30 Schizophrenia

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Key points

- Schizophrenia is a complex illness which varies greatly in presentation.
- Positive symptoms such as hallucinations, delusions and thought disorder, which commonly occur in the acute phase of the illness, usually respond to treatment with antipsychotic drugs.
- Negative symptoms such as apathy, social withdrawal and lack of drive, which occur commonly in the chronic phase of the illness, are more resistant to drug treatment.
- The term 'atypical' is used to describe the newer antipsychotic drugs that do not cause extrapyramidal side effects.
- The atypical antipsychotics are associated with a range of metabolic side effects including weight gain and diabetes.
- Typical antipsychotic drugs are often associated with anticholinergic, sedative and cardiovascular side effects in addition to extrapyramidal side effects.
- Long-term treatment with typical antipsychotic drugs is associated with the development of tardive dyskinesia.
- Most typical and atypical antipsychotic drugs have similar efficacy in the treatment of schizophrenia.
- Decisions about which antipsychotic drug to use should be a mutual decision based on an informed discussion involving individual preference, previous efficacy and side effects.
- Clozapine has a broader spectrum of activity than traditional antipsychotic drugs with some efficacy for treatment-resistant schizophrenia and negative symptoms.

The concept of schizophrenia can be difficult to understand. People who do not suffer from schizophrenia can have little idea of what the experience of hallucinations and delusions is like. The presentation of schizophrenia can be extremely varied, with a great range of possible symptoms. There are also many misconceptions about the condition of schizophrenia that have led to prejudice against sufferers of the illness. People with schizophrenia are commonly thought to have low intelligence and to be dangerous. In fact, only a minority shows violent behaviour, with social withdrawal being a more common picture. Up to 10% of people with schizophrenia commit suicide.

Classification

Since the late nineteenth century there have been frequent attempts to define the illness we now call schizophrenia. Kraepelin, in the late 1890s, coined the term 'dementia praecox' (early madness) to describe an illness where there was a deterioration of the personality at a young age. Kraepelin also coined the terms 'catatonic' (where motor symptoms are prevalent and changes in activity vary), 'hebephrenic' (silly, childish behaviour, affective symptoms and thought disorder prominence) and 'paranoid' (clinical picture dominated by paranoid delusions). A few years later Bleuler, a Swiss psychiatrist introduced the term 'schizophrenia', derived from the Greek words *skhizo* (to split) and *phren* (mind), meaning the split between the emotions and the intellect.

Two systems for the classification of schizophrenia are widely used: the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM IV; American Psychiatric Association, 1994) and the *International Classification of Diseases*, 10th edition (ICD 10; World Health Organization, 1992).

Symptoms and diagnosis

Acute psychotic illness

To establish a definite diagnosis of schizophrenia it is important to follow the diagnostic criteria in either DSM IV or ICD 10, but symptoms which commonly occur in the acute phase of a psychotic illness include the following:

- awkward social behaviour, appearing preoccupied, perplexed and withdrawn, or showing unexpected changes in behaviour
- initial vagueness in speech which can progress to disorders of the stream of thought or poverty of thought
- abnormality of mood such as anxiety, depression, irritability or euphoria
- auditory hallucinations, the most common of which are referred to as 'voices'; such voices can give commands to patients or may discuss the person in the third person, or comment on their actions
- delusions, of which those relating to control of thoughts are the most diagnostic; for example, patients feel that thoughts are being inserted into or withdrawn from their mind
- lack of insight into the illness.

These symptoms are commonly called positive symptoms.

Factors affecting diagnosis and prognosis

There is a reluctance to classify people as suffering schizophrenia on the basis of one acute psychotic illness, but there are a number of features which aid prediction of whether an acute illness will become chronic. These features include:

- age of onset, which, typically for schizophrenia, is late teenage to 30 years
- reports of a childhood which indicate the individual did not mix or was a rather shy and withdrawn personality
- a poor work record
- a desire for social isolation
- being single and not seeming to have sexual relationships
- a gradual onset of the illness and deterioration from the previous level of functioning
- grossly disorganised behaviour

Treatment

There is a wide range of antipsychotic drugs available for the treatment of a psychotic illness. Although most antipsychotic drugs are equally effective in the treatment of psychotic symptoms, some individuals respond better to one drug than another.

