specific role of each medicine and duration of treatment. Duration of treatment is particularly important to prevent highly potent medicines from being inadvertently continued beyond their intended course.

Symptom control

Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is one of the most frequently experienced side effects encountered by chemotherapy patients and is considered to be the most

distressing. In extreme cases, poor symptom control can result in patients refusing further treatment.

In selecting an appropriate anti-emetic regimen, relevant factors include the emetogenic potential of the chemotherapy drugs prescribed, the putative mechanism(s) of inducing emesis, and the likely onset and duration of symptoms. Individual patient characteristics also have to be taken into consideration. For example, predisposing factors which increase a patient's susceptibility to emesis following chemotherapy treatment are:

- Poor control with prior chemotherapy.
- Female sex.
- Younger age <50 years.
- A current or prior history of low chronic alcohol intake.
- History of sickness: pregnancy/travelling/surgery.
- Anxiety.
- Smoking.
- Radiation to gastro-intestinal tract, liver or brain.
- Other medications: various medications can cause nausea and vomiting such as anaesthetic agents, anti-depressants, anti-microbials, anti-fungals, iron, levodopa, carbidopa, NSAIDs.

Differences in the severity of emesis can also occur between patients receiving the same type of chemotherapy and even between treatment cycles in the same patient; however, modern drug treatment can successfully control CINV for the majority of patients.

The 5-hydroxytryptamine type 3 ($5HT_3$) receptor antagonists, which include dolasetron, granisetron, ondansetron, palonosetron and tropisetron, have become the standard management of acute CINV when treating patients with moderately emetogenic chemotherapy regimens. For highly emetogenic chemotherapy regimens such as those including cisplatinum, the use of the NK_1 inhibitor, aprepitant, together with a $5HT_3$ antagonist is becoming the gold standard. These agents are most effective in dealing with acute emesis (less than 24 h duration) when combined with a potent steroid such as dexamethasone.

It is important to achieve optimal control of nausea and vomiting at the outset to avoid subsequent anticipatory symptoms which can prove very difficult to treat.

The route of administration for anti-emetics is an important consideration. With intravenous chemotherapy, it may be simpler to administer all treatments by the intravenous route. Alternatives to the oral route may be useful when vomiting occurs and include the rectal and buccal route.

Pain control

Drug therapy remains the cornerstone of effective pain management but it is often undertreated, thus highlighting the importance of regular patient assessment and appropriate dose or drug treatment changes. For example, patients experiencing intolerable side effects to morphine may be transferred to oxycodone or transdermal fentanyl skin patches. Analgesia should be prescribed both regularly and for breakthrough pain, and stimulant laxatives should be prescribed to prevent constipation. Combinations of analgesics which have synergistic activity, for example, opiates plus NSAIDs, can be highly effective whilst minimising dose-related side effects of each agent.

The route of administration is also important. When patients are unable to manage oral medication, it is important to assess the use of alternative routes such as the rectal, subcutaneous, epidural and transdermal routes.

Bone marrow suppression

Myelosuppression following chemotherapy is common, and for some patients profound. The risk of systemic infection can be reduced by good oral hygiene and mouth care using antiseptic mouthwashes and anti-fungal prophylaxis. Patients must be advised to immediately report symptoms of infection and bruising. Platelet transfusions may be required, but fever or other evidence of infection occurring in a neutropenic patient when the neutrophil count is less than 1.0×10^9/L must be aggressively treated with broad-spectrum intravenous antibiotics to prevent overwhelming infection.

The duration and depth of neutropenia can be dramatically reduced by the administration of G-CSF which stimulate neutrophil production and, in cases of severe neutropenia, effectively rescue the patient. Once the patient's neutrophil count has recovered sufficiently, their use may be safely discontinued. These agents may also be used prophylactically in patients with a high risk of febrile neutropenia before receiving chemotherapy.

Blood transfusions are commonly required by patients at some stage of their treatment due to anaemia. Alternatively, erythropoietin may be useful in some patients receiving chemotherapy to shorten the period of anaemia and improve the patient's quality of life where blood transfusions are not possible.

Extravasation

Extreme care must be taken when administering cytotoxic drugs parenterally because of the dangers of extravasation. Extravasation, which is the accidental leakage of an intravenous drug into the surrounding tissue, can cause pain, erythema and severe local necrosis, resulting in permanent tissue damage. The patient must be asked to immediately report any pain or a stinging sensation at the injection site since the degree of damage is determined by the amount of drug extravasated and the speed at which it is detected. If extravasation is suspected, the administration of further chemotherapy must stop and remedial treatment must commence as soon as possible. The effectiveness of such therapy varies according to the agent extravasated.

Inpatient or outpatient treatment

The majority of patients receive chemotherapy in the outpatient clinic or day-care setting, where cytotoxics are administered mainly by short intravenous infusion at 3- or 4-week intervals. Other treatments include monoclonal antibodies,

Table 52.5 National Cancer Institute common toxicity criteria for anaemia (haemoglobin) (Cancer Therapy Evaluation Program, 1998)

Adverse event, Grade	0	1	2	3	4
Haemoglobin (Hgb)	WNL	<LLN–10.0 g/dL <LLN–100 g/L <LLN–6.2 mmol/L	8.0–<10.0 g/dL 80–<100 g/L 4.9–<6.2 mmol/L	6.5–<8.0 g/dL 65–<80 g/L 4.0–<4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L

WNL, within normal limits; LLN, lower limit of normal.

which usually require close monitoring of the patient for several hours in case of anaphylactic reactions. More complex treatments, such as cisplatinum-containing regimens which require prehydration with intravenous fluids, need the patient to attend all day.

Currently, inpatient treatment of chemotherapy only occurs for the small minority of treatments, and this number is declining further as novel ways of administering long infusions are being developed.

Domiciliary treatment

Oral cytotoxic drugs can safely be taken at home so long as the patient is informed and able to monitor side effects. Availability of a 24-h helpline is essential for these patients should they encounter problems whilst on treatment (National Chemotherapy Advisory Group, 2009). In the future, administration of intravenous treatments, such as the monoclonal antibody trastuzumab, may be carried out more frequently in the home setting, particularly when safety permits and where patient preference becomes an influential factor.

Monitoring anti-cancer therapy

As well as desirable outcomes, treatment with chemotherapy may result in a variety of undesirable outcomes; both require careful monitoring.

Toxicity

The toxicity resulting from treatment is routinely assessed following each cycle of chemotherapy, and may result in therapy being modified on subsequent cycles, for example, a dose reduction, a delay in treatment or, in some cases, an alternative treatment. A number of international rating scales are available for rating predictable acute reactions arising from chemotherapy, including that of the National Cancer Institute Common Toxicity Criteria (for an example, see Table 52.5). Standardising the assessment of treatment-related toxicity in this way allows comparison to be made between published reports of clinical trials.

Response to treatment

Throughout treatment, the response to therapy is closely monitored, noting changes in performance status, symptoms and objective measurements of the tumour. This may necessitate repeating some or all of the initial staging investigations. Should the initial treatment prove ineffective, an alternative can then be considered without delay. Assessment of response should be formally documented before proceeding to further therapy.

Definitions of response. These have been standardised by the WHO:

- *Complete response or remission* (CR). Disappearance of all recognisable tumour masses and/or biochemical changes directly related to the tumour and resolution of symptoms determined by two observations at least a month apart.
- *Partial response* (PR). Decrease by 50% or more in all tumour masses, measured by the product of the longest × the widest perpendicular diameters for at least a month.
- *Stable disease* (SD) *or no change* (NC). Changes smaller than those described above for PR or less than for progressive disease for at least a month.
- *Progressive disease* (PD). Occurrence of any new lesion or increase in the longest × widest perpendicular diameters of measurable disease by at least 25%.

Again, this allows comparison of results between different reported studies. An update of the WHO guidelines has been published (Therasse et al., 2000) called RECIST or Response Evaluation Criteria in Solid Tumours. To avoid confusion, it is important to stipulate in trial protocols which system will be used. Although clinical response indicates tumour sensitivity, it may not necessarily predict long-term survival nor does it measure other benefits such as quality of life.

Case studies

Case 52.1

Mrs BH, a 53-year-old post-menopausal mother of two teenage children, has recently completed six cycles of FEC(100)-T (5-fluorouracil, epirubicin, cyclophosphamide, docetaxel) as adjuvant chemotherapy for her node-positive early breast cancer. She tolerated her chemotherapy well and did not require any dose reductions or delays.

Her receptor status at diagnosis was oestrogen receptor positive and progestogen receptor negative (ER+/PR–); she was also HER2 positive.

Her oncologist has recommended that she commences adjuvant treatment with trastuzumab.

Questions

1. What treatment regimen for trastuzumab should be followed?
2. What side effects of trastuzumab should Mrs BH be informed about when giving consent for treatment?
3. What other treatments should be considered for this patient?

Answers

1. Trastuzumab targets the epidermal growth factor receptor (EGFR) and is indicated for the treatment of early breast cancer overexpressing HER2 following surgery, chemotherapy (neo-adjuvant or adjuvant) and radiotherapy if applicable as recommended by National Institute for Health and Clinical Excellence (2006a). The product license for trastuzumab recommends the dosing schedule used in the HERA study (Piccart-Gebhart et al., 2005), that is loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at three-weekly intervals administered as infusions over approximately 90 min. This is continued for 12 months, stopping sooner if disease reoccurs.
2. The most common side effects experienced by patients are infusion related, such as fever and chills, usually following the first or second treatment. Patients should be closely monitored for at least 6 h after the start of the first infusion and if the treatment has been well tolerated, for 2 h after the start of subsequent infusions. If a reaction occurs, the infusion should be stopped, appropriate symptomatic treatment administered and treatment recommenced at a slower rate only when the symptoms have subsided. Trastuzumab has been associated with cardiotoxicity and patients who have previously received anthracyclines are at increased risk. All patients should have their cardiac function closely monitored at baseline and every 3 months during the period that they are being treated with trastuzumab (National Institute for Health and Clinical Excellence, 2006a). There was an approximate 5% increase in the number of patients with a significant change in cardiac function in the HERA study (Piccart-Gebhart et al., 2005).
3. In view of her receptor status, this patient should be offered hormonal treatment. Depending on the perceived level of risk of recurrence as estimated using a model such as the Nottingham Prognostic Index (Galea et al., 1992), she should be offered either 5 years' treatment with an aromatase inhibitor or planned sequential treatment with tamoxifen switching to an aromatase inhibitor after 2–3 years' therapy. The long-term effect on cardiovascular health (tamoxifen) or bone health (aromatase inhibitors) together with the expected level of benefits should be used to guide choice of treatment. Further information can be found in national guidance for the early management of breast cancer with hormonal treatments (National Institute for Health and Clinical Excellence, 2006a).

Case 52.2

Mr BS, a 67-year-old man with a history of localised prostate cancer, is reviewed by his oncologist. Mr BS was previously treated with radical radiotherapy and more recently several lines of hormonal therapy.

His PSA has risen over the last 6 months and is now 80 ng/mL. It was 0.1 ng/mL on completion of radical radiation therapy. He also complains that his longstanding back pain controlled by low-dose NSAIDs has now become much worse and is out of control.

Questions

1. What is the most likely cause of Mr BS's back pain and raised PSA?
2. What treatment options should be discussed with the patient?
3. Why should he be referred for a dental examination before commencing any further treatment?

Answers

1. The fact that the PSA is markedly raised suggests a recurrence of prostate cancer. Moderate rises in the PSA would have warranted a change in hormonal therapy. The elevated PSA together with the increased back pain suggest metastatic bone disease as a result of distant recurrence of his prostate cancer. This could be confirmed with plain film X-rays or by bone scan. The risk of both local and distant recurrence depends on the stage at presentation.
2. Treatment options for recurrent prostate cancer include second-line hormonal therapy, chemotherapy with or without corticosteroids, and best supportive care. Localised radiotherapy to specific bone lesions could improve his back pain; this would depend on the distribution of treatable lesions identified. The choice of therapy depends on the symptoms, the site of relapse, performance status of the patient and the presence of other co-morbidities. Best supportive care can be provided with radiotherapy, bisphosphonates, steroids and analgesics, and is the only option for patients who are too ill to tolerate further systemic intervention. Tolerability of chemotherapy is of concern, particularly because most patients with prostate cancer are elderly and many have other medical problems. Mr BS has already received more than one line of hormonal therapy; his tumour is unlikely to respond to further hormonal manipulation. An alternative strategy that is available is the use of radioactive isotopes such as Strontium 89 for systemic treatment of multiple bone metastases. The use of chemotherapy in the treatment of hormone-refractory prostate cancer should be considered in patients with a Karnofsky performance status of 60% or greater. Further information on the use of docetaxel for the treatment of hormone-refractory metastatic prostate cancer is available (National Institute for Health and Clinical Excellence, 2006b).
3. Future treatment options for this patient may include use of bisphosphonates to stabilise his bone lesions and reduce his pain. Long-term use of bisphosphonates has been associated with osteonecrosis of the jaw; the risk is exacerbated by poor dental hygiene, concurrent dental procedures, chemotherapy, corticosteroids and malignant disease. Examination and preventive dental treatment should be considered for patients prior to commencing therapy with bisphosphonates in order to avoid any invasive procedures, for instance dental extraction, during bisphosphonate therapy.

Case 52.3

Mr SG, a 46-year-old patient, was diagnosed with Dukes' C colon cancer several months ago. Since then, he has undergone a left hemicolectomy. He is currently receiving capecitabine monotherapy as adjuvant treatment. He telephones the pharmacy department for advice on how to cope with the side effects he is currently experiencing.

Questions

1. What side effects are commonly associated with capecitabine?
2. How do these differ from those associated with intravenous 5-fluorouracil?
3. What advice should he be given?

Answers

1. Side effects most commonly associated with capecitabine treatment are mainly related to the skin and the gastro-intestinal tract.

- Palmar–plantar erythema (hand–foot syndrome) 57%
- Diarrhoea 47%
- Nausea 35%
- Stomatitis 23%
- Vomiting 18%
- Fatigue 16%

2. Although capecitabine is converted enzymatically to 5-fluorouracil, there is a difference in the frequency with which specific side effects are experienced, making it more akin to continuous infusions of 5-flourouracil. Patients receiving intermittent bolus therapy with 5-fluorouracil are more likely to experience the gastro-intestinal side effects, particularly diarrhoea or stomatitis, rather than the cutaneous reactions. Myelosuppression may also infrequently be a problem encountered by these patients.
3. Mr SG should be instructed to contact the emergency telephone number he would have been given with his treatment from the hospital looking after him.

   If detected early, side effects usually improve within 2–3 days. Treatment may be reinstated at the same dose if side effects are moderate, or at a reduced dose if more severe. Symptomatic relief for palmar–plantar erythema may be provided by the use of emollients. There is little evidence to support the use of specific antidotes.

Case 52.4

Mrs PQ, a 59-year-old women, has non-small-cell lung cancer. She has had a course of gemcitabine combined with carboplatin and now requires second-line chemotherapy. The doctor has suggested erlotinib.

Questions

1. What type of treatment is erlotinib and how is it given?
2. What common side effects should Mrs PQ be informed about when she is giving consent for treatment?
3. What other treatments should be considered for this patient?

Answers

1. Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. Epidermal growth factor receptor is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of epidermal growth factor receptor phosphotyrosine results in cell stasis and/or death. It is an oral tablet given once a day until disease progression or unacceptable toxicity.
2. Rash (75%) and diarrhoea (54%) were the most commonly reported adverse drug reactions (ADRs). In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in skin areas exposed to the sun. For patients who are exposed to the sun, protective clothing, and/or use of sun screen (with minimum SPF 15, e.g. mineral-containing) may be advisable. The rash generally starts about 8–10 days after starting treatment but usually improves after a few weeks. Diarrhoea is usually mild and can be controlled with anti-diarrhoeal drugs. Fatigue, nausea and vomiting and sore mouth are also quite common. Some people also develop sore, red eyes (conjunctivitis) or dry eyes.
3. Docetaxel is the other second-line treatment currently available for the treatment of non-small-cell lung cancer.

Case 52.5

Mrs GH is a 64-year-old post-menopausal women with metastatic breast cancer. She has had several cycles of chemotherapy including previous anthracyclines and she had her third cycle of capecitabine 8 days ago. Mrs GH is feeling 'a bit unwell' and her husband thinks she is not at all her usual self, and is, therefore, worried about her.

Questions

1. What side effect may Mrs GH be suffering from?
2. How would you explain to Mrs GH how to take a cycle of capecitabine?
3. What are the possible patient safety concerns regarding oral chemotherapy?

Answers

1. Mrs GH may be suffering from neutropenic sepsis. The signs can be difficult to identify with a small elevation in temperature and a general feeling of not being well. It is important that Mrs GH is prescribed IV antibiotics as soon as possible before she succumbs to the infection. Chemotherapy patients are all at varying degrees of risk for neutropenic sepsis due to the marked decrease in neutrophils in the body due to the chemotherapy. She should also have a blood test to check her neutrophil level, but administration of antibiotics should not wait for these results. Each hospital will have guidelines or a protocol in place to treat neutropenic sepsis in patients receiving chemotherapy.
2. Take the capecitabine dose morning and evening, 12 h apart with a glass of water. Mrs GH should take the capecitabine for 14 days and then stop for 7 days. In addition, it is important to make sure that Mrs GH understands her correct dose.
3. Healthcare workers and their staff must be made aware that the prescribing, dispensing and administering of oral anti-cancer medicines should be carried out and monitored to the same standard as injected therapy. This requires:

- Healthcare organisations to prepare local policies and procedures that describe the safe use of these oral medicines
- Treatment to be initiated by a cancer specialist
- All oral anti-cancer medicines to be prescribed only in the context of a written protocol and treatment plan
- Non-specialists who prescribe or administer on-going oral anti-cancer medication to have ready access to appropriate written protocols and treatment plans
- Staff dispensing oral anti-cancer medicines to be able to confirm that the prescribed dose is appropriate for the patient
- Patients to be fully informed and receive verbal and up-to-date written information about their oral anticancer therapy from the initiating hospital.

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Useful websites

British Oncology Pharmacy Association, Available at http://www.bopawebsite.org.

Cancer statistics, Available at http://info.cancerresearchuk.org/cancerstats/keyfacts/index.htm.

National Extravasation Information Service website, Available at http://www.extravasation.org.uk.

53 Rheumatoid arthritis and osteoarthritis

D. J. Pang and G. M. Brough

Key points

Rheumatoid arthritis

- Rheumatoid arthritis is the most common inflammatory arthritis affecting 1% of the population.
- It affects 5% of women and 3% of men over 65 years of age.
- The aetiology is unclear.
- Non-pharmacological treatment includes physiotherapy, occupational therapy, education and psychological support.
- On diagnosis of rheumatoid arthritis, early treatment with aggressive disease-modifying anti-rheumatic drugs (DMARDs) should commence to prevent joint destruction.
- Cytokine inhibitors are used in patients who do not respond to DMARD treatment. There are several agents available which target different cytokines in the inflammatory pathway.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may be considered for symptomatic relief and should be co-prescribed with a proton pump inhibitor.
- Steroids are useful for rapid relief of symptoms and in the early stages of DMARD introduction.

Osteoarthritis

- Osteoarthritis is uncommon under the age of 35 years.
- A wide variety of factors are thought to predispose a patient to osteoarthritis including genetic factors, age and mechanical overloading of the joint.
- Lifestyle changes such as maintaining optimal weight and undertaking regular exercise are an essential part of treatment.
- Paracetamol and topical NSAIDs are considered first-line treatments.
- Intra-articular steroids and opioids may be used for severe pain.
- Oral NSAIDs may be useful and should be co-prescribed with a proton pump inhibitor.

Rheumatoid arthritis

Rheumatoid arthritis is one of the most common inflammatory disorders affecting the population worldwide. It is a systemic inflammatory disease which affects not only the joints but a wide range of extra-articular organs. The disease, if not treated early, will lead to progressive joint deformity and increased morbidity and mortality.

Rheumatoid arthritis is a potentially fatal illness, with mortality increased twofold and an average decrease in life expectancy of 7–10 years. Patients with rheumatoid arthritis have an increased prevalence of other serious illnesses. The predominant conditions leading to this increased co-morbidity and mortality include infections, renal impairment, cardiovascular disease and lymphomas. The incidence of lymphoma is twofold higher than expected before taking into account the disease-modifying immunosuppressant drugs used in treating rheumatoid arthritis.

Epidemiology

Approximately 1% of the population worldwide is affected by rheumatoid arthritis, with females being two to three times more commonly affected. The prevalence of rheumatoid arthritis increases with age in both sexes; nearly 5% of women and 3% of men over the age of 65 years are affected by the disease. The peak age of incidence is about 30–50 years in women and slightly older in men. Rheumatoid arthritis also affects young children and its classification and treatment differs slightly from adults.

Aetiology and pathophysiology

The cause of rheumatoid arthritis remains unclear with hormonal, genetic and environmental factors playing a key role. Genetic factors contribute 53–65% of the risk of developing this disease. The HLA-DR4 allele is associated with both the development and severity of rheumatoid arthritis. Cigarette smoking is a strong risk factor for developing rheumatoid arthritis. A study of over 3000 women clearly linked the length of time that people had smoked with rheumatoid arthritis (Karlson et al., 1999). Patients with a smoking history of 25 years or more were increasingly likely to develop seropositive disease with nodules and erosions on radiology.

Pathologically, rheumatoid arthritis is characterised by the infiltration of a variety of inflammatory cells into the joint. The synovial membrane, which is normally acellular, becomes highly vascularised and hypertrophied, creating a so-called pannus formation. There is proliferation of synovial fibroblasts and an increase in the number of inflammatory

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cells present within the joint. The inflammatory cells involved in rheumatoid arthritis include T-cells (predominantly CD4 helper cells), B-cells, macrophages and plasma cells. Cytokines are released by these cells which cause the synovium to release proteolytic enzymes, resulting in the destruction of bone and cartilage. Key cytokines involved in rheumatoid arthritis include tumour necrosis factor (TNF)-α, interleukin-1, interleukin-6 and granulocyte macrophage colony-stimulating factor (GM-CSF). These play a crucial role in the pro-inflammatory reaction.

Clinical manifestations

There are different patterns of clinical presentation of rheumatoid arthritis. The disease may present as a polyarticular arthritis with a gradual onset, intermittent or migratory joint involvement, or a monoarticular onset. In addition, extra-articular manifestations may be present (Box 53.1). Extra-articular features occur in approximately 75% of seropositive patients and are often associated with a poor prognosis.

Disease onset is usually insidious with the predominant symptoms being pain, stiffness and swelling. Typically, the metacarpophalangeal and proximal interphalangeal joints of the fingers, interphalangeal joints of the thumbs, the wrists, and metatarsophalangeal joints of the toes are affected during the early stages of the disease. Rheumatoid arthritis–associated deformities affecting multiple joints of the hands are shown in Fig. 53.1. Other joints of the upper and lower limbs, such as the elbows, shoulders and knees, are also affected. Morning stiffness may last for 30 min to several hours, and usually reflects the severity of joint inflammation. Up to one-third of patients also suffer from prominent myalgia, fatigue, low-grade fever, weight loss and depression at disease onset.

Rheumatoid arthritis shows a marked variation of clinical expression in individual patients both in the number and pattern of joints affected, disease progression and the rapidity of joint damage. Disease activity may not abate in 10–20% of cases. Remission has been reported in a small proportion of patients but usually is very rare without disease-modifying anti-rheumatic drugs (DMARDs).

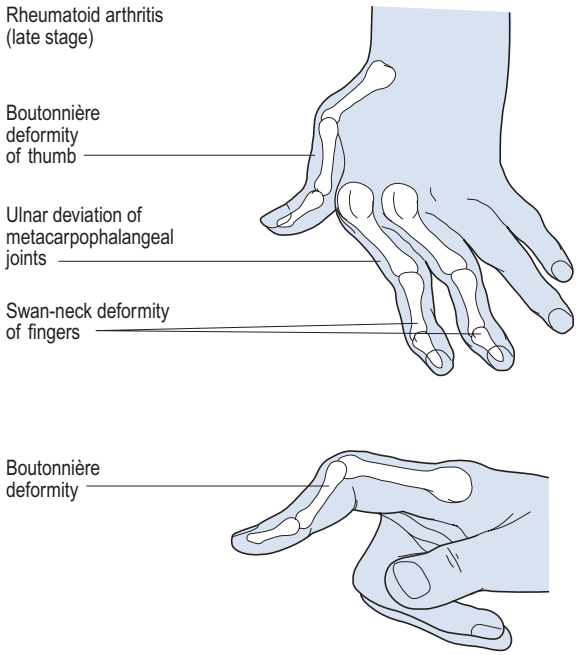


Fig. 53.1 Typical ulnar deviation, swan neck and boutonnière deformities.

Diagnosis

A clinical diagnosis of rheumatoid arthritis is made based on the patient's history, presenting symptoms and clinical findings. Family history is useful, as well as investigations including blood tests, ultrasound for the presence of synovitis and X-rays. The latter is used to demonstrate joint destruction which indicates a late manifestation of the disease.

Emphasis on early diagnosis and treatment is extremely important to prevent disease activity, duration and ultimately joint destruction. The American Rheumatism Association (ARA) criteria (Box 53.2) were principally designed for disease classification in patients with established disease and are not sensitive for patients in the early stages of rheumatoid arthritis (Arnett et al., 1988). The Disease Activity Score

Box 53.1 Examples of the extra-articular features of rheumatoid arthritis

Amyloidosis
Carpal tunnel syndrome
Episcleritis
Felty's Syndrome
Fever
Lymphadenopathy
Nodules; may be subcutaneous or within the lungs, eyes or heart
Osteoporosis
Pericarditis
Pleural and pericardial effusions
Scleritis
Vasculitis

Box 53.2 American Rheumatism Association criteria for the diagnosis of rheumatoid arthritis

- Morning stiffness in and around the joints for at least 6 weeks, lasting at least 1 h before maximal improvement
- Swelling of three or more joints for at least 6 weeks
- Swelling of the wrist, metacarpophalangeal or proximal interphalangeal joints for at least 6 weeks
- Symmetric joint swelling for at least 6 weeks
- Hand X-ray changes typical of rheumatoid arthritis that must include erosions or unequivocal bony decalcification around the joints
- Rheumatoid subcutaneous nodules
- Positive rheumatoid factor

The presence of at least 4 of these indicates a diagnosis of rheumatoid arthritis.

Box 53.3 Summary of DAS28 criteria in the assessment of rheumatoid arthritis

DAS28 is a composite formula. Four parameters are used to calculate a disease severity score:

1. Number of swollen joints out of a total of 28 specified joints
2. Number of tender joints out of a total of 28 specified joints
3. Erythrocyte sedimentation rate
4. Patient's interpretation of wellbeing, with 0 being at their best and 100 their worst

Programmed calculators are used to determine the final DAS28. DAS28 does not take into account other features of a patient's disease, such as synovitis and other clinical symptoms.

High disease activity: DAS28 of >5.1
Moderate disease activity: DAS28 of >3.2 to 5.1
Low disease activity: DAS28 of 2.6–3.2
Remission: DAS28 of <2.6

Box 53.4 American College of Rheumatology (ACR 20) response assessment in rheumatoid arthritis

At least 20% improvement in:
Swollen joint count
Tender joint count
and 20% improvement in any three of the following:
Patient assessed global disease activity
Evaluator assessed global disease activity
Patient pain assessment
Functional disability (using a health assessment questionnaire)
Acute phase response (ESR or CRP)
ACR 50 and 70 are determined as above but the relative improvement in response is 50% or 70%, respectively.

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

using 28 joint counts (DAS28) and American College of Rheumatology (ACR) response are some of the tools used by rheumatologists to assess disease activity and to monitor the patient's response to treatment (see Boxes 53.3 and 53.4).

Investigations

Inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are usually but not always elevated in active disease and are useful for monitoring response to treatment. Rheumatoid factor (RF) is an autoantibody directed against the host immunoglobulin and is most commonly found in rheumatoid arthritis. Routinely performed tests only detect immunoglobulin M rheumatoid factor (IgM RF) which is present in 75–80% of patients with rheumatoid arthritis (termed seropositive disease) and 5% of normal subjects. Those patients who do not have a detectable RF are said to be 'seronegative'. RF is not specific to rheumatoid arthritis and is also present in patients with chronic lung and liver disease, other connective tissue diseases, neoplasia, infections (particularly bacterial endocarditis) and cryoglobulinaemia.

Anti-cyclic citrullinated peptide antibodies (anti-CCP antibody) are a more specific test for rheumatoid arthritis with a specificity of 90–96% compared with the specificity of IgM RF of 85%. They are more useful for the early detection of rheumatoid arthritis in a patient with inflammatory arthritis. The sensitivity of both anti-CCP antibody and IgM RF is approximately 70%.

Antinuclear antibodies (ANA) and extractable nuclear antigens (ENA) are useful for establishing the differential diagnosis, such as other connective tissue diseases presenting or associated with an arthritis. ANA is almost universally positive in systemic lupus erythematosus and only positive in 20% of patients with rheumatoid arthritis.

Other abnormal laboratory tests include an elevated alkaline phosphatase, an elevated platelet count, a decreased serum albumin and a normochromic, normocytic anaemia. White cell count, particularly neutrophils, is elevated in patients with infected joints and is also elevated whilst the patient is on steroids.

Treatment

There are four primary goals in the treatment of rheumatoid arthritis:

- Symptom relief including pain control
- Slowing or prevention of joint damage
- Preserving and improving functional ability
- Achieving and maintaining disease remission

Once the diagnosis has been established, an individualised care plan with treatment goals should be agreed, including monitoring of disease severity using objective measures such as the ACR or DAS28 scores. The ultimate aim is to achieve disease remission, which can be defined by a number of methods including a target DAS28 of less than 2.6, CRP, or a reduction in signs and symptoms of disease activity. If remission cannot be achieved, the aim of therapy is to minimise joint destruction and to preserve function. The longer the period of remission or the best possible reduction in disease activity that can be achieved, the better the long-term outcome.

Patients should have access to a multidisciplinary team to address the pharmacological and non-pharmacological aspects of disease management. Education is extremely important as patients cope better if they understand their condition and have realistic expectations of the benefits and disadvantages of their treatment strategies. Patients may need psychological support and employment counselling to help them adjust to living with their condition. Occupational therapy aims to provide support and aid to allow patients to improve function and limit disability in their activities of daily living. This includes devices to alleviate tasks which may be troublesome for those with restricted manual dexterity, such as twisting lids to open bottles. Physiotherapy involves assessment of function and designing a programme to aid pain relief and rehabilitation. The programme should aim to improve general fitness through regular exercise, and tailor exercises to the individual patient to enhance joint flexibility and muscle strength. Alternative short-term pain relief options may also be explored such as transcutaneous electrical nerve stimulators

(TENS) and hydrotherapy. Surgical interventions, such as synovectomy and arthroplasty, may be useful to relieve pain and restore function.

Drug treatment

The pharmacological management of rheumatoid arthritis is evolving rapidly as more advanced therapies become available. The advent of biological therapies has brought new technologies which target different cytokine pathways involved in the pathogenesis of rheumatoid arthritis and have revolutionised disease management.

There are four main categories of drugs employed in the management of rheumatoid arthritis: non-steroidal anti-inflammatory drugs (NSAIDs) including cyclo-oxygenase (COX)-2 inhibitors, glucocorticoids, DMARDs and biological therapies. Simple analgesia also has a small role to play in basic symptom relief and includes paracetamol, codeine, and paracetamol and opiate combination products. These analgesics do not have any anti-inflammatory effect and will not aid disease modification. The aim of analgesia is to achieve symptom relief and reduce the need for long-term use of NSAIDs, COX-2 inhibitors and glucocorticoids.

Guidance for the treatment of rheumatoid arthritis has been issued and this is summarised in Fig. 53.2.

Non-steroidal anti-inflammatory drugs

The analgesic and anti-inflammatory properties of NSAIDs are used to reduce joint pain and swelling. However, as with simple analgesics, these drugs provide only symptomatic relief to improve joint function, and so should always be used in combination with other agents which modify the disease process.

The COX enzyme converts arachidonic acid into prostaglandins and thromboxanes. These prostanoids have a variety of physiological functions, and are also believed to be responsible for causing pain and swelling in inflammatory conditions. There are two main isoforms of the COX enzyme:

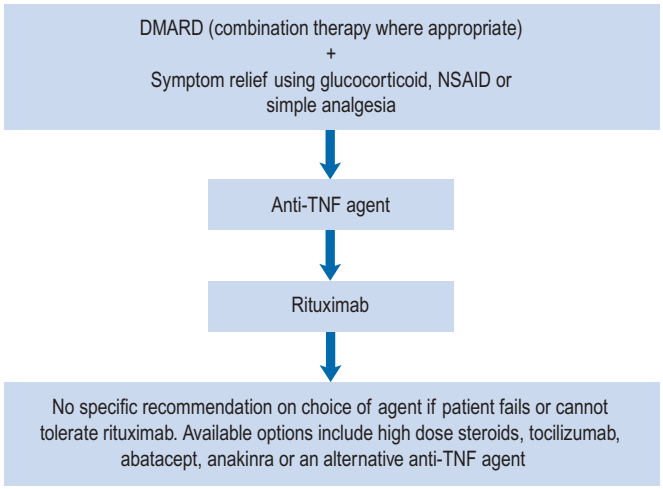


Fig. 53.2 Treatment algorithm for rheumatoid arthritis (NCCCC, 2009).

Table 53.1 NSAIDs currently licensed in the UK

Non-selective NSAIDs	COX-2 inhibitors
Aceclofenac	Celecoxib
Acemetacin	Etoricoxib
Azapropazone	
Dexibuprofen	
Dexketoprofen	
Diclofenac	
Etodolac	
Fenbufen	
Fluribprofen	
Ibuprofen	
Indometacin	
Ketoprofen	
Meloxicam	
Nabumetone	
Naproxen	
Piroxicam	
Tenoxicam	
Tiaprofenic acid	

COX-1 produces prostaglandins required for homeostatic functions, such as maintaining the gastric mucosa, support of renal function and platelet function. COX-2 is responsible for the production of inflammatory prostanoids.

NSAIDs vary in their selectivity for the COX-1 and COX-2 isoforms, and are categorised as either non-selective NSAIDs or selective COX-2 inhibitors, otherwise known as the coxibs (Table 53.1). Non-selective NSAIDs generally block both COX-1 and COX-2, whereas the coxibs have higher selectivity for the COX-2 isoform. However, COX-2 selectivity in NSAIDs varies according to the dose of drug given, which is demonstrated by the dose-related toxicity exhibited by some agents such as ibuprofen. The three most commonly used non-selective NSAIDs have differing levels of COX-1 or COX-2 selectivity: diclofenac is COX-2 'preferential', whereas ibuprofen and particularly naproxen preferentially inhibit COX-1. Originally, inhibition of COX-2 was thought to be involved solely with the anti-inflammatory, anti-pyretic and analgesic properties of NSAIDs. However, it is possible that COX-2 inhibition may also impair endothelial health, cause a prothrombotic state and promote cardiovascular disease.

Safety

In 2004, rofecoxib, a selective COX-2 inhibitors, was withdrawn from the worldwide market due to evidence of an increased risk of confirmed serious thrombotic events that included myocardial infarction and stroke, following long-term use. In the following years, similar evidence against the other COX-2 inhibitors and also against some of the non-selective NSAIDs accumulated.

At present, the exact cardiovascular risk for individual selective COX-2 inhibitors and NSAIDs is not known. Evidence from clinical trials of COX-2 inhibitors suggests that about 3 additional thrombotic events per 1000 patients/year may occur in the general population (MHRA, 2006).

A dose-dependent increase in cardiovascular risk is associated with use of celecoxib, high-dose diclofenac (150 mg/day) and high-dose ibuprofen (2400 mg/day). There does not appear to be an increased risk of myocardial infarction in association with low-dose ibuprofen (≤1200 mg/day). Naproxen is associated with a lower risk of arterial thrombotic events than COX-2 inhibitors. There may be some increased cardiovascular risk in all patients receiving any NSAID, irrespective of their baseline risk or duration of therapy. The key message is that patients should use the lowest effective dose and the shortest duration of treatment necessary to control symptoms to minimise the risk of adverse events.

The most common adverse events of NSAIDs are those that predominantly inhibit COX-1 and cause adverse gastro-intestinal effects. These range from minor symptoms, including dyspepsia, nausea and diarrhoea, to more serious events, such as gastric erosion, bleeding and duodenal and gastric ulceration. Patients are at a higher risk of serious gastro-intestinal complications if they are over 65 years of age, have a previous history of gastro-intestinal ulceration/bleeding or peptic ulcer disease, or are taking concomitant anti-platelet, anti-coagulation or steroid therapy. There are several gastroprotective agents available which may be used to reduce adverse events, including H_2 antagonists, misoprostol and proton pump inhibitors (PPIs). PPIs, such as omeprazole and lansoprazole, have been shown to be particularly effective at preventing gastric and duodenal ulcers with NSAIDs. All patients taking a non-selective NSAID or COX-2 inhibitor should receive concomitant treatment with a PPI to minimise gastro-intestinal adverse effects.

Aspirin inhibits the COX enzyme irreversibly through a different mechanism of action to the NSAIDs. Therefore, there is an increased risk of gastro-intestinal toxicity if aspirin and non-selective NSAIDs are used concomitantly, and the gastro-intestinal advantage of using a selective COX-2 inhibitor is severely reduced. Low-dose aspirin should only be co-prescribed with NSAIDs where absolutely necessary.

All NSAIDs may potentially cause adverse cardio-renal effects such as oedema, hypertension and heart failure. The distribution of COX-1 and COX-2 differs in the kidney, but there is no evidence to suggest differing degrees of isoform inhibition have an impact on the severity of cardio-renal adverse effects. Pharmacokinetic parameters, such as half-life and metabolism, may affect both thrombotic and cardio-renal properties of NSAIDs.

Choice of agent

Evidence suggests that all non-selective NSAIDs and COX-2 inhibitors are of similar efficacy, but vary in their toxicity profiles. However, there is individual patient variability in terms of response to a given NSAID, and so some patients may need to try several agents before reaching an effective and well-tolerated agent. Non-selective NSAIDs or COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. There are no recommendations on which agent to use first-line as all NSAIDs have analgesic effects of similar magnitude. However, as these drugs vary in terms of potential gastro-intestinal, liver and cardio-renal toxicity, it is advised that the choice of drug should take into account the patient's individual risk factors, including age.

Disease-modifying anti-rheumatic drugs

Joint damage is known to occur early in rheumatoid arthritis and is largely irreversible. The need for early intervention with DMARDs as part of an aggressive approach to minimise disease progression has become standard practice and is associated with better patient outcome. Early introduction of DMARDs also results in fewer adverse reactions and withdrawals from therapy (NCCCC, 2009).

The DMARDs that are commonly used for rheumatoid arthritis and have clear evidence of benefit are methotrexate, sulphasalazine, leflunomide and intramuscular gold (O'Dell, 2004). There is less compelling evidence for the use of hydroxychloroquine, D-penicillamine, oral gold, ciclosporin and azathioprine, although these agents do improve symptoms and some objective measures of inflammation. The exact mechanism of action of these drugs is unknown. All DMARDs inhibit the release or reduce the activity of inflammatory cytokines, such as TNF-α, interleukin-1, interleukin-2 and interleukin-6. Activated T-lymphocytes have been implicated in the inflammatory process, and these are inhibited by methotrexate, leflunomide and ciclosporin.

Patients should be made aware that the DMARDs all have a slow onset of action. They must be taken for at least 8 weeks before any clinical effect is apparent, and it may be months before an optimal response is achieved. Whilst early initiation of DMARDs is crucial, it is important to ensure the patient is maintained on therapy to maintain disease suppression. This itself is a challenge, due to the toxicity profiles of the majority of these drugs (see Table 53.2). The majority of the DMARDs require regular blood monitoring. Guidelines are available on the action to take in the event of abnormal blood results (Chakravarty et al., 2008).

Recommendations regarding the use of DMARDs in rheumatoid arthritis are summarised in Box 53.5 (NCCCC, 2009). Patients with a new diagnosis of rheumatoid arthritis should be offered combination DMARD therapy as first-line therapy as soon as possible, ideally within 3 months of the onset of persistent disease symptoms. The combination therapy should include methotrexate and at least one other DMARD, usually sulphasalazine and/or hydroxychloroquine. Evidence suggests that combination therapy appears to be superior in terms of benefits to symptoms, quality of life, remission rates and slowing of joint damage, when compared to monotherapy. Once sustained and satisfactory levels of disease control have been achieved, the doses of drugs should be cautiously reduced to levels that continue to maintain disease control.

In patients where combination therapy is not appropriate, for example where there are contraindications to a drug due to existing co-morbidities, DMARD monotherapy should be started, placing greater emphasis on fast escalation to a clinically effective dose rather than on choice of agent (NCCCC, 2009).

Table 53.2 DMARDs used in the treatment of rheumatoid arthritis

Name	Dose	Adverse reactions	Monitoring		Time period to benefit
			Baseline	Long-term	
Auranofin (oral gold)	3 mg two to three times daily	Rash, oral ulceration, proteinuria, myelosuppression	FBC Urinalysis U&E LFTs	FBC and urinalysis every 4 weeks	4–6 months
Azathioprine	1–3 mg/kg/day	Myelosuppression, hepatic impairment	FBC U&E LFTs TPMT assay	FBC and LFTs weekly for 6 weeks, then every 2 weeks until dose is stable for 6 weeks, then monthly. If maintenance dose is achieved and stable for 6 months consider reducing monitoring to every 3 months U&E every 6 months	6 weeks to 3 months
Ciclosporin	2.5–4 mg/kg/day (in two divided doses)	Hypertension, renal dysfunction, gingival hyperplasia, electrolyte imbalance, hyperlipidaemia	FBC U&E LFTs Fasting lipids CrCl BP	FBC and LFTs monthly until dose and trend stable for 3 months, then every 3 months thereafter U&E every 2 weeks until dose and trend stable for 3 months, then monthly thereafter Periodic lipid check Regular BP check – maintain ≤ 140/90	3 months
D-penicillamine	Usual maintenance 500–750 mg daily	Nausea, anorexia, myelosuppression, rashes, taste disturbances	FBC U&E Urinary protein	FBC and urinalysis every 2 weeks until dose stable for 3 months, then monthly thereafter	3–6 months
Hydroxychloroquine	200–400 mg daily	Ocular toxicity, GI and visual disturbances	FBC U&E LFT Visual acuity	Annual review with optometrist	2–3 months
Leflunomide	10–20 mg daily Loading dose is not commonly used in practice due to GI side effects	Weight loss, hypertension, GI disturbances, myelosuppression	FBC U&E LFTs BP Weight	FBC and LFTs monthly for 6 months, then every 2 months thereafter if stable Monthly bloods should be continued long-term if co-prescribed with another immunosuppressant or potentially hepatotoxic agent Regular BP and weight checks	8–12 weeks, although longer if the loading dose is not given
Methotrexate	7.5–25 mg once weekly	Hepatotoxicity, myelosuppression, pneumonitis, nausea and vomiting	FBC U&E LFTs Chest X-ray	FBC, U&E, LFTs every 2 weeks until MTX dose and monitoring stable for 6 weeks, then monthly thereafter until dose and disease stable for 1 year. Following this, reduction in frequency of monitoring may be considered depending on various patient factors, for example renal impairment	6 weeks to 3 months

Table 53.2 DMARDs used in the treatment of rheumatoid arthritis—cont'd

Name	Dose	Adverse reactions	Monitoring		Time period to benefit
			Baseline	Long-term	
Sodium aurothiomalate (IM gold)	10 mg test dose, then 50 mg weekly until significant response or total dose of 1000 mg has been given	Rash, oral ulceration, proteinuria, myelosuppression	FBC Urinalysis U&E LFTs	FBC and urinalysis every 4 weeks	Usually when 500 mg cumulative dose has been reached
Sulphasalazine	500 mg to 3 g daily	GI disturbances, myelosuppression, hepatotoxicity	FBC U&Es LFTs	FBC and LFTs monthly for first 3 months, then every 3 months thereafter. Reduce frequency after first year if dose and results are stable	3 months

BP, blood pressure; CrCl, creatinine clearance; FBC, full blood count; GI, gastro-intestinal; IM, intramuscular; LFTs, liver function tests; MTX, methotrexate; TPMT assay, thiopurine methyl transferase; U&E, Urea and electrolytes, including creatinine

Box 53.5 Key points regarding DMARD therapy (NCCCC, 2009)

Introduce DMARD therapy early (within 3 months ideally)
Use combination DMARDs involving methotrexate and at least one other DMARD
Use monotherapy where combination DMARD therapy is not appropriate, with rapid escalation to therapeutic dose
Withdraw cautiously when disease is stable to doses that maintain disease control

There are many factors that influence the choice of DMARD: relative efficacy, severity of disease, convenience, monitoring requirements, patient co-morbidities, cost, time period to benefit, prescriber's experience and success rates with the drug, side effects and patient adherence. Studies have shown that methotrexate has the best benefit to toxicity ratio. Both sulphasalazine and hydroxychloroquine are also favourable in terms of low incidence of serious adverse effects, although hydroxychloroquine alone does not slow radiological damage. Most patients started on a DMARD will not be taking it 3–4 years later because of adverse reactions or lack of efficacy. Despite promising results initially, some patients experience disease reactivation at a later stage and become unresponsive to treatment.

Methotrexate

Methotrexate is recognised as the gold standard DMARD in the management of rheumatoid arthritis. It is given as a once weekly dose and can be given orally or parenterally via the intramuscular or subcutaneous routes. Patients usually begin on oral therapy; parenteral methotrexate may be considered in those who do not respond adequately to the maximum tolerated oral dose, or in those who suffer from gastro-intestinal side effects. Doses used, whether administered by the parenteral or oral route, are similar, although bioavailability is greater with parenteral administration. Methotrexate is primarily excreted unchanged by the kidneys and so elderly patients or those with renal impairment may require lower doses. Methotrexate is a folic acid antagonist and acts by reversibly inhibiting dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Concomitant administration of oral folic acid reduces adverse effects of methotrexate and improves continuation of therapy and adherence. Doses used range from 5 mg weekly to 5 mg daily except on the day of methotrexate administration.

Methotrexate is associated with lung, liver and bone marrow toxicities. As a consequence, strict monitoring is advised and alcohol intake should be minimised. Methotrexate pneumonitis is usually seen within the first year of treatment, but can sometimes occur after long-term therapy. Myelosuppression can cause significant falls in blood cell counts. It is more likely to occur in the elderly, patients with renal impairment or patients who are also taking anti-folate drugs. A clinically significant drop in cell count calls for immediate withdrawal of methotrexate, and folinic acid rescue therapy. Patients should be counselled to report any of the following warning symptoms immediately to a healthcare professional: blood disorders, for example sore throat, bruising, mouth ulcers; liver toxicity, for example nausea, vomiting, abdominal discomfort, dark urine; and respiratory effects, for example shortness of breath, persistent dry cough.

Following a number of patient incidents involving methotrexate toxicity, guidance on safe use was issued by the National Patient Safety Agency (Box 53.6). Methotrexate-monitoring booklets are routinely given to patients when therapy is initiated. The booklet contains information to reinforce counselling points such as warning symptoms and drug interactions, and has sections where prescribers can enter in dose details (in number and strength of tablets) and record blood results. Methotrexate tablets are available as 2.5-mg and 10-mg strengths; most pharmacies will dispense the 2.5-mg strength only for non-chemotherapy indications such as rheumatoid arthritis.

