Chapter 19

Therapy-related issues: central nervous system

Pain: a definition

The International Association for the Study of Pain defines pain as '*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*'.

Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is always unpleasant and therefore is also an emotional experience.

Many people report pain in the absence of tissue damage or any likely pathophysiological cause. Usually this happens for psychological reasons. There is usually no way to distinguish their experience from that caused by tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus.[1] In view of this, pharmacists should be wary of expressing opinions about whether a particular patient is in pain or not.

Types of pain

Nociceptive pain

'Nociceptive pain' is pain that occurs when nociceptors (pain receptors) are stimulated. This is normal pain in response to injury of the body. The purpose of this type of pain is to discourage the use of injured body parts, which could potentially extend the injury further. This pain normally responds to conventional analgesics, such as paracetamol, NSAIDs, and opioids (Fig. 19.1).

Neuropathic pain

'Neuropathic pain' is pain initiated or caused by a primary lesion or dysfunction in the nervous system. The pain is often triggered by an injury, but this injury might or might not involve actual damage to the nervous system. It seems to have no physiological purpose. The pain frequently has burning, lancinating (stabbing), or electric-shock qualities. Persistent allodynia, pain resulting from a non-painful stimulus such as a light touch, is also a common characteristic of neuropathic pain. The pain can persist for months or years beyond the apparent healing of any damaged tissues. This pain might not respond to standard analgesics but might respond to unconventional analgesic treatments, such as antidepressants, anticonvulsants, and various other therapies, such as clonidine or capsaicin. (Fig. 19.1).

1 International Association for the Study of Pain. http://www.iasp-pain.org

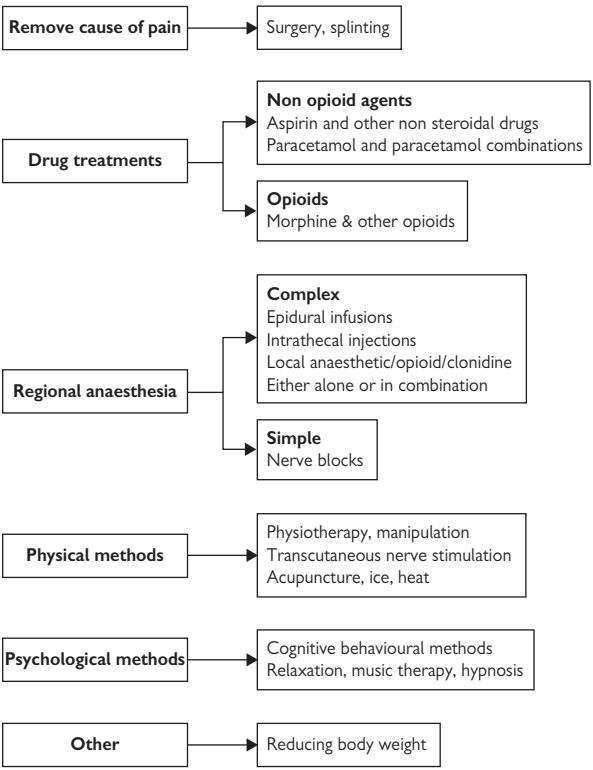

Fig. 19.1 Treating pain—methods available.

Assessment of pain

There are good validated scales for assessing pain. These are usually derived from assessment of both pain intensity and pain relief when analgesics are used. Both visual analogue scales (VASs), a line moving from 'no pain' to 'worst possible pain', and categorical scales, using words such as 'none', 'slight', 'moderate' or 'severe', are employed, often together. They can be useful to monitor progress in patients who are suffering from pain.

Categorical scales

Categorical scales use words to describe the magnitude of the pain. The patient picks the most appropriate word; most research groups use four words (none, mild, moderate, and severe). Scales to measure pain relief were developed later. The most common is the five-category scale (none, slight, moderate, good, and complete).

For analysis, numbers are given to the verbal categories (for pain intensity, none = 0, mild = 1, moderate = 2, and severe = 3, and for relief, none = 0, slight = 1, moderate = 2, good or lots = 3, and complete = 4).

The main advantages of categorical scales are that they are quick and simple. However, the small number of descriptors could force the scorer to choose a particular category when none describes the pain satisfactorily.

Visual analogue scales

VASs, lines with the left end labelled 'no relief of pain' and the right end labelled 'complete relief of pain', seem to overcome this limitation (Fig. 19.2). The standard VAS is 100mm long. Patients mark the line at the point that corresponds to their pain. The scores are obtained by measuring the distance between the 'no relief' end and the patient's mark, usually in millimetres. The main advantages of VASs are that they are simple and quick to score, avoid imprecise descriptive terms, and provide many points from which to choose. More concentration and coordination are needed, which can be difficult postoperatively or with neurological dis-orders.

Pain relief scales are perceived as more convenient than pain intensity scales, probably because patients have the same baseline relief (zero), whereas they could start with different baseline intensities (usually moderate or severe). They are based on the same approach of a 100mm scale but are asked to rate the amount of relief from 0 to 100mm. Relief scale results are then easier to compare. They can also be more sensitive than intensity scales. A theoretical drawback of relief scales is that the patient has to remember what the pain was like to begin with.

Global subjective efficacy ratings, or simply 'global scales', are designed to measure overall treatment performance. Patients are asked questions such as 'How effective do you think the treatment was?' and answer using a labelled numerical or categorical scale. Although these judgements probably include adverse effects, they can be the most sensitive way to discriminate between treatments.

Judgement of pain by the patient, rather than by a carer, is the ideal. Carers tend to overestimate the pain relief compared with the patient's version (Fig. 19.2).

Instructions

It is important that the use of the scale is explained to each patient. Patients are instructed to place a mark on the line to report the intensity or quality of the sensation experienced. Instructions should be written above the scale, e.g. INSTRUCTION: Put a mark on the line at the point that best describes HOW MUCH PAIN YOU ARE HAVING RIGHT NOW. Notice that what is measured is 'the perception right now', not a comparison such as: 'What is your pain compared with what you had before?'

Fig. 19.3 can be completed to show changes in pain intensity and/or pain relief across time. This can be valuable when introducing changes to analgesia and provides an ongoing assessment of progress.

A range of pain assessment tools including those in a range of languages and some for children, can be found at the Partners Against pain website.[1]

An example of a chart for patients with chronic pain is presented in Fig. 19.3. Patients are asked to assess their pain on a weekly basis and to bring their charts when attending clinics.

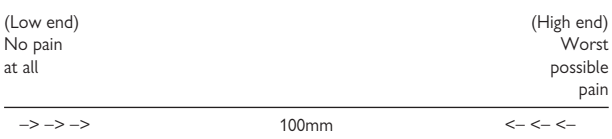

Fig. 19.2 Example of a VAS for pain intensity.

1 http://www.partnersagainstpain.com

Patients name

1. Please choose a suitable time and day of the week, and complete the chart on the same day and time every week.
2. Stop when the chart is full, or when the pain returns to the same intensity as it was before the treatment started.
3. If you have more than one pain (e.g. back pain and leg pain) we may ask you to complete a separate chart for each pain.

Type of treatment: . . . . . .
Date of treatment: . . . . . .

Main Area of Pain:

	Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
How bad has your pain been today?	None																	
	Mild																	
	Moderate																	
	Severe																	
	V Severe																	
How much pain relief have you had today from the injection?	Complete																	
	Good																	
	Moderate																	
	Slight																	
	None																	
Please record the name and number of pain killing tablets taken per week																		
How effective was the treatment this week?	Excellent																	
	Very Good																	
	Good																	
	Fair																	
	Poor																	

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Date when full pain returned . . . . . .

Fig. 19.3 Oxford chronic pain record chart.

Acute pain: incidence

Acute pain is common. A survey of >3000 patients newly discharged from hospital revealed the results shown in Table 19.1.

- Not all of the patients in the survey had undergone surgery, so this is not just a problem for surgical wards.
- Pain can be a problem after operations, dental procedures, and wound dressings. Some types of surgery have a less painful recovery than others, so analgesia must be tailored.
- The need for pain relief in medical settings such as MI, sickle cell crisis, musculoskeletal disease, and renal colic must be considered along with the needs of cancer, trauma, burns and obstetric patients.

Table 19.1 Responses to questions on pain by 3163 in-patients*

	Proportion of patients (%)
Pain was present all or most of the time	33
Pain was severe or moderate	87
Pain was worse than expected	17
Had to ask for drugs	42
Drugs did not arrive immediately	41
Pain was present all or most of the time	33

* http://www.medicine.ox.ac.uk/bandolier/painres/Painresstuff/whypain.html

Acute pain

NSAIDs and non-opioids

Effective relief can be achieved with oral non-opioids and NSAIDs. It is clear from the NNT chart (Fig. 19.4) that NSAIDs are superior to paracetamol and to paracetamol combined with codeine. Combining paracetamol with an NSAID can enhance pain relief for a number of patients in the acute phase post surgery. The current vogue of supplying separate paracetamol and codeine is to be discouraged (as a cost-saving exercise) because it leads to confusion in some patients, and there have been cases of (inadvertent) codeine overdosing leading to hospitalization.

There is wisdom in the saying that if patients can swallow, they should receive medicines by mouth. There is no evidence that NSAIDs given rectally or by injection work better or faster than the same oral dose. They do not ↓ the risk of GI damage either. Gastric upset and bleeding are important adverse effects. Ibuprofen is probably the safest in this respect; however, long-term NSAID treatment should be covered with a gastric-protecting agent such as a PPI. Beware also of using NSAIDs in patients with pre-existing kidney problems; an NSAID can precipitate acute renal failure, requiring dialysis.