There is controversy over how long people should remain on an antipsychotic drug following their first acute illness. Some would argue that, if the prognosis is poor, long-term therapy should be advocated. Others would want to see a second illness before advocating long-term therapy.

Chronic schizophrenia

Between 60% and 80% of patients who suffer from an acute psychotic illness will suffer further illness and become chronically affected. For these patients the diagnosis of schizophrenia can be applied.

As schizophrenia progresses, there may be periods of relapse with acute symptoms but the underlying trend is towards symptoms of lack of drive, social withdrawal and emotional apathy. Such symptoms are sometimes called negative symptoms and respond poorly to most antipsychotic drugs.

Causes of schizophrenia

Although the cause of schizophrenia remains unknown, there are many theories and models.

Vulnerability model

The vulnerability model postulates that the persistent characteristic of schizophrenia is not the schizophrenic episode itself but the vulnerability to the development of such episodes of the disorder. The episodes of the illness are time limited but the vulnerability remains, awaiting the trigger of some stress. Such vulnerability can depend on premorbid personality, the individual's social network or the environment. Manipulation and avoidance of stress can abort a potential schizophrenic episode.

Developmental model

The developmental model postulates that there are critical periods in the development of neuronal cells which, if adversely affected, may result in schizophrenia. Two such critical periods are postulated to occur when migrant neural cells do not reach their goal in fetal development and when supernumerary neural cells slough off at adolescence. This model is supported by neuroimaging studies which show structural brain abnormalities in patients with schizophrenia.

Ecological model

The ecological model postulates that external factors involving social, cultural and physical forces in the environment, such as population density, individual space, socio-economic status and racial status, influence the development of the disorder. The evidence in support of such a model remains weak.

Genetic model

There is undoubtably a genetic component to schizophrenia, with a higher incidence in the siblings of schizophrenics. However, even in monozygotic twins there are many cases where only one sibling has developed schizophrenia.

Transmitter abnormality model

The suggestion that schizophrenia is caused primarily by an abnormality of dopamine receptors and, in particular, D_2 receptors, has largely emerged from research into the effect of antipsychotic drugs. Such a theory is increasingly being questioned.

Other factors

Numerous other factors have been implicated in the development and cause of schizophrenia. These include migration, socio-economic factors, perinatal insult, infections, season of birth, viruses, toxins and family environment.

In reality, all of these factors may influence both the development and progression of schizophrenia. Social, familial and biological factors may lead to premorbid vulnerability and subsequently influence both the acute psychosis and the progression to chronic states. What is then likely is that the illness will feed back to influence social, familial and biological factors, thus leading to future vulnerability.

Drug treatment

Mode of action of antipsychotic drugs

Although the cause of schizophrenia is the subject of controversy, an understanding of the mode of action of antipsychotic drugs has led to the dopamine theory of schizophrenia. This theory postulates that the symptoms experienced in schizophrenia are caused by an alteration to the level of dopamine activity in the brain. It is based on knowledge that

dopamine receptor antagonists are often effective antipsychotics while drugs which increase dopamine activity, such as amfetamine, can either induce psychosis or exacerbate a schizophrenic illness.

At least six dopamine receptors exist in the brain, with much activity being focused on the D_2 receptor as being responsible for antipsychotic drug action. However, drugs such as pimozide, that claim to have a more specific effect on D_2 receptors, do not appear superior in antipsychotic effect when compared to other agents.

Research into the mode of action of clozapine has caused a change of attention to the mesolimbic system in the brain and to different receptors. Clozapine does not chronically alter striatal D_2 receptors but does appear to affect striatal D_1 receptors. It also appears to have more effect on the limbic system and on serotonin ($5HT_2$) receptors, which may explain its reduced risk of extrapyramidal symptoms. The term 'atypical' is used to categorise those antipsychotic drugs that, like clozapine, rarely produce extrapyramidal side effects (EPSEs).