Box 53.6 Summary of recommendations for the safe prescription of methotrexate

All prescriptions must specify a dose
The term 'as directed' should be avoided on prescriptions
The strength of tablets supplied should remain consistent to avoid confusion regarding dose
Issue all patients with a methotrexate monitoring booklet
Counsel patient:
- Strength and number of tablets to take
- Monitoring requirements
- Warning symptoms of methotrexate, for example sore throat, persistent cough, vomiting
- To inform other healthcare professionals that he/she is taking methotrexate

Sulphasalazine

Sulphasalazine has been shown to slow joint erosions and suppress inflammatory activity in rheumatoid arthritis. Blood dyscrasias usually occur within the first 3–6 months of treatment, therefore necessitating close monitoring in the initiation period. Patients should also be counselled to report warning symptoms of unexplained bleeding, bruising, purpura, sore throat, fever or malaise. Enteric-coated tablets are available to minimise gastro-intestinal side effects.

Hydroxychloroquine

Hydroxychloroquine is significantly less effective than other DMARDs and historically was reserved for milder cases of rheumatoid arthritis. It still has a place in therapy, particularly in combination with other DMARDs, as it seems to give some symptomatic relief to patients and is the least toxic of the DMARDs. It has also been used relatively safely in pregnancy. Regular visual assessment for retinopathy is recommended as long-term use of anti-malarial agents has been linked to ocular toxicity.

Leflunomide

Leflunomide has a long half-life of approximately 2 weeks, and consequently a loading dose may be given to achieve therapeutic drug levels more quickly. However, in practice, the loading dose is often omitted due to intolerable gastro-intestinal side effects such as diarrhoea. Leflunomide is associated with hepato- and haemato-toxicity, and should be used with caution if co-prescribed with drugs which also cause these adverse effects. Washout procedures using colestyramine or activated charcoal may be necessary when switching to another DMARD, in the event of a serious adverse effect or before conception in females.

Gold

Gold can be given via intramuscular injection as sodium aurothiomalate, or orally as auranofin. Intramuscular gold is more effective than oral. These drugs can be used over a long period of time provided the patient does not experience side effects such as proteinuria, blood disorders, rashes, gastro-intestinal side effects or bleeding.

Other DMARDs

D-Penicillamine is less commonly used, as side effects such as rashes, taste loss and vomiting, are common. It can be effective in some patients, but doses above 750 mg daily are associated with a high incidence of adverse effects. Azathioprine and ciclosporin can be used in refractory rheumatoid arthritis, but use is limited due to monitoring requirements and high incidence of side effects.

Glucocorticoids

Steroids can be given via the oral, intramuscular or intra-articular routes. They act by inhibiting cytokine release and give rapid relief of symptoms and decrease inflammation. Prednisolone is the most commonly used oral steroid. Intra-articular injections, such as triamcinolone or methylprednisolone, are administered into inflamed joints for local anti-inflammatory action, pain relief and to reduce deformity. The effects of the injection tend to last for approximately 4 weeks and should generally not be repeated more than three times a year into an affected joint. Intramuscular and, less commonly intravenous, injections are used as high-dose pulse therapy to control aggressive disease flares.

Steroids are also used as a bridging therapy and are particularly useful when introducing DMARDs which may take several months to take effect. There are various studies which demonstrate steroids are disease modifying in slowing radiological damage over 2 years. Doses of prednisolone 7.5 mg daily have been suggested to reduce the rate of joint destruction in moderate to severe rheumatoid arthritis of less than 2 years' duration (NCCCC, 2009).

Ideally, steroids should be reserved for short-term use in new-onset rheumatoid arthritis because of their long-term complications and adverse effects. However, because they exert such a potent anti-inflammatory effect, it may be difficult in some patients to withdraw therapy as the disease tends to flare with dose reductions. Gradual reducing regimens should be used with the aim to reach the lowest possible maintenance dose. A reducing rate as slow as 1 mg/month may even be necessary in some patients. Steroids can induce osteoporosis, which is a known complication associated with rheumatoid arthritis itself. Prophylactic therapy, such as calcium and vitamin D supplementation and bisphosphonates, should be considered in patients on steroids at a high dose or for an extended period of time. Gastroprotection may also be necessary in the form of H_2 antagonists or proton pump inhibitors. Other adverse effects associated with steroids are diabetes, increased risk of infection, hypertension and weight gain.

Biological therapies

Over the past decade, there have been significant advances in the treatment of rheumatoid arthritis due to emerging biological therapies. The so-called biologics in rheumatoid arthritis are

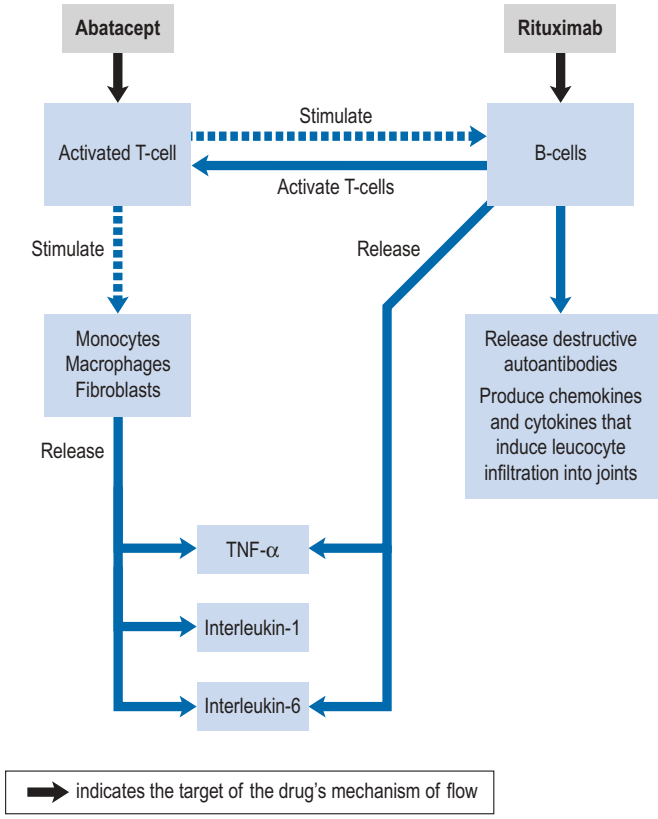


Fig. 53.3 Biologic agents and their targets in the inflammatory pathway.

genetically engineered monoclonal antibodies which selectively target different parts of the inflammatory pathways (Fig. 53.3). Activated T-cells release pro-inflammatory cytokines including TNF-α, interleukin-1 and interleukin-6. Adalimumab, etanercept, golimumab, infliximab and certolizumab pegol target TNF-α, anakinra and tocilizumab target the interleukins, whilst abatacept and rituximab act on T-cells and B-cells, respectively.

In current practice, biologics are used after a patient has failed DMARDs, although there is emerging evidence to suggest they should be used earlier in the disease. Combination DMARD therapy is increasingly advocated and may lead to earlier use of biologics. For example, a patient may now be trialled on two DMARDs, including methotrexate, over a period of 6 months and if the response is inadequate could be eligible for an anti-TNF agent within a year of diagnosis.

Anti-TNF agents

There are five anti-TNF agents available: adalimumab, etanercept, golimumab, infliximab and certolizumab pegol. All inhibit TNF-α which is an inflammatory cytokine found in high concentrations within the joint synovium of rheumatoid arthritis patients.

Infliximab was the first anti-TNF agent licensed for the treatment of rheumatoid arthritis. It is a chimeric human-murine monoclonal antibody that binds with high affinity to TNF-α, thereby neutralising its activity. Infliximab is the only anti-TNF agent which is given by intravenous infusion and must be given concomitantly with methotrexate. It is usually well tolerated, with the most common adverse effects being mild infusion reactions, such as headache and urticaria. Anaphylaxis and delayed hypersensitivity reactions have also been rarely reported. As infliximab is a part murine monoclonal antibody, it is thought to carry a higher risk of developing human anti-chimeric antibodies (HACAs). HACAs are associated with an increased frequency of infusion-related reactions and can be minimised by administering with an immunomodulatory therapy.

Adalimumab is a recombinant human monoclonal antibody that binds to and neutralises TNF-α. Etanercept is a human TNF fusion protein that binds to TNF cell surface receptors, thereby inhibiting interaction of TNF-α with its receptors. Certolizumab pegol is a pegylated antibody fragment which binds and neutralises TNF-α and is thought to have a relatively more rapid onset of action. Golimumab is the most recent addition to this family of agents and has the advantage of having a less frequent dosing schedule. (Table 53.3). Optimum clinical benefit is achieved when these drugs are used in combination with methotrexate. However, adalimumab, etanercept and certolizumab pegol can be used alone as monotherapy in patients for whom methotrexate is not appropriate or not tolerated.

Safety

The anti-TNF agents are generally well tolerated, with the main side effects being injection site reactions with the subcutaneous agents, and infusion-related reactions with infliximab.

Table 53.3 Biologic agents used in the treatment of rheumatoid arthritis and typical dose regimens in adults

Drug	Usual dose	Route
Adalimumab	40 mg every 2 weeks	Subcutaneous
Certolizumab pegol	400 mg at week 0, 2 and 4, then 200 mg every 2 weeks thereafter	Subcutaneous
Etanercept	25 mg twice weekly or 50 mg weekly	Subcutaneous
Golimumab	50 mg monthly	Subcutaneous
Infliximab	3 mg/kg at week 0, 2 and 6, then every 8 weeks thereafter	Intravenous infusion
Rituximab	1 g then 1 g 2 weeks later Max 2 courses/year	Intravenous infusion
Abatacept	750 mg at week 0, 2 and 4, then every 4 weeks thereafter[a]	Intravenous infusion
Anakinra	100 mg daily	Subcutaneous
Tocilizumab	8 mg/kg every 4 weeks	Intravenous infusion

[a]For a patient weighing between 60 and 100 kg; dose modifications are necessary for patients outside this weight range.

There are fewer monitoring requirements compared to the DMARDs and less frequent dosing, making these drugs potentially more appealing. However, the long-term safety of these drugs is being monitored in the UK by the British Society of Rheumatology Biologics Registry. This database collects data on efficacy and safety outcomes of all patients on biologics in a variety of rheumatological conditions including rheumatoid arthritis.

Patients using anti-TNF agents are more susceptible to serious infections such as sepsis, and opportunistic infections. A number of serious infections, including some fatalities, have been reported. Patients should not start anti-TNF therapy in the presence of infection. Those who develop infection whilst receiving treatment should stop and wait until the infection is controlled. The anti-TNF agents have long half-lives and temporary cessation of therapy should be considered prior to and after surgery. Reactivation of hepatitis B and latent tuberculosis has been reported. All patients should be screened for tuberculosis using appropriate tests, such as the tuberculin skin test and a chest X-ray. Active tuberculosis must be treated before an anti-TNF agent is initiated.

Malignancies, including lymphoma, have been reported in studies and post-marketing surveillance of the anti-TNF agents. Caution should be exercised with the use of anti-TNF agents in patients with previous malignancy.

All the anti-TNF agents except etanercept are contraindicated in New York Heart Association (NYHA) grade III/IV heart failure, and all should be used with caution in those with mild heart failure.

Place in therapy

Guidance on the use of adalimumab, etanercept, infliximab (NICE, 2007) and certolizumab pegol (NICE, 2010a) have been published, with the appraisal of golimumab pending. Adalimumab, certolizumab, etanercept or infliximab are recommended as treatment options in adults who meet the following criteria:

- Active rheumatoid arthritis with a DAS28 greater than 5.1 on at least two occasions, 1 month apart.
- Have undergone trials with two DMARDs, including methotrexate, unless contraindicated. A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.

Patients should be assessed for treatment efficacy using DAS28 every 6 months and continue treatment only if an adequate response is demonstrated 6 months after initiation. An adequate response is currently defined as an improvement in DAS28 of 1.2 points or more.

Changes in eligibility criteria have been suggested (Deighton et al., 2010) which recommend patients should have tried two DMARDs, but those with DAS28 > 3.2 and at least three or more tender joints and three or more swollen joints should be eligible for an anti-TNF agent. Whether NICE will adapt their guidance accordingly is unclear.

Use of the anti-TNF agents above their starting doses as listed in Table 53.3 is not advocated. According to their product licences, doses of adalimumab and infliximab may be escalated according to response, but this does not generally occur in practice.

Generally, the least expensive anti-TNF agent should be used although patient aspects may also affect choice of drug. There are differences between dosing frequencies of the anti-TNF agents, which should be discussed with the patient to ensure drug administration is easily incorporated into their lifestyle, thereby improving adherence. The subcutaneous agents are also available in pen formulations, making it easier for self-administration in patients who have problems with manual dexterity. Patients who are unable to self-administer the subcutaneous anti-TNF agents may choose to receive infliximab as a hospital day case. As infliximab is only licensed to be used in combination with methotrexate, adalimumab, certolizumab and etanercept are favoured in patients where methotrexate cannot be taken.

Rituximab

Rituximab is a chimeric human-murine monoclonal antibody which binds to the C20 antigen on B-lymphocytes to mediate B-cell lysis. It causes depletion of peripheral B-cells which play a role in the pathogenesis of rheumatoid arthritis. Recovery of B-cells appears to occur 6 months after treatment, with some patients showing prolonged B-cell depletion persisting up to 2 years after treatment (Emery et al., 2004).

Rituximab in combination with methotrexate is licensed for the treatment of severe active rheumatoid arthritis in patients who have had an inadequate response or intolerance to other DMARDs including one or more anti-TNF agent. Rituximab is also licensed for non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, both using a different dosing schedule to that of rheumatoid arthritis. A course of rituximab consists of two intravenous infusions administered as a day case in hospital: 1000-mg infusion followed by a second 1000-mg infusion 2 weeks later. The course may be repeated every 6 months depending on patient response. Disease response varies between patients in that some achieve disease remission after one course and do not require re-treatment, whilst others require further repeat infusions every 6–12 months.

Rituximab is generally well tolerated, and the most common adverse effects are infusion-related reactions including fever, changes in blood pressure and rash. Minor infusion-related side effects can be managed by reducing the rate of infusion and giving treatment for relief of symptoms such as paracetamol. The incidence of adverse effects is minimised by pre-medicating with methylprednisolone, paracetamol and an anti-histamine 1 h prior to the infusion. Hypersensitivity reactions and anaphylaxis are rare but serious side effects.

As with the anti-TNF agents, rituximab increases the risk of infections and should not be used in the presence of active or severe infections. Use has been associated with progressive multifocal leukoencephalopathy. It may also exacerbate

existing cardiac conditions such as angina pectoris and atrial fibrillation. Patients with a known history of cardiac disease should be closely monitored during treatment administration for changes in blood pressure and pulse. Anti-hypertensives may be omitted 12 h prior to the infusion. HACAs have been reported in some patients after the first course of rituximab. The presence of HACAs may be associated with worsening of infusion or allergic reactions, and possibly failure to deplete B-cells on further treatment.

In practice, rituximab is used in line with its product license, i.e. after failure of, or intolerance to, DMARD therapy including at least one anti-TNF agent. Patients may continue on rituximab therapy with infusions no more frequent than every 6 months, provided they demonstrate an adequate response of a DAS28 improvement of 1.2 points or more (NICE, 2010b).

Abatacept

Abatacept acts by blocking the full activation of T-cells thereby inhibiting the release of inflammatory cytokines. It is licensed for use in combination with methotrexate in the treatment of moderate to severe active rheumatoid arthritis in adults who have had an insufficient response or intolerance to other DMARDs including at least one anti-TNF agent and who cannot receive rituximab because they have a contraindication to rituximab, or when rituximab is withdrawn due to an adverse event (NICE, 2010a).

Anakinra

Anakinra blocks the binding of interleukin-1 to its receptor, thus inhibiting the inflammatory effects of interleukin-1. The evidence of its benefit in rheumatoid arthritis is weak and it is considered modestly effective. There are no trials directly comparing anakinra with other biologic agents; adjusted indirect comparisons suggest that anakinra may be significantly less effective at relieving the clinical signs and symptoms of rheumatoid arthritis than anti-TNF agents in combination with methotrexate. Anakinra is not cost effective in the treatment of rheumatoid arthritis and availability for routine use in the NHS has not been supported (NCCCC, 2009).

Tocilizumab

Tocilizumab acts by binding to interleukin-6 receptors. Interleukin-6 is a pro-inflammatory cytokine produced by a variety of cells including T- and B-cells, and has been implicated in the pathogenesis of rheumatoid arthritis and other inflammatory diseases. Tocilizumab is licensed for use in combination with methotrexate in the treatment of moderate to severe active rheumatoid arthritis in adults who have had an insufficient response or intolerance to other DMARDs including at least one anti-TNF agent. It is given as a monthly intravenous infusion at a dose of 8 mg/kg and requires regular monitoring of liver function tests and full blood count.

Tocilizumab is recommended for the treatment of rheumatoid arthritis in patients who fulfil the following criteria (NICE, 2010c):

- The patient has not responded adequately to one or more anti-TNF agents

and

- The patient cannot receive rituximab due to a contraindication or
- The patient cannot receive rituximab as they have experienced an adverse effect to treatment or
- The patient has not responded adequately to rituximab treatment.

Which biologic?

More biological therapies for the treatment of rheumatoid arthritis, with new mechanisms of action and targets in the inflammatory pathway, are expected to become available in the near future. Cost is a major factor in the use of biologics with many costing in the region of £10,000 per patient per annum. The decision as to which agent to use is further confounded by the absence of clinical trials that directly compare efficacy between the different biologics.

At present, anti-TNF agents remain the first-line biological therapy. Following failure or intolerance to one anti-TNF agent, patients should then be treated with rituximab. However, if patients cannot receive rituximab due to a contraindication, adverse effect, or intolerance to methotrexate, there remains a number of treatment options (see Fig. 53.4).

Rheumatoid arthritis and pregnancy

The management of rheumatoid arthritis during pregnancy is a common challenge, with disease activity improving in approximately 70–80% of patients. Disease activity usually decreases in the first trimester, and this lasts for a number of weeks to months into the postpartum period. Subsequently, 90% of patients will then experience a flare usually during the first 3 months.

Although case control studies of pregnancy outcome demonstrate a slight increase in spontaneous abortion in women with rheumatoid arthritis, most reports have failed to show an increase in fetal morbidity. Medication may potentially increase this risk, for example, steroids may restrict intrauterine growth. Women with active rheumatoid arthritis or other types of inflammatory arthritis may have children with lower birth weights.

None of the available drug treatments for rheumatoid arthritis are absolutely safe in pregnancy. A prescriber must carefully assess the risks and benefits of treatment in consultation with the patient. In patients with active rheumatoid arthritis during pregnancy, prednisolone is recommended at the lowest dose (below 20 mg daily if possible) to control the disease. Sulphasalazine and hydroxychloroquine are considered safe to prescribe by most obstetric physicians. Many of the DMARDs are contraindicated in pregnancy as they are known teratogens, and some require a washout period before conception, such as leflunomide.

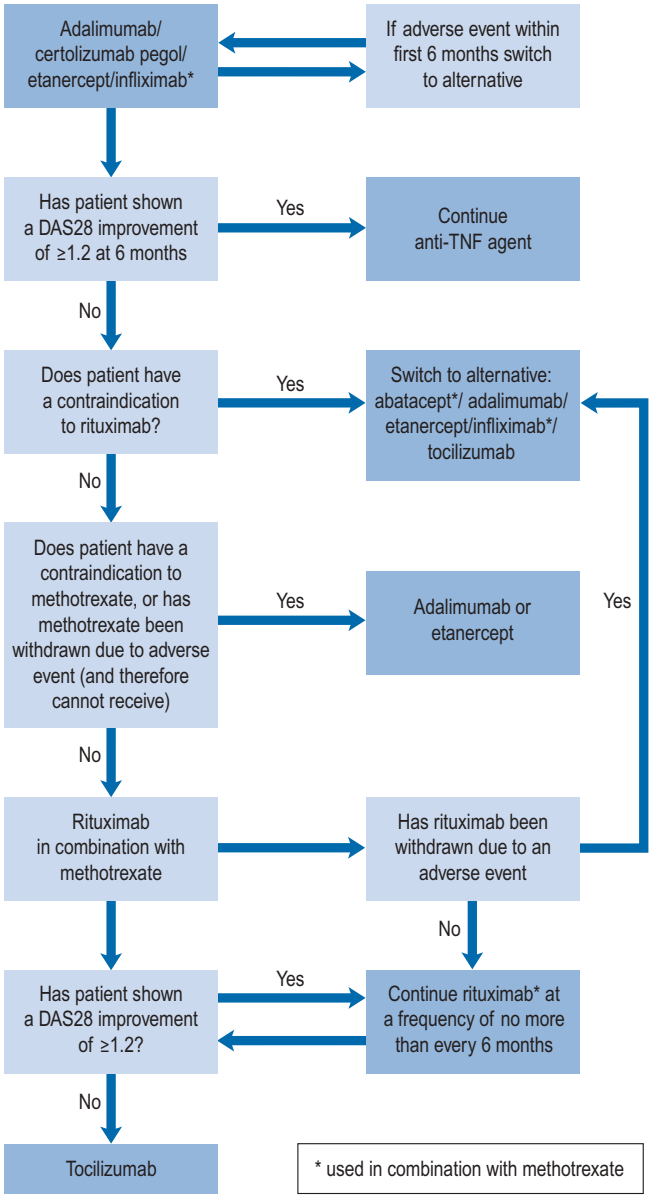


Fig. 53.4 Algorithm following introduction of an anti-TNF agent in the management of rheumatoid arthritis.

Patient care

Patient education and counselling are vital aspects in the management of rheumatoid arthritis. Patients should be encouraged to engage actively in their pharmacological and non-pharmacological treatment, and take responsibility for ensuring their medication regimen is safe and effective. Medicine information sheets are available from the Arthritis Research UK with further information available on their website (http://www.arthritisresearchuk.org/). Monitoring of the potentially toxic DMARDs is essential as non-adherence with the monitoring schedule may have serious consequences. Patients should be reminded of the warning symptoms that must trigger them to contact a healthcare professional. They should also be counselled to inform healthcare professionals of all the medication they are taking before starting a new medicine, and this includes use of over-the-counter products such as ibuprofen or aspirin.

Shared care agreements between secondary and primary care are often employed for DMARD therapy. This involves a primary care clinician continuing to prescribe and monitor drug treatment which has been initiated by a hospital specialist. Clear guidelines stating responsibilities of both parties, and the action required in the event of toxicity is defined within the document. The main advantage of shared care is that the patient will not be required to attend regular hospital appointments for blood tests and will be managed in primary care.

Some of the common therapeutic problems that are encountered in the management of rheumatoid arthritis are outlined in Table 53.4.

Osteoarthritis

Osteoarthritis is a chronic disease and the most common of all rheumatological disorders. It particularly affects individuals over the age of 65 years and is the major cause of hip and knee replacements in developed countries.

Osteoarthritis was previously thought to be the consequence of ageing, thereby leading to the term degenerative joint disease. However, it is now thought to be the result of a complex interplay of multiple factors including joint integrity, genetic predisposition, local inflammation, mechanical forces and cellular and biochemical processes.

Epidemiology

The prevalence of osteoarthritis increases with age. Generally, osteoarthritis is uncommon under the age of 35 years with 0.1% of people affected between the ages of 25–34 years, but 80% of people affected above the age of 55 years. It occurs in all populations irrespective of race, climate or geographical location. Obesity is the strongest modifiable risk factor and has been shown to particularly affect the knees. Trauma or injury due to diseases, such as rheumatoid arthritis, will predispose a joint to developing osteoarthritis.

A strong genetic component is thought to be present, particularly in women with hand involvement. An inherited defect in type II collagen genes is linked to the development of early-onset polyarticular osteoarthritis.

Aetiology

Osteoarthritis is a complex disease involving bone, cartilage and the synovium. It is generally believed to be an imbalance in erosive and reparative processes. There are a wide variety of factors predisposing an individual to this condition including the following:

- Increasing age
- Gender
- Genetic predisposition
- Congenital abnormality such as Perthes disease of the hip

Table 53.4 Examples of therapeutic problems encountered in the management of rheumatoid arthritis

Problem	Solution
NSAID not providing adequate symptom control	Consider alternative NSAID Review DMARD dose If patient has been on DMARD for a sufficient time period but with no improvement, consider alternative disease-modifying agent, i.e. another DMARD or a biologic agent Consider short-term systemic steroids for rapid relief of symptoms
Patient non-adherent with DMARD monitoring regimen	Education and counselling If patient still unwilling to comply, the safest option would be to consider swapping to DMARDs that require less stringent blood monitoring, for example hydroxychloroquine or sulphasalazine However, relative drug efficacy must also be considered
Nausea and vomiting with methotrexate	Ensure patient is taking folic acid Add anti-emetic therapy Change to parenteral methotrexate
Disease flares when trying to withdraw systemic steroids	Use a slower withdrawal regimen, for example decrease by 1 mg each month If patient cannot be withdrawn completely from steroids, consider reducing to lowest dose possible as maintenance treatment
Side effects of long-term steroids	Aim to use steroids for short-term treatment only Ensure concomitant treatment of PPI, bisphosphonate and calcium and vitamin D preparations are prescribed where appropriate
Patient cannot tolerate stinging at injection site associated with adalimumab or etanercept administration	Consider switching to infliximab

- Obesity
- Previous injury either due to sport or occupation
- Previous disease such as rheumatoid arthritis or gout
- Systemic disorders such as acromegaly
- Neuropathic joint disease such as a Charcot joint

Pathogenesis

The pathogenesis of osteoarthritis has been classified into four stages:

1. Initial repair
2. Early-stage osteoarthritis
3. Intermediate-stage osteoarthritis
4. Late-stage osteoarthritis

Initial repair is characterised by proliferation of chondrocytes synthesising the extracellular matrix of bone. Early-stage osteoarthritis results in degradation of the extracellular matrix as protease enzyme activity exceeds chondrocyte activity. There is net degradation and loss of articular cartilage. Intermediate osteoarthritis is associated with a failure of extracellular matrix synthesis and increased protease activity, further increasing cartilage loss. Finally, late-stage osteoarthritis may result in complete loss of cartilage with joint space narrowing in the most severe of cases. Bone outgrowths (osteophytes) appear at the joint margins, and there is sclerosis of the adjacent bone. Deformity is common at this stage.

Clinical manifestations

Osteoarthritis is traditionally classified by aetiology into idiopathic and secondary forms. Idiopathic can be further divided into localised and generalised depending on the number of joints involved. Localised osteoarthritis most commonly affects the hands, feet, hip, knees and spine, and less commonly the shoulder, temporomandibular, sacroiliac and wrist joints. Pain is increased by movement and loading on the joint, and may radiate beyond the joint itself, as in leg pain associated with spinal disease, and knee pain radiating from the hip. Stiffness in the early morning lasts for less than 30 min, unlike that due to rheumatoid arthritis; it may also occur after periods of rest and throughout the day.

In the hands, the most commonly affected joints are the distal interphalangeal joints or Heberden's nodes, the proximal interphalangeal joints (Bouchard's nodes) and the base of the thumb, the first carpometacarpal joint. Hip pain is particularly felt in the groin. Unlike rheumatoid arthritis, there is no extra-articular disease.

Investigations

Osteoarthritis is primarily diagnosed by its clinical presentation. Confirmation and progression can be achieved by radiography with the presence of joint space narrowing, bone

sclerosis, cysts and deformity. There is a lack of conformity between symptoms and radiological findings. On arthroscopy normal cartilage is smooth, white and glistening, while osteoarthritic cartilage is yellowed, irregular and ulcerated. Synovial fluid analysis should be carried out if one suspects infection or crystal arthropathy such as gout or pseudogout. Blood tests usually reveal a normal ESR and CRP.

Treatment

The aims of treatment are pain relief, optimisation of function and minimisation of disease progression. There are three core interventions which should be considered for every person with osteoarthritis where possible:

- Education, advice and access to information
- Strengthening exercises to improve muscle strength and aerobic fitness training
- Weight loss if overweight or obese

Guidelines are available for the management of osteoarthritis (NCCCC, 2008). If the three core interventions are not sufficient, paracetamol and topical NSAIDs can be added in to the treatment regimen. Paracetamol and topical NSAIDs are deemed 'relatively safe pharmaceutical options' compared to other available agents such as oral NSAIDs, opioids and intra-articular steroids. Other interventions which may also be considered include joint arthroplasty, transcutaneous electrical nerve stimulation (TENS), supports and braces, or manual therapy involving manipulation and stretching.

Paracetamol is the first-line drug treatment and should be used alongside core treatment. Regular dosing may be required as 'when required' administration may lead to reduced efficacy.

Topical NSAIDs, capsaicin and rubefacients are widely used for local relief of pain and inflammation. Topical treatments are perceived as self-management, and this has a positive effect on a patient's perception of their disease.

Due to the recent safety concerns with non-selective NSAIDs and COX-2 inhibitors, treatment regimens have moved towards opioids for uncontrolled pain. This should be balanced against adverse effects such as constipation and drowsiness, particularly in the elderly population.

There is a large amount of evidence supporting the efficacy of NSAIDs in reducing pain and stiffness in osteoarthritis. However, there is no strong evidence to suggest a consistent benefit over paracetamol. Non-selective NSAIDs or COX-2 inhibitors may be considered in patients where paracetamol and/or topical NSAIDs do not provide adequate pain relief, based on careful consideration of the patient's risk factors, as discussed earlier in the chapter. This does not include etoricoxib which is associated with a greater risk of causing fluid retention and aggravating hypertension. NSAIDs should be used at the lowest dose for the shortest period of time possible, and patients should also be prescribed a PPI.

Intra-articular steroids may be of benefit in reducing pain and inflammation in joints. Evidence suggests that they provide short-term reduction in pain, although improvement in function is less clear. They should be considered as an adjunct to core treatment for the relief of moderate to severe pain in osteoarthritis.

Hyaluronan is an endogenous molecule found in the synovial fluid. Its key functions are to increase viscosity of synovial fluid and lubrication within the joint. Synthetic intra-articular injections of hyaluronan are thought to provide pain relief and improve joint function, although there is limited evidence to support this. The synthetic hyaluronans are expensive and not currently recommended.

Nutraceuticals is a term which describes food supplements believed to have health benefits. The most widely used of these agents in osteoarthritis are glucosamine and chondroitin. They are available in a multitude of preparations, combinations, strengths and purities and can be purchased over the counter and via the internet. There is, however, little available evidence of efficacy to support their use.

Case studies

Case study 53.1

Mrs JS is a 46-year-old woman who has been referred by her primary care doctor to the rheumatology outpatient clinic in the local hospital. Her presenting complaint is a symmetrical pattern of inflammation in the joints of her hands, knees and shoulders, and severe pain and stiffness which are worse in the morning. She is a gardener and is finding it increasingly difficult to continue her job due to limited joint function. Her investigations and X-rays confirm a diagnosis of severe seropositive rheumatoid arthritis, including a high CRP and ESR. She takes citalopram for depression and has no other remarkable medical or drug history.

Questions

1. What treatment should be introduced for Mrs JS?
2. What key counselling points should be covered regarding her DMARD therapy?

Answers

1. DMARD treatment should be initiated immediately for Mrs JS as she has seropositive disease which is associated with a poorer outcome. She has no other co-morbidities which contraindicate her to any of the DMARDs. Combination treatment should be started with methotrexate and sulphasalazine as she has severe active disease. Folic acid should be also prescribed at 5 mg weekly. Some clinicians may opt for triple combination therapy of methotrexate, sulphasalazine and hydroxychloroquine.

   Her disease activity is impacting on her life and so rapid relief of symptoms is necessary. Methotrexate and sulphasalazine will take between 6 and 12 weeks to take effect. Multiple joints have been affected, and therefore local steroid injections are inappropriate. Oral prednisolone 30 mg daily should be started, with the aim to withdraw steroids after about 3 months.

   Prednisolone will usually alleviate pain and inflammation effectively and so a NSAID should not be required. However, if additional short-term relief is necessary, an as-required regimen with an NSAID, such as ibuprofen 400 mg three times a day or

naproxen 500 mg twice a day, may be offered. A PPI should be co-prescribed, for example omeprazole 20 mg daily. Paracetamol may also be taken, and may be substituted for co-codamol if the pain is severe and uncontrolled.

Other non-pharmacological measures should be considered, such as physiotherapy. Counselling and psychological support may be particularly important for Mrs JS. Most patients find it useful to have one key healthcare professional to refer to for advice and if they have any problems – this role is usually managed by a specialist nurse.

Mrs JS is started on methotrexate 7.5 mg weekly and sulphasalazine 500 mg twice a day as her disease-modifying treatments.

2. Mrs JS should be counselled on the following:
   - Her dose of methotrexate is 3 × 2.5 mg tablets and this should be taken as a single dose on the same day each week. This dose will be increased over the next few weeks.
   - Folic acid is given to minimise adverse effects of methotrexate, and should be taken weekly, but not on the same day as methotrexate.
   - Both DMARDs will take several weeks to take full effect.
   - She will need regular blood monitoring and she should be counselled about possible adverse effects on the liver and bone marrow.
   - Warning symptoms to report to a healthcare professional include any sign of infection, unexplained bleeding, bruising, purpura, sore throat, fever, malaise, dyspnoea, persistent dry cough, mouth ulcers, nausea or vomiting.
   - A methotrexate-monitoring booklet should be given to Mrs JS and she should be advised that it must be shown to any healthcare professional before receiving any additional medication or treatment.

Case study 53.2

Mr TP is a 58-year-old man who has been on methotrexate 20 mg weekly for the last 2 years for rheumatoid arthritis. He has found that his symptoms are worsening, and he has been taking more regular NSAIDs and analgesia in the last month for pain relief. He has tried sulphasalazine and leflunomide in the past, but was unable to continue therapy due to gastro-intestinal side effects.

Questions

1. How would you manage Mr TP's worsening disease activity?
2. After discussion with Mr TP and consideration of other co-morbidities, the treatment plan is to add in an anti-TNF agent. What additional information is required to ensure Mr TP meets eligibility criteria for treatment?
3. Mr TP admits that he is needle-phobic and does not like the idea of giving himself weekly or fortnightly injections. What treatment options are available to him?

Answers

1. Mr TP is on DMARD monotherapy, and so an additional agent may be beneficial. However, he has not tolerated sulphasalazine and leflunomide which are regarded as the more effective DMARDs, as well as methotrexate. Hydroxychloroquine could be added in alongside methotrexate, but this is unlikely to provide adequate disease modification.

   Another treatment option would be to introduce one of the biological agents. The anti-TNF agents are licensed to be used after failure of DMARDs, and would be the next logical step in Mr TP's treatment regimen.
2. Patients should demonstrate severe active disease, measured by two DAS28 assessments greater than 5.1, one month apart. A tender joint count and a swollen joint count should be carried out, ESR should be measured, and Mr TP's perception of his disease severity should be scored on a scale from 0 to 100 on a visual analogue scale. These parameters can then be used to calculate a DAS28 using an online calculator.
3. Adalimumab and etanercept are subcutaneous injections which are usually self-administered by patients. In some cases, a district nurse may be organised to administer the injection at the patient's home. For Mr TP, the thought of having such frequent injections is not desirable, and this may affect adherence to the medication regimen.

   Infliximab is given as an intravenous infusion in hospital, and he would not have to administer the drug himself. It has a less frequent dosing compared to the other anti-TNF agents, and it should be discussed with Mr TP whether he is happy to have an infusion every 8 weeks.

Case study 53.3

Mr AR is a 68-year-old man who has stable rheumatoid arthritis which is well controlled on his current drug regimen:

Sulphasalazine 1 g twice a day
Hydroxychloroquine 200 mg twice a day
Co-codamol 30/500 2 four times a day as required
Diclofenac 50 mg three times a day
Ramipril 5 mg once a day
Aspirin 75 mg once a day
Atorvastatin 40 mg once a day at night
Atenolol 50 mg once a day
He also has a history of myocardial infarction.

Question

Comment on his drug regimen.

Answer

High-dose diclofenac (150 mg/day) has been associated with an increased cardiovascular risk, and Mr AR has a history of myocardial infarction. As a consequence, his diclofenac should be stopped. In addition, Mr AR is on aspirin 75 mg daily, and so is as at a higher risk of gastro-intestinal adverse events if he is also taking an NSAID. In general, patients should not take NSAIDs concomitantly with low-dose aspirin unless absolutely necessary.

The reason for regular NSAID use should be investigated. The effectiveness of his DMARD regimen should also be considered, as his disease progression may be causing additional pain and inflammation of the joints. The next step in his disease-modifying treatment would be to consider a third DMARD, such as methotrexate. He may also be a candidate for anti-TNF therapy.

Alternative symptomatic relief that could be offered would be local steroid injections or modifications to his simple analgesia regimen, such as regular paracetamol with codeine as required. Some prescribers may consider using low-dose ibuprofen 400 mg three times a day on an as required basis, although the risk versus benefit regarding gastro-intestinal adverse effects should be considered.

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Useful websites

American College of Rheumatology.
http://www.rheumatology.org.

Arthritis Research UK.
http://www.arthritisresearchuk.org/.

British Society of Rheumatology.
http://www.rheumatology.org.uk/.

54 Gout and hyperuricaemia

T. Hawkins and A. Cunnington

Key points

- Gout is the most common inflammatory joint disease in men and is strongly age related.
- The prevalence of gout has increased over recent decades.
- It is caused by the deposition of monosodium urate crystals within articular and periarticular tissue.
- The degree of elevation of uric acid levels above the saturation point for urate crystal formation is a major determinant in precipitating an attack.
- Not all people with hyperuricaemia develop gout.
- Gout is normally the result of an interaction between genetic, constitutional and environmental risk factors.
- The aim of long-term therapy is to reduce the serum uric acid level sufficiently so that crystals can no longer form and existing crystals are dissolved.
- Non-pharmacological measures such as lifestyle and dietary modification play an important role in the management of gout.
- Unmanaged recurrent attacks can result in progressive cartilage and bone erosion, deposition of tophi, secondary osteoarthritis and disability.

Introduction

Gout is the most common inflammatory joint disease in men and the most common inflammatory arthritis in older women. It is caused by deposition of monosodium urate crystals in joints and soft tissues following chronic hyperuricaemia. Chronic hyperuricaemia is associated with disorders of purine metabolism due to under excretion or over production of uric acid, the final metabolite of endogenous and dietary purine metabolism. Gout usually presents as a monoarthritis in the first metatarsophalangeal joint (big toe) of the foot and is often referred to as podagra (from the Greek 'seizing the foot'). Subsequent attacks may be polyarticular. Other commonly affected joints include the mid-foot, ankle, knee, wrist and finger joints. Although the attack is extremely painful, it is usually self-limiting resolving spontaneously in 1–2 weeks. Acute attacks are managed with rest, ice and one of the following pharmacological agents: NSAIDs, colchicine or corticosteroids. Some patients may only ever experience one attack, but often a second attack occurs within 6–12 months, with increased risk of subsequent attacks. Patients with recurrent attacks require long-term prophylaxis with drugs that lower the serum urate level. The drug of choice is usually allopurinol, however, a small percentage of patients are unable to tolerate allopurinol and require treatment with an alternative urate-lowering agent such as febuxostat or a uricosuric agent such as benzbromarone, sulphinpyrazone or probenecid. It is essential that pharmacological measures are combined with non-pharmacological measures such as dietary and lifestyle modification to prevent recurrent attacks. Inappropriate management of gout can result in chronic tophaceous gout with polyarticular, destructive low-grade joint inflammation, joint deformity and tophi.

Epidemiology

Gout is one of the oldest recognised diseases and was identified by the Egyptians in 2460 BC. Hippocrates described it as 'arthritis of the rich' due to the association with certain foods and alcohol. Gout affects 1–2% of adults in developed countries, and in recent decades there has been a significant rise in its prevalence and incidence (Zhang et al., 2006). The USA has seen a doubling in the number of cases with the rate of gout increasing to 4.1% in older males. However, unlike the rest of the world, prevalence in the UK appears not to be rising and from 2000 to 2005 remained at 1.4% (Rider and Jordan, 2010). The increasing numbers in many developed countries have been attributed to trends in lifestyle leading to increased risk of gout, for example, obesity, metabolic syndrome, hypertension, alcohol consumption and increased age of the general population. Although the Maori population have a marked genetic predisposition to gout, prior to 1700 they did not experience this inflammatory joint disease. It was changes in diet and lifestyle following European settlement that led to the appearance and increasing prevalence in the country. New Zealand now has probably the highest prevalence in the World with one in eight men affected (Richette and Bardin, 2010). A similar pattern has also been seen in Eastern China, where gout was considered a very rare disease in the 1980s. Changes in diet and lifestyle due to Western influences have seen its prevalence rise to 1.1% in Eastern China in 2008.

In the UK, the presentation of gout in men before the age of 45 years is unusual, but in those over the age of 75 years prevalence is greater than 7% in men and 4% in women (Doherty, 2009; Jordan et al., 2007; Zhang et al., 2006).

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Gout is predominantly a disease of men with a male to female ratio of 3.6:1. In women, it tends to develop after menopause when levels of oestrogen, a known uricosuric, fall.

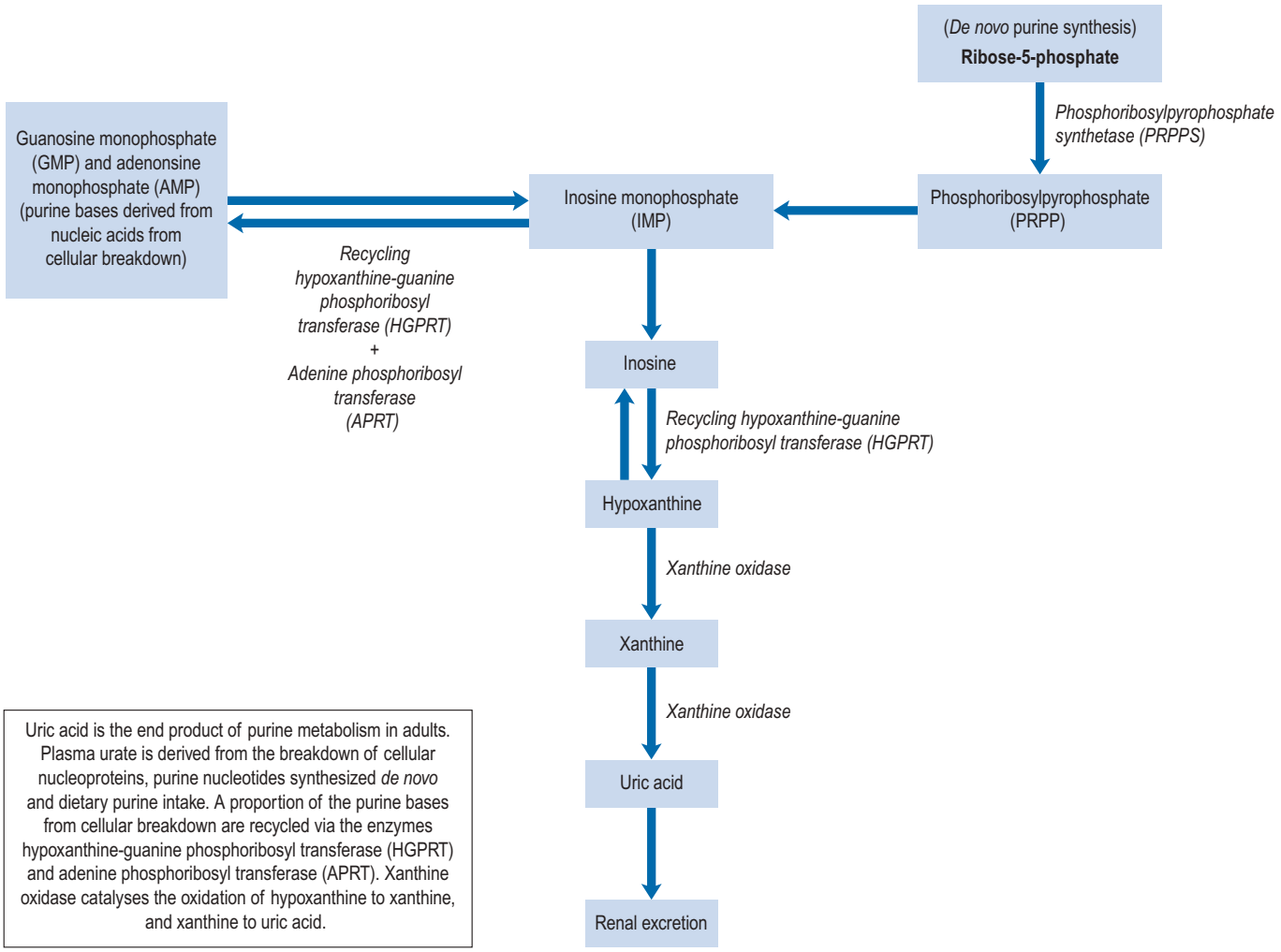
Although environmental factors are clearly implicated in the development of gout, studies have shown that inheritance also plays an important role. In recent years, research into the genetic background of gout has identified several renal urate transporters including URAT-1 and GLUT-9 and the genes that encode them, for example, *SLC22A12* and *SLC2A9*, respectively. Polymorphisms in these genes are associated with increased hyperuricaemia and gout (Dalbeth and Merriman, 2009; Doherty, 2009).

Pathophysiology

Uric acid is mainly a by-product from the breakdown of cellular nucleoproteins and purine nucleotides synthesised *de novo* with about a third coming from the breakdown of dietary purine intake (Fig. 54.1). Uric acid is a weak acid with a pK_a of 5.75, and at the physiological pH of the extra-cellular compartment 98% of uric acid is in the ionised form of urate. This is mainly present as monosodium urate due to the high concentration of sodium in the extra-cellular compartment. Human beings and higher primates lack the enzyme uricase that degrades uric acid to the highly soluble allantoin resulting in higher concentrations of urate close to the level of solubility. Monosodium urate has a solubility limit of 380 µmol/L; when the concentration exceeds 380 µmol/L, there is a risk of precipitation and the formation of monosodium urate crystals.

The production of urate is dependent upon the balance between purine ingestion, *de novo* synthesis in the cells and the actions of xanthine oxidase at the distal end of the purine pathway. Xanthine oxidase is the enzyme that catalyses the oxidation of hypoxanthine, the breakdown product from the catabolism of cellular nucleoproteins and purine nucleotides, to xanthine and xanthine to uric acid.

Gout can be classified as primary or secondary, depending on the presence or absence of an identified cause of hyperuricaemia.



Uric acid is the end product of purine metabolism in adults. Plasma urate is derived from the breakdown of cellular nucleoproteins, purine nucleotides synthesized *de novo* and dietary purine intake. A proportion of the purine bases from cellular breakdown are recycled via the enzymes hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and adenine phosphoribosyl transferase (APRT). Xanthine oxidase catalyses the oxidation of hypoxanthine to xanthine, and xanthine to uric acid.

Fig. 54.1 Purine pathway.

Primary gout is not a consequence of an acquired disorder, but is associated with rare inborn errors of metabolism and isolated renal tubular defects in the fractional clearance of uric acid. A rare group of enzyme defects result in an increased *de novo* purine synthesis such as hypoxanthine-guanine phosphoribosyl transferase deficiency (Lesch-Nyhan syndrome), phosphoribosyl pyrophosphate synthetase super activity, glucose-6 phosphatase deficiency and myogenic hyperuricaemia (Table 54.1).