The belief that NSAIDs should not be used after orthopaedic surgery because they inhibit healing is a myth.

Opioids

- These are first-line treatment for acute pain. Intermittent doses might provide effective relief, but patient-controlled analgesia is the preferred method. There are many stories of adequate doses being withheld because of misconceptions, fear, and ignorance.
- Dependence is not a problem in acute pain, and respiratory depression is only a problem if the patient is either not in pain or given doses larger than those needed to treat the pain.
- The key principle is to titrate the analgesic until either pain relief is obtained or unacceptable side effects are experienced.
- There is no evidence that one opioid is better than another, although pethidine (meperidine) should be avoided because of its toxic metabolites, which can accumulate, acting as a CNS irritant and eventually inducing convulsions, particularly if underlying renal failure is present. There is no evidence for the view that pethidine (meperidine) is best for renal colic pains.
- The metabolite of morphine (morphine-6-glucuronide) can accumulate in renal disease, with the effect of prolonging the action of morphine. Provided that the dose is titrated carefully, this should not be a problem.
- It makes good sense to select one opioid for the treatment of acute pain, so that everyone is familiar with its profile. In most settings, morphine does the job.

Regional anaesthesia

- Regional anaesthesia works by interrupting pain transmission from a localized area. The risk of neurological damage is the main concern.
- Pharmacists should be aware of the compatibility issues surrounding medicines for epidural or intrathecal use, in addition to careful monitoring of the doses used. Preservative-free morphine should be used as a rule (because of the potential neurotoxicity of preservatives), unless patients are in the terminal phase of illness.

Topical agents

- Topical agents can be useful in treating acute injuries, such as strains, sprains and soft tissue trauma. There is limited evidence for the benefits of rubifacients, which work by producing a counter-irritation to relieve musculoskeletal pains. The NNT is ~2, but this is based on three small trials (with 180 participants).
- There is good systematic review evidence to show that topical NSAIDs are effective in acute pain. The NNT for pain relief is 2–4 based on 37 placebo-controlled trials with a range of NSAIDs. Ketoprofen, felbinac, ibuprofen, and piroxicam are superior to placebo, but indometacin and benzydamine are no better than placebo. Adverse events for NSAIDs were no different than placebo.

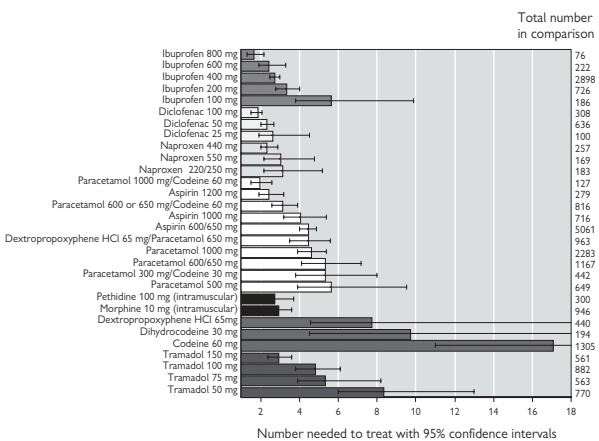

Fig. 19.4 Acute pain treatments: league table of the NNT.

Treating cancer pain

Since the introduction of the WHO three-step ladder (Fig. 19.5), potent opioids (usually morphine) have been the analgesics of choice for managing cancer pain.

Morphine is still considered the benchmark by the European Association for Palliative Care mainly because it is available in a number of different dose forms, it has extensive clinical experience, and it has an ability to provide analgesia. However, it is not always ideal, with wide individual variation in dose needs and active metabolites that can accumulate, particularly in renal failure. There is no maximum dose for morphine, but a systematic review showed that mean daily doses range from 25 to 300mg and, in unusual cases, can reach 2000mg daily. The adverse effects of morphine are not tolerated in ~4% of patients.

Drugs such as hydromorphone and oxycodone can be substituted, but these offer no real advantages. Transdermal fentanyl has become popular in recent years and can offer less constipation and daytime drowsiness.

Methadone can produce similar analgesia to morphine and has similar side effects, but it has a narrower dose range. It is the safest in renal failure; it also has a long and unpredictable half-life and its potency is often underestimated.

Spinal opioids

A few patients benefit from spinal opioids if they are unable to tolerate oral morphine. Spinal morphine in combination with a local anaesthetic is helpful for incident pain, and the addition of clonidine can help neuropathic pain. Spinal opioids are associated with greater risks, especially of epidural abscesses, cerebrospinal fluid leaks, and catheter problems.

Dealing with breakthrough pain

Cancer pain often presents as a continuous pain, with intermittent more serious pain breaking through. This can arise in up to 80% of patients with cancer pain. Four episodes daily is about the average, with each pain lasting ~30min. There are several dose strategies to manage breakthrough pain, with the usual 4h dose every 1–2h as needed (as an instant-release formulation). With transmucosal fentanyl, there seems to be little relationship between the rescue dose and the daily dose.

Use of NSAIDs with opioids

There is good evidence that NSAIDs can ↓ the total dose of opioids and ↓ their adverse effects. Gastric protective agents are needed for chronic long-term dosing.

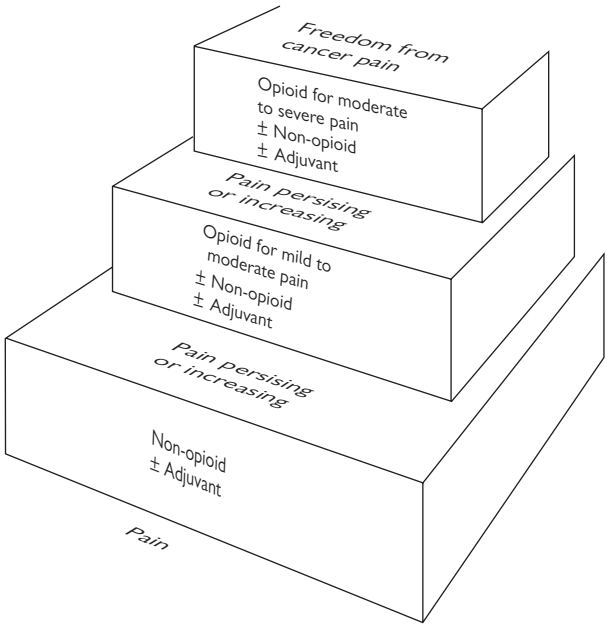

Fig. 19.5 WHO analgesic ladder.

Equianalgesic doses for opioids

Calculating equivalent doses is not an exact science, so care is needed. The literature contains much conflicting information, so key points are listed in the next section together with some external sources for suggested conversion factors.

Key points to consider when converting patients from one opioid to another

- Ratios for acute pain might not be the same as those for chronic pain.
- Ratio tables are for guidance only—they can be useful, but there can be wide variation between individuals. Therefore the dose needs to be started cautiously and titrated to effect.
- Monitor pain and pain relief—use of pain-assessment tools and adverse-effect monitoring should be considered.
- Tolerance to one opioid might not be carried over to another—this can lead to greater potency than expected. This can be anticipated by ↓ the equianalgesic dose by a further 30–50% and providing further analgesic rescue in the early stages.
- Be careful if treating patients with renal impairment—certain metabolites accumulate in renal impairment, so caution is needed. Fentanyl probably does not produce active metabolites in renal impairment, but caution is still advised.

Further reading

There is an opioid conversion software program for use on a handheld computer (and now a desktop version) at the Johns Hopkins Center for Cancer Pain Research. You can download the program free. Free registration is required. http://www.hopweb.org

Department of Anesthesiology and Critical Care Medicine at Johns Hopkins Medical Center has a useful website with additional suggested resources. http://www.hopkinsmedicine.org/anesthesiology/index.shtml

Pereira J *et al.* (2001). Equianalgesic dose ratios for opioids. *Journal of Pain and Symptom Management* **22**: 672–87.

Regnard C (1998). Conversion ratios for transdermal fentanyl. *European Journal of Palliative Care* **5**: 204.

Compatibility of drugs in pain and palliative care

There are a number of mixtures in common use, including opioids combined with drugs such as baclofen, midazolam, or local anaesthetics.

It is common to differentiate between chemical and physical compatibilities. Ideally, information for the former would be available for all mixtures, but in practice this is often hard to find. Some information is available in the peer-reviewed pharmacy literature and a search of international pharmaceutical abstracts can be helpful.

Time and temperature are two key components affecting chemical reactions, so it is wise not to leave mixtures sitting in syringe drivers for many hours in a warm room. An ↑ number of a drugs mixed together and the greater the concentration will ↑ the risk of incompatibility.

The majority of recommendations are desired from on physical compatibility, i.e. drugs are mixed and no obvious colour change or precipitation occurs, even when examined microscopically. Additionally, no change in pharmacological effect is seen when the drugs are administered.

Further reading

There are several useful sources for information on common opioid mixtures, as follows.

Trissel L (2005). *Handbook of Injectable Drugs* (13th edn). Bethesda, MD: American Society of Health System Pharmacists.

Dickman A *et al.* (2005). *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*. Oxford: Oxford University Press.

Twycross R, Wilcock A (2002). *Palliative Care Formulary*. Abingdon: Radcliffe Medical Press.

Trissell LA (2005). *Trissel's Stability of Compounded Formulations* (3rd edn). Washington, DC: American Pharmacists' Association.