Although the reason for the superiority of clozapine in schizophrenia treatment remains an enigma, a variety of theories have led to the development of a new family of antipsychotic drugs. Some mimic the impact of clozapine on a wide range of dopamine and serotonin receptors, for example, olanzapine, others mimic the impact on particular receptors, for example, $5HT_2/D_2$ receptor antagonists such as risperidone, others focus on limited occupancy of D_2 receptors, for example, quetiapine, while others focus on alternative theories such as partial agonism (aripiprazole).

Rationale for use of drugs

Although a variety of social and psychological therapies are helpful in the treatment of schizophrenia, drugs form the essential cornerstone. The aim of all therapies is to minimise the level of handicap and achieve the best level of mental functioning. Drugs do not cure schizophrenia and are only partially effective at eradicating some symptoms such as delusions and negative symptoms. At the same time, benefits have to be balanced against side effects and whether the need to suppress particular symptoms is important. For example, if the person has a delusion that he or she is responsible for famine in Africa, but this does not in any way influence that person's behaviour or mood, a common view would be that there would be little point in increasing antipsychotic drug therapy. However, others would argue that this 'untreated' delusion would make the person stand out or be subject to social stigma and the delusion should be more aggressively treated. If, on the other hand, this delusion led to great distress, or violent or dangerous behaviour, then an increase in antipsychotic drugs would usually be indicated.

It is now accepted that antipsychotic drugs can control or modify symptoms such as hallucinations and delusions that are evident in the acute episode of illness. Except for clozapine and the other atypicals, there is little evidence for antipsychotic drugs being of value in the treatment of the negative symptoms, although the matter remains controversial (Chakos et al., 2001). Antipsychotic drugs increase the length of time between breakdowns and shorten the length of the acute episode in most patients.

Drug selection and dose

Over the years there have been many changes to the range of antipsychotic drugs available. Despite the availability of newer agents many of the issues relevant to drug selection and dose have remained similar for the last 50 years and include:

Individual response

Drug selection should not be based on chemical group alone, since individual response to a particular drug or dose may be more important.

Side effects

For older, typical antipsychotic drugs, side effects such as hypotension, extrapyramidal symptoms and anticholinergic effects are key factors in the choice of drug. In contrast, with the newer atypical drugs, side effects such as diabetes, sexual dysfunction and weight gain affect adherence in many patients. Sedation remains a factor for all antipsychotic drugs.

The key side effects of concern are those categorised as EPSEs. Those that caused these side effects were called typical antipsychotic drugs and those that did not were called atypical. This classification system, however, has always remained subject to criticism as some atypicals will cause EPSEs when used at higher doses and the side effects of the different atypicals can vary considerably. EPSEs include:

Akathisia or motor restlessness. This causes patients to pace up and down, constantly shift their leg position or tap their feet.

Dystonia is the result of sustained muscle contraction. It can present as grimacing and facial distortion, neck twisting and laboured breathing. Occasionally the patient may have an oculogyric crisis in which, after a few moments of fixed staring, the eyeballs move upwards and then sideways, remaining in that position. In addition to these eye movements, the mouth is usually wide open, the tongue protruding and the head tilting backwards.

Parkinson-like side effects usually present as tremor, rigidity and poverty of facial expression. Drooling and excessive salivation are also common. A shuffling gait may be seen and the patient may show signs of fatigue when performing repetitive motor activities.

Another movement disorder more commonly associated with typical antipsychotics is tardive dyskinesia. Tardive dyskinesia normally affects the tongue, facial and neck muscles but can also affect the extremities. Individuals with tardive dyskinesia often have abnormalities of posture and movement of the fingers in addition to the oral-lingual-masticatory movements.