Secondary gout is the consequence of the use of specific drugs or develops as a consequence of other disorders. Certain diseases are associated with enhanced nucleic acid turnover, for example, myeloproliferative and lymphoproliferative disorders, psoriasis and haemolytic anaemia, and can lead to hyperuricaemia. Renal mechanisms are responsible for the majority of hyperuricaemia in individuals with over production representing less than 10% of patients with gout. The kidney excretes about two-thirds of the uric acid produced daily with the remainder being eliminated via the biliary tract with subsequent conversion to soluble allantoin by colonic bacterial uricase. Approximately 90% of the daily load of urate filtered by the kidneys is re-absorbed. This re-absorption process is mediated by specific anion transporters such as URAT-1 which is located on the apical side of the renal proximal tubular cells and is an important determinant of urate re-absorption (Richette and Bardin, 2010). The URAT-1 transporter is targeted by a number of drugs including benzbromarone, probenecid, losartan and sulphinpyrazone.

Table 54.1 Causes of primary and secondary gout

Primary gout	Secondary gout
Idiopathic	**Increased uric acid production**
Rare enzyme deficiencies	Lymphoproliferative/ Myeloproliferative
Hypoxanthine-guanine phosphoribosyl transferase deficiency (HPRT)	Chronic haemolytic anaemias
Phosphoribosyl pyrophosphate synthetase super-activity	Secondary polycythemia
Ribose-5-phosphate	Severe exfoliative psoriasis
AMP-deaminase deficiency	Gaucher's disease
	Cytotoxic drugs
	Glucose-6 phosphate deficiency
	High purine diet overproduction
	Reduced uric acid secretion
	Renal failure
	Hypertension
	Drugs (diuretics, aspirin, ciclosporin)
	Lead nephropathy
	Alcohol
	Down's Syndrome
	Myxoedema
	Beryllium poisoning

Risk factors

Hyperuricaemia is one of the main risk factors for gout and occurs in about 15–20% of the population (Doherty, 2009). Fortunately, only a minority of individuals with increased serum uric acid levels develop gout suggesting the importance of other contributing factors (Box 54.1).

Genetics

Common primary gout in men often shows a strong familial predisposition, although the genetic basis for this is not fully understood. A polymorphism of the *SLC22A12* gene which encodes for URAT-1 has been associated with under excretion of uric acid and hyperuricaemia in German Caucasians (Graessler et al., 2006). While in a Japanese cohort, another mutation of the *SLC22A12* gene has been shown to be protective for the development of gout (Taniguchi et al., 2005).

The recently identified glucose and fructose transporter (GLU9) also acts as a high-capacity urate transporter in the proximal renal tubules (Dalbeth and Merriman, 2009). Polymorphism in the gene which encodes for this transporter (SLC2A9) has been reported to influence serum uric acid levels, and a significant association with self-reported gout has been described (Dalbeth and Merriman, 2009).

Renal disease

Gout is frequently associated with kidney disease, each being a risk factor for the other. Hyperuricaemia is associated with primary kidney disease, but kidney damage may arise secondary to gout as a consequence of the deposition of urate crystals in the interstitium and tubules of the kidney. Historically, gout was associated with significant renal impairment; however, progressive renal failure directly due to gout is now rare and mainly limited to inadequately treated patients with primary purine overproduction associated with purine enzyme defects, rare forms of inherited renal disease, chronic lead intoxication and renal disease as a consequence of uncontrolled disease states associated with gout e.g. hypertension, type 2 diabetes and congestive cardiac failure. Men with gout have a two-fold higher risk of kidney stones than patients without gout (Jordan et al., 2007). The likelihood of stones increases with serum urate concentration, extent of urinary acid secretion and low urine pH.

Box 54.1 Risk factors for gout

- Genetics
- Renal disease
- Co-morbidities, for example, obesity, dyslipidaemia, glucose intolerance, hypertension
- Diet
- Alcohol consumption
- Medication

Co-morbidities

Metabolic syndrome is a multiplex risk factor for atherosclerotic cardiovascular disease that consists of atherogenic dyslipidaemia, raised blood pressure, increased blood glucose, and both prothrombotic and pro-inflammatory states. In the USA, metabolic syndrome is present in 63% of those with gout compared to 25% of those without gout (Choi et al., 2007). Other studies have shown obesity, weight gain and hypertension all to be independent risk factors for the development of gout (Choi et al., 2005).

Diet

Gout has often been associated with a rich lifestyle and excesses in diet. In particular, gout is higher in people who consume large quantities of red meat. There is also an increased risk associated with seafood consumption, but to a lesser extent than with red meat. In contrast, a diet high in purine-rich vegetables does not increase the risk, and the consumption of low-fat dairy products reduces the relative risk of gout with each additional dairy serving. The consumption of soft drinks sweetened with sugar (not diet drinks) has also been linked to an increase in the number of gout cases particularly in USA (Choi and Curham, 2008). The mechanism of action is thought to be an increase in uric acid levels caused by an increase in adenine nucleotide degradation. Vitamin C (ascorbic acid) has been shown to have a modest uricosuric effect (Huang et al., 2005). The consumption of cherries, but no other fruits, has also been shown to decrease uric acid levels.

Alcohol

Increased daily consumption of alcohol is associated with a higher risk of gout. Beer carries the greatest risk, probably due to its high purine content, followed by spirits. However, a moderate consumption of wine is not associated with an increased risk of developing gout (Jordan et al., 2007). The mechanism of action involved is thought to be the metabolism of ethanol to acetyl coenzyme A leading to adenine nucleotide degradation, with resultant increased formation of adenosine monophosphate, a precursor of uric acid. Alcohol also raises lactic acid levels in blood, which inhibits uric acid excretion.

Medication

A number of drugs are associated with increased uric acid levels (Box 54.2). The use of both loop and thiazide diuretics is the most common modifiable risk factor for secondary gout, especially in the elderly. It is thought loop and thiazide diuretics may precipitate an attack via volume depletion and reduced renal tubular secretion of uric acid. Aspirin has a bimodal effect; low doses inhibit uric acid excretion and increase urate levels, while doses greater than 3 g/day are uricosuric.

The prescribing of ciclosporin in organ transplant patients is an independent risk factor for new-onset gout in this group. The proposed mechanism of action is the interaction of ciclosporin with the hOAT10 transporter that mediates urate/glutathione exchange in the kidney (Bahn et al., 2008). Radiotherapy and chemotherapy in patients with neoplastic disorders can cause hyperuricaemia because of increased cell breakdown; to overcome this, prophylactic treatment may be given with allopurinol, commencing 3 days before therapy.

Box 54.2 Examples of drugs known to raise serum urate levels

- Alcohol
- Aspirin
- Ciclosporin
- Cytotoxic chemotherapy
- Diuretics (both loops and thiazides)
- Ethambutol
- Levodopa
- Pyrazinamide
- Ribavarin and interferon
- Teriparatide

Presentation and diagnosis

An acute attack of gout has a rapid onset, with pain being maximal at 6–24 h of onset and spontaneously resolving within several days or weeks. The first attack usually affects a single joint in the lower limbs in 85–90% of cases, most commonly the first metatarsophalangeal joint (big toe). The next most frequent joints to be affected are the mid-tarsi, ankles, knees and arms. The affected joint is hot, red and swollen with shiny overlying skin. Even the touch of a sheet on the affected joint is too painful for the patient to bear. The patient may also have a fever, leucocytosis, raised erythrocyte sedimentation rate (ESR), and the attack may also be preceded by prodromal symptoms such as anorexia, nausea or change in mood. Following resolution of the attack, there may be pruritis and desquamation of the overlying skin on the affected joint.

Monosodium urate crystals preferentially form in cartilage and fibrous tissues where they are protected from contact with inflammatory mediators. The deposition of crystals may continue for months or years without causing symptoms; it is only when the crystals are shed into the joint space or bursa that inflammatory reaction occurs precipitating an acute attack of gout. The shedding of crystals can be triggered by a number of factors including direct trauma, dehydration, acidosis or rapid weight loss. The acute phase response associated with intercurrent illness or surgery may also precipitate an attack; during this phase, there is increased urinary urate excretion with a lowering of serum uric acid which leads to partial dissolution of monosodium urate crystals and subsequent shedding of crystals into the joint space.

The shed crystals are phagocytosed by monocytes and macrophages, activating the NACHT–LRR–PYD-containing protein-3 (NALP3) inflammasome and triggering the release of interleukin-1β (IL-1β) and other cytokines, a subsequent infiltration of neutrophils and the symptoms of an acute attack (Dalbeth and Haskard, 2005). The NALP3 inflammasome (cryopyrin) is a complex of intracellular proteins that is

activated on exposure to microbial elements, such as bacterial RNA and toxins. Activation of NALP3 leads to the release of caspase-1, which is required for cleavage of pro-IL-1β to active IL-1β (Richette and Bardin, 2009). IL-1β has been shown to be critically associated with the inflammatory response induced by monosodium urate crystals (Rider and Jordan, 2010).

A third of patients will have normal uric acid concentrations during an acute attack of gout due to increased urinary urate excretion. The most appropriate time to measure serum urate for monitoring purposes is when the attack has completely resolved. The gold standard for the diagnosis of gout is the demonstration of urate crystals in synovial fluid or in a tophus by polarised light microscopy (Zhang et al., 2006). Crystals may be found in fluid aspirated from non-inflamed joints, even in those joints which have not previously experienced an attack. The crystals are large (10–20 μm) and needle shaped with a strong, intense, characteristic light pattern under polarised light. In contrast, the calcium pyrophosphate dehydrate crystals associated with pseudo-gout are small rhomboid crystals of low intensity. Gout and septic arthritis may co-exist and in order to exclude septic arthritis synovial fluid is sent for Gram staining and culture.

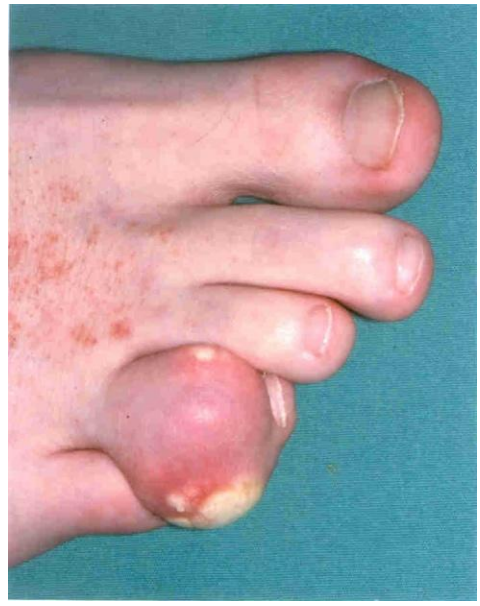


Fig. 54.3 Chronic tophaceous gout.

Course of disease

The course of gout follows a number of stages; initially, the patient may be asymptomatic with a raised serum uric acid level (Fig. 54.2). Some patients may only ever experience one attack, but often a second attack occurs within 6–12 months. Subsequent attacks tend to be of longer duration, affect more than one joint and may spread to the upper limbs. Untreated disease can result in chronic tophaceous gout, with persistent low-grade inflammation in a number of joints resulting in joint damage and deformity. The disease is characterised by the presence of tophi (Fig. 54.3), monosodium urate crystals surrounded by chronic mononuclear and giant-cell reactions. Tophi deposition can occur anywhere in the body, but they are commonly seen on the helix of the ear, within and around the toe or finger joints, on the elbow, around the knees or on the Achilles tendons. The skin overlying the tophi may ulcerate and extrude white, chalky material composed of monosodium urate crystals.

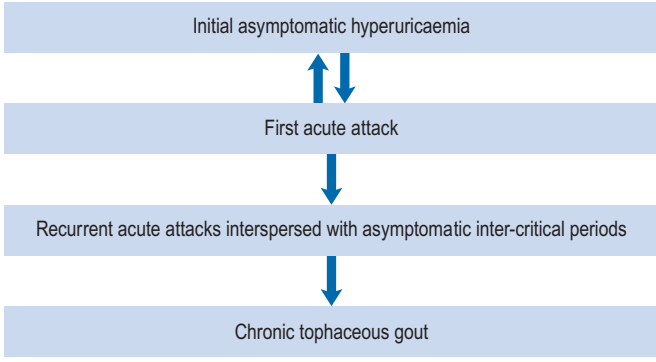


Fig. 54.2 Schematic representation of the stages of gout.

Treatment

The management of gout can be split into the rapid resolution of the initial acute attack and long-term measures to prevent future episodes (see Box 54.3).

Gout is often associated with other medical problems including obesity, hypertension, excessive alcohol and the metabolic syndrome of insulin resistance, hyperinsulinaemia, impaired glucose intolerance and hypertriglyceridaemia. This contributes to the increased cardiovascular risk and deterioration of renal function seen in patients with gout. Management is not only directed at alleviating acute attacks and preventing future attacks, but also identifying and treating other co-morbid conditions such as hypertension and hyperlipidaemia. Pharmacological measures should be combined with non-pharmacological measures such as weight loss, changes in diet, increased exercise and reduced alcohol consumption.

Management of an acute attack

Drugs used in the management of an acute attack include NSAIDs, colchicine and corticosteroids. NSAIDs are the recommended first-line agents, but in a number of patients their use is contraindicated and a second-line agent is indicated

Box 54.3 Treatment aims in gout

Rapid alleviation of the acute attack
Prevention of future attacks
Lower serum uric acid levels to below saturation point
Reduce risk of co-morbidities, for example, cardiovascular disease
Lifestyle modification

Box 54.4 Management of an acute attack of gout

Promptly and safely resolve pain
- First line: NSAID (use maximum dose)
- Second line: Colchicine
- Third line: Corticosteroid (consider first line in mono-articular disease)
- (±Simple and opiate analgesia if needed, for example, paracetamol, codeine dihydrocodeine)

Rest the joint 1–2 days and treat with ice

Remove contributing factors
- Review medication
- Review lifestyle

(Box 54.4). Where the pain is not adequately controlled by treatment, paracetamol and weak opiate analgesics, for example, codeine or dihydrocodeine may be added to the regimen to provide additional relief. Treatment should be continued until the attack is terminated, usually between 1 and 2 weeks. The affected joints should also be rested for 1–2 days and initially treated with ice which has a significant analgesic effect during an acute attack.

A complete medication review should be performed, and ideally medication which is likely to have contributed to the attack discontinued. Where loop and thiazide diuretics are being used for the management of hypertension alone, an alternative anti-hypertensive agent should be considered according to national guidance. Losartan, an angiotensin receptor blocker effective in hypertension, has been shown to have uricosuric properties and is a suitable agent in hypertensive patients with gout (Sica and Schoolwerth, 2002; Takahashi et al., 2003). In patients with heart failure, diuretics are often essential and cannot be discontinued. Certain NSAIDs may be preferable in patients on diuretics with both indometacin and azapropazone (no longer licensed in the UK) demonstrating an increase uric acid secretion. Moreover, the diuretic effect of furosemide appears unaffected by azapropazone and azapropazone's ability to promote uric acid secretion is sustained (Williamson et al., 1984).

Allopurinol should not be commenced during an acute attack as it may prolong or precipitate another attack. However, in patients already established on allopurinol therapy, allopurinol should always be continued during the attack. Aspirin at analgesic doses (600–2400 mg/day) should be avoided as it blocks urate secretion. The continuation or initiation of low-dose aspirin (75–150 mg/day) is recommended in patients with cardiac disease as the benefits outweigh the minimal effect on serum uric acid levels.

Non-steroidal anti-inflammatory drugs

Maximum doses of an NSAID should be commenced rapidly after the onset of an attack and then tapered 24 h after the complete resolution of symptoms. The usual treatment period is 1–2 weeks. NSAIDs act by direct inhibition of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) via blockade of the cyclo-oxgenase enzyme site. The subsequent inhibition of prostaglandin production reduces inflammation, but also results in additional activities on platelet aggregation, renal homeostasis and gastric mucosal integrity.

Although the NSAIDs differ in chemical structure, they all have similar pharmacological properties in terms of anti-inflammatory and analgesic action, and have similar drug interactions. For a number of years, indometacin was considered the NSAID of choice in gout largely because it was one of the first NSAIDs shown to be effective in the management of gout. However, it has not been shown to be of superior efficacy or safety when compared to other NSAIDs used in the management of acute gout (Jordan et al., 2007).

Azapropazone (1200–1800 mg/day) has been shown to have both anti-inflammatory and uricosuric effects during an acute attack. Unfortunately, use is associated with a higher risk of upper gastro-intestinal side effects when compared to other high-dose NSAIDs (diclofenac, ibuprofen, naproxen, indometacin and ketoprofen), and this significantly restricts its use.

Overall, there is no convincing evidence to promote the use of one NSAID over another in the management of acute gout.

In an effort to reduce the side effects of NSAIDs, and particularly the gastro-intestinal side effects, agents were developed to selectively block COX-2 and have minimal effect on COX-1. COX-2 selective agents are recommended for use in patients who are at high risk of developing gastro-intestinal side effects, but they are not recommended for routine use. It should be noted that the selective benefit of COX-2 inhibitors is lost in patients taking low dose aspirin. The selective COX-2 inhibitor etoricoxib in a daily dose of 120 mg has been shown to give comparable rapid relief of pain in acute gout to indometacin 50 mg three times daily but with fewer side effects (Schumacher et al., 2002). However, a systematic review and meta-analysis of studies involving etoricoxib have demonstrated an increased risk of cardiovascular thromboembolic events (Aldington et al., 2005). Although there are currently no data directly comparing the cardiovascular risk associated with selective and non-selective NSAIDs, it is recommended that the use of COX-2 inhibitors is avoided in patients with established heart disease, cerebrovascular disease or peripheral vascular disease.

NSAIDs should be avoided in patients with heart failure, renal insufficiency and a history of gastric ulceration. Care should also be exercised in elderly patients with multiple pathologies. When prescribing an NSAID, the need for gastric protection should be considered in patients at increased risk of a peptic ulcer, bleed or perforation.

Colchicine

Colchicine is an alkaloid derived from the autumn crocus (colchicum autumnale) and has been reported to have been used in the treatment of gout since the 6th century AD. Colchicine has a slower onset of action than NSAIDs but is recommended in patients where NSAIDs are contraindicated. It should be started as soon as possible after the onset of an attack.

Although the mode of action of colchicine in gout is not fully understood, it is thought to arrest microtubule assembly in neutrophils and inhibit many cellular functions. It suppresses

monosodium urate crystal-induced NALP3 inflammasome-driven caspase-1 activation, IL-1β processing and release, and L-selectin expression on neutrophils. Colchicine also blocks the release of a crystal-derived chemotactic factor from neutrophil lysosomes, blocks neutrophil adhesion to endothelium by modulating the distribution of adhesion molecules on the endothelial cells and inhibits monosodium urate crystal-induced production of superoxide anions from neutrophils (Nuki, 2008).

Although widely used, there are few studies that demonstrate the efficacy of colchicine. A single, randomised, controlled trial has compared the benefits of colchicine to placebo in acute gouty flare (Ahern et al., 1987). Patients were given 1 mg of colchicine followed by 500 µcg every 2 h until the attack stopped or they felt too ill to continue taking colchicine. Colchicine was found to be superior to placebo with an absolute reduction of 34% for pain and a 30% reduction in clinical symptoms such as palpation, swelling, redness and pain. The number needed to treat (NNT) with colchicine to reduce pain was 3 and the NNT to reduce clinical symptoms was 2. All participants given colchicine experienced gastro-intestinal side effects such as diarrhoea and/or vomiting. There are no studies comparing colchicine to either NSAIDs or corticosteroids in an acute flare of gout.

The current dose of colchicine licensed for the management of an acute attack of gout is 1 mg initially, followed by 500 µcg every 2–3 h until relief of pain is obtained or vomiting or diarrhoea occurs. A maximum of 6 mg should be given per course and treatment should not be repeated within 3 days. This dosage regimen frequently causes diarrhoea and other toxic side effects, particularly in elderly patients (Morris et al., 2003; Terkeltaub et al., 2008). It is therefore recommended that a dose of 500 µcg given twice or four times a day should be used to reduce toxicity. Intravenous colchicine is no longer licensed in the UK because use has been associated with a number of fatalities (2% mortality rate).

Common side effects associated with colchicine are abdominal cramps, nausea, vomiting, and rarely bone marrow suppression, neuropathy and myopathy. Side effects are more common in patients with hepatic or renal impairment. The dose of colchicine should be reduced in mild to moderate renal impairment, for example creatinine clearance 10–50 mL/min, and it should not be used in patients with severe renal impairment, for example creatinine clearance less than 10 mL/min. Care should also be exercised in patients with chronic heart failure due to colchicine's ability to constrict blood vessels and stimulate central vasomotor centres.

Colchicine is metabolised by CYP3A4 and excreted by p-glycoprotein; toxicity can be caused by drugs that interact with its metabolism and clearance, and this includes macrolides, ciclosporin and protease inhibitors. The absorption of vitamin B_{12} may be impaired by chronic administration of high doses of colchicine.

Corticosteroids

Corticosteroids are usually considered where use of an NSAID or colchicine is contraindicated or in refractory cases. They may be given intravenously, intramuscularly or direct into a joint (intra-articular) when only one or two joints are affected. In patients with a monoarthritis, an intra-articular corticosteroid injection is highly effective in treating an attack.

Intramuscular triamcinolone acetonide 60 mg has been shown to be as safe and effective as indometacin 50 mg three times daily in treating an acute attack of gout with earlier resolution of symptoms in the steroid group (Alloway et al., 1993). Common doses of intra-articular steroids are 80 mg of methylprednisolone acetate for a large joint such as a knee; 40 mg of methylprednisolone acetate or 40 mg of triamcinolone acetonide for a smaller joint such as a wrist or elbow. Oral prednisolone 30 mg daily for 5 days has also been shown to be equally efficacious to indometacin 50 mg three times a day for 2 days or 25 mg three times a day for 3 days plus paracetamol and has fewer adverse events (Man et al., 2007). Oral steroid regimens used in practice include prednisolone 30 mg daily for 1–3 days with subsequent dose tapering over 1–2 weeks. Intramuscular steroid injections (methylprednisolone acetate 80–120 mg) may sometimes be used to prevent the precipitation of a flare on initiation of prophylactic treatment for gout. Corticosteroids may have fewer adverse events than other acute treatments when used short term, particularly in the elderly.

Interleukin-1 inhibitors

IL-1β is critically associated with the inflammatory response induced by monosodium urate crystals (Rider and Jordan, 2010). Anakinra, an IL-1 receptor antagonist, has been shown to reduce the pain of gout and bring about complete resolution by day 3 in the majority of patients after a course of three 100-mg subcutaneous injections (McGonagle et al., 2007; So et al. 2007). Other IL-1 inhibitors, such as rilonacept, are under development.

Management of chronic gout

The presence of hyperuricaemia is not an indication to commence prophylactic therapy. Some patients may only experience a single episode and a change in lifestyle, diet or concurrent medication may be sufficient to prevent further attacks. Patients who suffer one or more acute attacks within 12 months of the first attack should normally be prescribed prophylactic urate-lowering therapy (see Fig. 54.4). There are, however, some groups of patients where prophylactic therapy should be instigated after a single attack. These include individuals with uric acid stones, the presence of tophi at first presentation and young patients with a family history of renal or cardiac disease. The criteria for starting prophylactic therapy for gout is detailed in Box 54.5.

The aim of prophylactic gout treatment is to maintain the serum urate level below the saturation point of monosodium urate (300 µmol/L). If the serum urate is maintained below this level, crystal deposits dissolve and gout is controlled. Prophylactic treatment should not be initiated until an acute attack of gout has completely resolved, usually 2–3 weeks

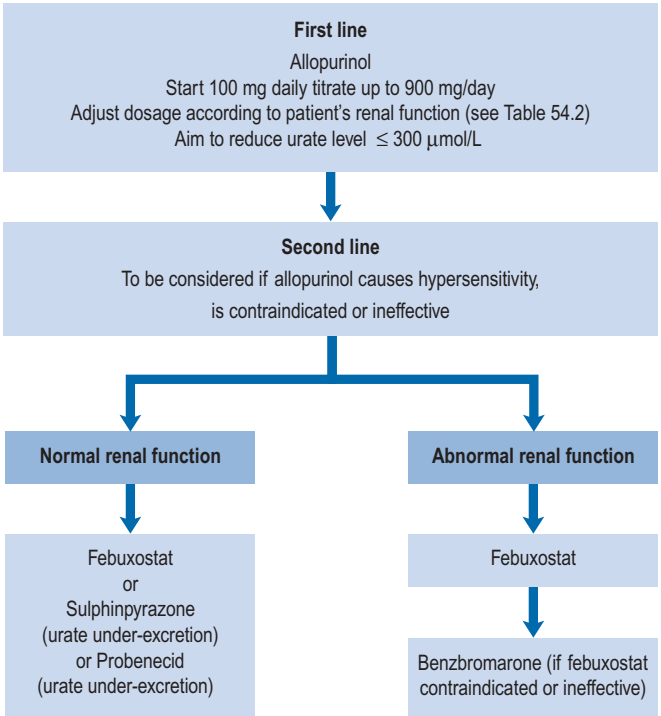


Fig. 54.4 Management of chronic gout in patients requiring urate-lowering therapy.

after symptom resolution. Once started, prophylactic treatment should be continued indefinitely even if further acute attacks develop.

Drugs that lower serum uric acid can be classified into three groups according to their pharmacological mode of action (Box 54.6).

Box 54.5 Criteria for starting prophylactic therapy for gout

One or more acute attacks within 12 months of the first attack
Tophi present at the first presentation of an acute attack
Presence of uric acid stones
Need to continue medication associated with raised uric acid levels, for example diuretics
Young patients with a family history of renal or cardiac disease

Box 54.6 Classification of prophylactic agents used to lower serum urate

Uricostatic agents: allopurinol, febuxostat
Uricosuric agents: benzbromarone, probenecid, sulphinpyrazone
Uricolytic agents: rasburicase, polyethylene glycol-uricase

Table 54.2 Recommended dose of allopurinol in patients with diminished renal function

Creatinine clearance (mL/min)	Dose
0	100 mg three times a week
10	100 mg alternate days
20	100 mg daily
40	150 mg daily
60	200 mg daily
>100	300 mg daily

Uricostatic agents

Uricostatic agents act on the enzyme xanthine oxidase. Xanthine oxidase catalyses the oxidation of hypoxanthine to xanthine and subsequently xanthine to uric acid (Fig. 54.1). Hypoxanthine comes from the catabolism of cellular nucleoproteins and purine nucleotides. Blocking the action of this enzyme reduces the production of uric acid. Agents in this group include allopurinol and febuxostat.

Allopurinol. Allopurinol is the prophylactic agent of choice in the management of recurrent gout. In order to become pharmacologically active, allopurinol must be metabolised by the liver to oxypurinol. Oxypurinol has a much longer half-life than allopurinol, 14–16 h compared to 2 h. Both allopurinol and oxypurinol are renally excreted, with oxypurinol undergoing re-absorption from the renal tubule. In patients with reduced renal function, the half-life of oxypurinol is increased with the risk of accumulation and toxicity. It is, therefore, essential that a patient's renal function is checked prior to the prescribing of allopurinol and the dose adjusted accordingly (Table 54.2).

In patients with normal renal function, the starting dose is 100 mg/day; this is gradually increased in 100-mg increments every 2–3 weeks until the optimal serum urate level (<300 µmol/L) or the maximum dose is reached. The maximum recommended daily dose in patients with normal renal function is 900 mg/day. A decrease in serum urate will occur within a couple of days of introducing allopurinol therapy with a peak effect at 7–10 days. The dissolution of tophi may take up to 6–12 months with effective therapy.

Approximately 3–5% of patients treated with allopurinol suffer from an adverse reaction. Intolerance usually manifests itself as a hypersensitivity reaction within the first 2 months of treatment. Adverse effects reported with allopurinol therapy include rash, fever, worsening renal failure, hepatotoxicity, vasculitis and even death. Severe toxic effects arise in less than 2% of patients. The risk of toxicity increases with renal impairment, age and concurrent drug therapy such as diuretics.

Prior to the availability of febuxostat, allopurinol desensitisation was attempted in patients with a mild hypersensitivity to allopurinol. This involved starting with a very low dose (50 µcg daily) and gradually increasing the dose over a period of several weeks to 100 mg daily. Desensitisation is now only considered where the reaction has been mild and there is an absence of alternative treatment options.

Azathioprine and mercaptopurine are metabolised by xanthine oxidase, co-administration of allopurinol reduces the metabolism of these two medicines leading to accumulation and toxicity. The dose of azathioprine or mercaptopurine

should be reduced to approximately a quarter of the normal dose when co-prescribed with allopurinol. In addition, full blood counts should be performed at regular intervals to identify potential toxicity. High-dose allopurinol (>600 mg/day) increases carbamazepine blood levels by approximately one third; the same effect is not associated with lower doses of allopurinol (<300 mg/day).

Febuxostat. Febuxostat is a more selective and potent inhibitor of xanthine oxidase than allopurinol and has no effect on other enzymes involved in purine or pyrimidine metabolism (Lawrence Edwards, 2009). It is licensed for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred including a history, or presence of, tophus and/or gouty arthritis. It is recommended as a second-line agent in patients who are intolerant of allopurinol or for whom allopurinol is contraindicated.

Febuxostat is more effective than fixed-dose allopurinol 300 mg in lowering uric acid concentrations in trials of up to 40 months' duration (Schumacher et al., 2008, 2009). However, a reduction in the incidence of episodes of acute gout has not been demonstrated.

The recommended starting dose for febuxostat is 80 mg once daily. If the serum uric acid is greater than 357 µmol/L, after 2–4 weeks, the dose should be increased to 120 mg once daily. The increased potency and good oral bioavailability of febuxostat leads to rapid decreases in serum uric acid levels permitting the testing of levels 2 weeks after starting therapy or adjusting the dose. No dosage adjustment is necessary in patients with mild or moderate renal impairment; however, there are no current recommendations for use in patients with severe renal impairment, for example creatinine clearance <30 mL/min. In patients with mild hepatic impairment, the dose should not exceed 80 mg daily; the use of febuxostat has not been studied in patients with severe hepatic impairment. Febuxostat should not be given to patients with ischaemic heart disease or congestive heart failure because of cardiovascular side effects. When initiating therapy with febuxostat, gout flare prophylaxis should be prescribed for at least 6 months.

The most common adverse effects include respiratory infection, diarrhoea, headache and liver function abnormalities. It is recommended liver function should be tested in all patients prior to the initiation of therapy and periodically thereafter based on clinical judgement. The use of febuxostat is not recommended in patients concomitantly treated with mercaptopurine or azathioprine and in patients taking theophylline, serum levels of theophylline should be monitored.

Uricosuric agents

Uricosuric agents increase uric acid excretion primarily by inhibiting post-secretory tubular absorption of uric acid from filtered urate in the kidney. They are indicated as second-line agents in those who are urate under-excreters and are dependent on the patient having an adequate level of renal function. These agents should be avoided in patients with urate nephropathy or those who are over producers of uric acid due to the high risk of developing renal stones. Patients receiving a uricosuric agent are required to maintain an adequate fluid intake, and the need for alkalinisation of urine should be considered to prevent urate precipitation

Benzbromarone. Benzbromarone has been shown to be effective in lowering serum urate levels and reducing the time to resolution of tophi (Kumar et al., 2005; Reinders et al. 2009). However, its use was associated with hepatoxicity and it was withdrawn from the UK. It is still possible to obtain benzbromarone on a named patient basis. The risk of hepatotoxicity has been estimated to be 1:17,000 patients. For those who are prescribed benzbromarone, regular liver function tests must be performed during the first 6 months of therapy, and the hepatotoxic risk associated with the medicine should be clearly explained to the patient at the outset.

The dose ranges from 50 to 200 mg daily. It remains active in mild to moderate renal impairment and is indicated where there is a contraindication to other agents used in the management of gout such as allopurinol and febuxostat (see Fig. 54.4). Diarrhoea may be troublesome in approximately 10% of patients.

Sulphinpyrazone. Sulphinpyrazone is effective in reducing the frequency of gout attacks, tophi and plasma urate levels at doses of 200–800 mg/day. It has the same mode of action on the kidney as benzbromarone and probenecid all of which inhibit URAT-1 transporter resulting in reduced urate re-absorption. However, in addition to this, sulphinpyrazone inhibits prostaglandin synthesis resulting in a similar adverse effect profile to NSAIDs, for example gastro-intestinal ulceration, acute renal failure, fluid retention, elevated liver enzymes and blood disorders. The use of sulphinpyrazone is reserved for use in patients with adequate renal function who are underexcretors of uric acid and intolerant or resistant to treatment with allopurinol.

Probenecid. Probenecid monotherapy is less effective than the other agents in this group and generally not recommended. It may have a role as an add-on agent when allopurinol alone is insufficient. Doses of 0.5–2.0 g/day have been used. As with sulphinpyrazone, it is ineffective in renal impairment. Dyspepsia and reflux may be troublesome in some patients, and it can interact with renally excreted anionic drugs. It is no longer marketed in the UK.

Uricolytics

Uricolytic drugs convert uric acid to allantoin through the actions of the enzyme urate oxidase (uricase). Allantoin is more soluble than uric acid and readily excreted by the kidney. Uricolytics are indicated for hyperuricaemia associated with tumour lysis syndrome and are not indicated for other forms of hyperuricaemia.

Rasburicase. Rasburicase, a recombinant form of the enzyme urate oxidase (uricase), is derived from a cDNA code from a modified *Aspergillus flavus* strain expressed in a modified strain of *Saccharomyces cerevisiae*. It is licensed to treat tumour lysis syndrome and is given intravenously at a dose of 0.2 mg/kg in short courses for 5–7 days. Rasburicase has a half-life of approximately 19 h. No dosage adjustment is required in patients with renal or hepatic impairment.

Rasburicase is generally well tolerated, but adverse effects include fever, nausea, vomiting, rash, diarrhoea, headache, allergic reactions and the development of auto-antibodies.

Polyethylene glycol-uricase (PEG-uricase). PEG-uricase is a pegylated, recombinant form of uricase. Pegylation of the molecule reduces the risk of patients developing auto-antibodies and lengthens the half-life of the drug. It is effective in reducing tophi. The use of PEG-uricase has been associated with severe infusion reactions in a small minority of patients; this and its high cost are likely to limit its use. It may have a role in severe, refractory cases or as a short-term treatment to remove tophi prior to the initiation of conventional urate-lowering therapies.

Preventing gout flare

When prophylactic treatment is commenced, there is a risk of precipitating an acute gout attack, or 'mobilisation flare', for approximately 12 months. Mobilisation flares are thought to be caused by the rapid fall in serum urate following the initiation of urate lowering. The risk of precipitating an acute attack can be reduced by delaying the initiation of long-term urate-lowering therapy until the acute attack has completely resolved and prescribing colchicine or an NSAID during the treatment initiation period.

Colchicine

Colchicine is the agent of first choice to prevent the precipitation of a flare when commencing chronic gout treatment. Low doses of colchicine (500 µcg orally twice a day) should be prescribed and continued for at least 6 months. There are no randomised controlled trial data assessing the effectiveness of colchicine as a single agent to prevent recurrent gout, but it has been shown to help reduce mobilisation flares for up to 6 months after starting allopurinol.

NSAIDs

If there are no contraindications to the use of NSAIDs, they may be considered second line to colchicine in patients' intolerant to colchicine. NSAIDs should be continued for a maximum of 6 weeks.

Patient care

It is important to inform patients about the disease, its curable nature, the aims of drug therapy and how to prevent and handle flares. The need for dietary and lifestyle changes should also be stressed. The UK Gout Society website can assist in providing patients with information about the condition and how it should be managed (http://www.ukgoutsociety.org/). In over-weight patients, gradual weight loss should be encouraged, very rapid weight loss should be avoided as it can cause ketosis and result in raised uric acid levels with the likelihood of precipitating an attack. Low purine diets are difficult to adhere to; a calorie-restricted diet with low carbohydrate (40% of energy), high protein (30% of energy) and unsaturated fat (30% of energy) should be recommended. The importance of avoiding or reducing alcohol consumption should also be emphasised.

Patients at risk of recurrent attacks should be issued with a suitable NSAID to treat the attack as soon as possible. The patient should be clear on what dose to take, when to initiate therapy, how long to take the medication for and any possible side effects to look out for. The patient should also be advised to avoid certain over-the-counter medicines which may exacerbate an attack, for example the use of aspirin as an analgesic.

Those taking long-term prophylactic therapy need to understand the importance of continuing therapy despite being asymptomatic. They should avoid running out of medication, as a short gap in therapy may precipitate an attack. Patients receiving uricosuric agents should be advised to maintain a fluid intake of at least 2 L/day to reduce the risk of uric acid stone formation in the kidneys.

Case studies

Case 54.1

Mr TH is a 50-year-old, slightly over-weight (95 kg) male who presents with an extremely painful big toe. He states that the pain started suddenly in the early hours of the morning and that he cannot even bear to put a sock over his foot. He can think of no recent trauma to his foot. He has no other symptoms and there is no previous significant medical history apart from high blood pressure for which he takes bendroflumethiazide (2.5 mg in the morning). On examination, the toe is red, hot, swollen and extremely painful on palpation. The patient also has an elevated blood pressure of 150 mm/95 mmHg. On questioning about his weekly alcohol intake, he states that he usually does not exceed 21 units/week, but that it was a friend's 50th birthday party recently and he might have had considerably more to drink than usual. Blood results show a slightly raised C-reactive protein, other parameters are normal including renal function; however, his serum urate is slightly raised (390 µmol/L). A diagnosis of acute gout is made.

Questions

1. What initial therapy would you recommend to treat the patient's acute attack of gout?
2. What risk factors could have contributed to the acute attack?
3. Should this patient be placed on therapy to prevent further attacks?
4. What lifestyle and dietary advice would you give to the patient to assist in preventing further attacks?

Answers

1. Initial therapy should be directed at promptly and safely resolving the pain. Drugs used in the management of an acute attack include NSAIDs, colchicine and corticosteroids. NSAIDs are indicated as first-line agents, but there are a number of patients

who cannot take these medicines, and this includes those with renal impairment, heart failure or a history of gastric ulceration. Caution should also be exercised in elderly patients with multiple pathologies as they are prone to develop side effects with NSAIDs, particularly gastric symptoms. Colchicine has a slower-onset action then NSAIDs (6 h vs. 2 h) and is usually indicated where NSAIDs are contraindicated. When only a single joint is affected, an intra-articular injection directly into the joint may be considered; however, this is often too painful for the patient to bear.

As the patient has no contraindications, it would be appropriate to start an NSAID at maximal dose for 2–3 days and then reduce and continue for a further 7–10 days. There is no evidence to promote the use of one NSAID over another in the management of an acute attack; the main issue is to start therapy as soon as possible at maximal dose provided there are no contraindications. When initiating an NSAID, the need for gastric protection should be considered particularly in those aged over 65 years, previous history of peptic ulcer disease or gastro-intestinal complications and other medicines associated with gastro-intestinal side effects.

COX-2 inhibitors such as etoricoxib selectively block the COX-2 pathway resulting in reduced gastro-intestinal side effects. These agents are recommended for patients with high risk of gastro-intestinal side effects, but they are not recommended for routine use. Etoricoxib has been shown to be as equally effective as indometacin with fewer adverse effects. However, a systematic review and meta-analysis of etoricoxib showed an increased risk of cardiovascular and thromboembolic events associated with its use. It is recommended that COX-2 inhibitors be avoided in patients with established heart disease, cerebrovascular disease or peripheral vascular disease.

Where the patient's pain is not adequately controlled by an NSAID, simple and low-potency opiate analgesia can be added to the regimen. The affected joint should be rested for 1–2 days and the affected area treated with ice.

2. Hyperuricaemia (raised serum uric acid levels) is one of the main risk factors for the development of gout; however, not all patients with a raised serum uric acid level will go on to develop gout. Studies have shown obesity, weight gain and hypertension all to be independent risk factors for the development of gout. Mr TH is slightly over-weight and has a history of hypertension. Measurement of his serum lipid levels should be considered as dyslipidaemia is commonly associated with gout.

   Loop and thiazide diuretics are one of the most common modifiable risk factors associated with gout. It is thought they exert their action via volume depletion and the reduced tubular renal secretion of uric acid. In patients with heart failure, diuretics are often essential and cannot be discontinued. Mr TH's bendroflumethiazide is being used for the management of hypertension and a change to an alternate hypertensive agent should be considered. Losartan, an angiotensin receptor blocker, has been shown to have both anti-hypertensive and urate-lowering properties and is suggested as a suitable agent in hypertensive patients with gout.

   Alcohol consumption is an important risk factor for the development of gout. The mechanism of action is thought to be due to the metabolism of ethanol to acetyl coenzyme A leading to adenine nucleotide degradation and a subsequent rise in the levels of adenosine monophosphate which is a precursor of uric acid. Beer drinking is associated with the highest risk due to its high purine content. It is recommended that males restrict their alcohol consumption to less than 21 units/week and that both male and female patients have at least 3 alcohol-free days per week. Beer, stout, port and fortified wines should be avoided. Two 125-mL glasses of wine per day are considered acceptable and two pub-sized measures of spirits are considered safer than half a pint of many beers.

3. In uncomplicated gout, specific long-term treatment to reduce plasma uric acid concentration should only be given if a second attack or further attacks of gout occur within 1 year. The need for preventative therapy is not indicated in this patient; he has uncomplicated gout and his bendroflumethiazide can be switched to an alternate anti-hypertensive agent which is not linked to an increase in uric acid levels. For some patients, changes in diet and lifestyle plus the removal of medicines contributing to the attack may be sufficient to prevent further flares. Where prophylactic therapy is indicated, it should only be commenced after complete resolution of the flare.
4. Lifestyle modification can be effective in preventing further attacks. Moderate physical exercise can be beneficial; however, intense muscular exercise should be avoided as it can lead to a rise in uric acid levels. In over-weight patients, gradual weight loss should be encouraged. Rapid weight loss can precipitate ketosis and a subsequent rise in the urate pool. Mr TH should be given appropriate dietary advice. It is the regular consumption of foods containing purines rather than the absolute purine content of a particular food that is important. The UK Gout Society (http://www.ukgoutsociety.org/) provides a fact sheet with dietary recommendations and the purine content of various foods for patients. Ideally, total daily purine intake should not exceed 200 mg/day, and foods such as shellfish, offal and sardines should be avoided. Dairy products have been shown to be beneficial in lowering serum uric acid, and even the addition of yoghurt on alternate days has been shown to reduce levels. The consumption of soft drinks sweetened with fructose or sucrose (not diet drinks) should be limited. Cherries whether sweet, tart, juice or fruit have a urate-lowering potential.

   As previously discussed, Mr TH should also moderate his alcohol consumption.

Case 54.2

Mr SB, a 45-year-old man, has recently been treated for his second acute attack of gout within 8 months of his first episode. The symptoms have now resolved and his primary care doctor is unsure if Mr SB should be commenced on prophylactic medication. Mr SB has no family history of renal disease, but his father died of a myocardial infarction aged 52. He takes no regular medication and has no other significant previous medical history.

Questions

1. Is it appropriate to initiate prophylactic treatment?
2. What prophylactic treatment would you recommend?

Answers

1. Patients who suffer one or more acute attacks of gout in a year should be commenced on prophylactic therapy. However, prophylactic therapy is recommended for some patients at the first acute attack. These include patients with uric acid stones, tophi and young patients with a family history of renal or cardiac disease. Mr SB is relatively young and there is a family history of cardiac disease. The initiation of prophylactic therapy should therefore be considered.
2. Allopurinol is the first-line choice for prophylactic treatment of hyperuricaemia. Patients with normal renal function should be commenced on 100 mg daily and the dose gradually increased by 100 mg increments at 2–3 week intervals until the serum urate level has been reduced to less than 300 µmol/L. Serum urate levels may be artificially low during an acute attack. The level should be checked following the acute episode and prophylactic therapy, if deemed appropriate, should not be commenced until

after the flare has resolved. Serum urate levels should fall within 2 days and peak at 7–10 days with the introduction of allopurinol and with dose increases.

Renal function should be checked prior to starting allopurinol to ensure that the correct dosage is prescribed based on the patient's creatinine clearance. Reduced renal function increases the half-life of allopurinol's active metabolite, oxypurinol. If the dose is not reduced according to renal function, the patient is at risk of oxypurinol accumulation and toxicity.

Mr SB does not take regular medication, but current medication should always be checked for interactions with allopurinol, for example azathioprine, mercaptopurine, carbamazepine.

As prophylactic treatment is being initiated, Mr SB is at risk of a mobilisation flare for approximately 12 months. Prophylaxis treatment for mobilisation flares should be recommended. First-line choice for the prevention of mobilisation flares is colchicine (500 µcg twice daily for 6 months). For patients who are intolerant to colchicines, NSAIDs offer a second-line choice, provided there are no contraindications to NSAID therapy. NSAIDs should be continued for a maximum of 6 weeks.

Case 54.3

Mrs DM, a 72-year-old woman, was admitted to hospital with dehydration and loss of consciousness, following a fall. On admission, she was taking bendroflumethiazide 2.5 mg each morning, candesartan 8 mg each morning, simvastatin 10 mg at night, paracetamol 1 g four times a day and the week before admission had been started on allopurinol 300 mg once a day for gout. On day 2 of her admission, she developed a rash and fever, her creatinine clearance was 23 mL/min and her ALT 156 international units/L. After investigation, she was diagnosed as having a hypersensitivity reaction to allopurinol. The allopurinol was stopped immediately.

Questions

1. What risk factors does this patient have for developing a hypersensitivity to allopurinol?
2. What prophylaxis treatment option would you recommend for following the allopurinol hypersensitivity reaction?

Answers

1. Severe toxic effects caused by allopurinol occur in less than 2% of patients taking allopurinol; however, the mortality risk is high in this group. The risk of allopurinol toxicity is increased for patients with renal impairment, old age and concomitant drugs. Mrs DM has all of these risk factors. Her renal function may have been impaired prior to admission due to her age, but this may have been further exacerbated by a period of dehydration caused from extended stasis following a fall. Bendroflumethiazide may have contributed to her fall, dehydration and history of gout. Her blood pressure requires close monitoring to ensure she is not suffering from postural hypotension or that the combination of two anti-hypertensive drugs is not causing her blood pressure to drop too low. Ideally, bendroflumethiazide should be avoided in this patient and if needed an alternate anti-hypertensive prescribed. Mrs DM's starting dose of allopurinol is considerably higher than that which would normally be recommended, the high dose in combination with renal impairment may have caused an accumulation of the active metabolite of allopurinol, oxypurinol, which would have increased the risk of toxicity. Renal function should be checked in all patients prior to commencing allopurinol. For normal renal function, a starting dose of 100 mg once a day is recommended. For abnormal renal function, the product data sheet should be consulted for appropriate dose reduction. Hypersensitivity reactions usually occur up to 2 months following the initiation of allopurinol. Allopurinol should be stopped immediately in patients with symptoms of hypersensitivity reaction.
2. The choice of second-line prophylaxis treatment to replace allopurinol should be based on both renal function and pathophysiology of the disease.

   Febuxostat is recommended in mild to moderate renal impairment, but there are no data in severe renal impairment. In patients with mild hepatic impairment, the dose of febuxostat must not exceed 80 mg once a day. Febuxostat is initiated at 80 mg daily but can be increased to 120 mg daily if the serum urate has not decreased adequately after 2–4 weeks of therapy. Febuxostat should not be used in patients with a history of cardiovascular disease.