Chronic pain

Overview

- Chronic pain is a major under-treated illness. The Pain in Europe study interviewed >46 000 people and it makes grim reading.
- Chronic pain is a widespread problem in Europe, affecting 1 in 5 adults. More than one-third of European households contain a pain sufferer. Two-thirds of chronic pain sufferers experience moderate pain, whereas one-third experience severe pain. The most common pain is back pain, and the most common cause of this is arthritis.
- People with chronic pain have been suffering on average for 7 years, with one-fifth of sufferers reporting a >20 year history. One-third of sufferers have pain all the time. Adequate pain control took >2 years to achieve in >50% of sufferers. Pain has a huge social impact. One in five sufferers have lost their job as a result of their pain. A similar number have been diagnosed with depression as a result of their pain. Generally, patients are satisfied with their care, but only 23% of sufferers have seen a pain management specialist and only 1 in 10 have been evaluated using pain scales.
- In terms of treatment, two-thirds of sufferers report that their pain control is inadequate at times, and one-third of sufferers believe that their doctor does not know how to control their pain.

What about the UK?

Almost 1 in 7 people in the UK suffer from chronic pain (~7.8 million people).

One-third of UK households are affected by chronic pain. 50% of chronic pain sufferers report the following:

- feel tired all the time
- feel helpless
- feel older than they really are
- do not remember what it feels like not to be in pain.

In addition, the following statistics here been reported.

- One in five sufferers say the pain is sometimes so bad that they want to die.
- Two-thirds of sufferers are *always* willing to try new treatments, but almost as many sufferers are worried about potential side effects of pain medication.
- Pain sufferers are proactive, with 80% of chronic pain sufferers treating their pain in some way, mainly with prescription medications.
- More than 1 in 5 (22%) sufferers have tried, and then stopped taking, prescription pain medication.
- Weak opioids are the most used class (50%) of pain medication.
- Other commonly prescribed drugs are paracetamol (38%) and NSAIDs (23%).
- The mean number of tablets taken every day is 5.7.

Despite this, much can be done to alleviate the suffering of patients with of chronic pain. The approach to treatment is the same as for acute pain, i.e. to titrate with analgesics until either pain relief or unacceptable side effects occur. In addition, there is a wide range of medicines other than analgesics that can provide relief.

Analgesics

In treating chronic pain, it is important to start with the simplest and most obvious treatments first, rather than move directly to unconventional analgesics. NSAIDs and/or paracetamol should be tried early. The combination of NSAIDs and paracetamol can be effective and can ↓ the dose of NSAID needed. The addition of a weak opioid can help in chronic pain. Patients on long-term NSAIDs should be given gastric protection and informed of the reasons for this. Approximately 1 in 120 patients who take an NSAID for >2 months without gastric protection develop a bleeding ulcer, and ~1 in 1200 patients die of a bleeding ulcer.

If simple analgesics are insufficient, there are other choices including so-called 'unconventional analgesics', such as antidepressants and anticonvulsant drugs. A strong opioid can be justified for some patients, provided that adequate steps are taken to screen patients before initiating treatment.

Non-pharmacological interventions can also help. Weight loss in overweight patients who suffer with arthritis can have a real benefit. Transcutaneous electronic nerve stimulation (TENS) can also be a useful addition. Radiotherapy can be effective in dealing with painful bony metastases. In specialist clinics, nerve blocks and epidural injections can also be helpful. A list of unconventional analgesics that can be effective in chronic neuropathic pain follows. It is usual to start at low doses and titrate the dose upwards until pain relief, unacceptable adverse effects, or the maximum dose is reached:

- Amitriptyline 50–150mg at night, or similar tricyclic antidepressants.
- Carbamazepine 100mg three times daily initially, ↑ slowly up to a maximum of 1200mg daily.
- Gabapentin, doses up to 3.6g daily
- Clonazepam 0.5mg twice daily, increasing to 1mg three times daily.
- Baclofen 5mg three times daily, increasing to 10mg three times daily.
- Pyridoxine 100mg up to five times daily.
- Capsaicin cream.
- Other anticonvulsants, such as pregabalin, lamotrigine, phenytoin, and sodium valproate.
- SSRIs can also be beneficial, but evidence for their use is very limited.

Antidepressant drugs for neuropathic pain

- Neuropathic pain refers to a group of painful disorders characterized by pain caused by dysfunction or disease of the nervous system at a peripheral or central level, or both. It is a complex entity, with many symptoms and signs that fluctuate in number and intensity over time. The three common components of neuropathic pain are steady and neuralgic pain paroxysmal spontaneous attacks and hypersensitivity.

- This type of pain can be very disabling, severe, and intractable, causing distress and suffering for individuals, including dysaesthesia and paraesthesia. Sensory deficits, such as partial or complex loss of sensation, are also commonly seen.
- The clinical impression is that both antidepressants and anticonvulsants are useful for neuropathic pain, but there are unanswered questions, including the following.
  - Which drug class should be the first-line choice?
  - Is one antidepressant drug superior to another?
  - Is there any difference in response to antidepressants in different neuropathic syndromes?
- The mechanisms of action of antidepressant drugs in the treatment of neuropathic pain are uncertain. Analgesia is often achieved at lower dosage and faster (usually within a few days) than the onset of any antidepressant effect, which can take up to 6wks. In addition, there is no correlation between the effect of antidepressants on mood and pain. Furthermore, antidepressants produce analgesia in patients with and without depression.
- Two main groups of antidepressants are in common use: the older tricyclic antidepressants, such as amitriptyline, imipramine, and many others, and a newer group of SSRIs. The clinical impression was that tricyclic antidepressants are more effective in treating neuropathic pain. However, SSRIs are gaining acceptance for pain relief.
- Tricyclic antidepressants exhibit more significant adverse effects which limit clinical use, particularly in the elderly. The most serious adverse effects of tricyclic antidepressants occur within the cardiovascular system:
  - postural hypotension
  - heart block.
  - arrhythmias.
- The most common adverse effects are:
  - sedation
  - anticholinergic effects (e.g. dry mouth, constipation, and urinary retention).
- SSRIs are better tolerated. They are free from cardiovascular side effects, are less sedative, and have fewer anticholinergic effects than tricyclic antidepressants.

Chapter 20

Therapy-related issues: infections

Basic microbiology

Micro-organisms are classified in many ways. The most important classifications are as follows.

- Category—e.g. viruses, bacteria, and protozoa.
- Genus—i.e. the 'family' that the micro-organism belongs to, such as *Staphylococcus*.
- Species—i.e. the specific name, such as *aureus*.

To name a micro-organism correctly, both the genus and the species name must be used—e.g. *Staphylococcus aureus*, *Haemophilus influenzae*.

Identifying micro-organisms

To diagnose and treat an infection correctly, the micro-organism must be identified. This is usually done by examining samples of faeces, blood, and sputum in various ways.

Microscopy

The sample is examined under the microscope. Sometimes the organism can easily be seen and identified—e.g. some helminths (worms) and their ova (eggs).

Dyes are used to stain cells so that they can be seen more easily. Differential staining uses the fact that cells with different properties stain differently and therefore can be distinguished. Bacteria are divided into two groups according to whether they stain with the Gram stain. The difference between Gram-positive and Gram-negative bacteria is in the permeability of the cell wall when treated with a purple dye followed by a decolorizing agent. Gram-positive cells retain the stain, whereas Gram-negative cells lose the purple stain and appear colourless, until stained with a pink counterstain (Fig. 20.1).

Mycobacteria have waxy cell walls and do not readily take up the Gram stain. A different staining technique is used, and then the sample is tested to see if it withstands decolorization with acid and alcohol. Mycobacteria retain the stain and thus are known as acid-fast bacilli (AFB), whereas other bacteria lose the stain.

Examination of stained films allows the shape of the cells to be seen, which can aid identification.

Bacteria are classified as follows:

- Cocci (spherical, rounded)—e.g. streptococci.
- Bacilli (straight rod)—e.g. *Pseudomonas* species.
- Spirochaetes (spiral rod)—e.g. *Treponema* species.
- Vibrios (curved, comma-shaped)—e.g. *Vibrio cholerae*.

Culture

Bacteria and fungi can be grown on the surface of solid, nutrient media. Colonies of many thousands of the micro-organism can be produced from a single cell. Colonies of different species often have characteristic appearances, which aids identification. For most species, it takes 12–48h for a colony to develop that is visible to the naked eye. Some organisms (e.g. mycobacteria) multiply much more slowly and can take several weeks to develop.

Samples can be grown in an environment from which O_2 has been excluded. Bacteria that grow in the absence of O_2 are known as 'anaerobes' and bacteria that need O_2 to grow are 'aerobes'. Bacteria are often described as a combination of their Gram-staining, shape, and anaerobic/aerobic characteristics. This helps to narrow the range of bacteria under consideration before lengthier tests identify the individual organism (Table 20.1). Other tests that can be used to identify the organism include the following.

- Detection of microbial antigen.
- Detection of microbial products—e.g. toxin produced by *Clostridium difficile*.
- Using gene probes.
- Polymerase chain reaction.

Discussion of these tests is beyond the scope of this topic. For further information the reader is referred to microbiology texts.

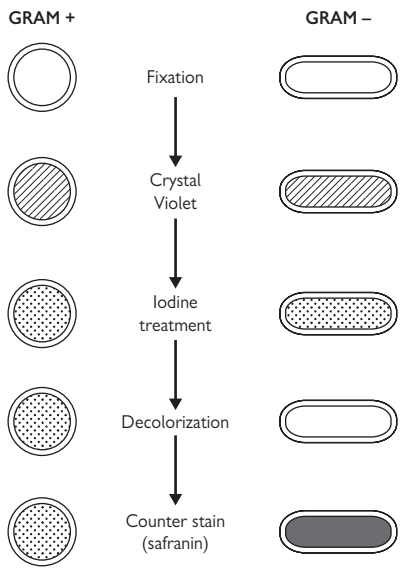

Fig. 20.1 Gram-staining procedure.