Epidemiological studies support the association between the prescribing of typical antipsychotic drugs and the development of tardive dyskinesia. Other factors which also appear to be associated include the duration of exposure to

antipsychotic drugs, the co-prescribing of anticholinergic drugs, the co-prescribing of lithium, advanced age, prior experience of acute extrapyramidal symptoms and brain damage. Many other factors have been postulated to be associated with tardive dyskinesia such as depot formulations of antipsychotic drugs, dosage of antipsychotic drug and antipsychotic drugs with high anticholinergic activity, but such associations remain unproven.

Although the mechanism by which tardive dyskinesia arises is unclear, the leading hypothesis is that after prolonged blockade of dopamine receptors, there is a paradoxical increase in the functional activity of dopamine in the basal ganglia occurs. This increased functional state is thought to come about through a phenomenon of disuse supersensitivity of dopamine receptors. The primary clinical evidence to support this theory arises because tardive dyskinesia is late in onset following prolonged exposure to antipsychotic drugs and has a tendency to worsen upon abrupt discontinuation of the antipsychotic drug.

Attempts to treat tardive dyskinesia have been many and varied. Treatments include use of dopamine-depleting agents such as reserpine and tetrabenazine, dopamine-blocking agents such as antipsychotic drugs, interference with catecholamine synthesis by drugs such as methyldopa, cholinergic agents such as choline and lecithin, use of GABA mimetic agents such as sodium valproate and baclofen, and the provision of drug holidays. Rarely are these strategies successful. Most successful strategies currently involve a gradual withdrawal of the typical antipsychotic drug and replacement with an atypical antipsychotic drug.

Concerns about the EPSEs and toxicity of typical antipsychotic drugs led to calls over the past 10 years for the 'atypicals' to be prescribed more widely. This approach was supported in national guidance which advocated that atypical antipsychotic drugs should be used for the treatment of a first illness. However, increasing concern about the side effects of the atypical antipsychotic drugs, which includes weight gain, diabetes and sexual dysfunction, has led many clinicians to question the benefits of the newer and more expensive atypical antipsychotics. In more recent guidance (National Institute for Health and Clinical Excellence, 2009), it has been advocated that:

- Oral antipsychotic medication should be offered to people with newly diagnosed schizophrenia.
- Information on the benefits and side effects of each antipsychotic agent should be provided and discussed with the patient.
- The decision as to which antipsychotic to use should be made in partnership with the patient and carer as appropriate.
- When deciding on the most suitable medication, the relative potential of the individual antipsychotics to cause EPSEs such as akathisia, metabolic side effects such as weight gain and other side effects including unpleasant subjective experiences should be considered.
- Combined antipsychotic medication should not be started, except for short periods (e.g. when changing medication).

Information on the advantages and disadvantages of the various antipsychotic drugs can be found in Table 30.1.

A significant factor that has influenced prescribing practice in schizophrenia in recent years has been an improved understanding of the role of clozapine in treatment-resistant schizophrenia.

Clozapine and refractory illness

Clozapine was developed as an antipsychotic drug during the 1960s. Unfortunately, use is associated with a 1–2% incidence of neutropenia and this initially resulted in the withdrawal of the drug from clinical practice. However, it was noted even at an early stage in the drug's history that it was free of the extrapyramidal side frequently seen with the other antipsychotic drugs. In the 1980s, clozapine was demonstrated to have a greater efficacy than other antipsychotics (Kane et al., 1988; Lieberman et al., 1994) and was subsequently reintroduced into clinical practice but with routine monitoring of blood mandatory.

Clozapine is now established as the drug of choice in treatment-resistant schizophrenia but it is not without problems (Tuunainen et al., 2000). In addition to neutropenia, it is associated with a greater risk of seizures, particularly if doses are above 600 mg daily. Some guidelines recommend the co-prescribing of sodium valproate to reduce this risk. In addition, use is associated with excessive drooling, hypotension and sedation during the early stages of treatment, requiring slow dose increases initially.