   In normal renal function, sulphinpyrazone or probenecid is indicated in urate under excretors when febuxostat is not appropriate. However, sulphinpyrazone can increase sodium and water retention and may worsen Mrs DM's heart failure. Probenecid is less effective than other uricosuric agents and is generally not used.

   Benzbromarone is effective in moderate renal impairment and may be considered if febuxostat is contraindicated or ineffective. Baseline liver function tests must be performed as well as regular monitoring during the first 6 months of therapy. Benzbromarone is only available on a named patient basis, patients must have failed or been intolerant of other therapies and understand that the use of benzbromarone is associated with liver toxicity.

   Allopurinol desensitisation should only be considered when all other prophylactic treatments have failed and is not appropriate for patients who have suffered a severe hypersensitivity reaction.

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55 Glaucoma

L. C. Titcomb and S. D. Andrew

Key points

- Glaucoma is a large group of disorders with widely differing clinical features.
- Chronic open-angle glaucoma (COAG) is a chronic progressive disease of insidious onset.
- The aim of treatment in COAG is to reduce the intraocular pressure (IOP) to a target pressure, specific to the patient, preventing further damage to the nerve fibres and the development of further visual field defects.
- A wide range of drugs is used to treat COAG. Laser treatment or surgery may be undertaken if the target pressure is not attained with medical therapy.
- COAG is a symptomless disease until well advanced. Concordance with therapy is an important issue.
- Acute primary angle-closure glaucoma (PACG) is a medical emergency that must be treated rapidly to prevent blindness.
- The aim of medical treatment in acute PACG is to reduce the IOP in preparation for laser treatment or surgery.
- A wide range of drugs can provoke an attack of PACG in susceptible individuals.

The term 'glaucoma' does not represent a single pathological entity. It consists of a large group of disorders with widely differing clinical features. It is, therefore, difficult to attempt a single definition of the term. High intraocular pressure (IOP) was previously used as a diagnostic criterion for glaucoma, but more recently, it has been recognised purely as the most important risk factor for the disease. This is because glaucoma can occur even in patients with normal IOP (normal-pressure chronic open-angle glaucoma, COAG). The 'normal' IOP (10–21 mmHg) is a statistical description of the range of IOP in the population and is not applicable to an individual subject. It is thought to increase with age, at the rate of approximately 1 mmHg every decade after the age of 40 years in the Western population. There is a circadian cycle of IOP, with maximum levels often occurring between 8 and 11 a.m. and minimum levels between midnight and 2 a.m. This may affect IOP readings taken in outpatient clinics at different times of the day. The normal diurnal variation is between 3 and 5 mmHg, and this is wider in untreated glaucoma. Although a raised IOP is not the only cause of glaucoma, it is the only parameter that can currently be changed by pharmacological intervention and therefore plays an important part in the evaluation of disease progression.

Current thinking is that once the rate of disease progression has been established, a 'target IOP' can be set. The target IOP is defined as a dynamic, clinical judgement about what level of IOP is considered by the healthcare professional treating the patient to be sufficiently low to minimise or arrest disease progression or onset and avoid disability from sight loss within a person's expected lifetime.

It is, however, extremely difficult to accurately assess in advance the IOP level at which further damage will occur for any one patient. As the correct target IOP is only discovered with hindsight, one limitation is that the chosen target IOP may not be low enough and a patient must get worse before it is realised that the target IOP was inadequate. There is no single safe IOP level for all patients, but in general, the aim is to achieve at least a 25–30% reduction from the initial IOP at which damage occurred. In advanced disease, the aim is to achieve an IOP level below 18 mmHg at all times. This can be used as a good method to set an initial target IOP. However, it is essential that the patient receives regular periodic re-evaluation so that the target IOP can be adjusted according to disease progression and treatment adjusted accordingly.

Epidemiology

The World Health Organisation has estimated that globally there are 12.5 million people blind from glaucoma with the total number affected by this condition at around 66 million. Approximately 13% of UK blindness registrations are ascribed to glaucoma, and around 2% of people older than 40 years have COAG, a figure which rises to almost 10% in people older than 75 years. With changes in population demographics, the number of individuals affected by glaucoma is expected to rise. Based on these estimates, there are around 500,000 people affected by COAG in England and Wales, who receive over a million glaucoma-related outpatient visits in the hospital eye service annually. Once diagnosed, affected individuals require lifelong monitoring for disease control and to detect possible progression of visual damage. Once lost, vision cannot be restored. Disease control with prevention or at least minimisation of ongoing damage is therefore paramount to maintain sight.

The diseases which make up the group known as glaucoma are usually classified according to the manner in which aqueous humour outflow is impaired.

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Chronic open-angle glaucoma

COAG, also referred to as chronic simple glaucoma, is associated with a relative obstruction to aqueous outflow through the trabecular meshwork and is a chronic progressive disease of insidious onset, usually affecting both eyes. It is frequently an inherited condition, with approximately 10% of first-degree relatives of COAG sufferers eventually developing the disease. Two conditions similar to COAG are normal-tension glaucoma, where the IOP is not raised on initial screening although signs of damage are present, and ocular hypertension (OHT), elevated IOP in the absence of visual field loss or glaucomatous optic nerve damage. It is estimated that 3–5% of those over 40 years have OHT, around one million people in England. OHT represents a major risk for future development of COAG with visual damage. Lowering IOP has been shown to protect against conversion to COAG.

Primary angle-closure glaucoma

Primary angle-closure glaucoma (PACG), or closed-angle glaucoma, is a condition in which closure of the angle by the peripheral iris results in a reduction in aqueous outflow. It occurs in predisposed eyes and is frequently unilateral. There are ethnic variations as the disease affects approximately 1 in 1000 Caucasian adults over the age of 40 years, about 1 in 100 Asians (especially mongoloids) and Hispanics, and 2–4 per 100 Inuits (Eskimos). It occurs in four times as many females as males.

Secondary glaucomas

Secondary glaucomas can arise for a number of reasons, including inflammation, intraocular tumour, raised episcleral venous pressure, or congenitally due to developmental abnormalities.

Aetiology

The factors that determine the level of IOP are the rate of aqueous humour production and the resistance encountered in the outflow channels. A fine balance between these is necessary to keep the pressure within the eye in the range of 16–21 mmHg.

Production of aqueous humour occurs in the ciliary epithelium by two mechanisms: secretion due to an active metabolic process, independent of the level of IOP, and ultrafiltration influenced by the level of blood pressure in the ciliary capillaries and the level of IOP.

Outflow of aqueous humour occurs by two routes. Approximately 80% of total outflow is through the trabecular meshwork into the canal of Schlemm and into the venous circulation via the aqueous veins. The uveoscleral pathway accounts for the remaining 20% through the ciliary body into the suprachoroidal space, to be drained into the ciliary body, choroid and sclera via the venous circulation.

Pathophysiology

The primary site of damage is thought to be the optic nerve head, rather than any other point along the nerve axon. This most easily explains the progressive loss of visual field. Studies of axoplasmic flow show a vulnerability of the nerves to elevated IOP as they pass through the optic disc.

In COAG, increased resistance within the drainage channels causes the rise in IOP. It is thought that the main route of resistance to aqueous outflow lies in the dense juxtacanalicular trabecular meshwork, or the endothelium lining the inner wall of Schlemm's canal.

In PACG, the rise in IOP is caused by a decreased outflow of aqueous humour, due to closure of the chamber angle by the peripheral iris. It occurs in predisposed eyes, and the predisposing factors can be anatomical or physiological. The anatomical characteristics are lens size, corneal diameter and axial length of the globe. The lens continues to grow throughout life. This brings the anterior surface closer to the cornea. Slackening of the suspensory ligaments increases this movement. Both factors occur very gradually and lead to a progressive shallowing of the anterior chamber. The depth of the anterior chamber and width of the chamber angle are related to corneal diameter, and those eyes predisposed to PACG are observed to have a corneal diameter less than that seen in normal eyes. A short eye, which is frequently also hypermetropic, has a small corneal diameter and a thick and relatively anteriorly located lens.

The physiological precipitating factors of PACG in predisposed eyes are not fully understood. Two theories currently exist. The dilator muscle theory suggests that contraction of the dilator muscle causes a posterior movement, which increases the apposition between the iris and anteriorly located lens and the degree of physiological pupillary block. The simultaneous dilation of the pupil renders the peripheral iris more flaccid, and causes the pressure in the posterior chamber to increase and the iris to bow anteriorly. Eventually, the peripheral iris obstructs the angle and the IOP rises (Fig. 55.1).

The sphincter muscle theory postulates that the sphincter of the pupil precipitates angle closure. The pupillary blocking force of the sphincter is greatest when the diameter of the pupil is about 4 mm.

Clinical manifestations

COAG is typically characterised by the following: an IOP greater than 21 mmHg, an open-angle, glaucomatous cupping and visual field loss. COAG, because of its insidious onset, is usually asymptomatic until it has caused a significant loss of visual field. In some eyes, subtle signs of glaucomatous retinal nerve damage can be detected prior to development of pathological cupping and detectable field loss. The earliest clinically significant field defect is a scotoma, which is an area of depressed vision within the visual field. Patients with COAG frequently show a wider swing in IOP than normal; therefore, a single pressure reading of 21 mmHg or less does not exclude

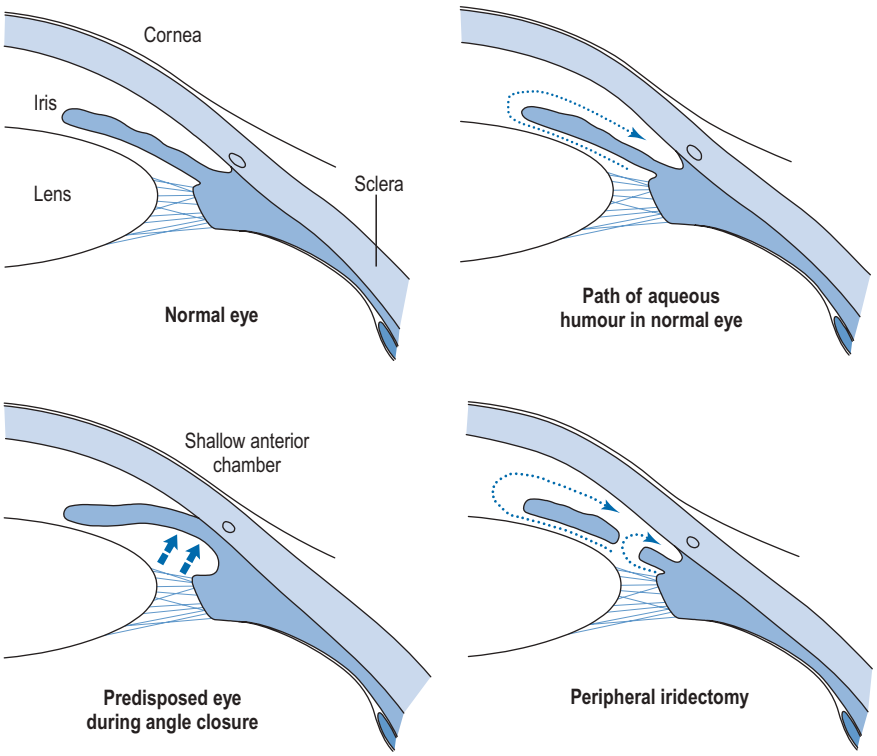


Fig. 55.1 Changes to the eye seen during closed-angle glaucoma.

the diagnosis. It may be necessary to measure IOP at different times of the day, or at periodic intervals.

Acute PACG is due to a sudden closure of the angle and a severe elevation in IOP. The symptoms include rapidly progressive visual impairment, periocular pain and congestion of the eye. In severe cases, nausea and vomiting may occur. The signs include injection of the limbal and conjunctival vessels, giving a 'ciliary flush'. The IOP usually lies between 50 and 80 mmHg and causes corneal oedema with epithelial vesicles. The anterior chamber is shallow and iridocorneal contact can be observed. The pupil is vertically oval and fixed in a semi-dilated position. It is unreactive to light and accommodation. The fellow eye usually has a shallow anterior chamber and a narrow angle. The optic nerve head is oedematous and hyperaemic.

Investigations

IOP may be measured by tonometry, such as indentation tonometry in which a plunger is applied to the cornea and the amount of indentation on the eye reflects the pressure within it. Tonography is a technique used to measure the outflow of aqueous humour from the eye, resulting from indentation of the eye, using a tonometer. Gonioscopy is used to estimate the width of the chamber angle, with the aid of a slit lamp. Perimetry is important for both the diagnosis and management of glaucoma by detecting early scotomata and larger changes in visual field. Other investigations which should be routinely offered to patients include a central corneal thickness measurement (CCT), as this has an effect on the measured IOP and may affect the efficacy of certain drug treatments (Johnson et al., 2008), and fundus examination for optic nerve assessment with dilatation using stereoscopic slit-lamp biomicroscopy. There are also guidelines for the monitoring of these patients and at what intervals their IOP, optic nerve head and visual fields should be checked (National Institute for Health and Clinical Excellence, 2009).

In patients with COAG, cupping of the optic disc becomes progressively apparent and is used in both diagnosis and assessment of the efficacy of treatment. The increased IOP appears to push the optic disc back into an excavation. This is known as glaucomatous cupping.

The colour of the optic disc will be observed to change from a creamy pink colour, due to the rich capillary network seen in the healthy eye, to increased pallor with advancing disease as the optic nerve tissue progressively atrophies.

Treatment

Chronic open-angle glaucomas

The aim of treatment in COAG is to reduce the raised IOP to the target value, preventing further damage to the nerve fibres and the development of further visual field defects to maintain the patient's visual function and quality of life. The key to effective treatment is careful and regular follow-up, including measurement of visual acuity, tonometry, gonioscopy, evaluation of the optic disc, CCT and perimetry, which is of primary importance.

The actual safe level of IOP is unknown, the importance of disc and field assessment being underlined by evidence that IOP does not rise above the 'normal' range in up to 50% of glaucomas (normal-pressure glaucomas). However, in many cases, maximal retardation of the disease process is achieved if the IOP is maintained in the lower teens. The effect on the visual field and the appearance of the optic disc are the only indications that IOP is being controlled at a safe level. A raised IOP without field or disc changes may not require treatment but will need regular review.

The initial treatment of COAG is usually medical. Topical administration is the preferred type of therapy, and there is a wide range of preparations available (Table 55.1). The chosen drug should be administered at its lowest concentration and as infrequently as possible to obtain the desired effect over the whole 24-h period as a high level of diurnal variation in IOP has been shown to be a more important factor in visual field development than the average IOP. A drug with few potential side effects should be chosen, with oral therapy retained as the final option. The prostaglandin analogues latanoprost and travoprost and the prostamide bimatoprost are indicated for first-line use, as are the β-blockers as these produce the greatest fall in IOP (Table 55.2). Carbonic anhydrase inhibitors and sympathomimetics, which result in a smaller fall in IOP, are reserved for patients unresponsive to first-line drugs, in patients in whom the first-line agents are contraindicated or as adjunctive therapy.

Table 55.1 Drugs used in the treatment of chronic open-angle glaucoma

Therapeutic category	Primary mechanism
Topical prostaglandins	Increase aqueous outflow
Topical prostamides	Increase aqueous outflow
Topical β-blocking agents	Decrease aqueous formation
Topical miotics	Increase aqueous outflow
Topical adrenergic agonists	Increase aqueous outflow and decrease aqueous formation
Topical carbonic anhydrase inhibitors	Decrease aqueous formation
Oral carbonic anhydrase inhibitors	Decrease aqueous formation

In most cases, the initial topical treatment is with a prostaglandin analogue or prostamide. If this is ineffective, another prostaglandin or prostamide may be substituted or a β-blocker used instead. Patients not reaching their target pressure on one first-line agent may be prescribed another concomitantly. Alternatively, a carbonic anhydrase inhibitor or a sympathomimetic may be added to one of the first-line drugs. Guidance on the treatment of people with OHT or suspected COAG has been published (National Institute for Health and Clinical Excellence, 2009). The treatment options (Table 55.3) take into account central corneal thickness and age, although age thresholds are only appropriate where vision is normal (OHT with or without suspected COAG) and the treatment is purely preventative. Pilocarpine is no longer recommended by NICE but is recommended as a second-line agent in European guidelines (European Glaucoma Society, 2008). Oral therapy with carbonic anhydrase inhibitors is usually reserved for use as the final stage of treatment in those complex glaucomas awaiting surgery (Fig. 55.2).

It has been proposed that the improved control of IOP with newer therapies has led to a reduction in surgery for glaucoma (Kenigsberg, 2007). However, some patients still require surgical intervention to reach their target pressure.

The most frequently performed surgical procedures create a fistula to act as a new route for aqueous outflow and the

Table 55.2 Comparison of reduction in intraocular pressure (IOP) with a range of ocular hypotensive drugs (adapted from van der Valk et al., 2009)

Drug	Relative IOP change from baseline at trough (%) (95% CI)	Relative IOP change from baseline at peak (%) (95% CI)
Bimatoprost	−28 (−29 to −27)	−33 (−35 to −31)
Travoprost	−29 (−32 to −25)	−31 (−32 to −29)
Latanoprost	−28 (−30 to −26)	−31 (−33 to −29)
Timolol	−26 (−28 to −25)	−27 (−29 to −25)
Betaxolol	−20 (−23 to −17)	−23 (−25 to −22)
Dorzolamide	−17 (−19 to −15)	−22 (−24 to −20)
Brinzolamide	−17 (−19 to −15)	−17 (−19 to −15)
Brimonidine	−18 (−21 to −14)	−25 (−28 to −22)
Placebo	−5 (−9 to −1)	−5 (−10 to 0)

Table 55.3 Treatment of people with ocular hypertension or suspected COAG (National Institute for Health and Clinical Excellence, 2009)

Central corneal thickness	More than 590 µm		555–590 µm		Less than 555 µm		
Untreated IOP (mmHg)	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>21 to 25	>25 to 32	>32
Age (years)	Any	Any	Any	Treat until 60	Treat until 65	Treat until 80	Any
Treatment	No treatment	No treatment	No treatment	β-blocker	Prostaglandin analogue	Prostaglandin analogue	Prostaglandin analogue

most frequently performed surgery of this type, trabeculectomy, appears more effective in controlling IOP than laser trabeculoplasty, in which a series of laser burns is applied to the trabecular meshwork to improve the outflow of aqueous humour. (Rolim de Moura et al., 2007).

Primary angle-closure glaucoma

The medical management of acute PACG is essentially to prepare the eye for surgical treatment. The aim of treatment is to decrease the IOP and associated inflammation. Analgesics and antiemetics are sometimes needed, dependent on symptom severity, to make the patient comfortable. It is usual to treat the unaffected eye prophylactically with miotics (Fig. 55.3).

Paralysis of the iris sphincter usually occurs at an IOP of more than 60 mmHg, due to ischaemia. Therefore, intensive miotic therapy, previously the treatment of choice in many cases of PACG, is usually ineffective and the IOP needs to be lowered by drugs that reduce aqueous humour production rather than by trying to pull the peripheral iris away from the angle with miotics. An intravenous loading dose of mannitol is usually the first drug of choice with intravenous acetazolamide a possible alternative. This is followed by oral treatment, sometimes in combination with corneal indentation, to physically force aqueous humour into the peripheral anterior chamber and artificially open the angle. This should allow the IOP to drop sufficiently to relieve iris ischaemia and allow the sphincter to respond to pilocarpine therapy.

Once the IOP has been reduced medically, the condition is treated surgically, by either surgical peripheral iridectomy or laser iridotomy, to remove an area of the peripheral iris to allow flow of aqueous humour through an alternative pathway (see Fig. 55.1). Filtration surgery is indicated if a large proportion of the angle has been permanently closed by adhesions between the iris and the cornea.

Drug treatment

Ocular prostanoids: prostaglandin analogues and prostamides

The National Institute for Health and Clinical Excellence (2009) guideline does not differentiate between the prostaglandin analogues and the prostamide bimatoprost, but recommends one of this class for the treatment of COAG, certain patients with OHT and certain COAG suspects (see Table 55.4)

The prostaglandin analogues, latanoprost, travoprost and tafluprost, are ester compounds thought to achieve a fall in IOP primarily by increasing the uveoscleral outflow with no significant effect on other parameters of aqueous humour dynamics, while the prostamide bimatoprost is thought to increase outflow through both trabecular and uveoscleral outflow pathways. However, there is still debate about the precise mechanisms of action of this group (Lim et al., 2008; Toris et al., 2008).

All the drugs in this class are licensed for the reduction of elevated IOP in open-angle glaucoma and OHT, and are administered once daily in the evening.

In a meta-analysis, these drugs have been shown to have a greater effect on both peak and trough readings of IOP than timolol, betaxolol, dorzolamide, brinzolamide or brimonidine, producing falls in IOP of 28–29% at trough and 31–33% at peak as shown in Table 55.2 (van der Valk et al., 2009).

Randomised head-to-head evaluations of prostaglandin therapy demonstrate similar efficacy, but differing hyperemia effects with bimatoprost and travoprost causing more hyperaemia than latanoprost (Eyawo et al., 2009; Honrubia et al., 2009). However, these studies were conducted before the introduction of the new formulations of bimatoprost 0.01% and the benzalkonium chloride–free travoprost.

The prostanoids have some interesting local side effects (Table 55.5). Pigmentation of the iris occurs in patients with mixed colour (green-brown or blue-brown) irides after 3–6 months of use and is a result of increased deposition of melanin in the melanocytes. An increase in the length and thickness of the eyelashes and pigmentation of the palpebral skin are also known side effects. Use of these drugs may lead to disruption of the blood–aqueous barrier in patients with aphakia and pseudophakia (no or false lens, respectively) and increase the risk of developing cystoid macular oedema; they should be used with caution in such patients. Reactivation of herpes simplex infection has been reported with bimatoprost, travoprost and latanoprost.

Latanoprost

Latanoprost, which is converted to its active free acid on entering the eye, was the first of the prostanoids to be launched and is the market leader. Like timolol amongst the

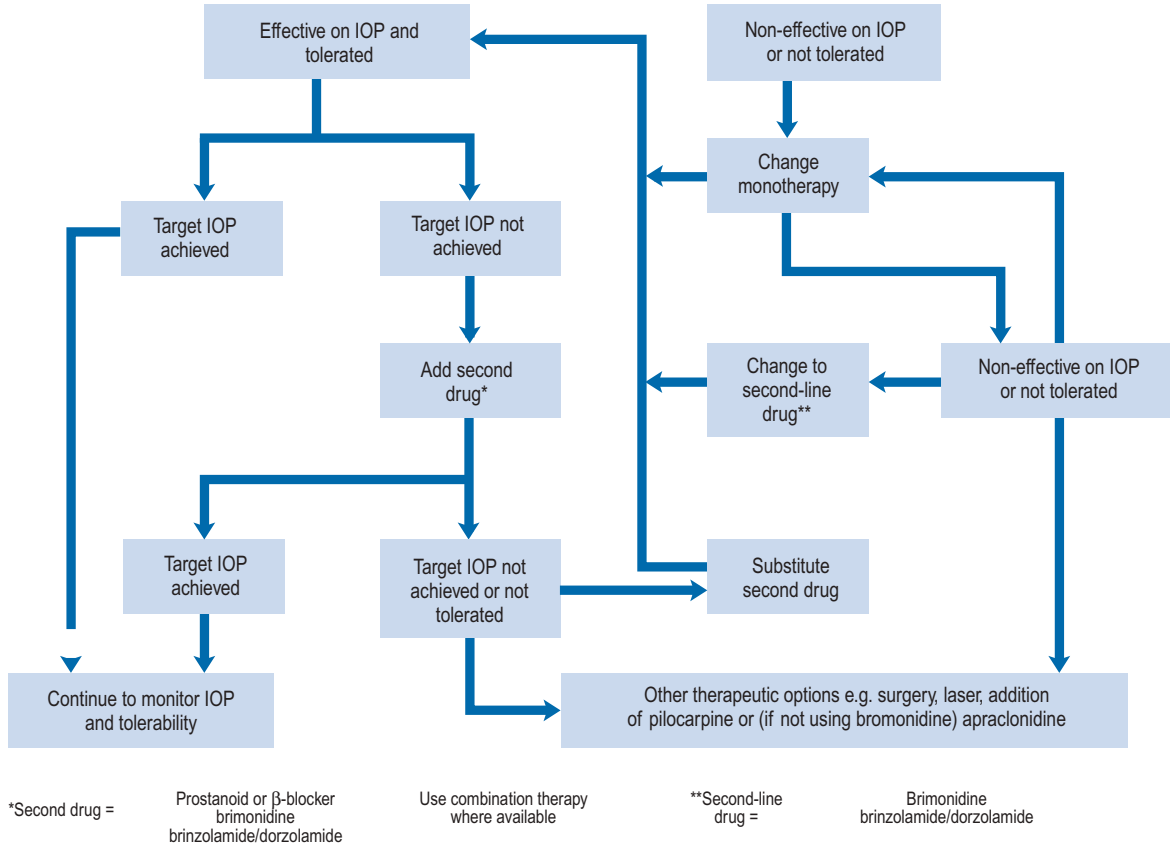


Fig. 55.2 Topical therapy for chronic open-angle glaucoma (COAG) based on recommendations of European Glaucoma Society (2008).

β-blockers, latanoprost is the drug in this class against which new drugs or combinations are assessed. It must be administered in the evening for maximum effect (Stewart et al., 2008). Latanoprost is generally very well tolerated. Serious adverse drug reactions were reported in only 17/3936 (0.43%) patients using latanoprost over a 5-year period (Goldberg et al., 2008), and patient persistence with latanoprost therapy is better than that with all other frequently used monotherapies (Rahman et al., 2009). Latanoprost is not heat stable and requires refrigeration; however, it is stable enough to be stored at room temperature for the 4-week in-use period applied in the UK. The concentration of the preservative benzalkonium chloride in latanoprost eye drops and bimatoprost 0.01% may prevent their use in certain patients. The benzalkonium chloride concentration in these formulations is 0.02%, which is four times that in bimatoprost 0.03% eye drops. The current formulation of travoprost, launched in January 2011, contains polyquaternium-1 rather than benzalkonium chloride.

Travoprost

Like latanoprost, travoprost is an ester pro-drug, converted to its active acid form by corneal hydrolytic enzymes as it is absorbed through the eye. Travoprost acid is a potent full agonist for prostaglandin $F_{2\alpha}$-receptors, producing 100% efficacy, whereas the comparable efficacy for latanoprost is 92%. It is highly selective, with no significant activity at non-prostanoid receptors and low affinity for the other prostanoid receptors responsible for pain, etc. It appears to be generally well tolerated by patients and is relatively free of systemic side effects, although abdominal cramp has been reported.

Patients treated with travoprost show good diurnal fluctuation control, and an ocular hypotensive effect was shown to last for over 3 days. Patients previously treated with β-blockers, α_2-agonists, carbonic anhydrase inhibitors, latanoprost and the dorzolamide-timolol fixed combination respond to travoprost. Administration time is not as important with travoprost as with latanoprost as no statistical difference was noted in the percentage fall in IOP whether travoprost was administered in the morning or in the evening (Stewart et al., 2008). Travoprost is a stable compound throughout a range of temperatures, and the commercially available product does not require refrigeration.

Tafluprost

Tafluprost is the first of the prostanoids available in a preservative-free form. In terms of efficacy and safety, it has been shown to be equivalent to a preserved preparation of tafluprost (Hamacher et al., 2008) and useful in patients allergic to, or intolerant of, benzalkonium chloride.

Tafluprost as adjunctive therapy to timolol results in consistently greater reductions in IOP compared with vehicle in patients with glaucoma or OHT that is inadequately controlled with timolol monotherapy (Egorov and Ropo, 2009).

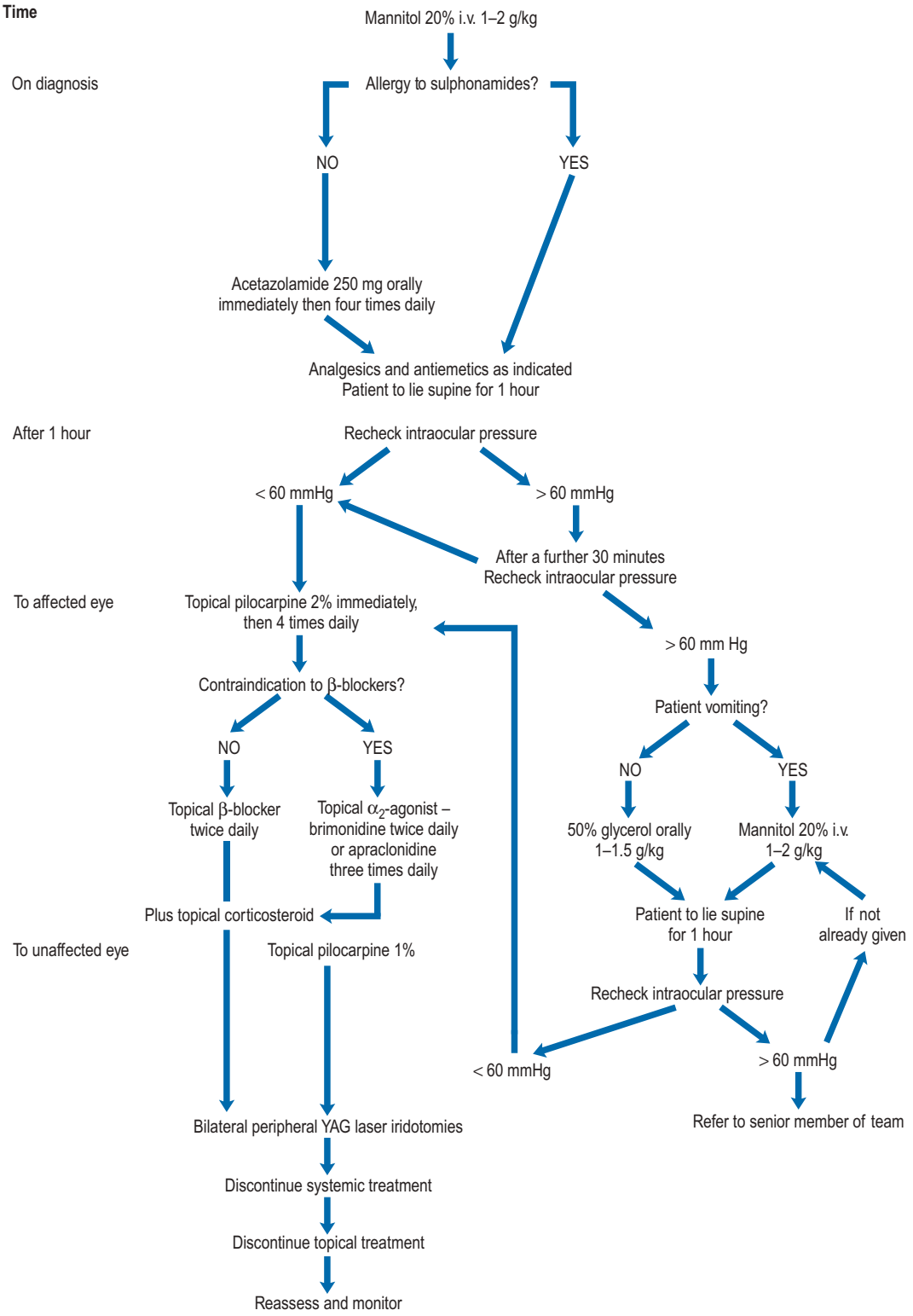


Fig. 55.3 Algorithm for the treatment of primary angle-closure glaucoma (PACG). YAG, yttrium aluminium garnet.

Bimatoprost

Bimatoprost is a fatty acid amide, pharmacologically similar to prostaglandin $F_{2\alpha}$1-ethanolamide (prostamide $F_{2\alpha}$).

Several mechanisms of action have been proposed including activity of bimatoprost or its free acid, 17-phenyl PGF_{2a}, at the prostaglandin $F_{2\alpha}$ receptor, prostamide mimetic activity, and inhibition of PGF synthase which leads to an increase in endogenous $PGF_{2\alpha}$. Although the free acid has been found in human eyes, its presence alone does not explain the 24-h efficacy of bimatoprost or its hypotensive superiority over

Table 55.4 Ocular prostanoids

	Bimatoprost		Latanoprost	Tafluprost	Travoprost
Trade name	Lumigan		Xalatan	Saflutan	Travatan
Pharmacological class	Prostamide		Prostaglandin analogue	Prostaglandin analogue	Prostaglandin analogue
Strength	0.03%	0.01%	0.005%	0.0015%	0.004%
Preservative	Benzalkonium chloride 0.005%	Benzalkonium chloride 0.02%	Benzalkonium chloride 0.02%	None	Polyquaternium-1 0.001%
Storage requirements	≤25 °C	≤25 °C	2–8 °C until opened then ≤25 °C for period of use of 4 weeks	2–8 °C	≤25 °C

latanoprost. The pharmacology of bimatoprost itself is not explained wholely by its interaction with known prostaglandin $F_{2\alpha}$ receptors. It is administered once daily in the evening; more frequent administration may lessen the IOP-lowering effect.

Bimatoprost lowers the IOP to a greater extent than any other topical ocular hypotensive (van der Valk et al., 2009), an effect (see Table 55.2) which is sustained for at least 4 years (Williams et al., 2008). It is superior to latanoprost in terms of response rate, fall in IOP and the percentage of patients reaching their target IOP. In some studies, bimatoprost is reported to be as effective as the fixed combination of latanoprost and timolol. Many patients are non-responsive to latanoprost as they do not achieve a fall in IOP greater than 10%, although a large proportion of patients show a 20% or more fall in IOP with bimatoprost. Patients not reaching their target on latanoprost achieved lower IOPs when switched to bimatoprost (Sonty et al., 2008). Such patients achieve better diurnal control with bimatoprost than with a fixed combination of dorzolamide and timolol (Sharpe et al., 2008).

Generally, bimatoprost causes similar ocular side effects to latanoprost and travoprost, but while all the ocular prostanoids cause subclinical ocular inflammation, bimatoprost and travoprost cause this to a lesser degree than latanoprost. However, bimatoprost causes hyperaemia more frequently than latanoprost, although this is described as mild. This may contribute to the higher discontinuation rate seen with bimatoprost therapy (Rahman et al., 2009). To address this issue, the manufacturers of bimatoprost have introduced a lower strength (0.01%) version containing a higher concentration of benzalkonium chloride to aid penetration of the drug. In a 12-month study, the bimatoprost 0.01% was equivalent to bimatoprost 0.03% in lowering IOP and demonstrated improved tolerability, including less frequent and severe conjunctival hyperemia (Katz et al., 2010).

β-Adrenoceptor antagonists

The exact mechanism of action of β-adrenoceptor antagonists (β-blockers) in lowering IOP has not been fully established but is thought to result from the blockade of ciliary β-receptors, preventing the cyclic AMP-induced rise in aqueous secretion, as they have been shown to reduce aqueous humour formation rather than increase outflow. Although there are both β_1- and β_2-receptors in the eye, the latter predominate and even cardioselective β-blockers are thought to work by blockade of β_2-receptors. Genetic factors have been shown to be important in patients' response to this group of drugs (Nieminen et al., 2007, Sidjanin et al., 2008).

Four drugs are available in the UK for topical administration: betaxolol, carteolol, levobunolol and timolol (Table 55.6). β-Blockers have a number of important properties in addition to β-adrenoceptor blockade. These include intrinsic sympathomimetic activity (ISA), cardioselectivity and membrane-stabilising activity, which are all of importance when considering the side effects seen with these agents (Table 55.7). The property of membrane stabilisation is relevant to the incidence of ocular side effects. The absence of anaesthetic properties reduces the number and severity of foreign body and dryness sensations, anaesthesia of the cornea and dry eye syndrome.

Ocular side effects of topically administered β-blockers are shown in Table 55.8.

It has been suggested that those β-blockers that show ISA are less likely to produce bronchospasm and peripheral vascular side effects. Carteolol is the only commercially available drug that shows ISA. The selectivity of cardioselective β-blockers diminishes with increasing dosage, even within the therapeutic range. Betaxolol is the only commercially available topical β-blocker that demonstrates cardioselectivity.

A degree of bradycardia is commonly seen with all β-blockers, and β-blocker eye drops have been identified as the cause of episodes of orthostatic hypotension and syncope in elderly patients (Müller et al., 2006). The use of topical β-blockers in patients on verapamil, diltiazem, disopyramide, quinidine or amiodarone could potentiate bradycardia and should be avoided. Topical β-blockers are generally avoided in patients with normal-tension glaucoma because the nocturnal fall in arterial pressure causes a potentially dangerous reduction in ocular perfusion.

The precipitation of bronchospasm in susceptible patients can occur with the administration of as little as one drop of timolol. Those β-blockers that show cardioselectivity or

Table 55.5 Side effects of prostanoids

Ocular	Systemic
Asthenopia	Abdominal cramp
Allergic conjunctivitis	Asthenia
Blepharitis	Asthma
Blepharospasm	Bradycardia
Browache	Dizziness
Cataract	Dyspnoea
Conjunctival follicles, papillae	Elevated liver function
Conjunctival hyperaemia	Headache
Cystoid macular oedema	Hirsutism
Corneal erosion	Hypertension
Conjunctival oedema	Hypotension
Deepening of lid sulcus	Infection (primarily URTIs)
Distichiasis	Peripheral oedema
Eye discharge	Skin rash
Eye pain	
Eyelash changes – increased number, length, thickness, pigmentation, misdirection, poliosis	
Eyelid oedema, eyelid retraction	
Eyelid and periocular skin darkening	
Foreign body sensation	
Increase in vellus hair on eyelids	
Increased iris pigmentation	
Iritis	
Lid margin crusting	
Localised skin reactions on the eyelids	
Ocular burning, dryness, irritation pruritus, fatigue	
Photophobia	
Punctate epithelial erosions	
Retinal haemorrhage	
Tearing	
Uveitis	
Visual disturbance	

URTIs, upper respiratory tract infection

Table 55.6 Ophthalmic β-blockers

Drug	Brand name	Strength (%)	Daily dosage frequency
Betaxolol	Betoptic® solution	0.5	2
	Betoptic® suspension[a]	0.25	2
Carteolol	Teoptic®	1	2
		2	2
Levobunolol	Betagan®[a] and generic form	0.5	1–2
Timolol	Timoptol®[a] and generic form	0.25	2
		0.5	2
	Timoptol-LA®	0.25	1
		0.5	1
	Nyogel®	0.1	1
	Cosopt®[a] (with dorzolamide 2%)	0.5	2
	Xalacom® (with latanoprost 0.005%)	0.5	1
	DuoTrav® (with travoprost 0.004%)	0.5	1
	Ganfort® (with bimatoprost 0.03%)	0.5	1
	Combigan® (with brimonidine 0.2%)	0.5	2
	Azarga® (with brinzolamide 1%)	0.5	2

[a]Available in unit dose and multidose forms.

Table 55.7 Pharmacological profile of ophthalmic β-blockers

	ß-blocking potency[a]	ISA	Cardioselectivity	Membrane-stabilising activity
Betaxolol	3–10	–	++	+
Carteolol	30	++	–	–
Levobunolol	6	–	–	–
Timolol	5–10	–	–	+

ISA, intrinsic sympathomimetic activity.
[a]Propranolol = 1

ISA are less likely to cause bronchoconstriction, and it has been demonstrated that respiratory function improved in patients whose treatment was changed from timolol to betaxolol or an adrenergic agonist, these same patients having previously been asymptomatic.

All topical β-blockers have been reported to cause bronchospasm; hence, 'at-risk' patients with a tendency to airway disease who require therapy for glaucoma should be treated with

Table 55.8 Ocular and systemic side effects of topical β-blockers

Ocular	Systemic
Allergic blepharoconjunctivitis	*Central nervous system*
Burning and itching	Anxiety
Blurred vision	Depression
Conjunctival hyperaemia	Fatigue
Corneal anaesthesia	Hallucinations
Dryness	Irritability
Foreign body sensation	Sleep disturbances
Macular oedema	*Endocrine*
Nasolacrimal duct obstruction	Hypoglycaemia (insulin induced)
Pain	*Gastro-intestinal*
Punctate keratitis	Nausea
Uveitis	Diarrhoea *Vascular* Arrhythmias Bradycardia Hypotension Peripheral vasoconstriction Reduced stroke volume *Respiratory* Bronchoconstriction Dyspnoea

extreme caution. Prescribers are advised that β-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease unless no alternative treatment is available. In such cases, the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. Lacrimal occlusion with intracanalicular plugs has been shown to almost completely prevent the bronchoconstriction caused by topical timolol in asthmatics by inhibiting or decreasing systemic absorption of the medication.

Ocular β-blockers are generally not contraindicated in diabetes, although a cardioselective agent may be preferable. However, they are best avoided in patients who suffer frequent hypoglycaemic attacks as they may mask the signs and symptoms of acute hypoglycaemia.

Systemic side effects of topically administered β-blockers are shown in Table 55.8.

The long-term benefits of β-blockers on visual function preservation have been shown to be less than would be expected. This may be due to adverse effects on the ocular microcirculation whereby the β-blockers interfere with endogenous vasodilation and cause optic nerve head arteriolar vasoconstriction. The various β-blockers demonstrate marked differences in their vasoconstrictive effect, with betaxolol possibly demonstrating the least vasoconstriction.

Betaxolol

In theory, because of its cardioselectivity, betaxolol should have fewer adverse effects on the pulmonary system. It should also have fewer adverse cardiovascular effects because of comparatively lower systemic β-receptor occupancy after ocular administration. Maximum occupancies for β_1 and β_2 receptors after ophthalmic administration were 52% and 88% for carteolol, 62% and 82% for timolol, and 44% and 3% for betaxolol, respectively. The lack of systemic effects of betaxolol compared with timolol has been highlighted by Easton who reported the case of an 85-year-old lady who developed atrial fibrillation on having her β-blocker eye drops changed from timolol to betaxolol (Easton, 2007)

However, betaxolol is less effective than other β-blockers as an ocular hypotensive agent (van der Valk, 2009). On initiation of treatment, the fall in IOP is slower than with other topical β-blockers. The 0.25% suspension is as effective as the 0.5% solution and is better tolerated by the patient (Yalvac et al., 2007). Experimental studies showed the drug reaches the retina after topical administration and displays a voltage-dependent L-type calcium channel-blocking activity, which probably leads to improved retinal perfusion. This effect may explain the significant improvement in visual field performance seen with betaxolol in a comparison study with timolol in open-angle glaucoma. The significant improvement with betaxolol occurred despite the more effective reductions in IOP with timolol.

Carteolol

It has been suggested that because of the ISA of carteolol, attributable to its metabolite 8-hydroxycarteolol found in the plasma, smaller changes are seen in pulmonary and cardiovascular parameters than are seen with the non-cardioselective β-blockers without ISA. Carteolol appears to be neutral in its effect on serum lipid levels, whereas timolol adversely affects high-density lipoprotein cholesterol (HDL-C) and the total cholesterol/HDL-C ratio. Carteolol is generally well tolerated and has been shown to be as effective as timolol at lowering IOP in the majority of patients. It has a greater vasodilator effect on the retinal and choroidal vasculature than timolol and levobunolol but less than that of betaxolol. It is the least lipophilic of the topical β-blockers and consequently is likely to show a lower incidence of central nervous system side effects.

Levobunolol

Levobunolol is the potent L-isomer of bunolol. It is metabolised to dihydrolevobunolol in the eye, prolonging the drug's half-life and making it one of only two topical β-blockers licensed for once-daily use. It is as effective with once-daily dosing as the usual twice-daily regimen. It is not cardioselective,

showing greater affinity for the β_2-receptor, and does not possess ISA. It is reported to be as effective as timolol 0.5% and metipranolol 0.6% (now discontinued) in lowering IOP and more effective than betaxolol 0.5%. The incidence of allergic contact dermatitis is greater with levobunolol than timolol (Jappe et al., 2006), and a greater percentage of patients on levobunolol than timolol or betaxolol discontinued the drug due to adverse effects (Rahman et al., 2009). Its effect on tear volume and corneal epithelial barrier function is similar to that produced by timolol, and it has less effect on non-invasive break-up time of the precorneal tear film. This may be attributable to its formulation which includes polyvinyl alcohol. Levobunolol appears to have no effect on the retinal and choroidal vasculature.

Timolol

This non-cardioselective β-blocker without ISA was the first to be introduced, and as such is the agent against which all newer β-blockers were compared. It is effective in the long-term treatment of glaucoma, often in conjunction with other antiglaucoma therapy in terms of IOP lowering. Many patients can be placed on once-a-day therapy provided the IOP is maintained at satisfactory levels. However, the presentation of timolol in a prolonged-release formulation (a polysaccharide-based, gel-forming solution) leads to a prolonged corneal contact time and increased penetration of timolol into the eye. This is the preferred form for once-daily administration. Both timolol eye gels, 0.1% and 0.5%, have been shown to be as effective as the 0.5% solution administered twice daily. The 0.1% gel has the advantage of a much lower drug load, giving rise to plasma levels of timolol 10 times lower than achieved after twice-daily dosage of timolol 0.5% eye drops. The concentration of timolol achieved in the aqueous humour following administration of the 0.1% gel formulation, despite being approximately 40% of that following administration of the 0.5% solution is sufficient to occupy 100% of β_1- and β_2-receptors (Volotinen et al., 2009). Timolol is available in combination products with the carbonic anhydrase inhibitors brinzolamide and dorzolamide, the prostaglandin analogues latanoprost and travaprost, the prostamide bimatoprost and the sympathomimetic brimonidine (see Table 55.6).

Sympathomimetic agents

The original sympathomimetic drug used in the treatment of OHT and open-angle glaucoma, adrenaline (epinephrine) and its lipophilic pro-drug dipivefrine have been discontinued. Adrenaline (epinephrine) is an α- and β-adrenoreceptor agonist. It decreases IOP by reducing aqueous inflow via an α-mediated vasoconstriction in the ciliary body and increased outflow due to a dilation of the aqueous and episcleral veins. Adrenaline (epinephrine) is a mydriatic and therefore its use is contraindicated in PACG and in patients who show a shallow anterior chamber, because of the risk of precipitating angle closure. More selective sympathomimetics apraclonidine and brimonidine are in use today.

Apraclonidine

Apraclonidine (a derivative of clonidine) was the first of the selective adrenergic agonists to be introduced. This drug, which acts predominantly on α_2 but also on α_1-receptors, reduces the rate at which aqueous humour is produced due to ciliary vasoconstriction. Eye drops containing apraclonidine 1% are used to control or prevent postsurgical elevation of IOP following anterior segment laser surgery.

Eye drops containing a 0.5% solution are licensed for the short-term adjunctive treatment of patients on maximally tolerated medical therapy who require additional IOP reduction to delay laser treatment or glaucoma surgery, but the benefit for most patients is less than 1 month. Apraclonidine 0.5% is as effective in lowering IOP as brimonidine 0.2%, but has less effect on blood pressure and heart rate. Although an off-licence use, apraclonidine is sometimes used in children in whom brimonidine is strictly contraindicated (Wright and Freedman, 2009).

Ocular and systemic side effects of α_2-agonists are shown in Table 55.9.