Table 20.1 Examples of pathogens from various types of bacteria

Gram-positive cocci	**Gram-negative cocci**
Staphylococci	Neisseria
Coagulase +ve, e.g. *Staph.aureus*	*N.meningitidis* (meningitis, septicaemia)
Coagulase –ve, e.g. *Staph.epidermidis*	*N.gonorrheae* (gonorrhoea)
Streptococci*	Moraxella
B-haemolytic streptococci	*M.catarrhalis* (pneumonia)
Strep.pyogenes (Lancefield group A)	**Gram-negative bacilli (rods)**
α-haemolytic streptococci	Enterobacteriaceae
Strep. mitior	*Escherichia coli*
Strep.pneumoniae (pneumococcus)	*Shigella species*
Strep. sanguis	*Salmonella* species
Enterococci (non-haemolytic)†	*Citrobacter freundii, C. koser*
E.mutans, E. faecalis	*Klebsiella pneumoniae, K.oxytoca*
Anaerobic streptococci	*Enterobacter aerogenes, E.cloacae*
Gram-positive bacilli (rods)	*Serratia morascens*
Aerobes	*Proteus mirabilis/vulgaris*
Bacillus anthracis (anthrax)	*Morganella morganii*
Corynebacterium diphtheriae	*Providencia* species
Listeria monocytogenes	*Yersinia Y.enterocolitica*
Nocardia species	*Y.pestis, Y.paratuberculosis*
Anaerobes	*Pseudomonas aeruginosa*
Clostridium	*Haemophilus influenzae*
C.botulinum (botulism)	*Brucella* species
C.perfringens (gas gangrene)	*Bordetella pertussis*
C.tetani (tetanus)	*Pasterurella multocida*
C.difficile (diarrhoea)	*Vibrio cholerae*
Actinomyces	*Camphylobacter jejuni*
A.israeli, A.naeslundii	
A.odontolyticus, A.viscosus	

Table 20.1 (*Contd.*)

Obligate intracellular bacteria	**Anaerobes**
Chlamydia	*Bacteroides* (wound infections)
C.trachomatis	*Fusobacterium*
C.psittaci	*Helicobacter pylori*
C.pneumoniae	**Mycobacteria**
Coxiella burnetii	*Mycobacterium tuberculosis*
Bartonella, Ehrlichia	*M.bovis*
Rickettsia (typhus)	*M.leprae* (leprosy)
Legionella pneumophilia	**'Atypical' mycobacteria**
Mycoplasma pneumoniae	*M.avium intracellulare*
	M.scrofulaceum, M.kansasii
	M.marinum, M.malmoense
	M.ulcerans, M.xenopi, M.gordonae
	M.fortuitum, M.chelonae, M.flaverscens
	M.smegmatis-phlei
	Spirochaetes
	Treponema (syphilis. yaws, pinta)
	Leptospira (Weil's dis., canicola fever)
	Borrelia (relapsing fever; Lyme disease)

*Streps are classified according to haemolytic pattern: (α–β or non-haemolytic) or by Lancefield antigen (A–G), or by species (e.g. Strep. pyogenes). There is crossover among these groups; this table is a generalization for the chief pathogens.
†Clinically, epidemiologically and in terms of treatment, enterococci behave unlike other streps.
Reproduced with permission from Longmore M *et al.* (2004). *Oxford Handbook of Clinical Medicine*, 6th edn. Oxford: Oxford University Press.

Modes of action of antibacterials

To avoid unwanted toxic effects on human cells, most antibacterials have a mode of action that affects bacterial but not mammalian cells.

There are many possible sites of action of antimicrobial agents. However, the most common mechanisms are as follows:

- inhibition of cell wall synthesis
- alteration of the cell membrane (usually antifungals)
- inhibition of protein synthesis
- inhibition of nucleic acid synthesis.

Inhibition of cell wall synthesis

- Mammalian cells do not have a cell wall (only a cell membrane) so this mode of action does not affect mammalian cells.
- Penicillins, cephalosporins, and other β-lactam antibacterials interfere with the synthesis of a substance called peptidoglycan. Peptidoglycan is an essential component of bacterial cell walls. If synthesis of peptidoglycan is inhibited, it is unable to support the cell wall and thus the bacteria lose their structure and eventually lyse (disintegrate) and die.
- Isoniazid also acts on the cell wall. It inhibits enzymes that are essential for synthesis of mycolic acids and the mycobacterial cell wall. The mode of action of ethambutol is not clear, but it might be the same as that of isoniazid.

Inhibition of protein synthesis

- The mechanism of protein synthesis is similar in bacterial and mammalian cells, but there are differences in ribosome structure (involved in protein synthesis) and other target sites, which ↓ the risk of toxicity to mammalian cells.
- Tetracyclines, aminoglycosides, macrolides, and chloramphenicol all work by inhibiting synthesis of proteins essential to the growth and reproduction of bacteria.
- Tetracyclines, macrolides, and chloramphenicol interfere with the binding of new amino acids onto peptide chains.
- Aminoglycosides prevent initiation of protein synthesis and cause non-functional proteins to be created.

Inhibition of nucleic acid synthesis

- Sulphonamides are structural analogues of para-amino benzoic acid (PABA). PABA is an essential precursor in bacterial synthesis of folic acid, which is necessary for the synthesis of nucleic acids. Mammalian cells are not affected as they use exogenous folic acid.
- Trimethoprim is an inhibitor of dihydrofolic acid reductase, an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid. This is one of the stages in bacterial synthesis of purines and thus DNA. Trimethoprim inhibits dihydrofolic acid reductase 50 000 times more efficiently in bacterial cells than in mammalian cells.
- Sulphonamides and trimethoprim produce sequential blocking of folate metabolism and therefore are synergistic.

- Bacteria use an enzyme called DNA gyrase to make the DNA into a small enough package to fit into the cell. This is called supercoiling. The quinolones inhibit DNA gyrase and supercoiling.
- Rifampicin inhibits bacterial RNA synthesis by binding to RNA polymerase. Mammalian RNA polymerase is not affected.
- Nitro-imidazoles (e.g. metronidazole) cause the DNA strand to break (cleavage).

Selection and use of antimicrobials

To treat or not to treat

The presence of micro-organisms does not necessarily mean that there is infection. The human body hosts a wide range of micro-organisms (mostly bacteria), but these rarely cause infection in an immuno-competent host. These organisms are known as 'commensals' and some have an important role in host defences. For example, *Clostridium difficile* is a pathogen that is normally suppressed by normal bowel flora. Eradication of the bowel flora (e.g. by broad-spectrum antibacterials) allows overgrowth of *C.difficile*, leading to diarrhoea and, sometimes, pseudo-membraneous colitis. Indiscriminate drug therapy can thus ↑ the risk of other infection.

Some organisms might be commensals in one part of the body and pathogens in another—e.g. *Escherichia coli* is part of the normal bowel flora but if it gets into the bladder it can cause urinary tract infection.

Some pathogenic organisms can reside on the host without causing infection. This is known as 'colonization', and signs and symptoms of infection are absent. A skin or nasal swab positive for meticillin-resistant *Staphylococcus aureus* (MRSA) does not usually require treatment except where elimination of MRSA carriage is required—e.g. prior to surgery.

Some infections are self-limiting and resolve without treatment. Many common viral infections resolve without treatment, and in any case most do not have specific antiviral drugs.

Choice of therapy

If infection is confirmed or is strongly suspected, appropriate therapy must be selected. Ideally, the pathogen is identified before antimicrobial therapy is started. However, identification of an organism by the laboratory usually takes a minimum of 24h and antimicrobial sensitivity tests can take a further 24h. For some slow-growing organisms, such as mycobacteria, culture and sensitivity results can take several weeks. Thus, in most cases, therapy will be started using 'best guess' (empirical) antimicrobials and tailored after culture and sensitivity results are known (Table 20.2).

Whenever possible, samples for culture and sensitivity tests should be taken before starting antimicrobial therapy so that growth is not inhibited. However, this delay might not be possible in very sick patients—e.g. those with suspected bacterial meningitis.

Factors that should be taken into account when selecting an antimicrobial are described as follows:

Clinical

- Does the patient have an infection that needs treating?
- Diagnosis/likely source of infection.
- Anatomical site of infection.
- Severity or potential severity of infection (and possible consequences—e.g. loss of prosthetic joint).
- Patient's underlying condition (if any) and vulnerability to infection—e.g. neutropenic patients more susceptible to sepsis.
- Patient-specific factors, e.g. allergies and renal function.

- Does the infection require empirical therapy or can antimicrobials be delayed until culture and sensitivity results are available?
- Foreign material, necrotic tissue, and abscesses are relatively impervious to antimicrobials. Abscesses should be drained and necrotic tissue debrided. If possible, foreign material should be removed.

Microbiology

- What are the pathogens?
  - Identified by microscopy or culture.
  - Presumed, according to epidemiology and knowledge of probable infecting organisms for the site of infection.
- Sensitivity of organisms to antimicrobial agents (Table 20.3):
  - national and local resistance patterns
  - culture and sensitivity data.