A regimen of gradual dose increases starting at 12.5 mg twice daily aiming to reach 300 mg in 2–3 weeks is normally recommended. However, this rate of dose increase is frequently too rapid, with tachycardia being a particular problem. In such cases, it is usual to slow down the rate of dose increase to a half or a quarter of that recommended. Although tachycardia is a common problem with clozapine initiation, if use is associated with fever, chest pain or hypotension this may indicate a high risk of myocarditis and the drug should be stopped (Committee on Safety of Medicines, 2002).

Polypharmacy

Polypharmacy remains a matter of concern in the management of individuals with schizophrenia. It usually arises because:

- There is a poor response to standard drug treatment.
- There are unrealistic expectations about the onset of action and the extent of treatment control.
- Prescribers feel inhibited about using high doses and resort to prescribing two or more antipsychotic drugs to achieve control, particularly in the acute situation. The consensus is that very high doses of antipsychotics do not improve the overall level of response (Royal College of Psychiatrists, 2006). Increasingly, though, prescribers are being encouraged to use clozapine at an earlier stage for patients who do not fully respond to treatment.

Table 30.1 Neuroleptics/antipsychotics and their commonly associated attributes and problems

Drug group	Drug	Comment
Butyrophenones	Haloperidol	Regarded as the gold standard reference antipsychotic Extrapyramidal side effects of parkinsonian rigidity, dystonia, akathisia Tardive dyskinesia with long-term use Drug most associated with neuroleptic malignant syndrome Sedation common Hormonal effects common Wide range of formulations including long-acting injection
	Benperidol	As haloperidol Claimed to reduce sexual drive, although little evidence to support the claim
Phenothiazines		
Piperidine	Pericyazine	Marked anticholinergic side effects of dry mouth, blurred vision and constipation Postural hypotension and falls in the elderly Lower incidence of extrapyramidal side effects
	Pipotiazine	As pericyazine but only available as depot formulation
Aliphatic	Chlorpromazine	As haloperidol but in addition postural hypotension, low body temperature, rashes and photosensitivity Increased sedative effects
	Promazine	As chlorpromazine but low potency Considered by some to have weak antipsychotic effect
	Levomepromazine (methotrimeprazine)	Very sedative and postural hypotension common Mostly used in terminal illness
Piperazine	Trifluoperazine	As chlorpromazine but greater incidence of extrapyramidal side effects and lower incidence of anticholinergic effects Tardive dyskinesia with long-term use Some antiemetic properties
	Fluphenazine	As trifluoperazine but also available as depot formulation
	Perphenazine	As trifluoperazine
Thioxanthines	Flupentixol	Similar to fluphenazine but also available as depot formulation
	Zuclopenthixol	Similar to chlorpromazine but also available as depot formulation
Diphenylbutylpiperidines	Pimozide	As haloperidol but concerns about cardiac effects at high dose limits use
Benzamides	Sulpiride	Lower incidence of extrapyramidal effects Few anticholinergic effects Useful adjunct to clozapine in refractory illness
	Amisulpride	As sulpiride
Dibenoxazepine tricyclics	Clozapine	Drug of choice for treatment-resistant schizophrenia Low incidence of extrapyramidal side effects or tardive dyskinesia Neutropenia in 1–2% of cases Enhanced efficacy against both positive and negative symptoms Sedation, dribbling, drooling, weight gain and diabetes
Thienobenzodiazepines	Olanzapine	Sedation, weight gain and diabetes Low incidence of extrapyramidal side effects and low impact on prolactin
	Quetiapine	Low incidence of extrapyramidal side effects and low impact on prolactin
	Zotepine	Similar to olanzapine but higher rate of prolactin elevation and higher rate of drug-induced seizures
Serotonin–dopamine antagonists	Risperidone	Extrapyramidal side effects at higher doses. High rate of prolactin elevation
	Paliperidone	As risperidone
	Ziprasidone	As risperidone
	Sertindole	Available on named patient basis only due to risk of sudden cardiac events
Partial dopamine agonist	Aripiprazole	Low level of side effects but light-headedness and blurred vision common

- Once control has been achieved there may be reluctance to reduce either dose or the number of drugs an individual is receiving for fear of re-emergence of symptoms.
- There is an imbalance between the perceived need in the hospital ward setting for sedation rather than an antipsychotic effect. The sedating side effects of antipsychotic drugs may be evident within hours; they are rapid in onset but may begin to wear off after 2–3 weeks. The antipsychotic effects on thought disorder, hallucinations and delusions may take some weeks to appear, although if there has been no response within 2–3 weeks a change of antipsychotic or change of dose may be indicated.