Brimonidine

More α_2-selectivity is seen with brimonidine, which results in miosis rather than mydriasis. Vasoconstriction of microvessels is also not seen. It is thought to increase uveoscleral outflow as well as reducing aqueous production. Brimonidine administered twice daily is almost as effective as timolol twice a day at peak. However, bromonidine is significantly less effective at trough, and some consider it to be more efficacious when administered three times a day, the frequency used in the USA. Brimonidine may be used as monotherapy to lower IOP in patients with open-angle glaucoma or OHT who are intolerant of β-blockers or in whom β-blockers are contraindicated, as there is no effect on pulmonary function

Table 55.9 Ocular and systemic side effects of topical α_2-agonists

Ocular	Systemic
Ocular pruritus	Dry mouth/nose
Discomfort	Headache
Tearing	Asthenia
Hyperaemia	Bradycardia
Conjunctival and lid oedema	Depression
Lid retraction, conjunctival blanching and mydriasis (reported after perioperative use of apraclonidine)	
Miosis (reported with brimonidine)	
Uveitis	

and only minimal cardiovascular effect. It may also be used as an adjunctive therapy in those patients whose IOP is not adequately controlled with a single agent as its IOP-lowering activity has been shown to be additive to that of β-blockers and prostaglandin analogues.

A database containing details of drug use in 956 glaucoma patients over 18 years shows that brimonidine had the highest proportion of discontinuations due to adverse effects (Rahman et al., 2009). It has high allergenicity and may increase the likelihood of allergy to preparations subsequently used.

A formulation of brimonidine, brimonidine-Purite 0.15%, given twice daily, has been shown to be as effective as brimonidine 0.2% twice a day. It has a more favourable safety and tolerability profile, a reduced incidence of allergic conjunctivitis and better patient satisfaction and comfort rating. In a 4-month study, co-administration of latanoprost and brimonidine 0.15% results in a greater fall in IOP than co-administration of latanoprost and brinzolamide or dorzolamide (Bournias and Lai, 2009). This product is not available in the UK.

Brimonidine is contraindicated in patients receiving monoamine oxidase inhibitors or antidepressants which affect noradrenergic transmission, and there is the possibility of brimonidine potentiating or causing an additive effect with CNS depressants. Its use is contraindicated in children in whom it causes drowsiness, ataxia, pallor, irritability, hypotension, bradycardia, miosis and respiratory depression (Lai Becker et al., 2009).

Experimental evidence in animals has demonstrated that brimonidine is a potential neuroprotective agent. However, to date, clinical trials have failed to translate into similar efficacy in humans (Saylor et al., 2009).

Commercially available preparations of sympathomimetic agents are shown in Table 55.10.

Miotics

Miotics act to increase the outflow of aqueous humour by a stimulation of ciliary muscle and an opening of channels in the trabecular meshwork. Miotics are directly acting parasympathomimetic agents that act at muscarinic receptors. The only such drug currently available commercially in the UK is pilocarpine.

Miosis is an unwanted incidental effect and can cause considerable difficulties to patients. Reduced visual acuity, especially in the presence of central lens opacities, spasm of accommodation, accompanied by severe frontal headache (browache) and diminished night vision may cause poor adherence in many patients.

Ocular side effects of pilocarpine are shown in Box 55.1. In eyes with narrow angles, PACG may be precipitated by an aggravation of pupillary block. Systemic side effects are due to parasympathetic stimulation and include anxiety, bradycardia, diarrhoea, nausea, vomiting and sweating (Box 55.2).

The onset of action of pilocarpine is 20 min, but its short duration of action necessitates four times daily dosing. The frequency of instillation of pilocarpine eye drops is a major disadvantage, and advances have been made to reduce the inconvenience of a four-times-daily dosage regimen. A slow-release gel preparation, Pilogel (Table 55.11), has been introduced. A single daily application, administered at bedtime, allows low IOP to be maintained for 24 h, with the patient sleeping through the more troublesome ocular side effects.

Box 55.1 Ocular side effects of topical pilocarpine

Allergic conjunctivitis
Blurred vision
Ciliary/conjunctival injection
Ciliary spasm
Induced myopia
Lens changes (chronic use)
Lid twitching
Pain
Pigment epithelial cells
Poor night vision
Posterior synechiae
Pupillary block
Retinal tear/detachments
Uveitis
Vitreous haemorrhage

Box 55.2 Systemic side effects of topical pilocarpine

Bradycardia
Bronchial spasm
Browache, headache
Diarrhoea
Hypotension
Lacrimation
Nausea and vomiting
Pulmonary oedema
Salivation
Sweating

Table 55.10 Available ocular products containing sympathomimetic agents

Drug	Trade name	Strength	Daily dosage frequency
Apraclonidine	Iopidine®	1%	1 h prior to surgery and on completion
	Iopidine®	0.5%	3
Brimonidine	Alphagan®	0.2%	2

Table 55.11 Commercially available forms of pilocarpine

Drug	Trade name	Strength	Daily dosage frequency
Pilocarpine	Generic presentation	0.5–4%	4
	Minims®	2%	4
	Pilogel®	4%	1

Carbonic anhydrase inhibitors

There are many forms of the enzyme carbonic anhydrase, three of which (CA-I, CA-II and CA-IV) are present in ocular tissues. In the ciliary epithelium, the inhibition of CA-II slows the formation of bicarbonate ions and their secretion into the posterior chamber of the eye. This reduces the sodium transport into the posterior chamber and decreases aqueous humour production, resulting in lower IOP. Inhibition of other forms of the enzyme results in many side effects.

Acetazolamide

This is the only systemic carbonic anhydrase inhibitor available in the UK. Although it is amongst the most potent ocular hypotensive agents available, it has limited use in the long-term management of glaucoma due to poor patient adherence following occurrence of side effects. The systemic side effects are shown in Box 55.3.

Paraesthesia occurs in almost all patients on commencement of therapy but usually disappears on continued therapy. The malaise complex can include fatigue, depression, weight loss and decreased libido.

Acetazolamide is also available in injection form, and given either intramuscularly or, preferably, intravenously. It is useful in the preoperative/emergency treatment of closed-angle glaucoma.

Topical carbonic anhydrase inhibitors

The topical carbonic anhydrase inhibitors dorzolamide and brinzolamide are useful alternatives to acetazolamide in glaucoma management. They are licensed as monotherapy for patients with OHT or open-angle glaucoma resistant to β-blockers or those in whom use of β-blockers is contraindicated. Dorzolamide is also licensed for the treatment of pseudo-exfoliative glaucoma, and limited clinical data in paediatric patients are available. Both drugs are licensed as adjunctive therapy to β-blockers and brinzolamide to prostaglandin analogues, although there is evidence to suggest that dorzolamide is as efficacious as brinzolamide when added to latanoprost (Nakamura et al., 2009).

Box 55.3 Side effects of systemic carbonic anhydrase inhibitors

Acidosis
Diarrhoea
Drowsiness
Elevated uric acid
Hypokalaemia
Nausea/vomiting
Malaise complex
Paraesthesia
Sulphonamide crystalluria
Sulphonamide sensitivity
Transient myopia

Table 55.12 Side effects of topical carbonic anhydrase inhibitors

Ocular	Systemic
Blurred vision	Dry mouth
Burning/stinging	Dyspnoea
Conjunctivitis	Headache
Eyelid pain/discomfort	Nausea
Fatigue	Taste perversion
Itching	
Nasolacrimal duct obstruction	
Ocular discharge	
Tearing	

Dorzolamide is used either alone three times a day or concurrently with a β-blocker or twice daily with a prostaglandin analogue. While the licence for brinzolamide states that the drug can be used twice a day as monotherapy, some patients may respond better to a three times daily dosage. Mean changes in IOP with brinzolamide administered twice daily and three times daily and dorzolamide administered three times daily are equivalent. However, the fall in IOP achieved with these agents is less than that seen with timolol 0.5% twice daily.

Side effects similar to those of systemic sulphonamides may occur and should be watched for. The most common side effects are shown in Table 55.12. Of the two topical carbonic anhydrase inhibitors, brinzolamide appears to cause less burning and stinging on instillation due to the neutral pH (7.5) of the formulation. This is reflected in a much greater discontinuation rate with dorzolamide (31%) than with brinzolamide (14%) (Rahman et al., 2009).

Animal studies suggested that both topical carbonic anhydrase inhibitors may improve ocular blood flow independent of the IOP; however, while this has been well established for dorzolamide in humans, data for brinzolamide are limited. It remains to be established whether this effect can help reduce visual field loss in patients with glaucoma.

Combination products

A large number of patients require more than one medication to achieve target pressure. A need for the patient to use two products concomitantly may lead to confusion, with multiple instillation of one product and non-use of the other. Also, if the second drop is instilled too soon after the first, wash-out of the first product with the second drop, overflow of the precorneal tear film and a dilution of both products may occur. In addition, the patient receives a larger dose of preservative which can irritate the eye and

is a common reason for non-tolerance of the regimen. The combination of two drugs in one topical ophthalmic preparation may improve adherence and result in a reduction in preservative load. Single rather than multi-drop combinations are recommended to improve adherence and maintain patients' quality of life.

For a combination of two drugs to be an acceptable alternative to the prescriber, the fixed combination must be more effective than either of the components used alone and at least as effective as the drugs administered separately, that is not demonstrate antagonism. In addition, adverse effects of the fixed combination must not be more numerous or more frequently encountered than with the components administered separately. There are six products in which timolol is combined with a second ocular hypotensive agent. They differ slightly in their therapeutic indications.

Fixed combination of timolol and dorzolamide

A combination of timolol 0.5% and dorzolamide 2% (Cosopt®) was the first topical ocular hypotensive combination to be marketed. It is indicated in the treatment of elevated IOP in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical β-blocker monotherapy is not sufficient. The fixed combination of dorzolamide and timolol is more effective than either timolol or dorzolamide alone, and as effective as its two components administered separately. In a review of its efficacy compared with other ocular hypotensives, an 80% response rate was reported for the fixed combination of dorzolamide and timolol (Yeh et al., 2008). It has also been reported to be a useful agent when used adjunctively with latanoprost, resulting in a further fall in IOP. Although generally well tolerated, the main problem with Cosopt® is burning and stinging on instillation. Although discontinuation of the combination in trials is low, Cosopt ® has been found to be the third most frequently discontinued eye product in practice (Rahman et al., 2009).

Fixed combination of timolol and latanoprost

A combination of timolol 0.5% and latanoprost 0.005%, marketed as Xalacom®, was first launched in the UK in 2001, shortly before the launch of travoprost and bimatoprost. Xalacom® is indicated for the reduction of IOP in patients with open-angle glaucoma and OHT who are insufficiently responsive to topical beta-blockers or prostaglandin analogues. It is administered once a day and has been shown to be more effective when administered in the evening than in the morning (Takmaz et al., 2008). It is unclear whether fixed combinations of prostaglandin analogues with timolol are superior to prostaglandin analogues alone.

Fixed combination of timolol and brimonidine

A combination of timolol 0.5% with brimonidine 0.2% is marketed as Combigan® and is indicated for the reduction of IOP in patients with COAG or OHT who are insufficiently responsive to topical beta-blockers.

The fixed combination has been shown to be superior in reducing IOP than either brimonidine or timolol alone and is as safe and effective as concomitant treatment with the individual components. Use of the combination product has been shown to result in a 24% fall in IOP (Papaconstantinou et al., 2009). Use of the brimonidine/timolol combination results in a greater number of side effects than timolol alone has fewer side effects than brimonidine alone (Sherwood et al., 2006) and fewer cases of allergy than brimonidine used alone (Motolko, 2008).

Fixed combination of timolol and travoprost

A fixed combination of travoprost 0.004% and timolol 0.5% (DuoTrav®) has been shown to be more effective than either of its components and is as efficacious as the components administered concomitantly while fewer side effects are reported with the combination product (Gross et al., 2007). The fixed combination of travoprost and timolol is indicated to decrease IOP in patients with open-angle glaucoma or OHT who are insufficiently responsive to topical β-blockers or prostaglandin analogues. Although the Summary of Product Characteristics states that the dose is one drop in the affected eye(s) once daily, in the morning or evening, it has been shown that an evening dose demonstrates better 24-h pressure control (Konstas et al., 2009).

Fixed combination of timolol and bimatoprost

A fixed combination of bimatoprost 0.03% and timolol 0.5% (Ganfort®) is available for the reduction of IOP in patients with open-angle glaucoma or OHT who are insufficiently responsive to topical β-blockers or prostaglandin analogues. The fixed combination has been shown to be more effective than either of its components used alone and as effective as the components used in their usual dosing regimen, that is bimatoprost once daily in the evening and timolol twice daily, used concomitantly. Conjunctival hyperaemia has been reported more frequently by patients on bimatoprost (39%) than the bimatoprost/timolol fixed combination (23%) with the lowest incidence in those receiving timolol (7%) (Brandt et al., 2008).

Fixed combination of timolol and brinzolamide

A fixed combination of brinzolamide 1% and timolol 0.5% (Azarga®) is a recently launched combination topical ocular hypotensive presentation. The combination is indicated to reduce IOP in adult patients with open-angle glaucoma or OHT for whom monotherapy has produced insufficient IOP reduction. It has greater IOP-lowering efficacy than brinzolamide or timolol alone (Kaback et al, 2008). Brinzolamide/timolol administration leads to a 30–33% fall in IOP at trough and 34–35% at peak and is better tolerated than, and preferred to, the dorzolamide/timolol combination, probably because of the neutral pH (7.2) of the suspension (Manni et al., 2009; Mundorf et al., 2008).

Hyperosmotic agents

Hyperosmotic agents are of great value during PACG emergencies due to their speed of action and effectiveness. The most commonly used agents are oral glycerol and intravenous mannitol, although both isosorbide and urea have been used in the past. Hyperosmotic agents act by drawing water out of the eye and therefore lower IOP. The maximal effect of glycerol is seen within 1 h and lasts for about 3 h, while mannitol acts within 30 min with effects lasting for 4–6 h.

Glycerol

Glycerol is given orally, usually as a 50% solution in water, the dose being 1–1.5 g/kg body weight given as a single dose. It is not a strong diuretic but may cause headaches, nausea and vomiting. Although it is metabolised to glucose in the body, it may be given to diabetics who are well controlled. All practitioners should be aware of the difference in dose in mL required for a 50% solution of glycerol formulated as a 50% w/v solution and one formulated as a 50% v/v solution (Table 55.13).

Mannitol

Mannitol is given as a 20% solution in water for intravenous administration. The dose is 1–2 g/kg body weight up to a maximum of 500 mL given over 30–40 min at a rate not exceeding 60 drops/min. It is a strong diuretic and as large volumes are required, it may cause problems due to cardiovascular overload, pulmonary oedema and stroke. Cerebral dehydration leads to headache and the patient may experience chills and chest pain. Mannitol is now generally preferred over acetazolamide as an initial treatment for PACG.

Patient care

Chronic open-angle glaucoma

When the condition is first diagnosed, patients should be told that the disorder cannot be cured but only controlled by the regular use of the prescribed treatment. As patients may not be aware of progression of the disease, the result of non-adherence with treatment should be made clear and the importance of regular attendance at clinics stressed.

The existence of a patient self-help group, the International Glaucoma Association (http://www.glaucoma-association.com), should be brought to the patient's attention. They will be able to put the patient in contact with their nearest support group.

The patient's technique for instillation of eye drops should be checked and corrected if necessary. Emphasis should be on the dose (one drop), the position of instillation, into the temporal side of the lower conjunctival sac, and the importance of punctal occlusion to minimise systemic side effects.

The preferred times for administration of topical medication should be discussed with the patient. Prostaglandins, prostamides and the gel form of pilocarpine are best administered at bedtime; a 12-hourly regimen should be employed for twice-daily drugs; 8-hourly for drugs given three times a day; and as near a 6-hourly regimen as practical for the

Table 55.13 Doses of hyperosmotic agents used in the treatment of POAG

Oral glycerol 50% at 1 g/kg				i.v. Mannitol 20% w/v[a]		
50% w/v solution		50% v/v solution		Weight	Dose at	Dose at
Weight (kg)	Dose (mL)	Weight (kg)	Dose (mL)	(kg)	1 g/kg (mL)	2 g/kg (mL)
40	80	44.5	70	40	200	400
50	100	50.8	80	50	250	500
60	120	57.2 63.5	90 100	60 70	300 350	– –
70	140	69.9 76.2	110 120	80 90	400 450	– –
80	160	82.6	130	100	500	–
90	180	88.9 95.3	140 150			
100	200	101.7	160			
For each additional 5 kg	Add 10 mL	For each additional 6.4 kg	Add 10 mL			

[a]Maximum dose 500 mL.

aqueous formulation of pilocarpine. β-Blockers given once daily should be administered in the morning. The importance of allowing a reasonable interval between drops should be emphasised. Sometimes, the order of instillation of different types of eye drop is important for pharmacological or practical reasons. For example, the instillation of pilocarpine should always precede that of a sympathomimetic to prevent pain in the eye resulting from a strong miosis following a weak mydriasis. The instillation of aqueous eye drops, which remain in the conjunctival sac for a maximum of 10 min, should precede that of viscous eye drops, for example hypromellose eye drops, or suspensions (e.g. dexamethasone 0.1% eye drops) where the contact time is prolonged.

Eye drops containing benzalkonium chloride should not be instilled if soft contact lenses are in situ. The patient should be instructed to remove the lens immediately before instillation and replace it approximately 30 min later.

As there is a hereditary component to COAG, patients should be told to advise first-degree relatives to be screened. Such people over the age of 40 years are entitled to free eye tests by their optometrist.

Primary angle-closure glaucoma

Patients found to have shallow anterior chambers and narrow angles are normally promptly listed for peripheral iridectomies. However, if the procedure is delayed, they should be advised of the symptoms of an attack of acute PACG and details of the factors that are likely to precipitate an attack so that they can be avoided. They should be advised that there are a number of prescription and non-prescription drugs that they should not take (Lachkar and Bouassida, 2007). When visiting the doctor and purchasing medicines from a pharmacy, the patient should always remember to mention their condition, and the prescriber should ensure that the drug is appropriate for a patient prone to angle closure. Examples of drugs contraindicated in this condition are listed in Table 55.14. Note that the absence of a drug from this list does not imply safety.

Table 55.14 Drugs contraindicated in narrow-angle glaucoma

Therapeutic class		Examples
Antimuscarinics	Topical Antispasmodic Motion sickness Bronchodilator Urinary retention	Atropine, cyclopentolate, homatropine, tropicamide Atropine, dicycloverine, hyoscine, propantheline Hyoscine, promethazine, cyclizine Ipratropium, tiotropium Darifenacin, fesoterodine, flavoxate, oxybutynin, propiverine, solifenacin, tolterodine, trospium
Drugs used in anaesthesia		Glycopyrronium, ketamine, suxamethonium
Antidepressants		Amitriptyline, amoxapine, citalopram, clomipramine, dosulepin, doxepin,duloxetine,fluvoxamine, imipramine, lofepramine, maprotiline, mirtazapine, nortriptyline, paroxetine, phernelzine, reboxetine, sertraline, trazodone, trimipramine, venlafaxine
Antipsychotics		Chlorpromazine, clozapine, flupentixol, fluphenazine, olanzapine, pericyazine, perphenazine, pipotiazine, promazine, risperidone, sulpiride, thioridazine, trifluoperazine, zuclopentixol
Antihistamines		Alimemazine, antazoline, cetirizine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, loratidine, pizotifen
Antiarrhythmics		Disopyramide
Antiepileptics		Carbamazepine, topiramate
Sympathomimetics		Adrenaline, cocaine, dipivefrine, ephedrine, isometheptene, naphazoline, phenylephrine, pseudoephedrine, salbutamol, xylometazoline
Drugs used in the treatment of ADHD		Atomoxetine, dexamfetamine, methylphenidate, ritodrine
Drugs used in the treatment of parkinsonism		Benserazide, carbidopa, entacapone, levodopa, orphenadrine, procyclidine, selegiline, trihexyphenidyl,
Non-steroidal anti-inflammatory drugs		Mefenamic acid
Sulphonamide derived drugs		Acetazolamide, co-trimoxazole, hydrochlorothiazide, sulphasalazine
Miscellaneous		Botulinum toxin, carboprost, paracalcitol, pilocarpine

Following an attack of angle closure and surgical treatment of the disorder, the patient should be told that the drugs previously contraindicated can be safely taken provided that iridectomy/iridotomy remains patent.

Patient adherence

The patient is more likely to comply with the prescribed treatment if the drug or drugs can be administered according to a simple, infrequent dosage regimen and cause no or few, local or systemic side effects.

Thus, a patient treated with a once-daily prostaglandin analogue or prostamide or once- or twice-daily β-blocker would be expected to adhere to the regimen better than someone treated with pilocarpine, with its unfortunate side effects and inconvenient four-times-a-day dosage regimen. Common side effects of topical and systemic medication should be fully discussed with the patient so that the hyperaemia encountered with the prostanoids and the paraesthesia with acetazolamide are not unexpected, leading to premature discontinuation of therapy.

As glaucoma is predominantly a disease of elderly people, physical disability may prevent successful treatment, however conscientious the patient. For example, rheumatoid arthritis may reduce the patient's ability to squeeze the bottle of eye drops, while the tremor of Parkinson's disease can make correct positioning of instillation difficult. Various aids have been introduced to help with correct positioning and squeezing of eye drops, and these should be made available to patients so disabled.

Patients with poor visual acuity can be helped by colour coding of eye drop labels and supplying bottles labelled with large print. Some manufacturers have endeavoured to enhance adherence by including dose-reminder caps and facilitating instillation by supplying aids to open or position the bottle. Other manufacturers have made their eye drop containers easier to squeeze or supply aids to squeeze the bottle. A list of such devices, some of which are available on prescription, others free of charge from manufacturers of drugs used in the treatment of glaucoma is available on the International Glaucoma Association's website (http://www.glaucoma-association.com/).

Where self-medication is impossible, a simple infrequent dosage regimen is more likely to be achieved when a relative, a neighbour or the district nursing service becomes responsible for administration of the medication. In these cases, a drug administered once daily, such as a long-acting timolol preparation or a prostaglandin analogue or bimatoprost, has an obvious advantage over one that should be administered at 12-hourly intervals. If pilocarpine is required and bedtime administration is possible, the prescribing of pilocarpine ophthalmic gel will be more practical than pilocarpine eye drops, the administration of which is totally impractical for anyone other than someone living with the patient.

Common therapeutic problems in glaucoma are listed in Table 55.15.

Table 55.15 Common therapeutic problems in glaucoma

Problem	Comments
Lack of adherence	Treatment perceived to be worse than disease Complex multiple drug regimens Frequency of dosing Inability to differentiate between different types of medication Inability to instil medication
Contraindication to therapy	Pilocarpine in uveitis β-Blockers in asthma, bradycardia, heart block, uncontrolled heart failure Prostaglandin analogues and prostamides in aphakia Wide range of topical and systemic drugs in shallow anterior chamber α_2-agonists in depression Carbonic anhydrase inhibitors in renal failure
Intolerance to drug	Miosis and ciliary spasm with pilocarpine Red eye with prostaglandin analogues, bimatoprost Bronchospasm with β-blockers Paraesthesia with acetazolamide
Use outside licensed indications	Paediatric patients Pregnant women Nursing mothers
Hypersensitivity	To active drug To preservative in multidose formulations

Case studies

Case 55.1

Mrs SJ, a 49-year-old nurse with asthma, visits her optometrist for an annual eye check because her father has glaucoma. Although the optometrist has never detected any problem before, on this occasion he decides to refer her to an ophthalmologist because her IOPs are 27 left eye and 20 mmHg right eye, even though there are no signs of glaucomatous damage.

The ophthalmologist confirms the optometrist's findings and measures this lady's central corneal thickness at 570 μm. In accordance with National Institute for Health and Clinical Excellence (2009) guidelines, she decides to initiate ocular hypotensive therapy in the left eye.

Question

What treatment should the ophthalmologist prescribe?

Answer

It is recommended that patients under 60 years of age with OHT or suspected COAG and a central corneal thickness of between

555 and 590 µm are treated with an ocular hypotensive agent (National Institute for Health and Clinical Excellence, 2009). The recommended therapy is a topical β-blocker which typically reduces IOP by approximately 25%. However, β-blockers are contraindicated in patients with asthma and the ophthalmologist needs to choose an alternative agent with equivalent or better efficacy.

If β-blockers are contraindicated, a prostaglandin analogue could be prescribed.

The ophthalmologist initiates latanoprost eye drops 0.005%, one drop in the left eye at night and arranges to see Mrs SJ again in 3 months to assess her response to therapy.

Case 55.2

Mr FT, a 67-year-old retired bank manager, has COAG in both eyes and a history of herpes simplex infection of the right eye. His IOP has been controlled on timolol eye drops 0.5% twice a day in each eye which he tolerates well. At this appointment, the optometrist working in the hospital's clinic noted an increased IOP in the right eye and deterioration in the visual field in that eye. She feels that Mr FT requires an additional ocular hypotensive agent in his right eye and asks the ophthalmologist in the clinic for an opinion.

Question

What treatments should the ophthalmologist consider for Mr FT?

Answer

Patients with COAG would normally be offered a prostaglandin analogue as first-line treatment, but in Mr. FT's case this therapy is contraindicated because of his history of herpes simplex infection. He is already on a β-blocker, the other group of drugs recommended as first-line therapy, so the ophthalmologist should consider surgical intervention or the addition of a second ocular hypotensive agent. Mr. FT is not at all keen on the idea of surgery and expresses a preference for further medical therapy. Other classes of ocular hypotensives which have an additive effect with timolol are the carbonic anhydrase inhibitors brinzolamide and dorzolamide and the sympathomimetic brimonidine. The ophthalmologist explains to the patient that he can continue to use timolol in both eyes and an additional drop in his right eye or use timolol in his left eye and a combination drop containing timolol and a second agent in his right eye. Mr FT decides on the latter option and leaves with a prescription for timolol eye drops 0.5%, twice daily for his left eye and Azarga® eye drops, twice daily for his right eye together with a date for a review appointment in 2 months.

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56 Drug-induced skin disorders

S. Walsh and D. Creamer

Key points

- Drug-induced skin reactions are common, accounting for 30% of all reported adverse drug reactions.
- Diagnosis requires a comprehensive drug history and knowledge of likely causative drugs.
- Treatment involves drug withdrawal and general supportive measures.
- All skin eruptions will cause morbidity but the severe reactions, such as Stevens–Johnson syndrome/toxic epidermal necrolysis, are associated with appreciable mortality.
- Certain individuals are at higher risk of drug eruptions, for example patients with HIV infection.
- Some types of drug reaction can cause systemic as well as skin involvement, affecting the hepatic, haematological and lymphatic systems.

Adverse drug reactions (ADRs) are an inevitable consequence of modern drug therapy. They are an important cause of iatrogenic illness in terms of morbidity and mortality. ADRs can cause serious harm to the patient, as well as carrying medico-legal and economic consequences. Fortunately, only about 2% of all drug-induced skin reactions are severe and very few are fatal. However, all drug-induced skin eruptions can cause morbidity, affect the patient's confidence in the prescriber and future adherence with medication. Therefore, it is important that all drug-associated rashes are carefully evaluated and documented. It is essential that the patient is made aware of his or her sensitivity, as subsequent exposure to the drug may cause a more severe eruption. At population level, both reporting of adverse events via the MHRA 'Yellow card scheme' and post-marketing surveillance of new drugs have a role in identifying patterns of drug eruption.

It is important to remember that the potential of an individual drug to cause a skin eruption is variable. Any drug can potentially cause any reaction pattern in the skin. Some drugs such as ferrous sulphate seldom produce a rash, while others, for example, carbamazepine, penicillin antibiotics and sulphasalazine, are far more likely to precipitate a skin eruption.

Diagnosis

It is often difficult to determine the cause of a drug-induced eruption because:

- Almost any drug can affect the skin
- Unrelated drugs produce similar reactions
- The same drug may produce different reaction patterns in different patients
- Some drug reactions are difficult to distinguish from specific skin diseases such as acne, eczema and psoriasis.

In most cases, diagnosis of a drug-induced skin eruption is based on the history and the temporal association of the onset of the rash to the commencement of the medication. Particular difficulties are presented by the patient taking combined preparations, for example co-tenidone, which contains both a diuretic and a β-blocker. Excipients contained in medication, such as preservatives, stabilisers or colours, may be the culprit rather than the drug itself. Changes in brand of medication may for this reason provoke a skin reaction in someone who appears to have been established on a drug for some time and suddenly develops a rash. Patients may be taking preparations acquired over the counter, or from an alternative practitioner, which they may not immediately volunteer when asked about current medication. If a patient presents with a rash and is currently taking, or has recently finished, medication it is important to:

- Take an accurate drug history, including over-the-counter medicines, herbal and homeopathic preparations and any injections. Record both generic and brand name of medicines.
- Ask if the patient has any history of drug sensitivity.
- Ascertain when the eruption started in relation to drug use (the latency of onset of the eruption).

Definitive diagnosis of a drug-induced dermatosis would require drug re-challenge; however, this is not recommended due to the possibility of provoking a more severe reaction on second exposure (Li Wan Po and Kendall 2001).

Drug-induced skin disorders

In this chapter, drug reactions will be considered under the following headings: drug reactions causing changes to skin function; mild drug-induced skin disorders; severe drug-induced skin disorders.

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Drug reactions causing changes to skin function

Some drugs alter the ability of the skin and associated structures (hair and nails) to perform their function normally.

Abnormal photosensitivity

Drugs may induce an excessive sensitivity to sunlight. Ultraviolet wavelengths of sunlight (290–400 nm) are able to interact with certain drugs in the skin to provoke abnormal photosensitivity. An eruption occurring on all uncovered skin implicates exposure to a systemic photosensitising agent, for example, a patient who commences bendroflumethiazide and subsequently develops sunburn on a cloudy day. A localised eruption indicates a reaction to a locally applied topical photosensitiser and subsequent exposure to light. This may be seen in individuals who are sensitive to a component of sunscreens such as benzophenone, a chemical sun block.

Drug-induced photosensitivity can be either phototoxic or photoallergic (Box 56.1). Phototoxic reactions, which are more common, resemble severe sunburn and can progress to blistering. They are dose dependent for both the drug and sunlight, occur within 5–15 h of taking the drug and subside quickly on drug withdrawal. Photoallergic rashes are usually eczematous, but may be lichenoid, urticarial, bullous or purpuric. They are not dose dependent and occur following exposure to normal amounts of sunlight exposure. The onset can be delayed by weeks or months, while recovery is often slow following drug withdrawal. Rarely, a photoallergic state can persist for years after the drug responsible has been discontinued.

Patients receiving known photosensitising drugs should be advised to avoid strong sunlight. They should also be advised to use a broad-spectrum topical sunscreen, providing both UVA protection (indicated by the 'star rating' on the bottle) and UVB cover (indicated by the sun protection factor, SPF).

Box 56.1 Drugs causing light-induced eruptions

Topical preparations
Topical non-steroidal anti-inflammatory drugs (NSAIDs)
Components of sunscreen such as para-aminobenzoic acid (PABA), benzophenone

Systemic drugs
Phototoxic reactions
Amiodarone
Nalidixic acid
NSAIDs
Chlorpromazine
Tetracyclines
Photoallergic reactions
Griseofulvin
NSAIDs
Sulphonamides
Sulphonylureas
Thiazide diuretics

Pigmentary changes

The skin's colour can be altered by drugs: hyper-pigmentation, hypo-pigmentation and discoloration can all potentially be induced by a variety of medicines (see Fig. 56.1 and Table 56.1). Pigmentary changes can be widespread or localised. The most common examples of localised pigmentation are the facial blue–black pigmentation in individuals on amiodarone or minocycline, and melasma facial pigmentation occurring in some women taking the combined oral contraceptive pill. Generalised pigmentary change induced by drugs is rare, but can occur with chemotherapeutic agents such as bleomycin. This may have the appearance of generalised hyper-melanosis, or may take on a more flagellate appearance with multiple linear areas of hyper-pigmentation.

The mechanism of drug pigmentation is not always known; however, proposed pathogenetic mechanisms are:

(1) Drug or drug metabolite deposition in the dermis and epidermis. An example of this would be agyria, in which systemic absorption of silver from, for example, topical silver sulphadiazine, causes a slate-grey discolouration of the skin.
(2) Enhanced melanin production with or without an increase in the number of active melanocytes. This appears to be the pathogenetic mechanism in melasma and also bleomycin-induced pigmentation (Moncada et al., 2009)

Nail changes

The growth and colour of finger and toenails can be modified by drugs. Abnormalities of texture and architecture of the nail unit can also be drug-induced. Blue discoloration of the nails can result from therapy with mepacrine, while a blue–black pigmentation may accompany treatment with minocycline and certain cytotoxic drugs such as hydroxyurea.

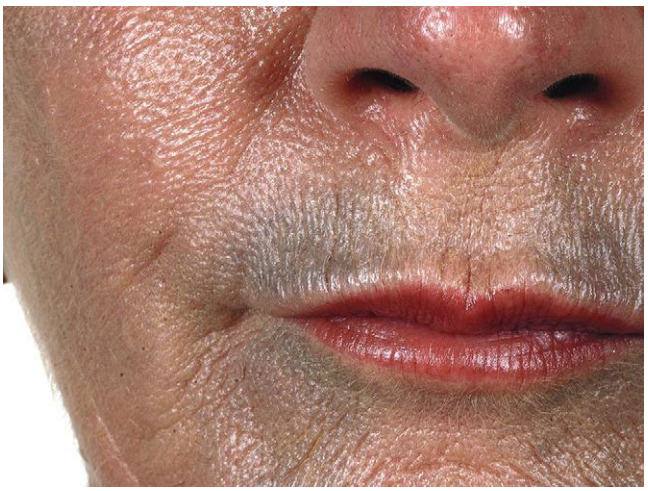


Fig. 56.1 Minocycline pigmentation: this female patient was taking minocycline for 2 years for treatment of rosacea and developed unsightly grey pigmentation round the mouth. This did not respond to stopping the medication.

Table 56.1 Drugs causing skin pigmentation

Drug	Pigmentation
Amiodarone	Blue-Grey
Anticonvulsants	Brown
Antimalarials	Blue-Grey
β-Blockers	Brown
Imatinib	Hypo/Hyperpigmentation
Imipramine	Blue/Grey
Mepacrine	Blue/black
Methyldopa	Brown
Oral contraceptives	Brown spots/patches
Phenothiazines	Brown/Blue-Grey
Psoralens	Brown
Tetracyclines	Blue-Black

Potassium permanganate solutions will dye nails brown. White nails (leuconychia) can result from treatment with chemotherapy agents, especially, cyclophosphamide, doxorubicin and vincristine. Beau's lines, transverse depression of the nail, represent interruption to the normal growth of the nail matrix, and are caused by systemic infection, metabolic upset, or occasionally by drugs. In the drug-induced form, the most common cause is again chemotherapy agents, similar to those which cause leuconychia.

Onycholysis is characterised by separation of the nail plate from the underlying nail bed. Any cytotoxic agent may induce onycholysis by direct toxicity to the matrix. Photo-onycholysis describes lifting of the nail plate and is caused by the combination of a photosensitising drug, for example minocycline, oxytetracycline and UVA exposure.

Hair changes

Drugs may exert an effect on the hair follicle itself or on the growth cycle of hair. The cycle of hair growth involves anagen (the growth phase of the hair), catagen (the resting phase) and telogen (the shedding phase). Either loss of hair or excessive growth of hair may result.

Loss of hair. Drug-induced alopecia (Box 56.2) may be partial or complete. The temporal relationship between the introduction of the drug and the subsequent loss of hair depends on the part of the hair cycle with which the drug interferes. Cytotoxic drugs interfere with the 'anagen' or growth phase of the hair cycle, and so loss is rapid and complete; it begins shortly after administration of the drug and the effect is dose dependent and fortunately reversible, but a delay of several weeks is common before regrowth begins.

Box 56.2 Drugs causing hair disorders

Alopecia
Acetretin
Anticoagulants
Anticonvulsants
Antithyroid drugs
β-Blockers
Cimetidine
Cytotoxic drugs
Gold salts
Interferons
Isotretinoin
Leflunomide
Lithium
Sodium valproate
Statins
Tacrolimus

Hirsutism/hypertrichosis
Acetazolamide
Anabolic steroids
Androgens
Corticosteroids (topical and systemic)
Ciclosporin
Danazol
Minoxidil
Oral contraceptives
Penicillamine
Phenytoin
Tamoxifen
Verapamil

Delayed hair loss following the introduction of a drug is a more insidious process and may not be noticed immediately by the patient. In this scenario, the drug is often interfering with the 'telogen' or shedding part of the hair cycle, moving follicles through this phase more quickly. Hair is shed at a rate that exceeds that at which the follicles can produce new hair, resulting in a thinning effect. Given the length of the hair cycle, this type of hair loss can occur 2–4 months after a drug is initiated. Retinoid therapy, including isotretinoin prescribed for acne, or acitretin for psoriasis, may induce a telogen alopecia.

Androgens promote shrinking of hair follicles and shorten duration of the growth stage of the hair-follicle cycle (anagen stage). Drugs with androgen activity can induce male-pattern baldness, for example exogenously administered testosterone, which may be prescribed for hypogonadism in men and occasionally in post-menopausal women as an adjunct to hormone replacement therapy. Oestrogens are known to prolong the anagen stage and counteract androgenetic alopecia. Oestrogenic stimuli may cause the hair follicle to shift into anagen phase and vice versa. Use of the oestrogen receptor antagonist tamoxifen in women with breast cancer can exacerbate female pattern hair loss. Tamoxifen competes for the oestrogen receptor and produces an environment with relative hyperandrogenism, which may augment the androgen action on follicles.

Excessive hair. Hirsutism is excessive hairiness, especially in women, in the male pattern of hair growth, while hypertrichosis is the growth of hair at sites not normally

hairy. Both conditions can be drug induced and in some cases the same drug can produce both patterns of hair growth (see Box 56.2). The capacity of minoxidil to produce hypertrichosis was noted during early trials of this drug as an antihypertensive. It is infrequently used for its originally intended purpose, as it produces profound postural hypotension, but its most noticeable side effect has been exploited as a topical preparation for the treatment of male pattern baldness.

Changes to the skin's immune system and skin malignancy

The skin's innate immune surveillance system detects and repairs UV-induced DNA damage thus limiting the tendency to cutaneous carcinogenesis. Drug-induced immunosuppression places an individual at an increased risk of skin cancer, notably squamous cell and basal cell carcinomas. As well as a reduction in immune surveillance, immunosuppression increases susceptibility to the human papilloma virus, some strains of which may predispose to the development of squamous malignancy. Patients taking drugs such as azathioprine, ciclosporin, tacrolimus, mycophenolate mofetil and chemotherapeutic agents should be counselled about the importance of sun protection to minimise the risk of development of malignant and pre-malignant skin cancers. Certain high-risk patients on immunosuppressant drugs, particularly renal transplant recipients, should undergo formal follow-up with skin monitoring by a dermatologist on a yearly basis.

Mild drug-induced skin disorders

Mild drug reaction patterns in the skin are numerous; some of the more commonly seen morphologies are discussed in this section.

Drug-induced exanthems

A drug-induced exanthem (widespread rash) is the most common type of drug reaction in the skin. Exanthems are characterised by erythema (redness) and may be morbilliform (resembling measles) or maculopapular (a mixture of flat and raised areas) (see Fig. 56.2). Less frequently there may be blisters, which may be small (vesicles) or larger (>5 mm, bullae), and the skin may feel hot, burning or itchy.

The proportion of the body surface area (BSA) involved varies from case to case but when severe, involving more than 90% of the BSA, the presentation is referred to as 'erythroderma', which is discussed later. In theory, any drug is capable of producing a drug-induced exanthem in the skin, but in practice, common causes include antibiotics (e.g. sulphonamides, ampicillin, isoniazid), anticonvulsants (e.g. phenytoin, carbamazepine) and antimalarials (chloroquine).

Most drug-induced exanthems begin within 7 days of commencing a drug, the mechanism being a delayed (type IV) hypersensitivity (Burns et al., 2004). If the drug can be identified, it should be stopped, appropriate symptomatic relief instituted with antihistamines and topical steroids. A clear record of the reaction should be made in the patient's notes.



Fig. 56.2 Drug exanthem: maculopapular, itchy eruption appeared 4 days following the introduction of a course of co-amoxiclav for a respiratory tract infection. Note the linear marks indicating excoriation (scratching) on the left posterior shoulder.

Both the patient and his primary care doctor should be made aware of the reaction for the purposes of future avoidance.

An exanthematous reaction commonly occurs following administration of ampicillin (or its derivatives, including amoxicillin) to patients suffering from glandular fever (infectious mononucleosis). It does not usually represent a true penicillin allergy, but a complex interplay between viral factors (infectious mononucleosis being caused by Epstein Barr virus) and drug epitopes (Burns et al., 2004). This reaction to the drug would not be expected to be seen in the same patient in the absence of the virus.

Urticaria and angioedema

Urticaria, also known as hives, describes the appearance of red, itchy weals on the skin (Fig. 56.3). Angioedema is a more serious, related condition in which the patient develops deep soft-tissue swellings, mostly notably on the face. Urticaria and angioedema can be either allergic, a reaction between an antigen and specific mast cell-bound IgE, or non-allergic.

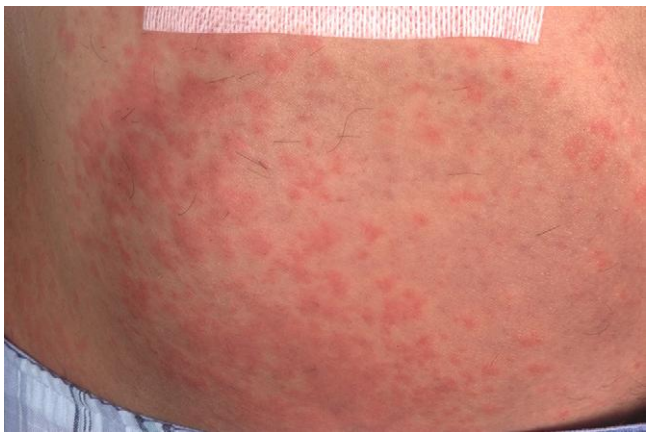


Fig. 56.3 Urticaria: patient developed the classic raised red itchy weals of urticaria following the commencement of ibuprofen for musculoskeletal pain.

Drugs are recognised triggers of urticaria and angioedema (Box 56.3) and can also exacerbate pre-existing urticaria. The most important culprits are the NSAIDs and opiates, both of which lower the threshold for mast cell degranulation. ACE inhibitors and angiotensin receptor blockers (ARBs), for example candesartan, can provoke angioedema in a susceptible individual.

Drug-induced urticaria/angioedema can be a cutaneous manifestation of anaphylaxis, and in this situation, urgent medical attention is needed with administration of adrenaline, antihistamine and intravenous corticosteroid.

Pruritus

Pruritus (itching) can accompany a drug rash, or may be an isolated symptom provoked by a medication. The most common trigger of drug-induced pruritus is the administration of opiate analgesics and their related synthetic derivatives such as tramadol. Opiate-induced pruritus is centrally mediated, rather than by peripheral nerves; therefore, antihistamines do not, in general, ameliorate the itch. This can pose a particular problem in the palliative care setting where opiate analgesics are required regularly.

Fixed drug eruptions

Fixed drug eruption is characterised by one or more inflammatory patches that recur at the same cutaneous or mucosal site(s) each time the patient is exposed to the offending drug (Fig. 56.4). The eruption usually involves the torso, hands, feet, face or genitalia, and is characterised by a deep red, circular, well-demarcated patch. They take between 2 and 24 h to develop following drug ingestion. On the first drug exposure, there is usually only one lesion, but subsequent exposure can result in multiple lesions.

The group of drugs with the potential to cause a fixed drug eruption is virtually limitless, but some of the drugs more commonly responsible are listed in Box 56.4.

Once the drug has been stopped, the lesions resolve and may leave an area of post-inflammatory hyperpigmentation. This may be the only physical sign at the time the patient presents. Topical steroids may ameliorate the symptoms.

Box 56.3 Drugs causing urticaria/angioedema

Antibiotics (particularly penicillins, and especially when given by the parenteral route)
Barbiturates
ACE inhibitors
Angiotensin receptor blockers
Levamisole
NSAIDs
Opiate analgesics
Phenolphthalein
Quinine
Rifampicin
Sulphonamides
Thiopental
Vancomycin



Fig. 56.4 Fixed drug eruption: female patient developed persistent macular inflamed areas on her upper chest wall 2 months after starting a new combined oral contraceptive pill. A fixed drug eruption was suspected and the lesions resolved after stopping the medicine.

Box 56.4 Drugs causing fixed drug eruptions

Ampicillin
Aspirin
Barbiturates
Dapsone
Metronidazole
NSAIDs
Oral contraceptives
Phenytoin
Quinine
Sulphonamides
Tetracyclines

Acneiform eruptions

Acne may be drug-induced or drug-exacerbated. One of the most commonly prescribed drugs to produce an acneiform eruption is corticosteroid, in either topical or oral form. Illicit use of anabolic steroids by athletes can also produce this effect, occasionally in its most severe form, acne fulminans. Other drugs which may worsen or provoke acne include ciclosporin, lithium and progesterone-only oral contraceptives.

A new class of anticancer drug, endothelial growth factor receptor antagonists, for example cetuximab, commonly produce an acneiform eruption. The papules and pustules which occur are more monomorphic than those seen in idiopathic acne. Interestingly, studies have shown that there is a positive correlation between the severity of the acneiform eruption and response of the cancer to the treatment (Saltz et al., 2003; Susman, 2004) Most drug-induced or drug-exacerbated acne can be managed with the same treatments as used in idiopathic acne, such as topical agents, oral tetracycline antibiotics, erythromycin, or in severe cases, oral retinoids. Examples of drugs which may cause an acneiform eruption are given in Box 56.5.

Box 56.5 Drugs causing acne

Androgens (in women)
Corticosteroids (oral and topical) and ACTH (including inhaled preparations)
Ciclosporin
EGFR antagonists (cetuximab)
Ethambutol
Haloperidol
Isoniazid
Lithium
Oral contraceptives
Phenobarbital
Phenytoin
Propylthiouracil

EGFR, Epidermal growth factor receptor.

Psoriasiform eruptions

Drugs can either exacerbate psoriasis in predisposed patients or induce psoriasiform rashes in previously unaffected patients (see Box 56.6). The psoriasiform eruptions mimic psoriasis and are characterised by itchy, scaly red patches on the elbows, forearms, knees, legs and scalp. Drugs which have a well-established effect of worsening pre-existing psoriasis include β blockers, lithium, antimalarials and ACE inhibitors.

Lichenoid eruptions

Drug-induced lichenoid eruptions (see Box 56.7) resemble lichen planus, occurring as flat mauve lesions. However, they may be atypical, showing scaling and confluence. The lesions can be seen at any site, but are found mainly on the forearms, neck and on the inner surface of the thighs. The eruption resolves with drug withdrawal, with or without topical steroids, but post-inflammatory hyperpigmentation is often long lasting.

Eczematous eruptions and contact dermatitis

Retinoid drugs (such as isotretinoin, acitretin and alitretinoin) and statins have a drying effect on the skin, and can exacerbate pre-existing eczema or precipitate eczema in a susceptible individual. Irritant contact dermatitis may be seen in preparations with an alcohol base, such as topical antibiotics, or with the application of topical preparations which are inherently irritant such as benzoyl peroxide, tar or dithranol.