Pharmaceutical

- Evidence of clinical efficacy:
  - against the organism.
  - at the site of infection.
- Bactericidal versus bacteriostatic agents:
  - Bactericidal drugs generally give more rapid resolution of infection.
  - Bacteriostatic drugs rely on phagocytes to eliminate the organisms and therefore are not suitable for infection in which phagocytes are impaired (e.g. granulocytopenia) or do not penetrate the site of infection (e.g. infective endocarditis).
- Spectrum of activity.
  - Narrow-spectrum antimicrobials are preferred if the organism has been identified.
  - Broad-spectrum antimicrobials might be required in empirical therapy or mixed infection.
  - Indiscriminate use of broad-spectrum antimicrobials ↑ the risk of development of drug resistance and super-infection, e.g. *C.difficile*.
- Appropriate route of administration.
  - Topical antimicrobials should be avoided, except where specifically indicated—e.g. eye or ear infection or metronidazole gel for fungating tumours.
  - Oral therapy is preferred and most antimicrobials have good bioavailability.
  - IV therapy might be necessary in the following circumstances:
    - — if the infection is serious
    - — if the drug has poor oral bioavailability
    - — if the patient is unconscious or unable to take oral drugs (e.g. perioperatively).
- Possible side effects or drug interactions.
- Pharmacokinetics:
  - tissue penetration—will the antimicrobial reach the site of infection?
  - clearance in liver/kidney impairment.
- Dose and frequency must be sufficient to give adequate blood levels but avoid unacceptable toxicity. Serum levels four to eight times the minimum inhibitory concentration (MIC) are considered adequate.

- Duration of treatment:
  - not too long—e.g. uncomplicated urinary tract infection only requires 3–5 days therapy.
  - not too short—e.g. bone infection might require therapy for several weeks or months.
- Local policies/restrictions on antimicrobial use.
- Cost.

Combined antimicrobial therapy

Combined antimicrobial therapy may be prescribed for certain indications.

- To give a broad spectrum of activity in empirical therapy, especially in high-risk situations such as neutropenic sepsis.
- To treat mixed infection if one drug does not cover all possible pathogens.
- To achieve a synergistic effect, thus ↑ efficacy but ↓ the dose required of each drug (and thus ↓ the risk of side effects)—e.g. penicillin and gentamicin in the treatment of streptococcal endocarditis. Relatively low doses of gentamicin are used, ↓ the risk of nephrotoxicity.
- To ↓ the probability of the emergence of drug resistance—e.g. treatment of TB requires a minimum of two drugs and antiretroviral therapy requires a minimum of three drugs.
- To restore or extend the spectrum of activity by including an enzyme inhibitor—e.g. co-amoxiclav.

Penicillin and cephalosporin hypersensitivity

Up to 10% of people are allergic to penicillins and up to 7% of these people are also allergic to cephalosporins. This can range from mild rash to fever to a serious anaphylactic reaction. Penicillins and cephalosporins should never be used again in a patient who has had a severe hypersensitivity reaction. If a patient has had a severe hypersensitivity reaction to penicillins, it is advisable to avoid cephalosporins unless there is no alternative. If the penicillin allergy is relatively mild (e.g. rash) cephalosporins can be prescribed cautiously.

Some patients state that they have had an allergic reaction when they have really only had nausea or a headache. This is not drug allergy and therefore it is safe to use penicillins and cephalosporins in these patients.

Ampicillin and amoxicillin can cause rashes in patients who have had glandular fever or leukaemia, or who are HIV positive. This is not a true allergic reaction and penicillins can be used again in these patients.

Monitoring therapy

It is essential to monitor and review antimicrobial therapy regularly, both to ensure that treatment is working and to avoid inappropriate continuation of therapy (Fig. 20.2) The pharmacist should monitor the following parameters.

- Temperature should ↓ to normal (36.8°C). (Note: drug hypersensitivity is a possible cause of persistent pyrexia.)
- Pulse, BP, and respiratory rate revert to normal.
- Raised white cell count decreases.
- Raised C-reactive protein decreases (normal <8).
- Symptoms such as local inflammation, pain, malaise, GI upset, headache, and confusion resolve.

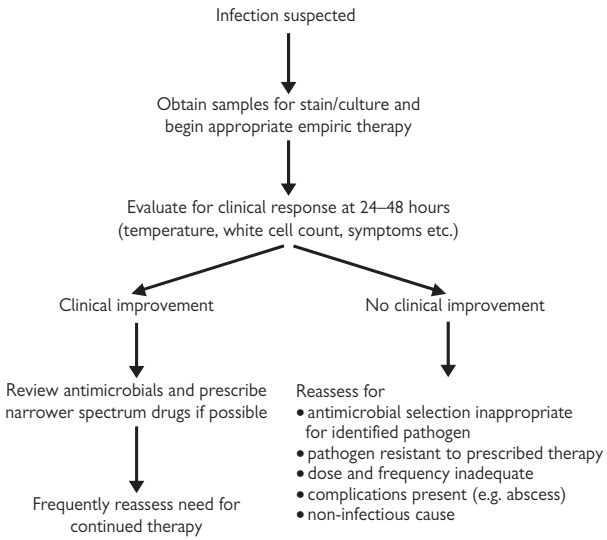

Fig. 20.2 Flowchart of selection and use of antimicrobials.

Reasons for treatment failure

- Wrong antimicrobial.
- Drug resistance.
- The isolated organism is not the cause of the disease.
- Treatment started too late.
- The wrong dose, duration, or route of administration.
- Lack of patient compliance.
- Difficulty getting the drug to the site of infection.
- ↓ immunity of the patient.

Further reading

Wickens H, Wade P (2005). How pharmacists can promote the sensible use of antimicrobials. *Pharmaceutical Journal* **274:** 427–30.

Wickens H, Wade P (2005). The right drug for the right bug. *Pharmaceutical Journal* **274:** 365–8.

Table 20.2 In vitro activity of antibacterials

✓= usually sensitive ? = variable sensitivity X = usually resistant or inappropriate therapy

Note: These are generalizations. There are major differences between countries, areas and hospitals. Check local Public Health or Microbiology laboratories for local sensitivity patterns. Antibacterials may not be licensed to treat the bacteria for which they are active.

	Gram positives								Anaerobes		Gram negatives										Atypicals		
	Staphylococcus aureus MSSA	*Staphylococcus aureus* MRSA	Staphylococcus epidermidis	Haemolytic streptococci (Strep A, C, G and Strep B)	*Enterococcus faecalis*	*Enterococcus faecium*	*Streptococcus pneumoniae*	*Listeria monocytogenes*	*Clostridium perfringens*	*Clostridium difficile*	*Bacteroides fragilis*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Haemophilus influenzae*	*Escherichia coli*	*Klebsiella spp*	*Proteus mirabilis*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Moraxella catarrhalis*	*Legionella spp*	*Mycoplasma pneumoniae*	*Chlamydia spp*
Penicillins																							
Phenoxymethylpenicillin	×	×	×	✓	✓	?	✓	×	✓	×	×	×	?	×	×	×	×	×	×	×	×	×	×
Benzylpenicillin	×	×	×	✓	✓	?	✓	✓	✓	×	×	✓	?	×	×	×	×	×	×	×	×	×	×
Ampicillin/Amoxicillin	×	×	×	✓	✓	?	✓	✓	✓	×	×	✓	?	?	?	×	✓	✓	×	×	×	×	×
Co-amoxiclav	✓	×	✓	✓	✓	?	✓	×	✓	×	✓	×	?	✓	✓	?	✓	✓	×	✓	×	×	×
Flucloxacillin	✓	×	?	✓	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Pip+tazobactam(Tazocin®)	✓	×	?	✓	✓	?	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×	×	×
Cephalosporins																							
Cefradine / Cefalexin	✓	×	?	✓	×	×	✓	×	×	×	×	×	×	×	✓	?	✓	×	×	×	×	×	×
Cefotaxime	✓	×	?	✓	×	×	✓	×	×	×	×	✓	?	✓	✓	✓	✓	✓	?	✓	×	×	×
Cefuroxime	✓	×	?	✓	×	×	✓	×	×	×	×	×	?	✓	✓	✓	✓	✓	×	✓	×	×	×
Ceftriaxone	✓	×	?	✓	×	×	✓	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	?	✓	×	×	×
Ceftazidime	?	×	?	✓	×	×	?	×	×	×	×	?	?	✓	✓	✓	✓	✓	✓	✓	×	×	×

	Gram positives								Anaerobes		Gram negatives										Atypicals		
	Staphylococcus aureus MSSA	*Staphylococcus aureus* MRSA	Staphylococcus epidermidis	*Haemolytic streptococci (Strep A, C, G and Strep B)*	*Enterococcus faecalis*	*Enterococcus faecium*	*Streptococcus pneumoniae*	*Listeria monocytogenes*	*Clostridium perfringens*	*Clostridium difficile*	*Bacteroides fragilis*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Haemophilus influenzae*	*Escherichia coli*	*Klebsiella spp*	*Proteus mirabilis*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Moraxella catarrhalis*	*Legionella spp*	*Mycoplasma pneumoniae*	*Chlamydia spp*
Carbapenems																							
Ertapenem	✓	×	✓	✓	?	×	✓	?	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	×	×
Meropenem/ Imipenem	✓	×	✓	✓	?	?	✓	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	×
Macrolides/ Lincosamides																							
Azithromycin	✓	×	×	✓	×	×	✓	×	✓	×	×	✓	?	✓	×	×	×	×	×	✓	✓	✓	✓
Erythromycin	✓	×	?	✓	×	×	✓	×	×	×	×	✓	?	?	×	×	×	×	×	✓	✓	✓	✓
Clarithromycin	✓	×	×	✓	×	×	✓	×	✓	×	×	×	?	✓	×	×	×	×	×	✓	✓	✓	✓
Clindamycin	✓	×	×	✓	×	×	✓	×	✓	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
Aminoglycosides																							
Amikacin	✓	✓	?	×	✓[1]	×	×	✓[1]	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×
Gentamicin	✓	✓	?	×	✓[1]	✓[1]	×	✓[1]	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×
Diaminopryimidines and sulphonamides																							
Co-trimoxazole	✓	?	?	?	×	×	✓	×	×	×	×	✓	?	?	✓	✓	✓	×	×	✓	✓	×	✓
Trimethoprim	?	?	?	?	✓	×	?	×	×	×	×	?	×	?	✓	✓	×	×	×	×	✓	×	×
Quinolones																							
Ciprofloxacin	✓	×	✓	×	×	×	×	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Levofloxacin	✓	×	✓	?	✓	×	✓	×	✓	×	×	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	✓
Moxifloxacin	✓	×	✓	✓	✓	?	✓	×	✓	×	?	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	✓