Neuroleptic equivalence

Although antipsychotic drugs vary in potency, studies on relative dopamine receptor binding have led to the concept of chlorpromazine equivalents as a useful method of transferring dosage from one product to another. Concern has been expressed about the variation between sources for such values, in particular about the quoted chlorpromazine equivalents of the butyrophenones and the conversion of depot doses to oral doses (Table 30.2). Likewise, there is no agreement on the equivalent doses of the atypicals.

For research purposes the concept of proportion of the maximum dose stated in the British National Formulary (BNF) has been developed as a standardised method for calculating average doses used in practice. However, this may not be a useful way of determining a dose when transferring a patient from one antipsychotic to another.

Table 30.2 Equivalence of typical antipsychotic drugs to 100 mg chlorpromazine (from Foster, 1989)

Drug	Usual dose (mg) equivalent of to 100 mg chlorpromazine	Variations in quoted dosage (mg) equivalent to 100 mg of chlorpromazine
Oral antipsychotics		
Promazine	200	100–250
Thioridazine	100	50–120
Trifluoperazine	5	3.5–7.5
Haloperidol	2	1.5–5
Sulpiride	200	–
Depot antipsychotics administered every 2 weeks (all administered as the decanoate)		
Zuclopenthixol	200	80–200
Flupentixol	40	16–40
Fluphenazine	25	10–25
Haloperidol	20	–

Augmentation strategies and polytherapy

Schizophrenia is a complex illness with a very varied presentation. In addition to the core symptoms, elements of other mental illnesses such as mania, depression and anxiety may predominate. Controversy remains about whether these associated symptoms should be treated separately or as a part of schizophrenia. In addition, there is debate about whether these presentations represent an alternative diagnosis, for example, schizoaffective disorder when the mood disorder is a primary component of the presentation. The current fashion is for these components of the illness to be treated separately, with much resulting polytherapy with SSRI antidepressants and antiepileptic drugs for mood control.

In addition to the above, complex prescriptions can arise when treatment with clozapine is perceived to be inadequate or doses are limited due to side effects. The theory behind the addition of a further drug can be either that the plasma concentration of the clozapine will be enhanced by the addition of another drug, or the second drug will enhance a particular receptor blockade which may be considered necessary in a specific patient (Cipriani et al., 2009; Paton et al., 2007). The augmentation strategy with the best evidence to support its use is the addition of sulpiride or amisulpride to clozapine. Other strategies include the addition of risperidone, lamotrigine or Ω3 fatty acids. However, many of the trials that support these augmentation strategies are small scale and a meta-analysis concluded that no single strategy was superior to another (Paton et al., 2007).

Long-acting formulations of antipsychotic drugs

Most long-acting (depot) formulations, including the long-acting olanzapine formulation, are synthesised by esterification of the hydroxyl group of the antipsychotic drug to a long chain fatty acid such as decanoic acid. The esters which are more lipophilic and soluble are dissolved in an oily vehicle such as sesame oil or a vegetable oil (viscoleo). Once the drug is injected into muscle it is slowly released from the oil vehicle. Active drug becomes available following hydrolysis for distribution to the site of the action. A long-acting injection of olanzapine has been marketed which contains a salt of olanzapine and pamoic acid suspended in an aqueous vehicle. This also is designed for intramuscular injection every 2–4 weeks.