Box 56.6 Drugs which exacerbate psoriasis

ACE inhibitors
Antimalarials – chloroquine, mepacrine
Biological therapy targeting tumour necrosis factor alpha (TNF-α) (occasionally – slightly paradoxical given that such drugs are also given to *treat* psoriasis)
β-Blockers (most frequently atenolol, oxprenolol and propranolol)
Corticosteroids, for example prednisolone
G-CSF
Lithium
NSAIDs

G-CSF, Granulocyte-colony stimulating factor.

Box 56.7 Drugs causing lichenoid eruptions

Antimalarials – chloroquine, mepacrine
Aspirin
ACE inhibitors
β-Blockers
Calcium channel blockers, for example amlodipine, nifedipine
Carbamazepine
Ethambutol
Gold salts
Imatinib
Interferon-α
Lithium
Methyldopa
NSAIDs
Penicillamine
Phenothiazines
Quinine
Sulphonylureas

Allergic contact dermatitis is a delayed (type IV) hypersensitivity reaction which can develop to any topical preparation, for example eye drops in a sensitised individual. Most commonly, this will be to excipients contained in the preparation, such as preservatives, for example sodium metabisulphite, fragrances or stabilisers, but may be to the drug itself. In all cases of irritant or allergic contact dermatitis, the patient should be counselled to stop the preparation. Patch testing carried out by a dermatologist is a useful way of investigating patients in whom a diagnosis of allergic contact dermatitis is suspected.

Erythema nodosum

Erythema nodosum is an acute inflammatory reaction with painful subcutaneous nodules, usually but not exclusively found on the shins. Erythema nodosum is usually a complication of infection with, for example, streptococcus or tuberculosis, or is a cutaneous manifestation of an inflammatory condition such as sarcoidosis. In its drug-induced form, it may be caused by oral contraceptives, sulphonamide antibiotics, salicylates, penicillins and gold salts.

Severe drug-induced skin disorders

Erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are all idiosyncratic, immunologically mediated severe drug eruptions. For our purposes, these diseases may be considered to be on a spectrum, from the mild and self-limiting at one end (EM) to the fulminating severe at the other (TEN).

Erythema multiforme

EM is an eruption of target-like lesions which are characterised by concentric red and pale rings with, in severe cases, central blistering. EM typically occurs on the limbs rather than the trunk but mucous membrane surfaces, such as the eye, the mouth and the genital tract, may also become involved. A significant proportion of EM cases are caused by infection,

Box 56.8 Drugs causing erythema multiforme

Allopurinol
Antiretrovirals, for example nevirapine
Barbiturates
Carbamazepine
Cimetidine
Dapsone
Gold salts
Isoniazid
Lamotrigine
Leflunomide
Macrolide antibiotics
Mefloquine
NSAIDs
Penicillins
Phenytoin
Rifampicin
Sulphonamides

particularly herpes simplex virus reactivation; however, in some patients, EM is triggered by a drug (see Box 56.8). Drug-induced EM will usually present within 2 weeks of starting a new medication. Once the responsible drug has been stopped, treatment is symptomatic with paracetamol, topical steroids and appropriate topical therapy for the mouth and other involved mucosal surfaces.

Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are terms used to describe a life-threatening, mucocutaneous drug hypersensitivity syndrome characterised by blistering and epidermal sloughing (Fig. 56.5). In SJS, there is epidermal detachment of <10% BSA, in TEN there is detachment of >30% of the BSA, while cases with 10–30% involvement are labelled SJS/TEN overlap. The systemic problems which accompany widespread epidermal loss such as high losses of heat and fluid, and the heightened risk of infection due to diminished barrier function can cause serious morbidity, similar to extensive burns. TEN carries a mortality rate of approximately 30%, but this can rise to 90% mortality in the presence of co-morbidities. HIV-infected patients and patients with systemic lupus erythematosus (SLE) have an enhanced risk of developing SJS/TEN. Drugs causing SJS/TEN are listed in Box 56.9.

Clinical features. A prodrome of fever, malaise, and upper respiratory tract symptoms may precede the eruption by a few days. Involvement of the mucous membranes of the eyes, mouth, and nose is a prominent early feature. Eye involvement results in blepharitis, haemorrhagic conjunctivitis, mucus secretion, and pseudomembranes. Ophthalmological input is required early if long-term sequelae such as blindness from corneal opacities and synechiae are not to occur. Urethral involvement must also be anticipated and the patient catheterised if strictures are not to complicate the disease course. Mouth involvement causes an erosive and haemorrhagic mucositis. On the skin, dusky red macules 1–3 cm in diameter appear at any site and evolve to become confluent. The skin lesions pass through vesicular and bullous phases before epidermal detachment occurs. Shearing pressure to the skin causes detachment of involved epidermis (positive Nikolsky's sign). In TEN, there is widespread epidermal loss and sloughing of the necrotic epidermis which peels back to leave large areas of exposed dermis. Denuded dermis exudes serum, becomes secondarily infected and readily bleeds. The patient is in severe pain and is usually extremely ill. The visceral manifestations that result from widespread epithelial loss include pneumonia, pancreatitis, thromboembolic disease, renal and hepatic impairment.

The patient with SJS/TEN will require full supportive care, preferably in an intensive care unit. Patients with SJS with less extensive involvement may be managed in a lower-dependency environment, but should be monitored closely



Fig. 56.5 Stevens–Johnson syndrome is a serious, idiosyncratic reaction of the skin and mucous membranes to a drug. It results in blistering and subsequently widespread epidermal loss and can have a high mortality rate.

Box 56.9 Drugs causing Stevens–Johnson syndrome and toxic epidermal necrolysis

Allopurinol
Antiretrovirals, for example nevirapine
Carbamazepine
Co-trimoxazole
Dapsone
Gold salts
Lamotrigine
Leflunomide
NSAIDs, for example meloxicam, diclofenac
Penicillins, for example amoxicillin, ampicillin
Phenobarbitone
Phenolphthalein
Phenylbutazone
Phenytoin
Sulphadiazine
Sulphasalazine
Tetracyclines, for example doxycycline

for signs of progression in the first 48 h of admission. A multidisciplinary approach, including dermatologists, ophthalmologists and intensive care physicians, is critical to a successful outcome. Following drug withdrawal, the management is supportive, including prompt treatment of infection, careful attention to thermoregulation, fluid balance and skin care, and introduction of appropriate eye and lid care. The literature has failed to identify one treatment which definitively improves outcomes, but agents which have been used include systemic steroids, ciclosporin and intravenous immunoglobulin.

Box 56.10 Common causes of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Allopurinol
Antiretrovirals, for example efavirenz
Carbamazepine
Cotrimoxazole
Lamotrigine
Minocycline
Phenobarbitone
Phenytoin
Sulphadiazine
Sulphasalazine
Vancomycin

Drug Reaction with Eosinophilia and Systemic Symptoms

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is sometimes known as Drug-Induced Hypersensitivity Syndrome (DIHS) and is a distinct, severe and potentially fatal drug-induced skin disorder. The drugs commonly associated with this syndrome are listed in Box 56.10.

Typically, the dermatosis of DRESS is an extensive, inflammatory, maculo-papular exanthem. Other skin signs may also be present including pustules, purpura, blisters, target-like lesions and facial oedema (Fig. 56.6). To meet the diagnostic criteria, there will also be a haematological abnormality, either a raised eosinophil count ($>1.5 \times 10^9$/L) or the presence of atypical lymphocytes on the blood film. There is prominent systemic involvement in DRESS, most commonly fever, lymph node enlargement and liver function abnormalities. Less typically, there is renal, pulmonary or cardiac involvement.

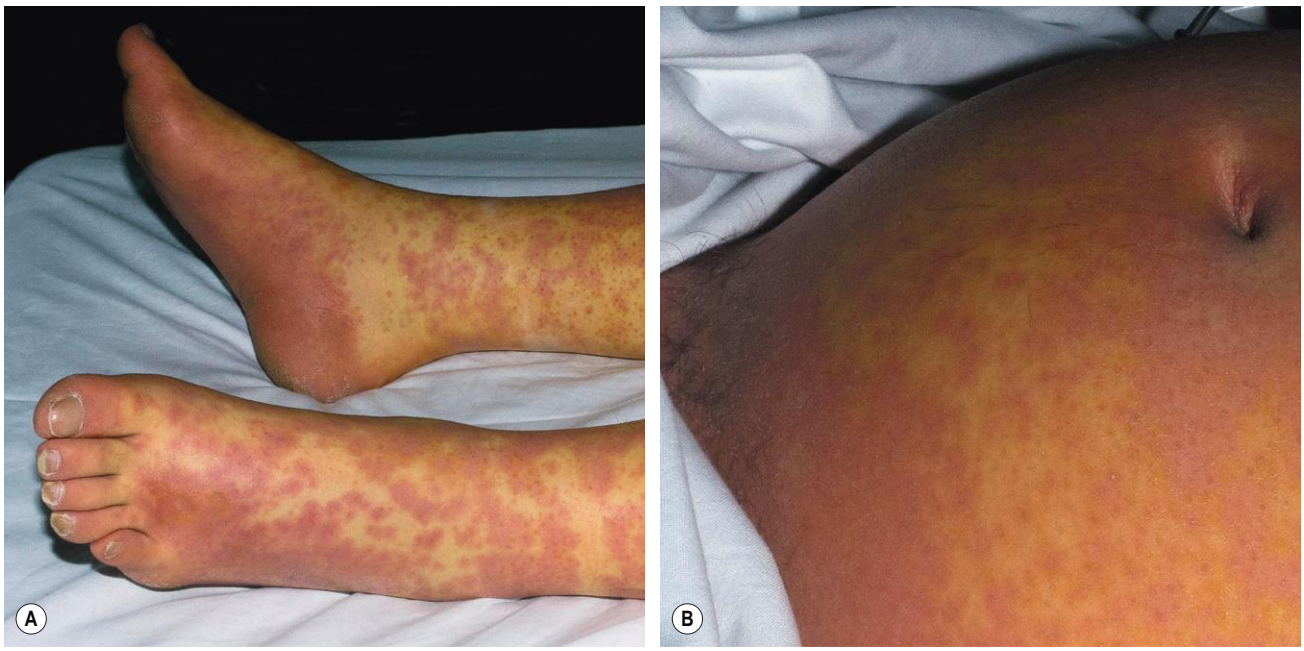


Fig. 56.6 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): female patient developed a severe systemic reaction following commencement of phenytoin for seizure prophylaxis after brain surgery. She had an erythematous urticated eruption as seen above accompanied by lymphadenopathy, derangement of liver function, and a circulating eosinophilia.

DRESS is characterised by its long latency of onset with the syndrome usually presenting between 2 and 8 weeks after commencement of the causative drug. This is an important point to note in the medication history, as often the drug responsible may be overlooked if it is considered to have been started 'too long ago'.

DRESS is accompanied by significant morbidity while the mortality has been estimated at 10%. Systemic steroids are usually administered, and may be beneficial, but there are no randomised controlled trials to support use. Management involves stopping the suspected drug, and supportive care dictated by extent of involvement.

Acute Generalised Exanthematous Pustulosis

Acute Generalised Exanthematous Pustulosis (AGEP) describes a reaction pattern to a drug consisting of widespread sterile, monomorphic pustules studding the skin in a generalised fashion. Such patients are generally systemically unwell with a fever and the complications of generalised skin inflammation including excessive heat and fluid loss. The differential diagnosis would include pustular psoriasis. Although the condition is self-limiting, potent topical steroids may accelerate resolution. The drugs which can cause AGEP are summarised in Box 56.11.

Erythroderma and exfoliative dermatitis

Erythroderma is the term used to describe any pattern of drug reaction in the skin where more than 90% of the BSA is involved. This is usually an extension of a severe drug-induced exanthem. The erythrodermic patient often feels shivery and may have lymphadenopathy and fever. The large surface area involved in erythroderma leads to substantial losses of heat and fluid from the body. This puts the patient at risk of electrolyte imbalances, hypothermia, and with the loss of skin barrier function, infection. Admission to hospital is indicated in cases of erythroderma, and management is supportive, with intravenous fluids, warming measures, and treatment of infection. Topical corticosteroids are often prescribed but must be used with caution since significant amounts will be systemically absorbed across the erythrodermic skin. During recovery, the patient will desquamate, referred to as the exfoliative phase. Drugs commonly provoking this pattern of reaction are similar to those which cause a drug-induced exanthem (Box 56.12).

Box 56.11 Drugs causing acute generalised exanthematous pustulosis

Allopurinol
Amoxicillin
Carbamazepine
Cefuroxime
Co-trimoxazole
Doxycycline
Macrolide antibiotics, for example, erythromycin, pristinamycin
Metronidazole
Lamotrigine
Phenytoin
Sulphasalazine
Vancomycin

Lupus erythematosus

Syndromes indistinguishable from Lupus erythematosus (LE) may occur following drug administration (see Box 56.13) and can be accompanied by seroconversion to antinuclear antibody (ANA) positivity. Serological clearance of ANA may occur after drug withdrawal, but this may take months or years.

The cutaneous manifestations of drug-induced LE include the characteristic butterfly-shaped rash on the face, photosensitive erythema on dorsal hands and neck, and annular lesions on limbs.

Box 56.12 Drugs causing exanthemous eruptions

Amoxicillin
Ampicillin[a]
Bleomycin
Captopril
Carbamazepine
Chlorpromazine
Co-trimoxazole
Gold salts
Nalidixic acid
NSAIDs
Phenytoin
Penicillamine

[a]Ampicillin rashes do not necessarily indicate penicillin hypersensitivity, but may seen when administered to a patient with glandular fever (see text).

Box 56.13 Drugs causing lupus erythematosus

Anticonvulsants: phenytoin
β-Blockers
Chlorpromazine
Griseofulvin
Hydralazine
Isoniazid
Lithium
Methyldopa
Oral contraceptives
Penicillamine
Phenytoin
Procainamide
Propylthiouracil
Sulphasalazine
Terbinafine
Biological therapy targeting tumour necrosis factor alpha (TNF-α), for example infliximab

Biological therapy targeting tumour necrosis factor alpha (TNF-α) such as infliximab and etanercept has been found to provoke lupus both in its systemic and limited cutaneous forms.

Vasculitis

Vasculitis is characterised pathologically by inflammation in vessel walls and clinically as palpable purpuric lesions most commonly found on the lower limbs. Cutaneous vasculitis without other organ involvement is the rule, but systemic involvement, such as renal, can occasionally occur. The purpuric areas on the legs may become ulcerated and require specialist dermatology input.

Drugs are the cause of approximately 10% of cutaneous vasculitis cases and should be considered in any patient with small vessel vasculitis (Box 56.14). Withdrawal of the causative drug is often sufficient to resolve the clinical manifestations without the need for treatment with systemic corticosteroids or more powerful immunosuppressants.

Skin necrosis

The term widespread cutaneous necrosis describes extensive skin infarction which often heralds a severe systemic coagulopathy. Widespread cutaneous necrosis can be triggered by a reaction to warfarin, or less commonly to heparin. In warfarin or coumarin skin necrosis, the buttocks and breasts are the most commonly involved sites. Discontinuation of the anticoagulant responsible is essential; however, ongoing management of the coagulopathy is critical and patients need to be assessed by a haematologist.

Box 56.14 Drugs that may cause cutaneous vasculitic reactions

ACE inhibitors
Allopurinol
Amiodarone
Aspirin
Carbamazepine
Carbimazole
Diltiazem
Erythromycin
Furosemide
Gold
Haematopoietic growth factors (G-CSF and GM-CSF)
Hydralazine
Interferons
Methotrexate
Minocycline
NSAIDs
Penicillamine
Propylthiouracil
Sulphasalazine
Sulphonamides
Thiazides
Thrombolytic agents

G-CSF, Granulocyte-colony stimulating factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor.

Patient care

Withdrawal of the likely offending drug should be the first intervention in cases of suspected drug eruption. This should be done in consultation with the prescribing physician, as an alternative drug may be required to control the patient's condition. General methods which will provide symptomatic relief in a mild, limited drug eruption include emollients, soap substitutes and oral antihistamines. A mild topical corticosteroid may also be appropriate. In cases where the eruption is more extensive, or if a mucosal surface is involved, specialist care provided by a dermatologist will be necessary.

Case studies

Case 56.1

A 36-year-old female patient with a long history of chronic idiopathic urticaria attends her local pharmacy for some advice. Her skin disease is usually well controlled with an occasional dose of cetirizine which she buys over the counter. She has recently begun taking ibuprofen for muscular pain associated with her marathon training, but has found to her dismay that her urticaria has become much worse and is flaring on a daily basis.

Questions

1. What is the likely cause of the deterioration in the control of urticaria?
2. What management should be advised?
3. What other group of drugs is likely to produce this effect?

Answers

1. Non-steroidal anti-inflammatory drugs (NSAIDs) are known to increase the frequency of attacks of urticaria in susceptible individuals. It is likely that the self-medicating with ibuprofen has lessened the patient's control of her urticaria.
2. In the first instance, the ibuprofen should be stopped. An alternative such as paracetamol could be advised for the musculoskeletal symptoms. An enquiry should be made as to whether or not any symptoms suggestive of angioedema, such as lip/tongue swelling, or difficulty breathing, have accompanied the urticaria, as this would imply a need for medical attention. In the acute phase, regular administration of an antihistamine such as chlorphenamine should help to relieve rapidly the symptoms. The patient should be warned that the ability of NSAIDs to worsen urticaria is a 'class effect' and that similar symptoms may be produced with drugs such as aspirin, meloxicam and naproxen.
3. Opiate analgesics lower the threshold for mast cell degranulation, which is the most important pathophysiological mechanism in the production of urticaria. Thus, morphine and related products such as codeine should be avoided.

Case 56.2

A 69-year-old male patient with a history of psoriasis attends the pharmacy looking for advice. In the past, his skin disease has always been well controlled with topical preparations. He was

recently admitted to hospital with a myocardial infarction and has noticed a marked deterioration in his psoriasis since discharge. During his admission, he was commenced on:

Aspirin 75 mg daily
Simvastatin 20 mg daily
Atenolol 25 mg daily
Enalapril 5 mg daily

Questions

1. What is the likely reason for the exacerbation of his psoriasis?
2. How should this be treated?

Answers

1. The patient's psoriasis could have worsened due to the stress of his recent illness, but it is probably secondary to the introduction of atenolol or enalapril. Both β-blockers and ACE inhibitors have been associated with the worsening of psoriasis.
2. Given the recent myocardial infarct, any interruptions or substitutions to treatment must be made in conjunction with the patient's primary care doctor or cardiologist. The worsening of psoriasis with β-blockers is likely to be a class effect, and therefore substituting a different β-blocker is unlikely to resolve the problem. The treating physician may wish to prescribe an alternative antihypertensive such as a calcium channel blocker. If this does not ameliorate the situation, then the ACE inhibitor may be suspected, and trial stoppage may be considered. An ARB (angiotensin receptor blocker) such as candesartan may be acceptable as an alternative.

Case 56.3

A 37-year-old man presents with swelling of his upper lip. He asks if this could be stress induced as he has had several previous episodes of localised swelling of the face over the last 6–12 months.
He has been taking bendroflumethazide and enalapril for hypertension for the last 3 years, but has not taken any other medications recently.

Questions

1. What condition do his symptoms suggest?
2. Could this be drug-induced?
3. How should the condition be treated?

Answers

1. This pattern of localised swelling of the face is characteristic of angioedema.
2. Angioedema is a known adverse effect of ACE inhibitors with an overall incidence of 0.5–1%. Although this commonly occurs in the first week of treatment, delayed-onset angioedema can occur even after many years of treatment.
3. Since angioedema can be life-threatening, any suspect drug should be stopped. There is a very low incidence of this occurring with an angiotensin II receptor blocker (ARB), and this may be a suitable alternative for this patient. The acute presentation of angioedema is treated with antihistamine and corticosteroids. If the patient presents with respiratory symptoms, subcutaneous epinephrine (adrenaline) is indicated.

Case 56.4

Miss AF is a 15-year-old renal transplant patient who attends the pharmacy 6 weeks following transplant. She is very distressed about the growth of facial hair and the worsening of acne.

Questions

1. What are the possible causes of Miss AF's skin complaints?
2. What other side effects should be enquired about?
3. How might these conditions be treated?

Answers

1. It is likely that Miss AF is receiving transplant immunosuppression that includes ciclosporin and prednisolone. The ciclosporin is most likely to have caused the growth of facial hair. Both the oral corticosteroid and the ciclosporin may have aggravated pre-existing acne or precipitated new-onset acne.
2. Ciclosporin may cause gingival hyperplasia, tremor, paraesthesia and nausea. Corticosteroids can cause increased appetite/weight gain, alterations of mood (euphoria, depression), sleep disturbance, gastritis and numerous other side effects.
3. Hirsutism is a side effect of ciclosporin that many young transplant patients have to cope with, and depilatory creams are commonly used. Tacrolimus is an alternative long-term immunosuppressant which is less likely to cause acne and hirsutism and which may be used in place of ciclosporin.

Case 56.5

An 85-year-old gentleman with rheumatoid arthritis, Mr DC, attends the local pharmacy with a persistent lesion on his left upper cheek, abutting the eyelid (Fig. 56.7), which has recently been bleeding. For the last 18 years, his rheumatoid arthritis has been treated with methotrexate. You know Mr DC is a retired naval officer, and his skin is severely sun damaged. He tells you he has had a number of basal cell carcinomas in the past and is concerned that this may be another.



Fig. 56.7 Case study 5 – a patient with basal cell carcinoma.

Questions

1. What is the likely diagnosis?
2. What risk factors does the patient have for this diagnosis?
3. How should he be advised?

Answers

1. This is likely to be another basal cell carcinoma (BCC). Basal cell carcinomas are the most common type of skin cancer in the western world, presenting as pearly papules with a central area of ulceration and creeping telangiectatic vessels at their surface. They usually occur on sun-exposed sites and are related to high cumulative levels of sun exposure.
2. Mr DC has a number of risk factors for developing a basal cell carcinoma:
   - Age: these lesions tend to occur in the older age group, presumably because of their high level of actinic damage accrued over many years. In addition, sunscreen was not as widely used in mid-to-late 20th century as it is today.
   - Immunosuppressed state: Mr. DC has been on an immunosuppressant for 18 years resulting in his tumour surveillance mechanisms being attenuated.
   - Occupation: it is likely that Mr DC will have served in some very sunny climates. A history of active service with the Armed Forces should always prompt health-care professionals to ask about the patient's history of sun exposure.
3. Firstly, the patient should be asked to consult his primary care doctor or dermatologist as the lesion will require treatment. If left unattended, basal cell carcinomas continue to grow and can become locally invasive. Secondly, Mr. DC should be advised of the importance of sun protection, using a high factor (30 or above) sunscreen, with good UVA protection (as indicated by the star rating system on the back of the bottle). A hat provides excellent cover for the scalp and face. The sun should be avoided completely between the hours of midday and 2 pm, when the levels of ultraviolet light are at their highest.

Case 56.6

A 56-year-old man, Mr SW, presents to the pharmacy in an alarmed state. In recent months, he has had several episodes of gout and was recently prescribed allopurinol. He has now taken four doses of the drug. Last night, Mr SW developed an unusual rash on his palms and soles, which this morning has developed blisters. The rash has now extended to involve his arms and legs. He also complains of 'mouth ulcers', a gritty feeling in the eyes, and pain on passing urine. Mr SW is not feverish now, but had a raised temperature overnight.

Questions

1. What is the likely diagnosis?
2. How should Mr SW be managed?

Answers

1. This patient is developing SJS. He has a blistering eruption which commenced peripherally, which is classical for this disorder. Mr SW now has evidence of mucosal site involvement, including the oral mucosa and conjunctivae, with urethral involvement suggested by his history of dysuria. Allopurinol is a common culprit for this condition.
2. Patients with suspected SJS need urgent dermatological assessment and often require inpatient care. The suspected drug should be withheld. Following admission to hospital, a full blood count, urinalysis, blood culture, skin swabs and a chest X-ray should be performed to screen for infection. An ophthalmological opinion should be sought to ensure that no synechiae (scarring) of the eyes forms because this can occasionally arise with the degree of inflammation seen in this patient. Catheterisation is required if urethral mucosal involvement is suspected, to prevent strictures forming due to scarring. Mr SW should not be exposed to allopurinol or related drugs again, as recurrence is likely.

Case 56.7

A 24-year-old female, Ms AM, was commenced on the combined oral contraceptive pill last month. Ms AM is concerned because she has noticed the appearance of raised red nodules on both shins, which are tender to touch, and have been becoming more numerous over the last 3 days. She has never had any such eruption before. There is no recent travel history, and Ms AM has no rashes elsewhere, nor does she have any arthralgia.

Questions

1. What is your diagnosis?
2. What is the likely cause of this eruption and what are the other possible causes?
3. What is the prognosis?

Answers

1. Ms AM has developed erythema nodosum, an inflammatory condition seen on the anterior legs, usually bilaterally. Erythema nodosum is a Latin term meaning 'red lumps', it represents a pathological process in which subcutaneous fat becomes inflamed.
2. The combined oral contraceptive pill is the most likely precipitant in this case. However, a full drug and medical history should be taken as other medicines may cause erythema nodosum, for example antibiotics or NSAIDs. A very common cause of erythema nodosum in young people is streptococcal throat infection. A travel history is important as the same clinical reaction pattern may be brought about by tuberculosis. Finally, a number of other medical problems such as ulcerative colitis and Crohn's disease, or sarcoidosis may also produce erythema nodosum.
3. The patient should see a dermatologist to have the other causes of erythema nodosum excluded. The management of erythema nodosum is supportive, with regular NSAIDs or paracetamol given for pain. The combined oral contraceptive pill should be stopped, and Ms AM switched to a different form of contraception.

Case 56.8

A 17-year-old girl, Miss AW, asks for some advice regarding a widespread itchy rash which has appeared suddenly over the last 24 h. Miss AW visited her primary care doctor 4 days ago complaining of a sore throat and a productive cough. Having auscultated the chest, the primary care doctor suspects a respiratory tract infection and prescribes amoxicillin. Five days later, Miss AW develops a widespread maculopapular rash. She attends the pharmacy for advice, and you suspect the rash to be drug-induced.

Questions

1. What is the cause of the eruption?
2. How should Miss AW be managed?
3. Should Miss AW be advised to avoid penicillin antibiotics in the future?

Answers

1. This is likely to be an amoxicillin-induced drug eruption.
2. The antibiotic should be stopped and the clinical indication for an alternative preparation assessed by the primary care doctor. An antihistamine and a mild/moderate potency topical corticosteroid should provide symptomatic relief. If the patient does not obtain relief with such treatment, if the rash is becoming widespread, or if there are any features of a systemic illness such as fever or enlarged lymph nodes, the patient should see the primary care doctor.
3. The reaction may be provoked by any antibiotic in the penicillin group, so the patient needs to be informed of the need to avoid all such antibiotics in the future.

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Eczema and psoriasis 57

A. Abdul-Wahab and N. Desai

Key points

- Eczema and psoriasis are common, chronic skin diseases with significant impact on quality of life.
- Emollient therapy is the mainstay of treatment for most types of eczema.
- Active inflammation should be treated with a topical steroid of appropriate potency.
- Eczematous skin is often secondarily infected and appropriate recognition of secondary bacterial and viral infections is mandatory.
- Systemic steroids should be avoided in psoriasis.
- New effective systemic agents are now available, including biologic agents, for which careful patient selection and regular monitoring are important.
- Eczema and psoriasis are inflammatory skin conditions commonly encountered in clinical practice. Although the conditions both manifest as erythematous, pruritic rashes, their morphology, distribution, long-term treatment options and outcomes may differ significantly. Both conditions can be functionally and socially disabling. Patient education, support and guidance with topical treatments are therefore extremely important.

Eczema

The terms 'eczema' and 'dermatitis' may be used interchangeably and describe the same clinical and histological entity. Eczema is an itchy erythematous (red) eruption consisting of ill-defined erythematous patches or papules. The skin surface is usually scaly and as time progresses, constant scratching leads to thickened, 'lichenified' skin.

Pathology and clinical features

Acute eczema is an inflammatory process leading to oedema in the epidermis. The oedema is seen histologically in the epidermis as 'spongiosis'. Oedema manifests as fluid that collects into tiny blisters which may then coalesce. This is seen histologically as intraepidermal vesicles and clinically as pompholyx blisters on thicker palmar and plantar skin, and as excoriated, ruptured crusted vesicles elsewhere. Tightly packed keratinocyte cells in the epidermis usually prevent transepidermal fluid loss and the entry of pathogens. This barrier function of the skin is lost in eczema. A schematic diagram demonstrating the normal skin epidermis and the effects on the barrier function during an acute eczema flare is shown in Fig. 57.1.

In the chronic form of eczema, prolonged rubbing and scratching results in a thickened epidermis and an increase in the upper horny cell layer of keratin, termed hyperkeratosis. Clinically, the skin appears thick, leathery, scaly and 'lichenified' with exaggerated skin markings, like tree bark (Fig. 57.2). Both acute and chronic stages are accompanied by a heavy chronic inflammatory cell infiltration of the dermis and epidermis. The main consequent symptom of these pathological processes is itch. The dictum of 'if it's not itchy, it's not eczema' holds true.

Clinical types

Atopic eczema

Atopic eczema is the commonest skin disorder of childhood, affecting between 10% and 20% of school age children in the UK. The aetiology is a combination of genetic, environmental and immunological factors.

The term 'atopy' describes an exaggerated propensity to form IgE to common allergens. In later life, approximately half of eczema patients will develop associated atopic disorders such as asthma and allergic rhinitis. The molecular pathology in atopic eczema is complex. The epidermal Langerhans cells have high-affinity IgE receptors through which the T-helper cells (T_h2 and T_h1) release cytokines and mediate skin inflammation.

Atopic eczema is diagnosed clinically and the criteria for definition include chronic itchy skin with three or more of the following: a history of flexural involvement of the skin creases, visible flexural involvement, dry skin, other atopic disease or onset within the first 2 years of life. The clinical course and distribution change through puberty and adulthood. In infants, common areas affected are face, neck and nappy area. Through childhood, flexural sites such as folds of the elbows and backs of the knees are classically involved (see Fig. 57.3). Symptoms usually improve with age and approximately 60% have resolution of symptoms by the age of 16.

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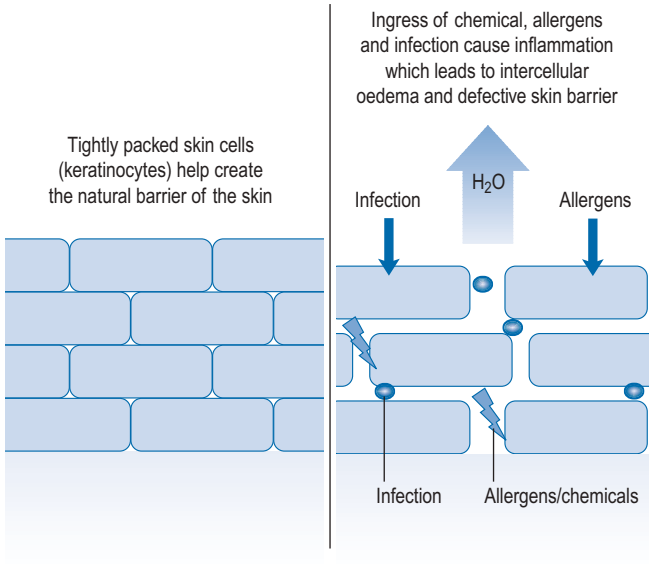


Fig. 57.1 Schematic diagram demonstrating the normal skin epidermis (left) and the effects on the barrier function (right) during an acute eczema flare.



Fig. 57.2 Dry, excoriated, lichenified chronic eczema (courtesy of M. Carr).



Fig. 57.3 Flexural eczema in childhood (courtesy of M. Carr).

Exacerbating factors

A number of factors can aggravate atopic eczema:

- Extremes of temperature
- Irritants: soap, detergents, shower gels, bubble baths and water
- Stress
- Infection, either bacterial or viral
- Contact allergens
- Food allergens
- Inhaled allergens
- Airborne allergens.

The commonest trigger in the paediatric population is secondary infection, either bacterial or viral. Bacterial colonisation is common on the skin of those with atopic dermatitis and may result in the invasive infection triggering an acute flare. *Staphylococcus aureus* and *Streptococcus* spp. are most often responsible (Fig. 57.4).

Viral infections such as herpes simplex and molluscum contagiosum may also complicate atopic eczema. Eczema herpeticum is caused by the widespread dissemination of herpes simplex virus in eczematous skin and is a dermatological emergency. It requires urgent assessment and treatment with systemic aciclovir.

In some cases of severe atopic eczema, food allergy may be a contributory factor, particularly if a clear temporal relationship is detected by the parents. These cases should be referred to a paediatric allergy specialist, with access to a paediatric dietician, as unsupervised dietary restriction should be avoided in children. Most children tend to grow out of food allergies over time with the exception of nut and shellfish allergies.

Contact dermatitis

Contact dermatitis is classified as either allergic contact dermatitis (ACD) or irritant contact dermatitis (ICD).

Allergic contact dermatitis

ACD is a delayed type IV hypersensitivity reaction that develops in response to an antigen to which the host immune system has been previously sensitised. As a consequence, symptoms rarely develop on first exposure to the stimulus and



Fig. 57.4 Impetigo complicating atopic eczema (courtesy of M. Carr).

may only manifest months or years later following repeated re-exposure.

Many common compounds can lead to ACD. The most common compounds implicated are:

- Metals, for example nickel and cobalt
- Neomycin, a topical antibiotic found in over-the-counter preparations sold in some countries
- Fragrance ingredients, for example Balsam of Peru
- Rubber compounds
- Hair dyes, for example p-phenylediamine
- Plants, for example poison ivy.

Diagnosis relies heavily on a detailed patient history as well as recognising the pattern and distribution of the eczematous rash. Although the signs are usually localised to the area exposed to the allergen, secondary generalised eczema may develop.

The standard confirmatory investigation is patch testing and is used to differentiate allergic from ICD. This involves application of a standard, with or without a specialised range of compounds, to the patient's back over 72 h. This is followed by examination for a cutaneous reaction at day 2 and day 4. Identification of relevant compounds allows the patient to avoid the substance in the future, and this will hopefully reduce symptoms. Common areas of the body affected by ACD, with corresponding probable sensitisers, are listed in Table 57.1.

Irritant contact dermatitis

This is the most common form of occupational dermatitis and the commonest cause of hand eczema (Fig. 57.5). Unlike ACD, ICD is not immunologically mediated. The mechanism involves disruption of the epidermal permeability barrier and a direct cytotoxic effect depending on the irritant. Patients with pre-existing epidermal barrier dysfunction such as atopic eczema are at higher risk. The occupation of the individual may also be a risk factor, especially those working as builders, hairdressers, gardeners, healthcare workers and chefs. Irritants include detergents, oils, water, inorganic acids, alcohols and plastics. Preventative skin care is key and this includes the use of barriers such as emollients or cotton gloves in addition to avoiding suspected irritants.

Table 57.1 Common locations for allergic contact dermatitis and possible sensitisers

Location	Possible sensitising agents
Periorbital	Airborne allergens, nail polish, contact lens solution
Umbilicus	Nickel hypersensitivity to belt/jean button
Neck	Antiseptic in soap, cosmetics
Hairline	PPD in hair dye, hair perming solution
Hands	Latex or rubber accelerators in gloves, nickel, fragrances, protein contact dermatitis in food preparation, irritant contact dermatitis due to water

PPD, p-phenylediamine.



Fig. 57.5 Contact dermatitis to cement in a building worker (courtesy of M. Carr).

Seborrhoeic dermatitis

This common disorder is usually confined to areas with high sebum production. The likely aetiological mechanism is overgrowth of the commensal yeast *Malassezia furfur* (Pityosporum ovale). The clinical features are pink-yellow greasy patches with 'bran-like' scale which occur in the sebaceous-rich scalp, nasal folds, medial eyebrow, pre-sternal region and flexural sites. In the first few months of life, it manifests as coherent scaling of the scalp with inflammation and ooze, known as 'cradle cap'. In adults, the symptoms are usually mild with a chronic, relapsing course. Extensive and severe seborrhoeic dermatitis can be seen in patients with underlying HIV infection or Parkinson's disease. Treatment usually includes topical imidazoles.

Discoid eczema

Discoid eczema is also known as 'nummular dermatitis' and is a type of chronic eczema presenting with disseminated coin-shaped eczematous lesions of the extremities. Middle-aged males are most commonly affected.

Stasis eczema

Stasis eczema is also called stasis dermatitis, gravitational dermatitis or varicose eczema. It is a clinical component of chronic venous insufficiency seen in addition to other features which include varicose veins, skin discolouration, peripheral oedema, leg discomfort and non-healing ulcers. Clinical features include scaly eczematous plaques confined to the lower legs. Multiple topical medicines and dressings often lead to a secondary ACD. Management of stasis eczema should address the underlying cause.

Asteatotic eczema

Asteatotic eczema, also called eczema craquele, usually affects the lower legs and appears as dry, cracked skin likened to 'cracked paving'. This is associated with increasing age, low

humidity and frequent bathing. Treatment consists of emollients and mildly potent topical steroids.

Treatment

First-line treatment of eczema should include an emollient and soap substitute for washing. Topical steroids are used for anti-inflammatory effect. Systemic treatments for adult atopic eczema include oral prednisolone, ciclosporin and azathioprine. If there is a secondary bacterial infection, then this should be treated with oral antibiotics. The antibiotic(s) should be chosen based on sensitivity determined by wound swab.

Emollients

Emollients, topical hydrating agents consisting of fat or oil to soften the skin, are the mainstay of eczema management. Emollients are effective first-line treatments for all types of eczema, and regular, liberal use will reduce topical steroid requirements. The greasier products have more emollient effect (see Fig. 57.6). They are often underused and the need to educate the patient regarding use of sufficient quantities is vital. Dry skin is aggravated by soap and bath products, and therefore an emollient soap substitute for washing is advisable.

Topical corticosteroids

Topical steroids act as anti-inflammatory agents and are extremely useful and important in managing eczema. In recent years, the public have veered from overuse of topical steroids causing long-lasting side effects, to high levels of anxiety regarding possible side effects concerning their use. This can commonly lead to under treatment in children. Therefore, patient/carer education regarding appropriate topical steroid use is a crucial part of eczema management.

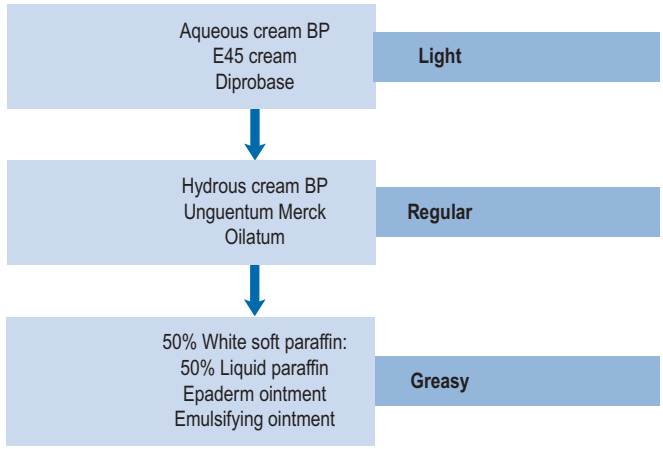


Fig. 57.6 Commonly used emollients used in dry skin conditions (adapted from MeReC, 1998).

Topical steroids are classified into four main groups according to potency: mild, moderately potent, potent and very potent (Table 57.2). The choice of topical steroid is dependent on the site and severity of skin disease. Potent and very potent steroids should be avoided on delicate sites such as the face, genitals and flexures. The periorbital region should be treated with caution due to the thin skin increasing the likelihood of absorption and risk of cataracts or glaucoma. Treatment should be reviewed regularly and tailored accordingly. It is also important to remember that any form of occlusion will increase the absorption of steroid applied.

Side effects are mainly local and include striae (stretch marks), telangiectasia (visible dilated small blood vessels), epidermal thinning, purpura (bruising), acne and perioral dermatitis. Lower frequency side effects include poor wound healing, spread or worsening of untreated infections and hypertrichosis. Hypopigmentation is a temporary side effect of long-term topical steroid use and is frequently

Table 57.2 Comparative potencies of topical corticosteroid preparations

UK Steroid Group	Trade name	Strength	Relative strength compared to hydrocortisone
Hydrocortisone 0.5–2.5%	Hydrocortisone	Mild	1
Fluocinolone acetonide 0.0025%	Synalar 1:10 dilution®		
Betamethasone valerate 0.025%	Betnovate RD®	Moderately potent	2.5× stronger
Clobetasone butyrate 0.05%	Eumovate®		
Fluocinolone acetonide 0.00625%	Synalar 1 in 4 dilution®		
Fludroxycortide 0.0125%	Haelan®		
Betametasone valerate 0.1%	Betnovate®	Potent	10× stronger
Mometasone furoate 0.1%	Elocon®		
Clobetasol propionate 0.05%	Dermovate®	Very potent	50× stronger

exploited in illegal 'skin bleaching' agents. Rarely, adrenal suppression or Cushing's syndrome due to systemic absorption may occur.

Local and systemic side effects are extremely rare with appropriate use and duration of topical steroid treatment. Patients should be advised to spread preparations thinly either once or twice daily. The recommended amount used can be quantified using a fingertip unit (Fig. 57.7). The quantity in this unit is sufficient to cover an area the size of two adult palms. Table 57.3 details the quantities for application to different sites required for twice-daily treatment for 1 week.

Base

Topical corticosteroids are available in ointment (oil based), cream (water based), aqueous or alcoholic solution, gel, foam or shampoo formulation for the scalp. In general, ointment preparations are preferable to creams in eczema management because they are absorbed better and have fewer preservative chemicals. Alcoholic solutions may lead to irritation and should not be applied to acutely inflamed or broken skin.

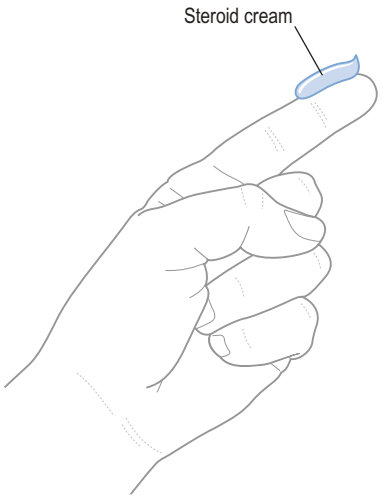


Fig. 57.7 Recommended amount of a topical steroid corresponding to one fingertip unit.

Table 57.3 Minimum quantity of topical application required for twice daily treatment for 1 week (courtesy of M. Carr).

Age	Whole body	Trunk	Both arms and legs
6 months	35	15	20
4 years	60	20	35
8 years	90	35	50
12 years	120	45	65
Adult (70 kg)	170	60	90

Allergies

Both immediate and delayed hypersensitivity reactions to topical corticosteroids can occur, although not commonly. These can be reactions to either the steroid molecule itself or the vehicle in which it is found. Allergic reactions to one topical steroid may cross-react to others. Therefore, allergy testing is mandatory for such patients. Betamethasone may be less likely to cause allergic reactions than other topical preparations.

Antibiotics and steroid combinations

Combination preparations can be useful in treating mild bacterial infection of eczematous skin. Long-term use should be limited due to the risks of sensitisation and antibiotic resistance. In general, invasive infection is best managed with oral antibiotics.

Calcineurin inhibitors

The past decade saw the introduction of topical calcineurin inhibitors for the treatment of chronic eczema. These non-steroid immunomodulators inhibit calcineurin phosphatase which is important in T-lymphocyte activation. The main side effect is burning or stinging on initial application, but this usually improves after a few days. Although a theoretical risk of increased malignancy exists with these agents, studies have not shown an association between exposure to topical calcineurin inhibitors and increased rates of cutaneous malignancy. Calcineurin inhibitors should not be used on infected skin and are generally not very useful in severely inflamed eczematous skin. Their greatest value appears to be in maintenance therapy.

Tacrolimus ointment (Protopic®) is a calcineurin inhibitor derived from the oral transplant medicine FK506. The 0.1% and 0.03% preparations are indicated in the treatment of moderate to severe atopic dermatitis in adults and children over the age of 2 years. Tacrolimus is now also used in clinical practice as a second-line agent for other steroid responsive dermatoses.

Pimecrolimus 1% cream (Elidel®) is indicated for short-term or intermittent long-term use in mild to moderate atopic dermatitis. Studies have shown that it is effective, well tolerated and has minimal adverse effects in the long-term control of eczema in children aged over 2 years (Langley et al., 2008). Furthermore, this has resulted in the reduced use of topical steroids leading to a lower risk of steroid-induced side effects (Kapp et al., 2002).

Antihistamines

Pruritis is the most distressing feature of eczema. Oral antihistamines have no direct effect on pruritis in eczema; their main effect is sedation. Sedating antihistamines may cause day time drowsiness, and caution should be taken when driving and also if prescribed to school age children.

Topical imidazoles

Ketoconazole as a shampoo or cream is effective in reduction of *Pityosporum ovale* on the skin and is therefore useful in the treatment of seborrhoeic dermatitis. As the disease runs a chronic, relapsing course regular or intermittent use is usually necessary.

Coal tar preparations

Tar creams and ointments can be used in the management of hyperkeratotic, lichenified eczema. These are less cosmetically acceptable than other topical preparations, but coal tar is an effective anti-pruritic.

Bandaging

In children with atopic eczema, occlusion with bandages is useful to prevent scratching and potentiate the action of ointments and creams on the skin. Wet wrapping involves the application of emollients and steroids under a double layer to keep the inner layer moist. Parents can be trained to apply these bandages at home.

Systemic therapies

Systemic steroids

Oral prednisolone can be used as a short-term treatment in the management of severe acute eczema that needs rapid control. Long-term treatment with oral steroids is now rarely used due to the risk of side effects including hypertension and osteoporosis.

Ciclosporin

Ciclosporin is a systemic immunosuppressant that blocks activation of T-lymphocytes. It is effective as a short-term bridging therapy in severe chronic adult eczema and has a rapid onset of action. Intermittent courses at doses of 2.5–5 mg/kg/day are useful, but dose-related renal nephrotoxicity is inevitable and limits treatment duration to a maximum of 8–12 months. Other side effects include hypertension and increased risk of malignancy. A detailed patient history is required to determine if there is a previous history of gynaecologic or prostate malignancy. During treatment with ciclosporin, patients also require close monitoring of renal function and blood pressure.

Azathioprine

Azathioprine is a purine analogue that inhibits DNA synthesis and can be effective as monotherapy in adult eczema. Bone marrow suppression and toxicity are the major concerns. A higher risk of marrow suppression occurs in individuals with low levels of thiopurine methyltransferase (TPMT), and this should be assessed at screening. Patients with borderline TPMT levels require a lower dose of azathioprine. Patients with low levels of TPMT should not be offered this treatment.

Methotrexate

Methotrexate is occasionally used in unresponsive adult atopic eczema, but randomised controlled trials are lacking. A small prospective trial has shown that methotrexate can be effective and well tolerated as a second-line therapy for the treatment of moderate to severe atopic eczema in adults (Weatherhead et al., 2007).

Mycophenolate mofetil

Mycophenolate mofetil is an oral systemic agent that prevents T- and B-cell proliferation, thereby reducing inflammatory cytokine release. This can be used as an alternative in severe adult atopic dermatitis where azathioprine or ciclosporin are contraindicated. Side effects are gastro-intestinal upset, bone marrow suppression and an increased risk of infection.