(continued)

Table 20.2 (*Contd.*)

	Gram positives								Anaerobes		Gram negatives											Atypicals		
	Staphylococcus aureus MSSA	*Staphylococcus aureus* MRSA	Staphylococcus epidermidis	*Haemolytic streptococci (Strep A, C, G and Strep B)*	*Enterococcus faecalis*	*Enterococcus faecium*	*Streptococcus pneumoniae*	*Listeria monocytogenes*	*Clostridium perfringens*	*Clostridium difficile*	*Bacteroides fragilis*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Haemophilus influenzae*	*Escherichia coli*	*Klebsiella spp*	*Proteus mirabilis*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Moraxella catarrhalis*	*Legionella spp*	*Mycoplasma pneumoniae*	*Chlamydia spp*
Glycopeptides																								
Vancomycin (IV)	✓	✓	✓	✓	✓	?	✓	✓	✓	×[2]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Teicoplanin	✓	✓	?	✓	✓	?	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Nitromidazoles																								
Metronidazole	×	×	×	×	×	×	×	×	✓	✓	✓	×	×	×	×	×	×	×	×	×	×	×	×	×
Oxazolidinones																								
Linezolid	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	?	×	×	?	×	×	×	×	×	×	×	×	×	✓
Tetracyclines																								
Doxycycline	✓	?	×	?	×	×	✓	✓	✓	×	?	×	×	?	×	×	×	×	×	×	×	×	×	✓
Miscellaneous																								
Chloramphenicol	?	×	×	✓	?	?	✓	×	?	×	✓	✓	✓	✓	✓	?	?	?	×	✓	✓	✓	✓	✓
Quinupristin / dalfopristin(Synercid®)	✓	✓	✓	✓	×	✓	✓	✓	✓	?	✓	×	✓	?	×	×	×	×	×	✓	✓	✓	✓	✓

[1]Sensitive if used synergistically with penicillins/glycopeptides.
[2]IV vancomycin ineffective for *Clostridium difficile*.

Table 20.3 Diseases, potential causative bacteria and typical treatment choices*

Specific condition	Potential bacterial pathogens	Typical empirical treatment
Meningitis	*Streptococcus pneumoniae, Neisseria menigiditis, Haemophilus influenzae.* Group B streptococcus (seen in neonates). Less commonly, *Escherichia coli* and *Listeria monocytogenes.* Other Gram negative bacteria and *Staphylococcus* spp usually associated with neurosurgery	Cefotaxime and ceftriaxone provide broad cover and good central nervous system penetration. Ampicillin or amoxicillin is required to cover *Listeria* spp (elderly and neonates). Causative agents can also be mycobacterial, viral or, rarely, fungal and these will require appropriate therapy.
Brain abscess	*S.aureus*, anaerobic streptococci, *Bacteroides* spp, Gram negatives, such as Escherichia, Proteus, *Klebsiella* spp	Cefotaxime or ceftriaxone, meropenem if broader cover required (avoid imipenem due to CNS side effects). The condition can occasionally be fungal or parasitic.
Otitis media	*Strep. pneumoniae, H.influenzae, Moraxella catarrhalis, S.aureus*, mixed anaerobes	Antibacterial therapy not always necessary. Amoxicillin or co- amoxiclav. Can also be viral (e.g. influenza, respiratory syncitial virus, enteroviruses).
Otitis externa	*Pseudomonas aeruginosa* ("swimmer's ear), *S.aureus* (pustule)	Topical gentamicin. Less commonly fungal (*Candida albicans*, *Aspergillus* spp).
Upper respiratory tract infections		
Pharyngitis/tonsillitis	*Strep. pyogenes* (group A)	Phenoymethylpenicillin but note that 50% of sore throats are viral in origin.
Epiglottitis	*H.influenzae, Strep. pyogenes* (group A)	Ceftriaxone or cefotaxime.
Sinusitis	*Strep. pneumoniae, H.influenzae*, mixed anaerobes, *S.aureus, M. catharrhalis*	Co-amoxiclav. Sinusitis may be viral (e.g. rhinovirus, influenza) or occasionally, fungal.

(continued)

Table 20.3 (*Contd.*)

Specific condition	Potential bacterial pathogens	Typical empirical treatment
Lower respiratory tract infections‡		
Community-acquired	*Strep. pneumoniae, H.influenzae, M. catharrhalis*, atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and, rarely, *Legionella pneumophila*).	Amoxicillin oral or ceftriaxone intravenous (depending on severity) ± macrolide if atypical organisms are suspected or clarithromycin ± rifampicin for Legionella.
Hospital-acquired	*E.coli, Ps. aeruginosa,* and other gram negative organisms, methicillin-resistant *S.aureus* (MRSA)	Broad spectrum antibacterials are required until a definitive diagnosis is made e.g. meropenem/imipenem/piperacillin + tazobactam (Tazocin®), vancomycin + quinolone if MRSA suspected. Infection can be viral. Fungal infection is more likely in immunocompromised patients.
Endocarditis	*Enterococcus* spp, Viridans group streptococci, *S.aureus,* coagulase-negative staphylococci.	Benzylpenicillin and gentamicin (synergistic action) or flucloxacillin and gentamicin if staphylococci are suspected (often seen in injecting drug users).
Gastrointestinal infections	*E.coli, Shigella* spp, *Campylobacter jejuni, Salmonella* spp, *S aureus, Bacillus cereus* (toxin mediated)	Gastrointestinal infections are generally self-limiting and often viral. Fluid replacement may be all that is required. Expert advice should be sought if antibacterials are considered necessary. In severe disease, ciprofloxacin is used for *Salmonella* spp and erythromycin for *Campylobacter.*
Urinary tract infections	*E.coli,* enterococci, *Klebsiella* spp, *Enterobacter* spp, *Pseudomonas* spp (UTI)/Pyelonephritis *Proteus* spp	For UTI use amoxicillin, cefradine/cefalexin, trimethoprim or nitrofurantoin depending on local resistance patterns. For uncomplicated UTI in a young woman, three days treatment should be sufficient. A longer course may be required in men. Recurrent or complicated UTIs require further investigation, consideration of resistant organisms and use of second-line agents. Co-amoxiclav or ceftriaxone (± single dose of gentamicin) are often used for pyelonephritis.

Skin and soft tissue infection (cellulitis)	*S.aureus, Strep. pyogenes* (group A)	Penicillin +/– flucloxacillin (oral or intravenously depending on severity). Always check (and treat) for co-existing athlete's foot which can be an entry point for organisms.
Septic arthritis	*S.aureus, Strep. pneumoniae,* occasionally Gram negatives guided by culture results.	Flucloxacillin or ceftriaxone empirically, but therapy should be guided by culture results
Osteomyelitis	*S.aureus, Strep. pneumoniae,* coagulase negative staphylococci (usually associated with implanted material). Many other organisms infrequently cause disease.	Flucloxacillin or ceftriaxone empirically, but therapy should be guided by culture results. Infections involving prostheses will require longer therapy.
Sepsis Neutropenic	*S aureus* (MRSA), *Strep. viridans,* coagulase-negative staphylococci, *E.coli, Klebsiella* spp, *Ps aeruginosa* or *Pneumocystis jiroveci* (*carinii*) pneumonia (PCP).	Meropenem/imipenem/piperacillin+tazobactam plus gentamicin. Vancomycin if staphylococcus species (including MRSA) suspected. Co-trimoxazole for PCP. If fever persists consider fungal or viral infections
Non-neutropenic	*S.aureus* (MRSA), *Streptococcus.* spp, *E.coli, Pseudomonas* spp.	Therapy depends on source of infection. Empirically – flucloxacillin/ ceftriazone +/– gentamicin. Vancomycin if MRSA suspected. Meropenem/imipenem/piperacillin + tazobactam initially in septic shock

* Pathogens/therapy may differ in children and neonates—seek specialist advice.

† Patients with MRSA or high risk of MRSA, add vancomycin or teicoplanin.

‡ See also British Thoracic Society Guidelines for the management of community acquired pneumonia in adults. *Thorax* (2001) **56** (suppl 4) 1–64 www.brit-thoracic.org.uk.

Adapted with permission from Wickens H and Wade P (2005) The right drug for the right bug. *The Pharmaceutical Journal,* **274** 365–8.

Antimicrobial prophylaxis

Indiscriminate and prolonged courses of antimicrobials should be avoided, but in some situations short- or long-term antimicrobial prophylaxis might be appropriate to prevent infection (and thus further courses of antimicrobials).

Surgical prophylaxis

Antibacterial drugs are given to ↓ the risk of the following.

- Wound infection after potentially contaminated surgery—e.g. GI or genitourinary surgery and trauma.
- Losing implanted material—e.g. joint prosthesis.

It is important that there are adequate concentrations of antibacterials in the blood at the time of incision ('knife-to-skin time') and throughout surgery. Thus it is important to administer antibacterials at an appropriate time (usually 30–60min) before surgery starts and repeat doses of short-acting antibacterials if surgery is delayed or prolonged. It is rarely necessary to continue antibacterials after wound closure. More prolonged therapy is effectively treatment rather than prophylaxis.

The choice of antibacterial depends on the type of surgery and local bacterial sensitivities. Vancomycin or teicoplanin should be used for patients with proven or suspected MRSA colonization.[1] Drugs are usually administered by IV infusion to ensure adequate levels at the critical time.