Phototherapy

Phototherapy can be effective in select cases of atopic dermatitis. Narrow-band UVB is the therapy of choice (Gambichler et al., 2005; Meduri et al., 2007). The potential side effects of all types of phototherapy include burning, premature ageing and a small increased risk of skin cancer. A small proportion of patients have photosensitive eczema, and this should be determined by taking a detailed patient history before prescribing phototherapy treatment. A treatment course requires a patient to attend two or three times a week for at least 6 weeks.

Dietary supplements

Current evidence suggests that probiotics are not an effective treatment for eczema and may carry a small risk of adverse events such as infection and small bowel ischaemia. There is no evidence for use of evening primrose oil. The use of Chinese herbal medications in atopic eczema is under close scrutiny, and conflicting results have been obtained. Liver function should be monitored as hepatitis is a known side effect of some Chinese herbal medicines.

Interactions with drugs used in the treatment of eczema and psoriasis are shown in Table 57.4.

Patient care

It is important to recognise that eczema affects many aspects of a patient's life and has considerable effects on the family. Quality-of-life factors affected include body image, irritability and loss of sleep due to profound itch and limitations to work and hobbies (Fig. 57.8). A multidisciplinary approach is often needed in overcoming these issues, and healthcare workers including primary care doctors, dermatologists, specialist nurses, pharmacists and teachers may be involved. Patients with eczema should aim to lead as normal a life as possible, and school staff and employers can play an important part in achieving this goal.

Patient and parental education is important as treatments are designed to control and manage the disease. Although atopic eczema is likely to improve throughout childhood, expectations of an immediate cure need to be addressed. Advice and support through contact with other patients and their families can be obtained from the National Eczema Society (www.eczema.org). An algorithm for the management of eczema is shown in Fig. 57.9.

Psoriasis

Psoriasis is a chronic inflammatory disorder of the skin and joints. The current prevalence in Europe and North America is estimated to be between 1% and 3%. The usual presentation is with well-demarcated red plaques with an overlying scale.

Table 57.4 Interactions with drugs used in the treatment of eczema and psoriasis (courtesy of M. Carr)

	Interacting drug	Outcome
Methotrexate	Aspirin	Increased plasma concentration and toxicity of methotrexate
	NSAIDs	Increased plasma concentration and toxicity of methotrexate
	Probenecid	Increased plasma concentration and toxicity of methotrexate
	Phenytoin	Increased bone marrow toxicity
	Sulphonamides	Increased toxicity
	Trimethoprim	Increased antifolate effect of methotrexate
Azathioprine	Allopurinol	Enhanced effect and toxicity of azathioprine
	Warfarin	Inhibition of anticoagulant effect
	Cimetidine	Enhanced myelosuppression
	Indometacin	Increased risk of leucopenia
Ciclosporin	NSAIDs	Increased risk of nephrotoxicity
	Aminoglycosides	Increased risk of nephrotoxicity
	Co-trimoxazole	Increased risk of nephrotoxicity
	Ciprofloxacin	Increased risk of nephrotoxicity
	Ketoconazole	Increased plasma concentration of ciclosporin
	Itraconazole	Increased plasma concentration of ciclosporin
	Erythromycin	Increased plasma concentration of ciclosporin
	Oral contraceptives	Increased plasma concentration of ciclosporin
	Calcium channel blockers	Increased plasma concentration of ciclosporin
	Phenytoin	Decreased plasma concentration of ciclosporin
	Carbamazepine	Decreased plasma concentration of ciclosporin
	Rifampicin	Decreased plasma concentration of ciclosporin
Acitretin	Methotrexate	Increased plasma concentration of methotrexate

Aetiology

The aetiology of psoriasis is a combination of genetic and environmental factors. In most cases, there is a genetic predisposition and up to 70% of patients report a family history of psoriasis. Recent advances in genome-wide association studies have led to the identification of at least nine chromosomal psoriasis susceptibility loci. Multiple genes are likely to influence disease susceptibility, severity and clinical subtype. The strongest association is with HLA-CW*06.

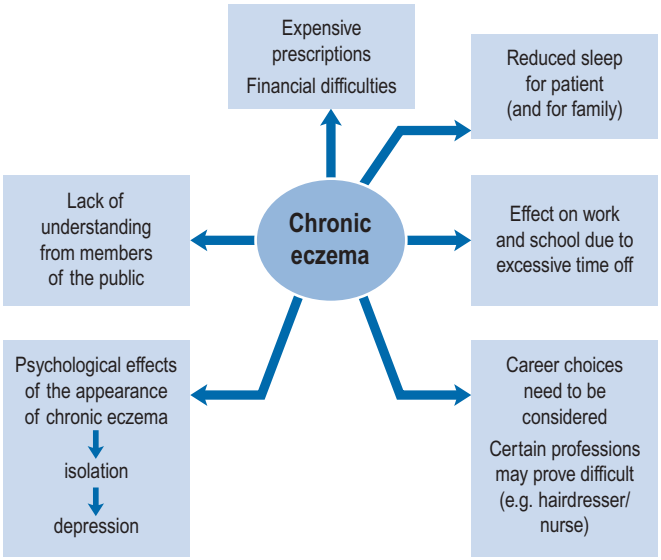


Fig. 57.8 The social and psychological effects of chronic eczema.

Precipitating factors

Non-inherited factors also have a role in triggering psoriasis in predisposed individuals. These are described as follows.

Infections

Bacterial infections have been implicated as triggers for psoriasis. Streptococcal infections, particularly pharyngitis, frequently precede the onset of guttate psoriasis. HIV infection can aggravate psoriasis. The severity of the psoriasis is greater in this patient population.

Drugs

Drugs can exacerbate or induce psoriasis in predisposed individuals. The most common causative agents are lithium, ß-blockers, anti-malarials, non-steroidal anti-inflammatory drugs (NSAIDs), tetracyclines and rapid withdrawal of systemic corticosteroids.

Alcohol and smoking

Excess alcohol consumption may exacerbate established psoriasis. Additionally, psoriasis is associated with high rates of alcoholism due to the psychological stresses of the disease.

Smoking is strongly associated with palmoplantar psoriasis; up to 95% of patients with this variant are smokers at disease onset. Smoking cessation should be actively addressed due to a likely improvement in disease status and associated risk reduction of ischaemic heart disease. It has been suggested that psoriasis,

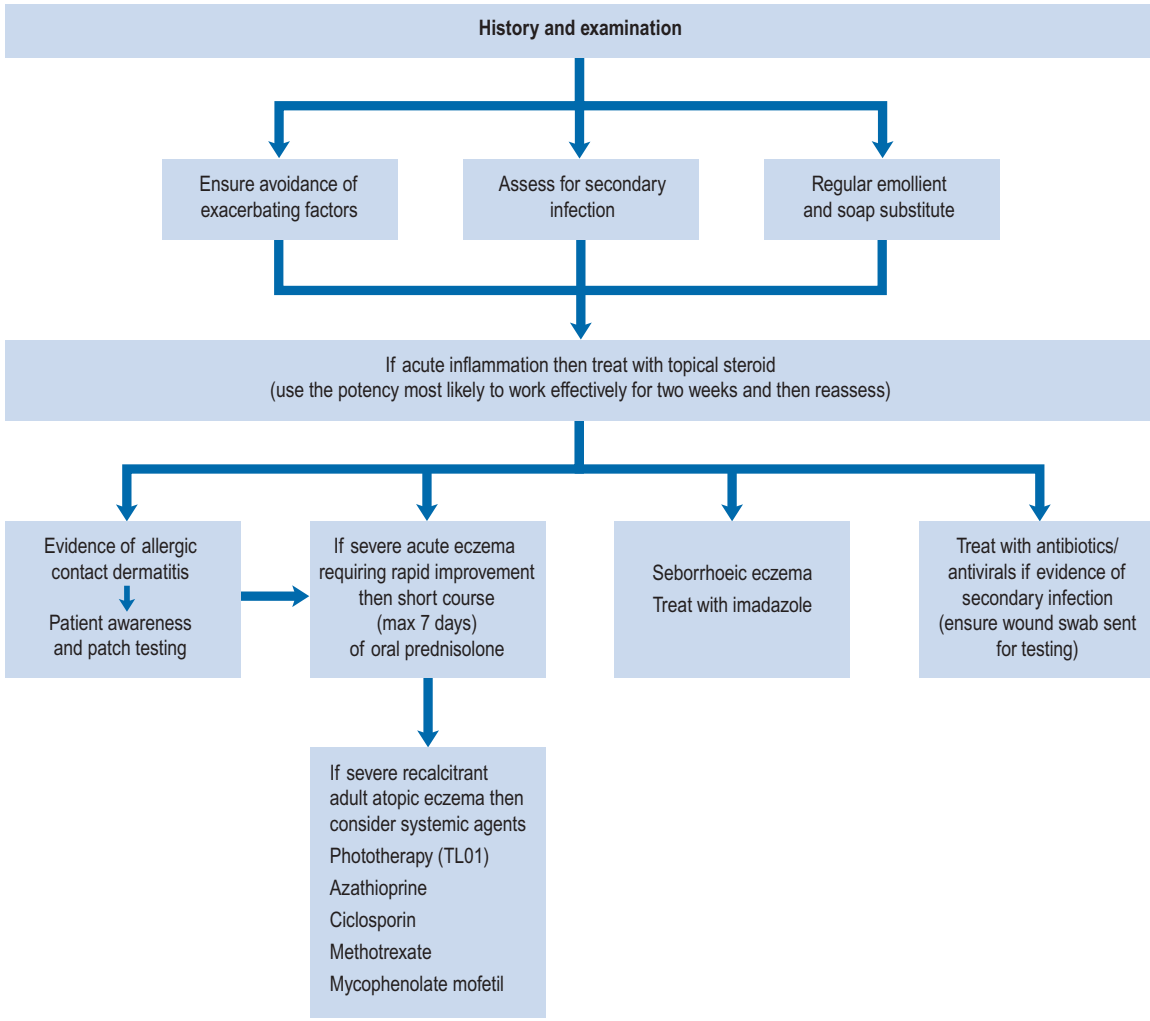


Fig. 57.9 Algorithm for the management of eczema.

particularly if severe, may be an independent risk factor for atherosclerosis, myocardial infarction and stroke (Mehta et al., 2010).

Emotional stress

Anecdotal observations and frequent patient reports identify stress as an important trigger factor for psoriasis. Clinical evidence has demonstrated that the onset and severity of psoriasis can correlate with prior stress (Kirby et al., 2008). Furthermore, psychological distress and depression can occur as a consequence of psoriasis.

Koebner phenomenon

The Koebner phenomenon refers to psoriatic lesions which occur at sites of injury to the skin, such as a cut, burn, scratch or surgical scar, in patients with psoriasis.

Pathology and clinical features

The clinical features of psoriasis, well-demarcated, erythematous scaly plaques, are explained by the histological features (Fig. 57.10). Common sites affected include the scalp, buttocks, elbows, knees and nails.



Fig. 57.10 Chronic scaly plaque psoriasis on an elbow (courtesy of M. Carr).

Histologically, the epidermis is thickened (acanthosis), with a thickened upper horny layer (hyperkeratosis) which is reflected by the clinical features of thick, scaly skin. The build of scale is due to increased epidermal turnover. The differentiation of cells through the epidermis terminating in the keratin horny layer normally takes approximately 40 days. Epidermal turnover in

psoriatic skin may be as rapid as 7 days. In the dermis, the capillaries are dilated, tortuous and closer to the surface of the skin. This explains Auspitz's sign which is the appearance of pinpoint bleeding after scraping off psoriasis scales.

Inflammatory cells are present in all layers of psoriatic skin; granulocytes are predominant and form microabscesses in the epidermis. Lymphocytes and Langerhans cells are also increased. The presence of lymphocytes in the epidermis led to hypotheses of an immunological cytokine-mediated process causing epidermal hyperproliferation and changes in vascular structure. T-cells, dendritic cells and cytokines such as tumour necrosis factor alpha (TNFα), interleukin (IL)-12 and IL-23 all contribute to its pathogenesis. This is confirmed by the therapeutic effect of drugs that suppress T-lymphocyte function, such as ciclosporin, in psoriasis.

Clinical types

Psoriasis vulgaris

Psoriasis vulgaris, also known as chronic plaque psoriasis, is the most common variant. It can occur at any age but most often begins in young adulthood and has a chronic relapsing course. The typical psoriatic lesion is a red, sharply demarcated plaque with overlying silvery scale. The distribution is usually symmetrical and involves extensor sites such as the elbows and knees. The sacrum, scalp and nails are also commonly affected. The plaques may itch but not usually to the severity of eczematous plaques. Treatment is aimed at management of disease rather than cure.

Guttate psoriasis

Guttate psoriasis is more commonly seen in children and young adults and is characterised by a widespread scaly eruption of small 'teardrop-like' scaly plaques (Fig. 57.11). The presentation is often acute and can appear 10–14 days after a streptococcal upper respiratory tract infection. Topical treatments or UVB phototherapy are usually effective. Spontaneous resolution is common; however, guttate psoriasis may be the first manifestation of psoriasis in predisposed individuals.



Fig. 57.11 Guttate psoriasis showing Koebner phenomenon in scratch mark (courtesy of M. Carr).

Scalp psoriasis

Involvement of the scalp may be the only manifestation of psoriasis in some patients, but may also occur in psoriasis vulgaris. This appears as scaly demarcated plaques extending to the hairline and around the ears. Hair loss is rare.

Psoriatic nail disease

The nails are frequently affected in psoriasis. In a small proportion of patients, the nails are the only area affected. Changes include nail pitting, nail ridging, onycholysis (separation of the nail from the nail bed), hyperkeratosis under the nail and complete nail destruction. These symptoms can be cosmetically disfiguring. Topical treatments are rarely effective for psoriatic nail disease. Systemic treatments such as methotrexate, when prescribed for generalised psoriasis, may also improve nail disease.

Palmoplantar psoriasis

At these sites on the palms and soles, there is sharp demarcation of the involved areas (Fig. 57.12). Palmoplantar psoriasis can take two forms: either inflamed hyperkeratotic fissured skin which can be very painful or sterile pustules on an erythematous base which dry to leave small brown macules (palmoplantar pustulosis). The pustular form is much commoner in smokers.

Flexural psoriasis

Psoriasis can occur at flexural sites such as the axillae, groin, submammary areas and genitalia. Due to friction and moisture within skin folds, lesions differ in appearance from classical psoriasis and tend to be red and glazed rather than scaly. Affected areas tend to be clearly demarcated. Secondary infections,



Fig. 57.12 Pustular psoriasis of sole (courtesy of M. Carr).



Fig. 57.13 Erythrodermic psoriasis, courtesy of St John's Institute of Dermatology, London.

particularly with *Candida* are common. Potent steroids are not advised at these sites due to the high risk of skin atrophy.

Erythrodermic psoriasis

Erythroderma, or exfoliative dermatitis, is a severe, potentially life-threatening condition in which more than 90% of the body surface is red and scaly (see Fig. 57.13). This can occur as a consequence of either eczema or psoriasis. Skin function is impaired and patients suffer dehydration, electrolyte imbalance, temperature dysregulation and serious secondary infection. These patients need urgent hospital admission, medical supportive therapy and topical treatment. Initially, bland emollients such as white soft paraffin and mild to moderate topical steroids should be used. Underlying conditions, such as psoriasis, can then be treated with appropriate systemic agents.

Generalised pustular psoriasis

This is an acute, unstable form of psoriasis manifesting as widespread sheets of tiny sterile pustules on an erythematous base. The patient is usually systemically unwell with fever and general malaise. Pustular psoriasis may be precipitated by the withdrawal of systemic or very potent topical steroid. Therefore, oral steroids are avoided in the management of stable psoriasis.

Psoriatic arthropathy

Approximately 25% of psoriatic patients suffer with an associated arthropathy. There are five patterns of psoriatic arthropathy; monoarthopathy, rheumatoid arthritis-like, osteoarthritis-like, sacroiliitis-like and arthritis mutilans. Rheumatoid factor is negative in these patients. Some treatments effective for skin psoriasis are also effective in psoriatic arthropathy including methotrexate, and biological agents with action against TNFα.

Treatment

Many patients with psoriasis have mild disease and require only emollient therapy to prevent drying and fissuring of the elbows and knees. Other treatment options should take into account the type of psoriasis, patient occupation and lifestyle factors as well as disease severity. This will ensure improved patient compliance and better outcome.

Topical therapy

First-line treatment of mild to moderate psoriasis should include an emollient as well as a topical treatment. Mild to moderate topical steroids are useful for delicate skin sites such as the face and flexures. Dithranol and tar products are effective, but limitations of use include irritation, messy application and potent odour. Topical treatments may be technically difficult to apply to the scalp area; patient education and demonstration is key. Topical vitamin D analogues are well tolerated.

Vitamin D analogues

Vitamin D analogues inhibit keratinocyte differentiation and production. The most commonly prescribed Vitamin D analogue is calcipotriol. This is commonly used within primary care for mild localised psoriasis and is available as a lotion, ointment, cream or scalp treatment. Patients should be advised to avoid use on delicate skin sites such as the face and flexures due to irritation. Hypercalcaemia due to systemic absorption can occur if the maximum weekly dose exceeds 100 g. Efficacy may be enhanced when used in combination with a topical steroid.

Steroids

Topical steroids are cosmetically acceptable and easy to apply. Mild to moderately potent steroids are of greatest value in acutely inflamed psoriasis to reduce inflammation. Reduction of inflammation is important as it then allows other treatments to be introduced that would otherwise irritate acutely inflamed plaques. Topical steroids have a number of limitations. The use of potent steroids on large areas of psoriasis is associated with

risks of local atrophy and systemic absorption. Furthermore, there is a rebound effect on withdrawal. Potent steroids should be reserved for localised disease, such as thicker acral sites, often in combination with salicylic acid if there is hyperkeratosis. In general, very potent steroids should be avoided.

Coal tar

Along with dithranol, coal tar is one of the oldest topical treatments for psoriasis. Coal tar has anti-inflammatory, antibacterial, anti-pruritic and antimitotic effects. A variety of preparations are available including bath preparations, shampoos, creams and ointment. Coal tar concentrations of 1–10% can be used, but use of higher concentrations should occur in a supervised setting. Coal tar in combination with topical steroids can be effective, for example Alphosyl HC®. The efficacy of tar is enhanced when used with UVB light therapy (Goerkerman regimen). The main limitations of tar are irritation of delicate skin sites, odour and temporary staining of skin and clothing. The theoretical risk of carcinogenesis due to polycyclic aromatic hydrocarbons has not been demonstrated in long-term clinical practice.

Dithranol

Dithranol (anthralin in the USA) is a synthetic anthracene derivative which has an anti-proliferative and anti-inflammatory effect on the skin. It is one of the older treatments used for stable, chronic plaque psoriasis. Although effective, practical drawbacks include burning and irritation of normal skin, staining of clothes as well as a strong odour. In current practice, dithranol is most commonly used as a short contact regimen within a dermatology day centre setting. The starting concentration of dithranol is usually 0.5% which can be increased slowly if tolerated up to 3%.

Salicylic acid

This is useful to reduce scale, particularly while treating hyperkeratosis of the palms and soles. It can be mixed with coal tar, steroid or urea.

Topical retinoids

Retinoids are less effective than vitamin D analogues in the treatment of psoriasis. Irritation is a possible side effect to therapy.

Topical treatment of psoriasis at special sites

Scalp

Tar shampoo is effective in mild scalp psoriasis. However, a descaling agent is required as part of therapy for thicker plaques. Coconut oil compounds, peanut oil and greasy emollient with salicylic acid can be used as descaling agents. A topical steroid can then be applied for inflammatory disease. Treatment does require considerable time and commitment from the patient.

Genitals

The genital regions are prone to irritation and mild to moderate topical steroids can be used. In addition, it is also important to inform patients that treatments used on other parts of the body may be too potent and irritant for genital areas.

Nails

Before treatment of psoriasis, fungal infections of the nails should be excluded. Topical treatments often have poor efficacy in psoriasis affecting the nail, and systemic therapy is preferred.

Phototherapy

The majority of psoriatic patients exhibit improvement of symptoms on sunny holidays, with only 10% of patients reporting deterioration in symptoms on sun exposure. Phototherapy has an immunosuppressive effect on skin and has been used in the treatment of psoriasis for over 80 years. Narrow-band UVB (311–313 nm) is preferable to broadband UVB (290–320 nm) due to increased safety and reduced risk of burning.

PUVA

PUVA (psoralens plus UVA light) has a valuable role in the treatment of stable moderate to severe psoriasis. Psoralens are drugs that are activated by long-wave ultraviolet light (320–400 nm), thereby interfering with DNA synthesis and reducing epidermal turnover. The two psoralens available in the UK are 8-MOP (methoxypsoralen) and 5-MOP. These are taken orally 2 h before exposure to UVA light. The eyes are always protected due to the risk of cataracts and patients are given sunglasses to wear for 12 h after treatment. The treatment is usually given twice a week for a 6-week period. Total cumulative dosage is carefully monitored.

The commonest adverse effect is nausea due to ingestion of oral psoralens. The most serious adverse effect is an increased risk of long-term cutaneous malignancy. Those with fair skin types and on past or present immunosuppresion are at greatest risk. Due to these risks, PUVA is usually reserved for patients resistant to UVB therapy.

Systemic therapy

Systemic therapy is indicated in severe widespread psoriasis, intolerant of or rapidly relapsing after topical therapy and phototherapy. Objective measures of disease severity and impact on quality of life are used routinely to assess need for systemic therapy and treatment response and include the Psoriasis Area and Severity Index (PASI) and the Dermatology Quality of Life Index (DLQI). Systemic treatments commonly prescribed in psoriasis include methotrexate, acitretin and ciclosporin. Drug interactions are important and a detailed patient drug history is important. New biologic agents are used in severe disease which is unresponsive to oral immunosuppressant treatment. Common adverse effects and monitoring requirements of systemic treatments of eczema and psoriasis are presented in Table 57.5.

Table 57.5 Common adverse effects and monitoring requirements for systemic treatments of eczema and psoriasis

Therapy	Adverse Effects	Monitoring requirements
Methotrexate	Hepatic fibrosis; myelosuppression; nausea; pulmonary fibrosis; teratogenic (contraindicated in both males and females for 4 weeks before and 3 months after treatment)	FBC U&E LFT Pro-collagen III peptide (P3NP) ±Liver biopsy Chest X-Ray (screening)
Hydroxyurea	Myelosuppression; skin reaction; teratogenic; liver toxicity (narrow therapeutic window)	FBC U&Es LFT
Ciclosporin	Renal nephrotoxicity Hypertension Gingival hypertrophy	FBC U&E LFT Lipid profile Blood pressure Urinalysis
Acitretin	Teratogenic (including up to 2 years post-treatment) Dryness of mucous membranes and skin Hyperostoses, increased serum triglyceride Occasional hepatotoxic reaction	FBC U&E LFT Lipid profile
Fumaric Acid Esters	Gastro-intestinal side effects Flushing Lymphopenia Proteinuria Renal failure	FBC U&E LFT Urinalysis
Azathioprine	Myelosuppression Deranged liver function Gastro-intestinal effects	TPMT pre-treatment FBC/U&E/LFT

U&Es, urea and electrolytes; LFTs, liver function tests; FBC, full blood count; TPMT, thiopurine methyl transferase genetic polymorphism screening.

Methotrexate

Methotrexate is a folic acid antagonist used in moderate to severe psoriasis. In males and females of non-childbearing potential, this tends to be the first-line systemic agent. It is also effective in psoriatic arthropathy. Methotrexate is given as a once weekly oral low dose regimen, with an initial test dose of 5 mg increasing up to 30 mg weekly. Acute toxicity occurs due to the effect of methotrexate on folic acid metabolism of rapidly dividing cells in the bone marrow and gastro-intestinal tract. This can cause myelosuppression or gastro-intestinal bleeding. In such cases, folinic acid rescue can be used to oppose the folate antagonist effect at a dose of 120 mg folinic acid over 12–24 h intravenously or intramuscularly in divided doses, followed by 15 mg/kg orally every 6 h for 48 h. Hepatic fibrosis is the commonest long-term risk and regular monitoring of liver function is necessary. Some patients complain of nausea and other gastro-intestinal side effects as well as lethargy. Folic acid 5 mg taken on the days methotrexate is not prescribed can reduce these adverse effects.

Patient monitoring in methotrexate therapy is detailed in Table 57.5. Liver function tests do not reliably predict hepatic fibrosis; supportive investigations are therefore required. Liver biopsy remains the gold standard. Recently, the measurement of serum pro-collagen three peptide levels has led to a reduction of liver biopsies for detection of hepatic fibrosis in these patients (Chalmers et al., 2005).

Acitretin

Acitretin, a vitamin A derivative that inhibits epidermal proliferation, is effective for disorders of keratinisation including chronic plaque psoriasis. The starting dose is usually 25–30 mg daily for 2–4 weeks increasing to 75 mg daily for short periods and according to clinical response. Mucocutaneous side effects, hair loss and lethargy are common. Acitretin should be avoided in women of childbearing potential because of the teratogenic risk. However, it is a safer option for patients with chronic infection for whom immunosuppression is contraindicated. Patients should be warned that a rebound response is occasionally seen when stopping treatment, and therefore a long-term maintenance dose is usually advised.

Ciclosporin

Ciclosporin is an effective treatment for all variants of psoriasis with a fairly rapid mode of action. The dose is 2–5 mg/kg. Similar to eczema management, continuous ciclosporin treatment for more than 1 year is not advised due to renal nephrotoxicity. Adverse events include hypertension, hypertrichosis, paraesthesia, tremor and increased risk of infections. There is also of an increased risk of skin cancer in conjunction with ciclosporin use in patients who have previously had phototherapy.

Hydroxyurea/hydroxycarbamide

Hydroxyurea/hydroxycarbamide is a drug with similar effects on bone marrow and germ cells to methotrexate but without the hepatotoxic effects. Relapse occurs on stopping treatment.

Fumaric acid esters

Fumaric acid esters have been used since the early 1960s and affect both keratinocytes and T-cell activity. It is licensed in Europe, but not in the UK, for severe, relapsing, chronic, plaque psoriasis. The main side effects are gastro-intestinal upset and flushing.

Biologic therapy

Biologic therapies or 'biologics' are drugs designed to block specific molecular steps important in immune-mediated disease. They have been used successfully in rheumatoid arthritis, inflammatory bowel disease and are now licensed for use in chronic plaque psoriasis. Their use is recommended for patients with severe plaque psoriasis defined as a PASI ≥ 10 and DLQI > 10 who have failed at least two standard systemic agents including methotrexate, ciclosporin and acitretin or one systemic agent and phototherapy (Smith et al., 2009).

TNFα antagonists

TNFα is a pro-inflammatory cytokine that plays a central role in the pathogenesis of psoriasis. The tumour necrosis factor antagonists: infliximab, adalimumab and etanercept all have potent immunosuppressant action and have proven efficacy in severe psoriasis. Serious adverse effects include infection, in particular reactivation of tuberculosis, exacerbation of severe cardiac failure, demyelinating disease and a potential risk of malignancy (solid organ tumours and lymphoma). Careful patient selection and regular monitoring are important.

Etanercept is a genetically engineered receptor fusion protein with affinity for soluble TNFα. The dose is 25 mg twice weekly via subcutaneous injection. Higher doses of 50 mg twice a week are used in psoriatic arthropathy. The most frequent side effects are injection site reactions.

Infliximab is a chimeric monoclonal antibody against TNFα. It is also used in Crohn's disease, ulcerative colitis, ankylosing spondylitis and rheumatoid arthritis. Clinical trials have demonstrated rapid onset and good efficacy in psoriasis.

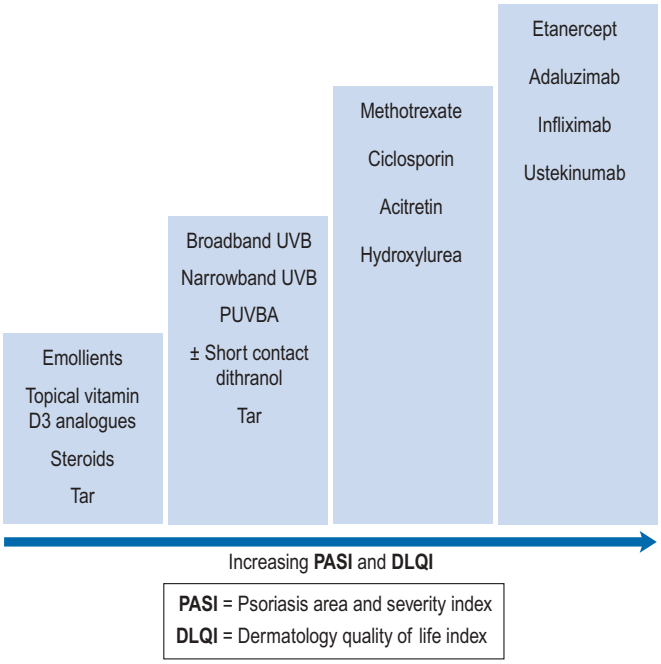


Fig. 57.14 Treatment algorithm for psoriasis.

Infliximab is administered at a dose of 5 mg/kg by intravenous infusion every 8 weeks after a loading dose at weeks 0, 2 and 6. Observation and nursing care on a day unit are therefore required.

Adalimumab is humanised monoclonal antibody against TNFα that is administered in a bolus of 80 mg subcutaneously and then 40 mg on alternate weeks.

Other biologic agents used in psoriasis

Ustekinumab is the newest available biologic agent used in the treatment of psoriasis. It is a fully human monoclonal antibody that prevents IL-12 and IL-23 from binding receptor proteins. A dose of 45 mg (or 90 mg in patients weighing >100 kg) is administered subcutaneously at week 0, 4 then every 12 weeks. In light of the limited patient exposure to this treatment, ustekinumab is reserved for use as a second-line biologic agent where TNF therapy has failed or cannot be used.

Efaluzimab, a T-cell modulator, was withdrawn in 2009 due to an increased risk of progressive multifocal leucoencephalopathy.

A treatment algorithm for psoriasis is shown in Fig. 57.14.

Patient care

Psoriasis is a chronic disease associated with significant psychosocial disability and reduction in quality of life. As well as effects related to depression; impact on body image and sexual relationships should be considered. Coexistent psoriatic arthropathy may have a severe impact on function and lead to significant time away from work or education. Support and

understanding of individual patients' needs and lifestyles will improve adherence to treatment. Psoriasis can be associated with alcohol misuse, and a drug and alcohol history should always be sought. Systemic and biologic treatments require regular attendance and blood tests, and therefore patients with poor attendance records may not be suitable for such treatment. Ultimately, responsibility lies with the patient to ensure regular treatment.

The chronicity of this disease may lead to treatment 'fatigue' and frustration with messy topical therapies. There are numerous alternatives and newer formulations are generally less messy. Treatments can be expensive and information on the entitlement to benefits to replace clothing ruined by ointments or washing machines worn out by constant use is available. The Psoriasis Association (www.psoriasis-association.org.uk) provides an excellent service for this, together with practical advice from fellow sufferers about day-to-day problems.

Case studies

Case 57.1

A 3-year-old child with known atopic eczema is seen in clinic with a widespread, excoriated, dry rash (see Fig. 57.15). Her eczema symptoms started at the age of 6 weeks. Her sleep has always been poor due to the marked itch symptoms at night. She has had two recent courses of oral antibiotics for presumed bacterial skin infection. Her normal skin treatment involves hydrocortisone 1% ointment to affected areas twice daily. Her parents are concerned regarding the possible triggers of her eczema flares and are keen to pursue possible allergy testing.



Fig. 57.15 Case study 1 – a young child with moderate/severe atopic eczema courtesy of St John's Institute of Dermatology, London.

Question

What advice could be given to the child's parents?

Answer

Fig. 57.15 shows a young child with moderate/severe atopic eczema. Ill-defined, dry, erythematous patches of eczema are visible. A few of the patches around her ankles appear crusty and eroded. This may represent secondary infection.

Management should include regular topical emollient therapy. The correct quantities should be emphasised. A regular soap substitute should be prescribed.

Wound swabs should always be taken before prescribing an oral antibiotic for presumed infected eczema.

A moderately potent steroid ointment should be administered daily, along with a regular, greasy topical emollient. When a moderately potent or potent topical steroid is prescribed for a child, medical follow-up must be arranged. Regular use of potent steroids is not advised and will lead to local side effects including skin atrophy. If the treatment is ineffective, a short admission to hospital or regular day care should be arranged for further intensive topical treatments or dressings.

Time should be spent explaining to the parents the aetiology of atopic eczema. Although eczema is usually a chronic disease with no 'cure', it should also be explained that approximately 60% of children will have minimal or no symptoms after the age of 16.

Allergy testing is commonly requested by parents, but as most children will grow out of their symptoms as well as food sensitivities, formal testing is not always appropriate. Allergy testing may involve blood tests, including RAST tests, and skin prick tests. These may not be a pleasant experience for a young child. A positive result does not directly correlate with the effect of allergen avoidance on the course of atopic eczema. High street or internet allergy tests have no benefit in atopic eczema.

Case 57.2

A 22-year-old male nurse attends outpatients complaining of dry, painful eczema affecting his hands. He had previously suffered with childhood eczema and asthma. Since starting his new job, his symptoms have developed causing severe pain, fissures, itch and dry skin. His finger pulps are particularly affected. He attended occupational health and was then advised to see a dermatologist.

Question

What is the likely cause of his symptoms and what advice should be given?

Answer

The aetiology of hand dermatitis is often complex and multifactorial. An atopic predisposition, irritant factors as well as allergic contact type IV hypersensitivity may all play a part. In view of his atopic eczema during childhood, he is at greater risk of irritant and ACD than the general population. The need for this patient to constantly wash his hands with antiseptic hand wash and excessive contact with water is likely to be an exacerbating factor. Alternatives to antiseptic washes include a moisturising soap substitute, for example Dermol 500®.

A potent topical steroid and emollient with a good barrier effect should be prescribed. Tape impregnated with a steroid preparation,

for example Haelan® tape may be useful to protect fissured areas on his hands. Patch testing would be the next step to investigate a possible allergic contact component to his symptoms.

Young adults with moderate or severe eczema should be given career guidance to avoid occupations at higher risk of leading to ICD, for instance hairdressing, domestic cleaning or working in a healthcare environment that requires constant hand washing.

Case 57.3

A 28-year-old male management executive with lifelong atopic eczema has attended with worsening severity of his eczema. He has been using emollients and moderately potent topical steroids for many years and feels that these are no longer having an effect. Over the past year, he has required two short courses of oral steroids. His sleep is affected and he cannot afford to take any further time off work.

Question

What are the treatment options for this man?

Answer

This patient needs effective treatment before he becomes erythrodermic. High-dose systemic steroids over a 2-week period may have a rapid effect but are not a long-term option. His topical regime should be explored to ensure adequate quantities of emollient are being used. In addition, his aims, expectations and medical issues should be explored with a view to possible systemic treatment.

If more than a few weeks of treatment are anticipated, ciclosporin is a possible treatment option. Pre-treatment screening should include blood pressure, urinalysis and blood tests including renal function. A short course of ciclosporin treatment no longer than 12 months would alleviate his symptoms, improve his mental well being and give him a break from his chronic skin disease. If longer-term systemic management is anticipated, azathioprine would be an option, but efficacy would only be evident after approximately 8 weeks of treatment.

Case 57.4

A 9-year-old boy with known atopic eczema presented with a vesicular, blistering eruption over his face and trunk (see Fig. 57.16). His mother noticed the blisters 48 h ago and brought him to hospital as he was unwell and feverish. He had been using topical steroids and emollients regularly for his moderate atopic eczema. His sister has recently been suffering with cold sores.

Question

Fig. 57.16 shows the young patient with eczema herpeticum. What advice would you give this patient and his mother?

Answer

Eczema herpeticum, Kaposi's varicelliform eruption, is an important and serious complication that can occur in eczema patients. This is a medical emergency and early treatment with aciclovir may prove lifesaving. This widespread eruption occurs following inoculation of herpes simplex virus to skin damaged by eczema. This then spreads rapidly and can affect the eyes and lungs. It usually



Fig. 57.16 Case study 4 – a young patient with eczema herpeticum courtesy of St John's Institute of Dermatology, London.

manifests in young children with atopic eczema. Typically, the tiny blisters, vesicles, develop in large numbers on eczematous skin and patients are systemically unwell. The blisters or erosions appear 'punched out' and may be pustular. Eye involvement, as suggested in Fig. 57.16, necessitates urgent ophthalmological review as herpes simplex ocular infection can lead to corneal ulceration, stromal keratitis, iritis and permanent visual loss.

Children with atopic eczema and their parents should be educated to recognise the signs and symptoms of eczema herpeticum.

Case 57.5

A 33-year-old electrician presents to clinic with a 5-month history of a mildly itchy eruption occurring around the nasal area and eyebrows (see Fig. 57.17). He describes it as occasionally scaly and is very concerned regarding the cosmetic appearance. On examination, he also has mild scale and erythema affecting the scalp. The dandruff shampoos he usually purchases from his local community pharmacy have been ineffective. The diagnosis is seborrheic dermatitis.

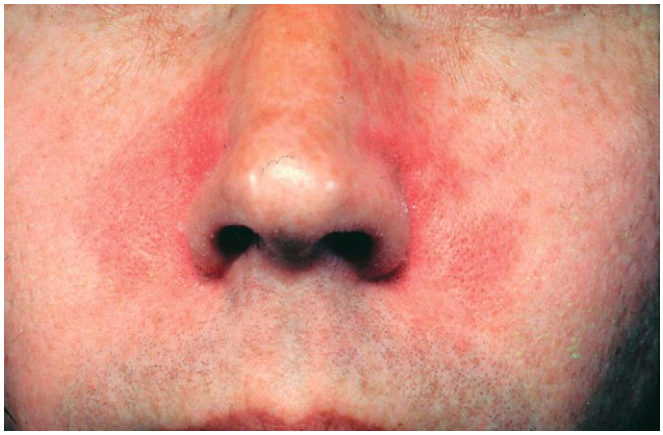


Fig. 57.17 Case study 5 – man with seborrheic dermatitis, courtesy of St John's Institute of Dermatology, London.

Question

What options would you offer for topical treatment?

Answer

Ketoconazole shampoo and ketoconazole 2% cream will reduce the population of *Pityosporum ovale* on the skin which may benefit symptoms. If symptomatic and itchy, a mild topical steroid with antifungal may be an option. In addition, patients should be counselled that seborrheic dermatitis is a common condition which may be chronic and periodic exacerbations may occur.

Case 57.6

A 55-year-old woman presents with a history of longstanding chronic plaque psoriasis. Since the age of 16, she has had numerous topical treatments which have not adequately managed her symptoms. Over the past 18 months, she has noticed swelling and pain over the proximal joints of both hands, which is much worse in the morning. On examination, she has early signs of deformity. NSAIDs have not alleviated her symptoms, and her function at work is now affected.

Question

What management options should be offered for this patient?

Answer

Psoriatic arthopathy affects up to 30% of patients with psoriasis. The resulting pain and functional disability of this arthropathy can be debilitating. However, non-steroidal anti-inflammatory medicines improve symptom control. Other treatment options include methotrexate, ciclosporin and TNFα antagonists. These medicines would also have a beneficial effect on this patient's psoriasis. Both rheumatology and dermatology services are required in the management of such patients.

Case 57.7

A 45-year-old man with psorasis has been complaining of an itchy scaly scalp for the last 8 months. He has seen his primary care doctor who as prescribed a topical steroid preparation (Betacap®), but this treatment has had little effect. He is troubled by thick scale and severe itch at night.

Question

What treatment options could be considered?

Answer

Treatment of scalp psoriasis differs from other forms of psoriasis because of the presence of thick hair. Topical treatments can be difficult and messy to apply. In addition, phototherapy is not usually effective at this site. Almost all topical preparations used to treat psoriasis on the body have equivalent scalp preparations, although the application method varies. Coal tar shampoos are usually suitable first-line treatments for scalp psoriasis. Aqueous and alcoholic scalp preparations will not penetrate thick scale which needs to be softened with emollient preparations first. Arachis oil, provided the patient is not peanut allergic, or coconut oil are commonly used for this. Salicylic acid and coal tar preparations are often effective, and sometimes these are mixed with a coconut oil base (Sebco®, Cocois®). These preparations should be left on for approximately 1 h and then washed off. Topical steroids may be effective for inflamed skin, but will not penetrate thick scale. Intermittent rather than prolonged use of topical steroids is advised.

Case 57.8

A 45-year-old man has become increasingly disabled with palmoplantar pustular psoriasis. He has had frequent crops of inflamed pustules on the palms and soles which dry up to form crusts and scaling followed by painful fissuring of the skin. This has made his job as a joiner increasingly difficult, and he has had prolonged periods of absences through illness. He has tried emollients, topical steroid applications and steroid combinations but with only temporary relief.

Question

What are the best options for the treatment of this man?

Answer

Firstly, the patient should be advised to use regular emollient therapy. A topical treatment should also be prescribed such as a potent topical steroid in combination with a base such as propylene glycol or salicylic acid. Occlusion with either cotton gloves or cling film can improve skin penetration. However, this condition can be chronic and very disabling for manual workers, and therefore systemic therapy may be advised. In such cases, oral acitretin may be given for long-term use. The patient's fasting lipids and liver function should be monitored. If oral acitretin is contraindicated, hand and foot PUVA can be used. Patients diagnosed with palmoplantar pustulosis should be advised to stop smoking and be provided with appropriate support. This is because palmoplantar pustulosis has been found to improve after cessation of smoking (Michaëlsson et al., 2006).

Case 57.9

A 24-year-old man presents at the clinic with a 10-year history of plaque psoriasis affecting his elbows, knees and sacral area, with a few small plaques elsewhere. He is otherwise fit and well. He regularly plays football and is embarrassed by the appearance of his skin. He has tried Betnovate RD® ointment (0.025%), which smoothed the plaques a little, and calcipotriol ointment, which removed the scale from the plaques but did not clear them.

Question

What treatment could this patient try next?

Answer

As the patient only has a few localised plaques, a treatment course of short contact dithranol creams may be suitable. A starting concentration of 0.5% dithranol is tolerated by most patients. The dithranol strength can then be increased every 5–7 days. The effect can be enhanced by UVB treatment twice

weekly at a dermatology department. The usual staining and burning with dithranol is minimised by short contact therapy, and any discolouration fades quickly after the treatment has stopped.

Case 57.10

A 35-year-old male patient with chronic plaque psoriasis has been reviewed. He has severe plaque psoriasis occurring on more than 50% of his body surface area. He has tried topical treatments and has also had UVB and PUVA therapy with little improvement. A course of methotrexate has failed to improve his symptoms and his work and psychological wellbeing are suffering. His PASI score is 25 and DLQI is 13.

Question

What treatment options could now be offered?

Answer

This patient would be considered eligible to receive treatment with any of the licensed biologic agents. Eligibility is based on having severe disease. This is defined as PASI score greater than 10 and a DLQI greater than 10 in addition to being unresponsive/intolerant to standard systemic therapy. Pre-treatment screening for infection including active or latent tuberculosis, congestive cardiac failure, demyelination and malignancy is required.

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58 Wounds

S. Holloway and K. Harding

Key points

- Acute wound healing should progress through an orderly sequence of events to re-establish tissue integrity.
- A functional blood vessel network is fundamental for wound healing.
- Changes occur in the repaired tissue for up to 2 years with the scar tissue becoming stronger with time.
- A number of intrinsic and extrinsic factors can affect the healing process and include age, diabetes, infection, nutrition, smoking and drugs.
- Wounds are costly to treat and therefore accurate assessment of a patient and his/her wound is important.
- Assessment should be part of an ongoing process with opportunity for regular re-assessment.
- Acute wounds such as surgical incisions heal quickly with minimal complications; chronic wounds such as diabetic foot ulcers, leg ulcers and pressure ulcers take longer to heal.
- The management of patients with diabetic foot ulcers needs to include treatment of their diabetes as well as local wound management and off-loading techniques to reduce foot pressures.
- Venous leg ulcers are the most common cause of ulceration in the population and require the external application of compression bandages/hosiery to aid healing. These ulcers can be complicated by gravitational eczema; therefore, treatment of the surrounding skin is of equal importance.
- The majority of pressure ulcers are preventable. Management of patients requires a multi-disciplinary approach with the use of pressure-reducing/pressure-relieving support surfaces and repositioning as adjunctive measures to ensure appropriate care.

A wound can be thought of as any break in the integrity of the skin (Enoch and Leaper, 2005), although when this is due to minor trauma it might be termed a cut or an abrasion. Such wounds tend to heal fairly quickly by the process of regeneration of tissue and cells and generally do not pose any long-term problems. However, the time it takes for a wound to heal will depend on a number of factors related to the nature of the wound, the individual and environment. Many of these factors will be dealt with at different points throughout this chapter.

Structure of the skin

The skin is made up of the epidermis and dermis below which is the sub-cutis, muscle and bone. Within the epidermis, there are four layers:

- Stratum corneum
- Stratum granulosum
- Stratum spinosum
- Stratum basale.

Within the very thin structure of the epidermis, some of the key cells required for healing are present, in particular keratinocytes, dendritic cells and melanocytes.

The dermis is separated into the papillary and reticular dermis and is thicker than the epidermis. It is joined to the epidermis by structures known as rete ridges or 'pegs'. In uninjured tissue, this arrangement helps the skin to maintain its normal function, something which can be affected when a wound occurs or as an individual's skin changes with age. Like the epidermis, the dermis also contains many of the key cells/structures that are required for the normal healing response to occur; these include:

- Fibroblasts; for the production of collagen
- Endothelial cells; to stimulate blood vessel growth
- Leucocytes; such as lymphocytes, neutrophils and macrophages
- Smooth muscle cells
- Extracellular matrix.

The functions of the skin and factors that affect skin condition are listed in Table 58.1. How these roles link to wounds and wound healing will be explored in more detail later.

Wound healing

In adults, a scar is the normal end product of most injuries, with occasionally excessive scarring, that is hypertrophic or keloid complicating matters. However, wound healing can also be scarless, such as in fetal skin or the oral mucosa

Table 58.1 Functions of the skin and factors affecting skin condition

Functions of the skin	Factors affecting skin condition
Protective covering	Dryness
Moisture retention	Age
Sensation	Environment
Regulation of body temperature	Nutrition
Release of waste	Hydration
Absorption of nutrients, that is Vitamin D	

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(Desai, 1997a; Wysocki, 2007). This type of healing presents an interesting concept and may offer some significant developments in the future. There are also many individuals for whom healing is delayed, and includes wounds often referred to as 'chronic' or 'non-healing'. Other terminology is used in clinical practice to describe how wounds heal and includes:

- Primary intention
- Delayed primary closure
- Secondary intention.



Fig. 58.1 Example of wound healing by primary intention.

Essentially, healing by primary intention (Fig. 58.1) describes where the wound edges are opposed, that is brought together by sutures, staples or glue and wound healing occurs mainly by connective tissue formation. Delayed primary healing is used where there may be a risk of contamination or infection, that is if the patient has undergone emergency abdominal surgery. In this instance, some of the layers of tissue are stitched, and the sutures are placed in readiness for the remainder of the wound to be closed after 48 h when the risk of infection is less. In contrast, secondary healing (Fig. 58.2) describes a situation where the wound is left open to heal by the normal processes. This type of healing is relevant to many of the types of wounds that will be discussed later.