Medical prophylaxis

Medical prophylaxis is appropriate for specific infections and for high-risk patients, as follows.

- Contacts of sick patients—e.g. meningitis and TB.
- Immunosuppressed patients—e.g. organ-transplant recipients, HIV-positive patients, and splenectomy patients.
- Malaria.
- Post-exposure prophylaxis, following exposure to HIV or hepatitis B.

Further reading

Prophylaxis regimens can be found in the *British National Formulary* and on www.sign.ac.uk.

Rahman MH, Anson J (2004). Peri-operative antibacterial prophylaxis. *Pharmaceutical Journal* **272**: 743–5.

1 Gemmell CG *et al.* (2006).Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in the UK. *Journal of Antimicrobial Chemotheraphy* **57**: 589–608.

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Optimizing antimicrobial use

↓ antimicrobial use might not actually ↓ the rate of resistance, but it might limit the rate at which new resistance emerges. Pharmacists have an important role in optimizing antimicrobial use—often known as 'antimicrobial stewardship'. In the UK, the Department of Health has specifically promoted the role of pharmacists in monitoring and optimizing antimicrobial use. In many hospitals, specialist antimicrobial pharmacists work alongside microbiologists and infectious diseases doctors to promote good antimicrobial stewardship through education, audit, and production of prescribing policies. However, all pharmacists, whether in hospitals or the community, have a role in ensuring 'prudent use' of antimicrobials.

Strategies for antimicrobial stewardship

- Use of non-antimicrobial treatment as appropriate, e.g. draining abscesses and removing infected invasive devices such as catheters.
- Improved systems for resistance testing and better communication of resistance data in the hospital and community settings to enable better-directed therapy.
  - Avoid continued use of ineffective drugs.
  - Enable switching from broad-spectrum to narrower-spectrum antimicrobials.
- Faster diagnosis of infection to ↓ the amount of unnecessary empirical therapy.
- Ensuring that empirical therapy considers the following adjustments, as necessary.
  - Therapy is stopped if infection is ruled out.
  - Therapy is changed, as necessary, when culture results are available.
- Production of antimicrobial prescribing policies and promoting adherence to guidelines.
- Ensuring choice, dose, and duration of therapy, including the following.
  - Monitoring serum levels and adjusting doses for antimicrobials that require TDM.
  - Ensuring that kinetic factors are taken into account—e.g. nitrofurantoin is not excreted into the urine in adequate concentrations to be effective in patients with renal impairment.
- Avoiding unnecessary/overlong use of broad-spectrum antimicrobials.
- Appropriate use of antimicrobials for surgical prophylaxis, including avoiding prolonged courses.
- Use of combination therapy if there is a high risk of resistance emerging—e.g. rifampicin should never be used alone for TB or other infections.
- Avoiding co-prescribing of antimicrobials that have the same or an overlapping spectrum of activity—e.g. co-amoxiclav and metronidazole.
- Considering rotational use of antimicrobials (cycling) in some circumstances.
- Educating patients to take antimicrobials correctly and that some infections do not require antimicrobial therapy.

Points to consider when reviewing a prescription for an antimicrobial

- Is it the right choice for the infection (or appropriate empirical therapy)?
- Does it comply with local policies/restrictive practices?
- Could a narrower-spectrum antimicrobial be used?
- Should it be used in combination with another antimicrobial?
- Is more than one antimicrobial with an overlapping spectrum of activity being used, and if so, why?
- Will the antimicrobial be distributed to the target (infected) organ?
- Is the dose correct taking into account the following?
  - Renal impairment.
  - Severity of infection.
  - Patient weight.
- Is TDM and subsequent dose adjustment required?
- Is the route of administration appropriate?
- Is the duration of therapy appropriate?
- Does the patient understand the dosing instructions and importance of completing the course?

Further reading

Wicken H, Wade P (2005). Understanding antibiotic resistance. *Pharmaceutical Journal* **274**: 501–4.

European Surveillance of Antimicrobials. http://www.ua.ac.be/esac

Department of Health. *The Path of Least Resistance*. London: Department of Health. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4120729.pdf

Patient information sheets on:

- *C.difficile*: http://www.dh.gov.uk/assetroot/04/11/34/79/04115884.pdf
- MRSA: http://www.dh.gov.uk/assetroot/04/11/58/84/04113479.pdf

Get Smart for Healthcare (advice for clinicians, fact sheets, and posters). http://www.cdc.gov/getsmart/healthcare/resources/factsheets/hc_providers.html

Antimicrobial prescribing guidelines

Antimicrobials are the second most frequently prescribed class of drugs, after analgesics. In England, about 50 million prescriptions for antimicrobials are dispensed each year. Approximately 80% of antimicrobial prescribing is in the community, and although the emergence of 'superbugs' is less of a problem than in hospitals, resistance and cost are still an issue. Education of patients and GPs to reduce pressure to prescribe has contributed to a reduction in antimicrobial usage in the community. The remaining 20% of antimicrobial prescribing is in hospitals. However, this class represents some of the more expensive drugs used in secondary care and antimicrobial resistance in the hospital setting is an increasing problem, notably with MRSA.

Both WHO and the UK Department of Health have emphasized the need for 'prudent use' of antimicrobials. WHO defines this as: '*the cost-effective use of antimicrobials which maximises their clinical therapeutic effect, while minimising both drug-related toxicity and the development of antimicrobial resistance*'.

A good antimicrobial prescribing policy or guidelines will contribute to prudent (and thus cost-effective) use of antimicrobials.

Type and format of guidance

Antimicrobial prescribing guidelines come in many formats. Before starting to write guidelines, both the format and the intent must be decided:

- advisory or mandatory
- policy, guidelines, restricted list
- educational.

It has been shown that prescribers prefer an educational approach and this may have the best long-term impact. However, it may be necessary to give mandatory advice on the use of certain high-cost/sensitive drugs.

The format must be easily accessible to prescribers at the time of prescribing. Computer-based guidelines offer the opportunity to provide additional educational material and may be linked to a computerized prescribing package. This may be the best approach in the community where most GP practices use electronic prescribing. However, few hospitals in the UK use electronic prescribing and most doctors will not have a computer at the bedside. Thus most hospital guidelines are presented as a booklet, card, or Filofax insert which can be kept in the pocket. An ideal format is a pocket-size ready reference linked to more detailed electronic guidelines.

The amount of detail will be determined by the presentation. As a minimum the recommended drug and an alternative (if needed) due to allergy, (adult) dose, route, and duration should be included. More detailed policies might also include side effects, contraindications, use in children, in the elderly, and in pregnancy, etc.

Style and layout must be clear and easy to follow. In lengthier guidelines an index or contents list should be provided. Use plain English throughout and avoid Latin abbreviations such as 'tds' (if space permits). Note that different countries use different abbreviations, which may cause confusion for visiting staff—e.g. the US abbreviation 'qd' means once a day but may

be misinterpreted as the UK 'qds' or four times a day. During the drafting process it is advisable to 'pilot' the guidelines to ensure that potential users interpret them in the way intended.

Hard-copy guidelines should be robust, using card (laminated if possible) rather than paper and good-quality printing.

Target audience

This should be identified. Are restrictions just applicable to junior doctors or to senior medical staff as well? Write the guidelines as if they are aimed at a doctor who has newly joined the hospital/GP practice and who needs to find what to prescribe in a situation quickly and easily.

Authors

Hospital antimicrobial guidelines are usually produced as a collaboration between microbiology and pharmacy. To ensure local ownership, consultants in the relevant specialities should be invited to contribute or comment—e.g. surgeons for surgical prophylaxis. In the community, guidelines may be produced by a committee of GPs from one or more practices, usually with the assistance of the prescribing adviser. Ideally, local primary and secondary care policies should be linked.

Content

Guidelines should:

- be evidence based and recommendations referenced as appropriate
- advise on when **not** to prescribe, as this is as valid as advice on when and what antimicrobial to prescribe
- discourage unnecessary use of the parenteral route
- include contact numbers for microbiology, pharmacy medicines information service
- be cross-referenced to other relevant hospital/practice guidelines.

Cost may be included but may become outdated before the guidelines are due for revision. As a minimum, the following areas should be covered.

- Surgical prophylaxis.
- Meningitis prophylaxis.
- Empirical treatment (first and second choice) for:
  - meningitis
  - urinary tract infection
  - lower respiratory tract infection
  - sepsis.

Other areas which should be included are as follows.

- Prophylaxis in asplenic patients.
- Empirical treatment for:
  - GI infection
  - MRSA
  - upper respiratory tract infection
  - skin infection.

A suggested list of recommended areas to cover is provided at http://www.jac.oxfordjournals.org/content/60/suppl_1/i87.full

Updating

The guidelines should state the issue date and frequency of review. As a minimum, guidelines should be reviewed and updated as necessary every 2 years.

Monitoring and audit

Adherence to the guidelines should be monitored. For example, a specific area such as vascular surgery prophylaxis can be audited. If there is significant non-adherence, the reasons should be established and addressed.

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Antimicrobial resistance

Resistance is an almost inevitable consequence of antimicrobial use. As bacteria, viruses, or other micro-organisms reproduce, mutations can spontaneously occur. These mutations might provide some protection against the action of certain antimicrobials. 'Survival of the fittest' means that when these micro-organisms are exposed to antimicrobials, the fully sensitive ones are suppressed but resistant ones survive, reproduce, and become the dominant strain. Most attention has been focused on bacterial resistance, but the principles discussed here apply to all micro-organisms.