Any injury to the skin will result in a sequence of events aimed at repairing the defect. Figure 58.3 shows the process of wound healing and is divided into four phases:

- Haemostasis
- Inflammation
- Proliferation
- Remodelling or maturation.



Fig. 58.2 Example of wound healing by secondary intention. Wound bed shows healthy granulation tissue and epithelial tissue can be seen at the wound edges.

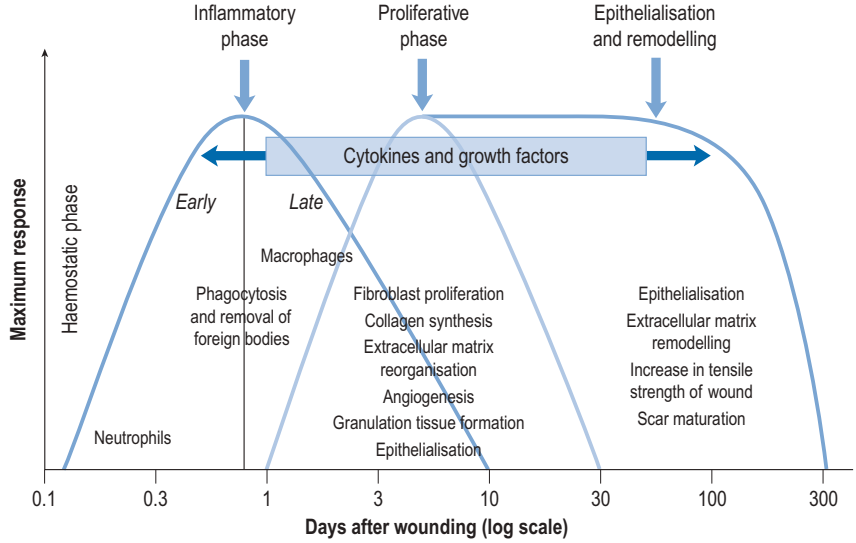


Fig. 58.3 Phases of wound healing (from Enoch et al 2008).

An insult to the tissues causes a number of systemic processes to occur simultaneously. Platelets aggregate and adhere to the sub-endothelium; coagulation factors as well as growth factors are also released. Through changes in the platelet structure and function, thrombin and fibrin are released to aid clot formation and reduce excess blood loss. Once this has occurred, haemostasis is said to have been established. The initial fibrin matrix provides the scaffold for the subsequent structure. This process relies on the individual having a normal clotting response and may be affected by drugs or systemic disease.

Following haemostasis, the inflammatory phase extends from day 0 through to about day 10 in normal healing and involves neutrophils (early inflammation), and macrophages (late inflammation). Neutrophils phagocytose bacteria and kill foreign bodies by producing oxygen metabolites such as hydroxyl radicals, hydrogen peroxide and superoxide ion. In normal healing, the numbers of neutrophils decrease in number over time leading to an increase in the number of macrophages present. The key function of macrophage is to digest bacteria, dead tissue and old neutrophils. There is some evidence to suggest that in wounds which are not healing it may be the inflammatory phase and its related cells that are at fault. The classic signs of inflammation are well reported and include:

- Redness
- Swelling
- Heat
- Pain.

These signs are normal and should not be considered as indicating the presence of infection.

The proliferative phase begins approximately 1 day post-injury and should be resolving by about day 30. There are three main activities that occur during this time and include:

- Granulation tissue formation – requires new blood vessels and formation of collagen
- Contraction of the wound
- Epithelialisation.

The presence of a functional blood vessel network is fundamental for wound healing to progress. Angiogenesis, the formation of blood vessels, is required to supply oxygen to the wound environment and it is through the migration of capillaries through the provisional matrix that the vasculature is re-established. Endothelial cells migrate and proliferate to eventually join the existing blood supply to the injured area. Once this has occurred, granulation tissue can form to begin to repair the defect. The provisional tissue laid down (Fig. 58.2) is made up of fibrin, fibronectin, collagen and glycosaminoglycans. Through the action of fibroblasts, collagen is produced and the continued presence of macrophages ensures the wound is kept 'clean'. Collagen production is essential for healing to progress and in particular Types I, III and IV are required.

In conjunction with the laying down of granulation tissue, the wound edges begin to contract at around day 8, and this process assists wound closure. The key cell involved is the myofibroblast which applies tension to the surrounding matrix to induce contraction. The normal process of contraction should not be confused with contracture, which is an abnormal feature of scarring.

Around the same time, it may also be possible to see signs of epithelialisation occurring (Fig. 58.2). Keratinocytes, the cell associated with this process, are initiated hours after injury; they migrate from the edge of a wound over the provisional matrix laid down or they dissect through it. Hair follicles can act as islands of regenerating epithelium in some areas. The wound bed can be easily damaged during the proliferative phase, with simple things like incorrect dressing choice causing significant damage. Moist wound healing (MWH) principles (Winter, 1962) are encouraged to support the normal physiological process of healing.

The final phase of the healing process is termed remodelling or maturation. During this time, the initial collagen that has been laid down is synthesised by enzymes ultimately leading to a more ordered network that increases in structure and strength over time. However, this repaired area is never as strong as normal tissue and is always at risk of breakdown should circumstances occur. These final changes can take place for up to a year or more after the initial insult.

Factors affecting wound healing

Generally, wound healing should progress as described above; however, a number of factors that affect healing have been identified (Grey and Harding, 2008). A summary of these is provided in Table 58.2, some of which include:

- Age
- Diabetes
- Infection
- Nutrition
- Smoking
- Drugs.

Age

Younger patients appear to have an increased rate of healing, and there are differences in fetal healing that mean the regeneration process is superior with little or no inflammation or scarring (Desai, 1997b). In comparison, wound repair in the elderly is slower (Ashcroft et al., 2002), and management may be more challenging because of concurrent disease processes. This is a particular problem in the proliferative and remodelling phases where tissue appears to be more friable and fragile. The overall effects of age on wound healing appear to be:

- Decreased inflammatory response
- Delayed angiogenesis
- Decreased collagen synthesis and degradation
- Slower epithelialisation.

Table 58.2 Intrinsic and extrinsic factors affecting wound healing

Intrinsic factors systemic local		Extrinsic factors
Age	Blood supply	Nutrition
Uraemia	Changes in oxygen tension	Smoking
Jaundice	Vessel trauma	Radiotherapy
Diabetes	Abnormal scarring	Infection
Anaemia	Haematoma	Drugs
Hormones	Local infection	Iatrogenic influences
Malignant disease		Wound dressings

Diabetes

Diabetes poses many problems for patients with wounds and management is often challenging because of concurrent peripheral neuropathy (PN), peripheral arterial disease (PAD), neuro-ischaemia and infection (Table 58.3).

Infection

Bacterial invasion of wounds is very common. In fact, any break in the skin integrity places the wound at risk of local contamination or infection and if untreated can lead to systemic infection. The spectrum of infection from colonisation through to infection is demonstrated in Fig. 58.4. The difficulty may be in recognising when such circumstances are present. The normal inflammatory signs were discussed earlier, and these should be borne in mind when examining a patient's wound. However, there are additional local signs that may be present in wounds healing by primary or secondary intention (Fig. 58.5) that suggest an infective process; these include:

- Increased pain
- Delayed wound healing
- Wound bleeds easily
- Friable, fragile tissue
- Pocketing/bridging of tissue
- Wound breakdown (dehiscence).

Infection in a wound can often be diagnosed by clinical signs and symptoms alone and unless a systemic infection is suspected, that is the patient complains of flu-like symptoms, can

Table 58.3 Complications of diabetes

Peripheral neuropathy	Causes damage to nerves that leads to a lack of the protective pain sensation, but the blood supply remains good. Very common and can lead to foot deformities and abnormal walking patterns. Neuropathy should be considered in terms of sensory, autonomic and motor changes. The foot is usually warm, numb and dry with palpable foot pulses
Peripheral arterial disease	Often develops as a result of atherosclerosis but develops at a faster rate in diabetic patients. Can affect the large (macro) and small (micro) vessels leading to decreased blood flow to the legs and feet, which can ultimately lead to minor or major amputations. The foot is often cool, clammy with absent or reduced foot pulses
Neuro-ischaemia	A combination of peripheral neuropathy and peripheral arterial disease
Infection	More common in diabetic patients, probably because they have an associated defective immunity. The neutrophil and lymphocyte response is slow (partly due to vascular problems); therefore, the inflammatory and subsequent phases are impaired. Hence, these patients have an increased tendency to develop infections

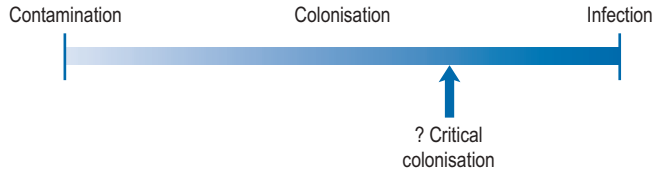


Fig. 58.4 Schematic representation for the outcome of bacterial invasion.



Fig. 58.5 Infection in a granulating wound.

be treated locally with topical antimicrobial dressings rather than oral antibiotics.

In recent years, there has been increased recognition that bacteria have the ability to build up colonies that present a challenge in terms of the management of bacterial load. Known as biofilms, they have the ability to resist removal and have been implicated in delayed healing of a number of wound types. The removal of dead and devitalised tissue from the wound bed seems to have some effect in preventing the growth of biofilms (Wolcott and Rhoads, 2008); however, this method is not suitable for all wounds; hence, other approaches are being sought.

The choice of topical treatment for the management of local wound infection will be dealt with in a later section.

Nutrition

The nutritional requirements for wound healing have been the subject of debate with limited evidence as to the exact dietary components for individual wound types. In general, if the patient has a balanced diet, this should be sufficient for the normal processes to take place. However, a diet that is lacking in vital nutrients can lead to delayed wound healing and wound breakdown. In the extreme, the patient can become malnourished with surgical patients most at risk of protein energy malnutrition (PEM). Box 58.1 outlines the nutritional factors that should be considered in the assessment of individuals, many of which have been incorporated in nutritional risk assessment tools. Individuals at most risk of nutritional deficiencies are those affected by:

- Ill-health in old age
- Cancer
- Chronic neurological disease

Box 58.1 Nutritional assessment and treatment options

General nutritional assessment to include
Current appetite
Food intake
Patient's ability to eat/chew/swallow
Presence of dentures

Specialist nutritional assessment
Anthropometric measurements such as:
Body Mass Index (BMI), % weight loss, haemoglobin, skin fold thickness, grip strength, serum albumin
Gut function
Total energy requirements

Nutrients required for healing
Protein
Zinc
Copper
Iron

Vitamins required for healing
A
B complex
C
E

Treatment options
Modified normal diet: increase high energy/protein foods
Modified normal diet plus nutritional supplementation
Total enteral support
Naso-gastric feeding
Total parenteral nutrition
Percutaneous endoscopic gastrostomy (PEG)

- Chronic inflammatory bowel disease
- Surgery (pre- and post-operatively)
- Stroke
- Acute and chronic pain
- Immuno-deficiency disease such as HIV and AIDS.

Smoking

Smoking is known to be detrimental to health generally, and in addition the effect of nicotine and carbon monoxide on skin and muscles is well documented (Møller et al., 2002). These substances reduce the oxygen levels in the tissues and can lead to the formation of thrombi. A good blood supply and adequate vascularisation is important for normal wound healing. There has been debate about the period of time patients should abstain from smoking to reduce relevant, potential complications. This has been suggested to vary from 4 (Sorensen et al., 2003) to 8 weeks (Møller et al., 2002). However, the role of nicotine replacement interventions in further reducing complications is less clear.

Drugs

There are certain drugs that are suggested to have an effect on the healing process. These include NSAIDs, corticosteroids and immunosuppressive agents (Grey and Harding, 2008),

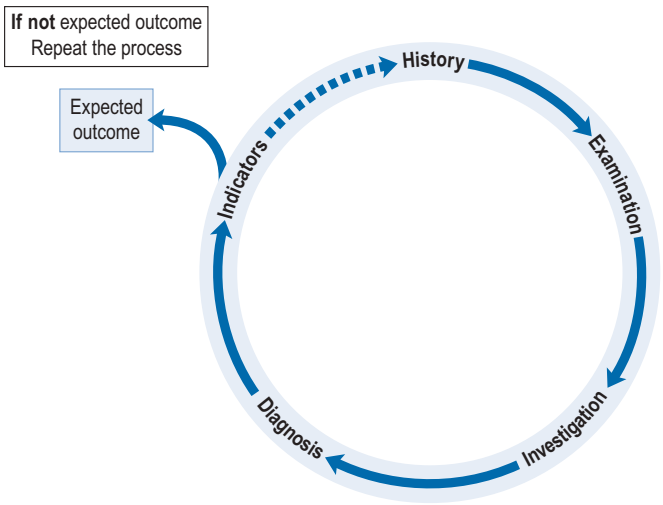


Fig. 58.6 Assessment of a patient with a wound.

which affect the inflammatory response, collagen synthesis and mitosis, respectively. Whilst drugs do not generally cause wounds, there have been recent reports that nicorandil, used for the treatment of angina, may cause peri-anal wounds that resolve on cessation of the medication (Baker et al., 2007).

Wound assessment

Wounds are costly to treat; therefore, it is important to appreciate the various considerations that need to be taken into account when assessing a patient. Assessment should not be viewed as a one-off occurrence but instead should be undertaken as part of an ongoing process with the emphasis on the patient, not just their wound.

A structured approach to the assessment of a patient with a wound is required. The six key elements of the original wound healing matrix are listed here and the key concepts depicted in Fig. 58.6:

- Phase of wound healing
- Aetiology
  - Acute, that is surgical, trauma, burns
  - Chronic, that is leg ulcers, diabetic foot ulcers, pressure ulcers
- Clinical manifestation
  - Size
  - Shape
  - Characteristics, that is exudate, odour, tissue type
- Environment and care
  - Primary care
  - Secondary care
- Healthcare system and resources
- Site of the wound.

Diabetic foot ulcers

Epidemiology

It was estimated that there were 1.4 million people diagnosed as diabetic in 2002 with these figures expected to double by 2010 (Cradock and Shaw, 2002). The cost of treating individuals with diabetes accounts for at least 9% of the acute healthcare costs in the UK. These costs, however, do not take into account the personal cost to the individual, such as a reduction in the ability to work and time they may need to take off work (Waters and Holloway, 2009). Diabetic foot problems are the most common cause for admission, and patients admitted to hospital for in-patient care are often hospitalised for 4–6 weeks, which obviously increases the financial costs considerably.

One of the major risks to patients with diabetic foot disease is that of amputation, which could be minor, that is mid-foot to toe; or major, that is mid-foot and above. National Service Frameworks for diabetes (Department of Health, 2001) have emerged to address this and, in turn, have been built upon (Department of Health, 2007a,b). Of concern is that up to 85% of amputations are preceded by foot ulcers. Therefore, if the incidence of foot ulcers can be reduced, this might lead to a reduction in amputations.

Aetiology

Individuals with diabetes are at risk of a number of systemic complications (see Chapter 44).

The two main causes of foot ulceration in patients with diabetes are:

- Neuropathy
- Ischaemia

PN causes damage to the nerves that leads to a lack of the protective pain sensation and is present in 75% of patients with diabetes. In this group of individuals, the blood supply to the extremities remains good, but the foot becomes insensate and can subsequently become deformed. This leads to an abnormal walking pattern and potentially tissue breakdown from abnormal pressures placed upon the foot. The characteristics of the diabetic foot are set out in Table 58.4. Unfortunately, the early systemic changes associated with the onset of diabetes may be present for up to 12 years before a diagnosis is

Table 58.4 Clinical features of a diabetic foot with neuropathy or arterial disease

Characteristic	Peripheral neuropathy	Peripheral arterial disease
Temperature	Warm	Cool
Foot pulse	Present/'bounding'	Absent/reduced
Pain	Commonly no pain NB Painful diabetic neuropathy is a rare but potential feature	Pain on walking (intermittent claudication) Depends on degree of neuropathy
Site of ulcers	Toes and metatarsal heads	Lateral (outer) border of foot
Callus (hard skin)	Present	Absent

made, by which time damage has already begun to occur and is often irreversible.

PAD usually occurs as a result of atherosclerosis. This often results in a reduction in blood flow to the lower limbs and pain on walking (claudication), pain at rest with possible progression to gangrene and amputation. PAD is common in the elderly and is not just a complication of diabetes, although people who have diabetes are at an increased risk of developing it. Foot ulceration due to PAD is less common, accounting for approximately 5% of cases.

Neuropathy can be related to lack of sensation (sensory neuropathy) and may also cause atrophy and weakness of muscles in the foot (motor neuropathy). In addition, there are effects on the autonomic nervous system which can cause changes in blood flow and sweat secretion (autonomic neuropathy). Each of these elements needs to be considered as each has significant effects on the lower limb in individuals with diabetes.

Clinical signs

The clinical features of a diabetic foot with PN and PAD are summarised in Table 58.4 and their typical presentations shown in Fig. 58.7 and Fig. 58.8, respectively. There are a number of factors that place patients at increased risk of ulceration including foot deformity; ill-fitting footwear; mechanical injury, for example treading on a sharp object; thermal injury, for example heat from a fire, or stepping into a hot bath; and chemical trauma typically caused by an over-the-counter preparation purchased to remove hard skin. National guidelines outline the processes that should be in place to ensure the monitoring of patients deemed at risk (Department of Health, 2001, 2007a,b; National Institute of Health and Clinical Excellence, 2004). One of the key issues to consider is that the feet of patients with diabetes do not ulcerate spontaneously, instead any one, or combination, of the factors discussed could be to blame.



Fig. 58.7 Diabetic foot ulcer caused by peripheral neuropathy.



Fig. 58.8 Peripheral arterial disease in a patient with diabetes.

Diagnosis

It is essential that individuals with diabetes are cared for within a multi-disciplinary framework with the responsibilities for management of the patient clearly defined.

Initial assessment should include a clinical examination of the foot and may also require objective testing, for example an X-ray. The key features of this examination are set out in Table 58.5. In addition, further tests such as a full blood count, examination of urine, alternate imaging methods,

Table 58.5 Examination of the diabetic foot

Clinical examination		Objective test
Shape and deformities	Toe deformities Foot deformities Callus	X-ray
Sensory function	Vibration Protective sensation	Biothesiometry Semmes–Weinstein filament
Motor function	Wasting Weakness Ankle reflexes	Electrophysiological tests
Autonomic function	Reduced sweating Callus Warmth Appearance of veins on the foot	Quantitative sweat test
Vascular status	Foot pulses Temperature Swelling	Non-invasive Doppler studies, ankle brachial pressure index and/or toe pressure indices

that is magnetic resonance imaging, colour duplex scans and angiograms, may be indicated.

Infection in the diabetic foot is a real risk and a common complication. It has been estimated that 20–50% of diabetic ulcers are infected. The severity of the infection will depend on the nature of the bacteria, but commonly cellulitis and osteomyelitis occur in patients with neuropathic ulcers with gangrene being more associated with PAD. Bacterial cultures from ulcers are usually polymicrobial with both Gram-positive and Gram-negative organisms as well as anaerobic bacteria. There should be concern if any of the following features occur:

- Difficulty walking and/or applying shoes
- Swelling in part or all of the foot
- Redness or other discolouration
- Foot becomes hotter than normal
- Discharge or unusual odour
- Open sores or blisters
- Nausea, vomiting or high temperature
- Difficulty maintaining blood glucose control.

Treatment

Infection

The signs of infection are often delayed or insidious in patients with diabetes. Virtually all diabetic foot infections require antimicrobial therapy, but this alone is rarely sufficient. If soft-tissue infection is superficial, then oral, relatively narrow spectrum antibiotics for 1–2 weeks are indicated (Lipsky and Berendt, 2006); however, if there is cellulitis and spreading infection, parenteral antibiotic therapy may be required for up to 4 weeks. In addition to antibiotics, the patient may require hospitalisation if removal of dead or devitalised tissue is required. An X-ray of the foot may also be advisable if the tissue loss is over the bone, and referral to a vascular or orthopaedic specialist may be necessary for surgery.

Other considerations

Treatment of a diabetic foot ulcer should also include:

- Podiatry
- Skin and wound care
- Provision of footwear to remove/redistribute weight
- Offloading options to include orthoses/custom-made insoles
- Patient education
- Pain relief
- Control of diabetes
- Multidisciplinary team approach.

The range of treatment options will be determined by whether there is neuropathy and/or PAD present, as well as the presence of ulcers and/or infection. The debridement of callus and devitalised tissue is essential as it enables the true dimensions of the ulcer to be established (Edmonds and Foster, 2000). Dressings are important but should not be viewed in isolation to the other essential aspects of treatment listed above. Key aspects in the choice of dressing for diabetic foot ulcers are how it will perform in a shoe, whether it will withstand pressure and shear forces, how well it will absorb any fluid from the wound and how often the dressing needs to be changed and cost effectiveness.

Prevention of recurrence

Many of the considerations discussed above are also important in terms of preventing a recurrence of ulceration and should be borne in mind when planning the management of individuals with diabetes. Ideally, ulceration should be prevented via intensive screening programmes, although unfortunately this is not always achievable. In addition, the maintenance of tight control over blood glucose and blood pressure is required together with the monitoring of cholesterol and initiation of antiplatelet therapy. Guidelines (National Institute of Health and Clinical Excellence, 2008) recommend the following:

- Blood pressure ≤140/80
- Blood glucose <7 mmol/L or $HbA1_c$ <6.5%
- Total cholesterol <5.0 mmol/L
- Antiplatelet therapy for those with or at risk of cardiovascular disease.

Leg ulcers

Epidemiology

The prevalence of leg ulcers in the Western world is 0.11–0.18% (Briggs and Closs, 2003). There is a preponderance of 2.8:1 female to male ratio, with venous disease being the main cause of ulceration. The risk of leg ulceration increases with age.

The estimated cost in the UK of all leg ulcers is between £200–600 million pounds with the costs of individual ulcer treatment between £557–1366 over a year (Tennvall and Hjelmgren, 2005). Between 60% and 90% of patients are managed in the community.

Aetiology

Leg ulcers can be classified as follows:

- Venous
- Arterial
- Mixed, that is ulcers that have a venous and arterial component
- Diabetic; typically on the foot, rather than the leg
- Autoimmune, for example rheumatoid arthritis.

Venous ulcers

Ulcers of venous origin account for the majority of all leg ulcers. There are a number of reasons why they occur and include failure of the calf muscle pump to work effectively, which leads to pooling of fluid in the lower limb and oedema. This can lead to high pressures in the lower limb on walking, known as venous hypertension. This swelling can lead to poor

oxygenation of the tissues and trapping of harmful substances such as growth factors and enzymes. Ultimately, this can lead to tissue breakdown precipitated by simple trauma such as knocking the leg.

The calf muscle pump relies on an adequate level of mobility; therefore, anything that might affect this such as increasing age, obesity and trauma predisposes the individual to a sequence of events if they also have poor venous return.

Risk factors associated with the development of venous ulcers include deep vein thrombosis (DVT), varicose veins, or surgery/trauma to the leg.

Clinical signs

Venous disease. As a result of venous hypertension and leakage of fluid, red blood cells are deposited in the tissues causing discolouration known as haemosiderin. This can often be seen on the lower limb and may be red or brown in colour. Varicose veins may also be visible as will oedema (swelling) and a characteristic change known as lipodermatosclerosis (LDS). Over time, the limb may develop a typical inverted 'champagne bottle' appearance. Venous ulcers are typically shallow and develop in the gaiter area (Fig. 58.9). Patients may also have associated gravitational eczema.



Fig. 58.9 Venous leg ulceration.

Diagnosis

The key element is the accuracy of the assessment and should include:

- Clinical history
- Clinical investigation
- Assessment of the limb
- Assessment of the ulcer.

Table 58.6 summarises the key aspects of the assessment of an individual with a leg ulcer.

Assessment of ankle brachial pressure index (ABPI). The use of a hand-held Doppler device is used to assess the arterial blood flow. Ideally, this test should be undertaken on any patient presenting with a leg ulcer. Furthermore, it should be carried out on first presentation as well as at subsequent intervals depending on whether the ulcer is improving or not. Essentially, the ankle brachial pressure index compares the patient's brachial (arm) and ankle systolic pressures:

$$\text{ABPI} = \frac{\text{highest ankle systolic pressure}}{\text{highest brachial systolic pressure}}$$

The patient should rest for 20 min before the assessment and the pressures should be measured supine (lying down). Two measurements should be taken from the foot and the highest value used in the calculation.

The ankle brachial pressure index is not a definitive measure of arterial status but merely serves as an indicator of blood flow. Other clinical signs and symptoms also need to be taken into account.

As a general principle, the ankle brachial pressure index or ratio should be ≥ 1.0 in individuals with no arterial disease. However, this should not be relied upon in the presence of diabetes as calcification of arteries can occur and lead to falsely high ABPI readings. In this instance, a Duplex scan would be a more reliable indicator of vascular status. Furthermore, both hypo- and hypertension can affect the readings.

Table 58.6 Factors to be taken into account in the assessment of an individual with a leg ulcer

Clinical history	Clinical investigations	Assessment of both limbs	Assessment of the ulcer
Family history	Blood pressure	Oedema	Year first ulcer occurred
Varicose veins	Ankle brachial pressure index	Site of ulcer	Site of ulcer/previous ulcers
Deep vein thrombosis/pulmonary embolus	Full blood count	Depth of wound	Size of ulcer(s)
Phlebitis		Appearance of wound bed	Number of previous episodes
Surgery or fracture of the leg		Surrounding skin	Time free of ulcers
Heart disease/stroke		Perfusion of feet	Past treatment (successful or not)
		Presence of pulses	Previous/current uses of compression bandaging
Diabetes		Ankle brachial pressure index	
Peripheral arterial disease			
Chest pain/angina			
Smoker			
Rheumatoid arthritis			
Medication			
Allergies			

Treatment

The mainstay of treatment for confirmed venous ulceration is compression bandaging. Known as graduated compression, specific bandage systems are used to apply external pressure to aid venous return. The ABPI must be ≥ 0.8 for this treatment to be used. Although there is much debate about which bandage system is preferable, the choice should be based on an individual patient assessment and may include:

- Short stretch systems
- Multi-layer systems

The aim of most systems is to create pressures of 40 mmHg at the ankle decreasing up to the knee to assist in venous return. In addition to bandaging, the patient should be encouraged to keep mobile, which could be as simple as undertaking ankle exercises to improve blood flow. Leg elevation and rest should also form part of overall management.

Even where arterial disease has been excluded as a complication, the patient should be monitored carefully for signs of compromised blood flow as serious injury such as skin necrosis or in the extreme amputation may be required.

Other treatment options may include antibiotics if systemic infection is suspected or topical antimicrobial dressings for local infection which include iodine- or silver-based products.

Intermittent pneumatic compression, surgery, skin grafting, bioengineered skin and pharmacological treatments such as oxypentifylline have all been suggested as adjuvant therapies to compression therapy (Robson et al., 2006).

General wound care should include cleansing of the ulcerated area with saline or tap water to maintain cleanliness and hygiene as well as debridement of any dead or devitalised tissue. Dressings should be simple and as low adherent as possible as they have to perform well under the bandage system. There is a need to be aware of the potential of contact sensitivity to the dressings, bandages, or skin treatments used.

Gravitational eczema is commonplace in patients with venous disease and is related to the changes caused by venous hypertension. The patient may complain of intense itching, and scratch marks may be visible on examination. It is important to distinguish eczema from contact sensitivity and cellulitis as each of these requires a different treatment. Treatment of eczema will include a combination of a topical corticosteroid such as clobetasone butyrate (Eumovate®) or mometasone furoate (Elocon®) creams and emollients such as Epaderm® or similar mixtures of white soft paraffin and liquid paraffin to manage this inflammatory condition.

Prevention of recurrence

Once a venous ulcer is healed, compression hosiery (in the form of stockings) are required. This hosiery is classed as 1, 2 or 3 depending on the level of pressure applied. Class 3 stockings and tights provide strong support (25–35 mmHg at the ankle) and are the preferred choice to prevent recurrence of venous ulcers. Table 58.7 provides the compression values for hosiery. Ideally, they will need to be worn for life or at least a minimum of 5 years. Unfortunately, recurrence is common often because of the inconvenience associated with the wearing of stockings. Patient education and follow-up is essential. Community leg ulcer clinics have been established in many areas of the UK and have shown to be effective in supporting patients.

Table 58.7 British national formulary compression values for hosiery

Compression class	Level of support	Compression hosiery (British Standard)
Class 1	Light	14-17 mm Hg*
Class 2	Medium'	18-24 mm Hg*
Class 3	Strong	25-35 mm Hg*

*compression provided at the ankle

Arterial ulcers

Arterial ulceration is commonly associated with atherosclerosis and peripheral artery disease, much of which has been discussed previously in relation to diabetic foot disease. Both macro- and micro-disease may be present.

Clinical signs

The classic clinical features of arterial insufficiency are:

- Intermittent claudication/rest pain
- Colour changes, for example pallor
- Muscle atrophy/weakness
- Poor perfusion, for example cool limb
- Loss of skin hair
- Thickening/hardening of the nails
- Ulceration
- Gangrene.

Arterial ulcers often appear 'punched out' (Fig. 58.10) and have a pale wound bed. The significant feature is pain, with many patients reporting pain on walking known as intermittent claudication. As the disease progresses, patients may also report that their pain is worse at rest, particularly when their legs are elevated. This feature affects their ability to sleep, eat and keep mobile which can ultimately mean they are unable to leave the house.

Diagnosis

A simple test known as Buerger's Test (see glossary) is normally used to look for positive signs of disease. If it is possible, a Doppler test should also be undertaken to calculate the patient's ankle brachial pressure index. Typically, an ankle brachial pressure index of 0.6–0.8 indicates a degree of arterial disease, whilst a value ≤0.6 is considered to be indicative of considerable disease. In addition, a colour Duplex scan is usually required to ascertain the extent of the disease. If treatment is required, an angiogram will usually be undertaken to examine the affected vessels.



Fig. 58.10 Arterial leg ulceration.

Treatment

An angioplasty may be carried out to improve the blood supply. Where this is not possible, vascular reconstruction may be advised to try and prevent further progression. Treatment will also include pain relief, prevention of infection and nutritional support. In addition, smoking cessation advice may be needed as might pharmaceutical intervention for cholesterol or lipid lowering purposes.

Prevention of recurrence

The main risk for individuals with arterial disease is amputation (minor or major). The patient plays a key role in prevention as many of the predisposing factors are lifestyle issues such as giving up smoking, eating a healthy diet and exercise. It may also be necessary to continue taking medication as discussed previously.

Mixed ulcers

While the term 'mixed ulceration' is used in clinical practice to describe ulcers with an element of venous and arterial disease, technically it is not a diagnosis. Patients present with venous and arterial symptoms, and an ankle brachial pressure index is likely to be between 0.6 and 0.8. Treatment is directed at the symptoms causing most concern, with compression bandaging only used under close supervision. The management options are as discussed previously for venous and arterial ulcers.

Pressure ulcers

Epidemiology

Previously referred to as *bed sores* or *pressure sores*, this wound type is now generally referred to as a pressure ulcer (National Institute of Health and Clinical Excellence, 2005) and defined as:

> *localised injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear. A number of contributing or confounding factors are also associated with pressure ulcers, the significance of these factors is yet to be elucidated.*
>
> (European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel, 2009)

The prevalence of pressure ulcers across five European countries was 18.1% (Clark et al., 2004). This helps us establish the burden of pressure ulcers perhaps locally, nationally and globally but does not necessarily provide information on the quality of care (European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel, 2009). Table 58.8 provides the most recent data on incidence.

Common sites of pressure ulcers

Pressure ulcer damage can occur anywhere on the body, but are most common over bony prominences including:

- Sacrum
- Heels
- Buttock
- Trochanter.

Sacral damage often occurs from the patient slipping down the bed or whilst sitting in a chair with shear forces causing the most damage. Injury to other areas is more likely to be due to direct pressure over a bony prominence. In acutely ill patients, equipment such as nasal cannula can even cause pressure damage to the nose.

Aetiology

As the name implies, this sort of wound is caused by external pressure on the tissues which, if sustained, leads to decreased capillary flow, ischaemia and capillary thrombosis. In turn, fluid escapes from the vasculature into the surrounding tissues causing oedema, accumulation of metabolic waste and cell death.

There are different types of pressure that may be implicated in the onset of damage, and it is both the type and duration of pressure that is of importance. The types of pressure are listed as follows:

- Capillary closing pressure
- Vertical pressure
- Tissue interface pressure
- Shear and friction forces.

Table 58.8 Incidence of pressure ulcers in UK

	Grade distribution	Annual incidence
Grade I	34.9%	140,000
Grade II	41.2%	170,000
Grade III	12.9%	50,000
Grade IV	11.0%	50,000

In addition to pressure, other factors that may influence the development of the damage are:

- Reactive hyperaemia
- Reperfusion injury
- Patient age: extremes of age most at risk
- Nutritional status: extremes of weight most at risk
- Mobility status
- Condition of peripheral circulation
- Continence status.

Clinical signs

Early signs of damage may present as a red area on the skin that remains even after the pressure has been relieved, or damage may present as broken skin or an abrasion. Pressure ulcers are now classified using four categories or stages (rather than grades):

Category/stage I: Non-blanchable redness of intact skin

Intact skin with non-blanchable erythema (in normal tissue if you use light finger pressure on an area it turns white, once the pressure is released it returns to the normal colour very quickly; where damage is present the tissue does not 'blanch', i.e. turn white) of a localised area usually over a bony prominence. Discolouration of the skin, warmth, oedema, hardness or pain may also be present. Darkly pigmented skin may not have visible blanching but may be painful, firm, soft, warmer or cooler as compared to adjacent tissue.

Category/stage II: Partial skin loss or blister

Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanguinous filled blister.

Category/stage III: Full thickness skin loss (fat visible)

Full thickness tissue loss. Sub-cutaneous fat may be visible but bone, tendon or muscle is not exposed. Some slough may be present. May include undermining and tunnelling.

Category/stage IV: Full thickness tissue loss (muscle/ bone visible)

Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunnelling.

Diagnosis

Pressure ulcers are usually diagnosed on clinical appearance and presenting history. Using the classification system outlined above, it is also possible to determine the stage of ulcer.

X-rays of the ulcer may be required, especially if it is over a bony area, to exclude any underlying infection in the bone (osteomyelitis). In addition, blood tests to examine inflammatory markers may also be useful in determining the presence of infection.

If undermining or tunnelling is present, further ultrasound scans may be required to examine the full extent of the wound and to identify any collection of fluid.

Treatment

The care of patients with pressure ulcers will depend on the category/stage of the damage, but there are interventions common to all patients and these include (National Institute of Health and Clinical Excellence, 2003, 2005):

- Appropriate support surface (mattress and seating/ cushions) to redistribute pressure and reduce shear forces
- Repositioning (turning) schedule to meet the needs of the individual
- Wound cleansing with normal saline or potable water
- Debridement of dead or devitalised tissue using an appropriate method
- Dressings that meet the wound characteristics
- Treatment of infection via local or systemic route as appropriate
- Skin care and hygiene, particularly if the patient is incontinent
- Negative pressure wound therapy may be a suitable adjuvant therapy
- Surgical reconstructive intervention in complex cases.

Other therapeutic interventions include electrical stimulation, laser therapy and ultrasound.

Prevention of pressure ulcers

The majority of pressure ulcers are preventable. Prevention strategies should take into account the aetiology of the ulcer and also the risk factors discussed. Important considerations in terms of prevention include:

- Patient repositioning
- Use of equipment
- Skin care
- Nutritional support.

An individual's potential risk of developing damage should be assessed with a view to identifying those that are vulnerable. Once an individual is deemed to be at risk of skin breakdown, the aim should be to improve tissue tolerance which can be achieved using the elements described above.

Principles of wound management

There are a number of principles to wound management including:

- Knowledge of wound healing physiology
- Assessment of the patient
- Assessment of the wound/ulcer
- Assessment of the tissue type
- Recognition of factors affecting healing
- Knowledge of dressings available
- Availability of resources.

The health care professional needs to be clear about the aim of management, and the expected outcome before the most appropriate treatment can be selected. Table 58.9 outlines the main considerations to be taken into account. Whilst wound healing is often viewed as the eventual outcome in some instances this may not be feasible; therefore, alternative aims should be identified to demonstrate success.

Assessment of the tissue type should include examination of the following:

- Dead, devitalised tissue, that is slough, necrosis
- Infected tissue
- Granulating, that is pink
- Epithelial tissue, that is pink, silvery tissue at the edges of a wound.

Once this information has been established, then the choice of local treatment should be more apparent. The selection of a dressing will depend on:

- Treatment objective
- Stage of healing
- Tissue type
- Site and size of the wound
- Frequency of the dressing change
- Comfort/cosmetic appearance
- Where/by whom the dressing is to be changed
- If the dressing is available.

Table 58.9 Criteria to consider in choosing appropriate wound management

Aim	Criteria
Protect from	Drying out Infection Further damage
Debride using	Autolytic methods Mechanically Sharp/Surgical Larvae
Control	Bleeding Exudate Pain Odour

Box 58.2 lists the main types of dressings available. Dressings alone will not heal a wound, and other aspects of care may need to be taken into account including:

- Compression bandages for patients with venous ulcers
- Pressure relieving equipment for individuals with or at risk of pressure ulcers
- Footwear and off-loading devices for patients with diabetic foot disease

Box 58.2 Wound management products

Basic wound contact dressings, that is knitted viscose/polymer dressings

Low adherent dressings – indicated for clean granulating wounds with a light amount of exudate. NB Dressing may stick so be cautious of trauma on removal

Absorbent dressings – are also low adherent and suitable for mild and moderate (but not viscous) exudate

Advanced wound dressings

Hydrogel – generally donates liquid to aid autolytic debridement of sloughy, necrotic wounds. Available in amorphous or sheet form depending on the size and shape of the wound. Choice will depend on the amount of exudate present.

Vapour permeable films and membranes – also allow the passage of water vapour and oxygen but remain impermeable to water and bacteria. They allow viewing of the wound and are flexible and conform to awkward wound shapes. Mainly suitable for partial thickness wounds and formulated with and without an absorbent pad for exudate management. Use would be avoided in infected and highly exuding wounds.

Soft polymer – often with added silicone. Designed to be non-adherent and are useful if the skin/wound is fragile and where further damage is to be avoided. They can be used on wounds that have light to moderate exudate but may require a secondary absorbent dressing if large amounts of exudate are present.

Hydrocolloids – semi-permeable to water vapour and oxygen, and gel in the presence of exudate. Promote autolytic debridement and are also useful on granulating wounds as they can be left in place for a number of days. Generally, these dressings are indicated for moderate to heavy exudate, careful monitoring for maceration of the wound edges and surrounding skin would be important.

Foam – suitable for most types of wounds but requires a moist wound interface. Can absorb various levels of exudate with some having better fluid handling capacity than others. Presented in adhesive and non-adhesive forms, the choice of which is often based on the integrity of the patient's surrounding skin.

Alginate – usually fibrous dressings, made from seaweed, some have haemostatic properties. Require moisture so are not suitable for dry wounds. They are suitable for exuding wounds and can aid autolytic debridement. Available as packing material (ropes) or flat sheets, the choice of which depends on the size and shape of the wound. May require a secondary dressing to hold in place.

Capillary action – contraindicated in bleeding wounds but useful for exuding wounds, particularly when slough is present. Absorbent core absorbs and contains the exudate which minimises the risk of maceration. A secondary dressing is also required.

Odour absorbent – utilise activated charcoal to absorb odour from wounds. Some require a suitable primary contact layer whilst others are layered and provide a non-adherent wound contact interface. The cause of the odour should always be established as underlying infection may require additional treatment.

Continued

Box 58.2 Wound management products—cont'd

Antimicrobial – used to treat local rather than spreading or systemic infection. Can be used to reduce the levels of bacteria in the wound. The amount of exudate should be a consideration when choosing an antimicrobial dressing.

Honey – medical honey is anti-inflammatory as well as antimicrobial and can aid with debridement of the wound and combating odour. Caution should be exercised in diabetic patients and its use should be avoided if a patient is allergic to bees/bee stings.

Iodine – available as povidone-iodine or cadexomer-iodine, preparations are useful in clinically infected wounds. Iodine is effective against a wide range of bacteria, but its effect can be diluted if large amounts of exudate are present. Cadexomer-iodine is effective at debriding wounds. Iodine can cause sensitivity and systemic absorption can occur especially from large wounds or prolonged use.

Silver – used when infection is suspected. Available in different presentations and can be used on all wound types that have clinical signs of infection and where exudate is present. Skin discoloration can occur and systemic absorption can occur therefore use is contraindicated in pregnancy and neonates.

Specialised dressings

Protease-modulating matrix – acts on the proteolytic enzymes in chronic wounds and re-establishes normal enzymatic activity. Can be used on non-healing wounds that do not seem to be progressing.

Silicone keloid dressings – used to reduce hypertrophic and keloid scarring, therefore are not appropriate for open wounds. A staged approach to application is advised with increasing wear time being indicated. Dressings can be washed and re-used.

Adjunct dressings and appliances

Surgical absorbents – useful as secondary layer over a primary wound contact layer. Absorb exudate but allow leakage of exudate ('strike-through'). Can adhere to the wound bed and fibres may be shed, therefore should be used cautiously.

Wound drainage pouches – use when other exudate absorbing dressings are not sufficient to manage the fluid levels; wound drainage bags may be useful as a means to containing the leakage.

Complex adjunct therapies

Topical negative pressure – useful for acute and chronic cavity wounds and shallower wounds healing by secondary intention; topical negative pressure or vacuum-assisted closure aims to stimulate angiogenesis, remove excess exudate, reduce the bacterial burden and stimulate the production of granulation tissue.

Sterile larvae (maggots) – useful for debridement of sloughy wounds. Once applied they can remain *in situ* for 3 days before replacing. Now available contained within a net bag to simplify application.

Growth factors – Becalpermin (Regranex®) licensed for full thickness, diabetic neuropathic foot ulcers.

Bandages

Compression (multi-layer) – provide compression for treatment of venous ulcers. Correct application of bandage is essential as the incorrect application technique can be hazardous. A Doppler assessment to establish the patient's ankle brachial pressure index (ABPI) is essential prior to application. Systems include high compression, short stretch and multi-layer (4 layer and 2 layer). Choice is often dependent on patient preference.

Compression hosiery – prevents recurrence of venous ulcers. Ankle brachial pressure index should be established prior to application. Class III is preferred.

Compression garments – for management of lymphoedema. Used in conjunction with intermittent pneumatic compression systems.

Skin care

Skin barriers that protect the peri-wound area are important as wound exudate contains enzymes that can cause damage to tissues. Simple silicone-based creams or petroleum-based ointments can be useful in providing a protective layer for fragile skin.

- Topical negative pressure for cavity wounds healing by secondary intention.
- Nutritional supplementation
- Drugs to influence healing
- Surgical interventions.

Case studies

Case 58.1

A 64-year-old diabetic man has an ulcer on the sole of his foot. He cannot recall how he sustained the injury and the wound is not painful. The patient feels otherwise well (Fig. 58.11).

Questions

1. What is the most likely cause of the ulceration?
2. What are the key concerns in ensuring appropriate management?
3. What are the options for assessment and treatment?

Answers

1. From the position and the appearance, this is likely to be a neuropathic diabetic foot ulcer as these commonly present on the plantar (sole) aspect of the foot. They are usually painless and can leak large amounts of exudate if they are deep. Note the signs of macerated tissue around the edges of the wound.



Fig. 58.11 Case 58.1

2. The most common complication of this sort of ulcer is infection. Local infection of the wound bed can quickly lead to spread of infection (cellulitis) in patients with diabetes as they have a slower immune response and do not mount a defence mechanism quickly. In addition, an assessment of the patient's glucose control should be undertaken as poor glucose management can exacerbate complications. Finally, a review of the patient's footwear should be considered as the patient may require further off-loading techniques to assist wound healing.
3. Assessment of the foot should be undertaken to establish the extent of the neuropathy. Vascular assessment is also required to examine the blood flow to the limb. Local wound assessment should include a description of the tissue present, the size of the wound (to include depth) and the amount of exudate as this will determine not only the topical dressing to be applied but also whether further investigations are required.

   As the ulcer has some depth, the wound will need packing gently with a dressing that has good fluid handling capacity. A secondary dressing will be needed to secure the contact layer, and the footwear should be suitable enough to accommodate the dressing without causing further pressure.

Case 58.2

A 71-year-old lady has ulceration on the gaiter area of her lower leg (Fig. 58.12).

Questions

1. What is the likely cause and how would this be established?
2. What treatment does the patient require?
3. What advice would be required in the short and long-term?



Fig. 58.12 Case 58.2

Answers

1. The ulcer is typical of a venous ulcer, caused by venous hypertension which damages the veins and causes leakage of cells and fluid ultimately leading to tissue breakdown often caused by minor trauma. A medical history should be taken to establish likely predisposing factors; the limb should be assessed for colour, oedema and the presence of pain. The ulcer is likely to be shallow, with irregular edges and surrounding skin may demonstrate changes associated with venous disease such as haemosiderin, LDS or gravitational eczema.
2. Local treatment will include a non-adherent dressing if the wound bed is clean and granulating. Surrounding skin will require emollients for hydration and/or topical steroids if eczema is present. The most important treatment will be the application of graduated compression using a multi-layer bandage system.
3. The patient should be encouraged to take gentle exercise (sufficient to ensure ankle flexion) and also elevate the leg when sitting. The patient must continue to wear the compression bandages (day and night) until healed unless pain, discomfort or skin colour changes occur, in which case they should seek medical attention. In the long-term, the patient should be assessed for compression hosiery which should be continued for at least 5 years post-healing to prevent recurrence.

Case 58.3

A 59-year-old spinally injured, wheelchair-bound patient has a pressure ulcer extending into the underlying tissues (Fig. 58.13).

Questions

1. What is the likely stage/category of the ulcer?
2. What are the factors that have led to the development of the ulcer?
3. What are the key concerns in selecting the most appropriate product (s) to manage (a) the ulcer (b) the patient?

Answers

1. This is likely to be a Stage/Category III ulcer as on further examination no bone can be felt at the base of the wound (bleeding noted in the image is due to probing of the ulcer and is also due to the presence of local infection in the tissues).



Fig. 58.13 Case 58.3

2. The patient has sustained a spinal injury and as a consequence their mobility will be limited, and they will not sense the need to change position regularly as they have lost the sensory clues to undertake this. The ulcer has probably been caused by direct pressure over a bony prominence which has led to the compression of tissue and vessels leading to damage.
   (a) An assessment of the ulcer should be undertaken to include the size of the ulcer, presence of undermining or tunnelling, the type of tissue in the wound bed (to include presence of bone) and the amount of exudate. A cavity wound such as this should be packed gently and secured with a non-adhesive type dressing as skin stripping may occur on dressing removal otherwise. An antimicrobial dressing could be used.
   (b) The patient's wheelchair and cushion should be assessed to determine whether they are suitable. The patient should also be asked about how often they relieve the pressure when sitting and be reminded that ideally this should be every 15 min. The patient should be encouraged to remain off the affected area until it has healed and the use of an appropriate mattress should be discussed. Other aspects such as skin care (to include the peri-wound area), skin hygiene and nutrition should also be reviewed.

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