Mechanisms of resistance

- Change in cell wall permeability, thus ↓ drug access to intracellular target sites. The relatively simple cell wall of Gram-positive bacteria makes them inherently more permeable and therefore this resistance mechanism is more common in Gram-negative than Gram-positive bacteria.
- Enzyme degradation of the drug—the best known is breakdown of the β-lactam ring of penicillins, cephalosporins, and carbapenems by β-lactamases.
- Efflux pumps actively remove the drug from the cell.
- Mutation at the target site.
  - Alteration of penicillin-binding proteins leads to resistance to β-lactam antibiotics.
  - Changes in the structure of the enzyme reverse transcriptase leads to resistance to reverse transcriptase inhibitors.

Some organisms can develop multiple resistance mechanisms—e.g. *Pseudomonas aeruginosa* manifests resistance to carbapenems through production of β-lactamase, ↑ in efflux pumps, and changes to the bacterial cell wall.

Implications of antimicrobial resistance

Antimicrobial resistance leads to ↑ in the following.

- Morbidity:
  - patients might be sicker for longer
  - hospital stays are ↑
  - alternative antimicrobials might be more toxic
  - residential placements might be difficult
  - isolation and institutionalization.
- Mortality.
- Cost.
  - Newer, potentially more expensive antimicrobials might have to be used.
  - Extended hospital stay.
  - More nursing time.
  - ↑ use of disposables (e.g. aprons and gloves).
  - In some cases, equipment might have to be discarded.

New strains of resistant bacteria are appearing at an alarming rate. Within the hospital environment, MRSA has been a problem for many years but the emergence of vancomycin-resistant MRSA (VRSA) and community-acquired MRSA (C-MRSA) is of significant concern. Other increasingly problematic resistant organisms are as follows:

- vancomycin-resistant enterococci (VRE)
- extended-spectrum β-lactamases (ESBLs)
- *Acinetobacter baumanii.*

At present, agents to treat these resistant organisms are available, but they tend to be expensive, with a higher risk of side effects. However, the production of new drugs is not keeping up with development of new resistant bacteria, and the possibility of resistant species emerging for which there is no antibacterial therapy available is very real.

Measuring resistance

In vitro resistance tests generally require the organism to be cultured in the presence of antimicrobials.

Disk diffusion

Disk diffusion involves culturing bacteria on an agar plate that has had samples (impregnated disks) of an antibacterial placed on it. If there is no growth around the antibacterial, the bacteria are sensitive to the antibacterial, but if the bacteria grow around the sample, this means that they are resistant. Partial growth represents intermediate susceptibility.

E-test

The E-test is based on similar principles to disk diffusion, but here an impregnated strip containing a single antibacterial at ↑ concentrations is placed on the agar plate. Bacterial growth is inhibited around the strip after it reaches a certain concentration. This is equivalent to the MIC.

These tests can be problematic for slow-growing bacteria, such as mycobacteria, and for organisms that are difficult to culture, such as viruses. Newer tests involve amplifying and examining the genetic material of the organism to look for mutations that are known to be associated with resistance. This technique is used for HIV-resistance testing.

Risk factors for antimicrobial resistance

Excessive and inappropriate antimicrobial use results in selective pressures that facilitate the emergence of resistant micro-organisms. It is estimated that up to 50% of antimicrobial use is inappropriate. Unnecessary antimicrobial use contributes to resistance without any clinical gain. This includes the following.

- Use of antimicrobials for infections that are trivial or self-limiting.
- Use of antibacterials to treat infection of viral origin—e.g. the common cold.
- Over-long antimicrobial prophylaxis or treatment courses.

Even appropriate antimicrobial therapy is ↑ worldwide, in addition to ↑ use of broad-spectrum antibacterials and prolonged courses. This is due to the following reasons.

- ↑ numbers of severely ill hospital patients.
- More frequent use of invasive devices and procedures.
- Presence of more severely immunocompromised patients in hospitals and the community. ↑ opportunity for dissemination of infection ↑ the possibility of spread of resistant organisms between patients. This is facilitated by the following.
  - Overcrowding in hospital and community healthcare facilities.
  - ↑ hospital throughput.
  - Poor cleaning and disinfection of rooms, equipment, and hands.

Strategies to ↓ or contain antimicrobial resistance

Three main strategies are required to ↓ or contain antimicrobial resistance.

- Prevention of infection through the following mechanisms:
  - vaccines.
  - prophylaxis.
  - ↓ use of invasive devices.
  - good hygiene.
- ↓ dissemination of antimicrobial-resistant organisms (see 🕮 p.440, 'Infection control').
- Limiting or modifying antimicrobial use.

Further reading

Standing Medical Advisory Committee, Subgroup on Antimicrobial Resistance (1998). *The Path of Least Resistance*. 🔗 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4120729.pdf

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Infection control

Infection control is important in hospital and community residential facilities for the following reasons.

- To prevent cross-transmission of infection.
- To prevent the spread of resistant micro-organisms.

Special attention should be paid to infection control in areas where patients are most vulnerable:

- intensive care units
- neonatal units
- burns wards
- vascular wards
- units treating immunocompromised patients.

Special attention should also be paid to infection control where procedures or devices make patients more vulnerable:

- urinary catheters
- intravascular devices
- surgical procedures
- respiratory care equipment
- enteral or parenteral feeding.

Infection control should be an integral part of the culture of any institution. This requires the following considerations.

- There is an infection control lead clinician or nurse.
- There are written procedures for infection control.
- Staff (including temporary staff and locums) receive education and training on infection control procedures.
- There are adequate supplies and facilities—e.g. availability of aprons and gloves.
- There is documentation of additional infection control requirements, as necessary, for individual patients.
- Healthcare staff are immunized, as needed, for hepatitis B, TB, chickenpox, and influenza.
- There are written procedures for managing occupational exposure to blood-borne viruses, and staff are made aware of these procedures.

Universal precautions

Strict attention to hygiene is essential. All body fluids and contaminated equipment, including linen, from all patients should be handled as if infected. This is known as 'universal precautions' and includes taking appropriate measures to ensure the following.

- Prevent contamination—e.g. wearing apron and gloves and bagging dirty linen.
- Dispose of waste safely—e.g. use of clinical waste bins and sharps boxes.
- Protect staff against occupational exposure to blood-borne viruses—e.g. hepatitis B and C, and HIV.

Isolation of patients

It might be necessary to nurse patients in isolation in the following circumstances.

- They are a potential source of infection—e.g. MRSA, *C.difficile* diarrhoea, and TB.
- They are particularly vulnerable to infection ('reverse barrier nursing')—e.g. severely neutropenic patients.

Isolation procedures include the following.

- Nursing patients in a side room or, if more than one patient has the same infection, in a cordoned-off area.
- Wearing protective clothing when in contact with the patient. This includes staff who might be in contact with the patient elsewhere in the hospital (e.g. hospital porters).
- Ensuring that equipment is disinfected immediately after use.
- Ensuring that aprons, gloves, and other disposables are disposed of safely (usually bagged within the room).
- Ensuring that visitors take appropriate measures to prevent cross-contamination—e.g. handwashing and wearing protective clothing for particularly vulnerable patients.

Handwashing or decontamination

Hand hygiene is an essential part of infection control. It is effective for prevention of cross-contamination, but unfortunately compliance is often poor—particularly if staff are overworked and stressed.

Education of all staff (clinical and non-clinical) on hand hygiene is essential, in addition to ensuring adequate facilities for washing or decontamination. The usual procedures include the following.

- Staff 'bare below the elbows' in clinical areas (i.e. wearing short or rolled-up sleeves, no wrist watches or bracelets, no rings except wedding rings) in order to facilitate hand hygiene.
- Hands must be decontaminated before and after any episode of patient contact, including handling patients' possessions at the bedside–e.g. when checking patients' own drugs.
- Visibly soiled or potentially grossly contaminated hands should be washed with soap and water; otherwise alcohol gel can be used (with the exception of potential exposure to *C.difficile* as the spores are resistant to alcohol).
- Attention should be paid to ensuring the whole of the hand is decontaminated, including the following:
  - wrists
  - thumbs
  - between the fingers
  - backs of hands.

Pharmacists and infection control

To avoid contamination of medicines, in addition to presenting a professional appearance, a high standard of cleanliness should be maintained in pharmacy shops and dispensaries. Special attention should be paid to ensuring that the following areas are kept clean and tidy.

- Dispensing benches, especially areas where extemporaneous dispensing is carried out.
- Drug refrigerators.
- Toilets.
- Storage areas (often neglected).

Pharmacy staff should have access to handwashing facilities with soap and hot water. Aprons, gloves, and (as appropriate) masks should be used when preparing extemporaneous preparations. Tablets and capsules should not be handled—use counting trays and tweezers or a spatula, and disinfect these frequently.

Note that the type of patient contact experienced in a community pharmacy is extremely unlikely to lead to transmission of infection, including MRSA and TB.

Pharmacists do not often have 'hands-on' contact with patients but they should still observe infection-control procedures. These include the following.

- Decontaminating hands on entering and leaving clinical areas, and before and after direct patient contact.
- Wearing gloves and an apron when in close or prolonged contact with high-risk patients—e.g. those with MRSA.
- Wearing gloves, as appropriate, for 'hands-on' patient contact—e.g. wound care.
- Checking that new staff, trainees and locums, or temporary staff, if necessary, have immunity to chickenpox, TB. and hepatitis B.

In the UK, NICE[1] has published guidelines on infection control in primary and community care (including antimicrobial treatment and prophylaxis) in the following areas:

- standard principles
- care of patients with long-term urinary catheters
- care during enteral feeding
- care of patients with central venous catheters.

1 NICE guidance: http://guidance.nice.org.uk/CG2/Guidance/pdf/English