Although the ideal long-acting antipsychotic formulation should release the drug at a constant rate so that plasma level fluctuations are kept to a minimum, all the available products produce significant variations (Table 30.3). This can result in increased side effects at the time of peak plasma concentrations, usually after 5–7 days, for oil-based depots and increased patient irritability towards the end of the period, as plasma concentrations decline. For many patients though, oil-based long-acting formulations result in a very slow decline in drug availability after a period of chronic administration (Altamura et al., 2003). When transferring a patient from depot formulations to oral administration, it may be many months before the effect of the depot finally wears off.

Table 30.3 Comparison of depot antipsychotics

Drug	Ester	Vehicle	Time to peak (days) from single dose	Half-life (days)
Haloperidol	Decanoate	Sesame oil	3–9	21
Flupentixol	Decanoate	Viscoleo oil	7	17
Zuclopenthixol	Decanoate	Viscoleo oil	4–7	19
Fluphenazine	Decanoate	Sesame oil	0.3–1.5	6–9
Pipotiazine	Palmitate	Sesame oil	10–15	15
Risperidone		Microspheres	32	8–9
Olanzapine	Pamoate	Aqueous	3	10
Paliperidone	Palmitate	Microspheres	13	25–49

Long-acting risperidone injection involves a microsphere formulation. The microspheres delay the release of risperidone for 3–4 weeks. Once release has commenced, the risperidone reaches a maximum concentration 4–5 weeks after the injection with a decline over the subsequent 2–3 weeks. This more rapid decline has an advantage that by 2 months after the last injection, little of the risperidone will remain. The delay in onset is often a reason for relapse as it is necessary to maintain oral supplementation for at least 6 weeks and this may be overlooked.

In addition to the principles of drug choice and dosage selection that apply to oral drugs, with depot therapy there is also a need to consider the future habitation of the patient. If the patient is to live an independent lifestyle, depot formulations are indicated, but if the person is to remain in staffed accommodation and receive other medicines routinely administered by a nurse, the use of depot formulations may not be logical.

Advantages and disadvantages of long-acting formulations

Non-adherence with oral medicines is a major problem in patients with any long-term illness and the administration of depot formulations guarantees drug delivery. It has been argued that, although depot injections are expensive, they have economic advantages because they reduce hospital admissions, improve drug bioavailability by avoiding the deactivating processes which occur in the gut and liver, and result in more consistent plasma levels of drug.

Depot formulations have the disadvantage of reduced flexibility of dosage, the painful nature of administration and, for the older depots, a high incidence of EPSEs. In addition, risperidone long-acting injection has the disadvantage of considerable delay in onset, whilst the olanzapine depot is associated with a post-injection syndrome consistent with olanzapine overdose. Although this side effect is relatively rare there is a requirement for patients to be observed for 3 hours following injection thereby limiting its acceptability.

Anticholinergic drugs

Anticholinergic drugs are prescribed to counter the EPSEs of typical antipsychotics, and at one time were routinely prescribed. It is generally accepted that, with the possible exception of the first few weeks of treatment with antipsychotic drugs known to have a high incidence of EPSEs, anticholinergic drugs should only be prescribed when a need has been shown. A number of studies have looked at the discontinuation of anticholinergic agents and reported re-emergence of the symptoms. Up to 60% of patients may be affected by re-emergence of symptoms and between 25% and 30% of patients will have a continuing need for anticholinergic drugs. The anticholinergic drugs are not without problems, having their own range of side effects that include dry mouth, constipation and blurred vision. Trihexyphenidyl in particular, is renowned for its euphoric effects and withdrawal problems can include cholinergic rebound. One of the benefits of the atypical antipsychotic drugs is the reduced need for co-prescription of anticholinergic drugs. However, EPSEs can still occur with atypical antipsychotic drugs, particularly at high dose.

Interactions and antipsychotic drugs

There are claimed to be many interactions involving antipsychotic drugs but few appear to be clinically significant. Propranolol increases the plasma concentration of chlorpromazine, and carbamazepine accelerates the metabolism of haloperidol, risperidone and olanzapine. When tricyclic antidepressants are administered with phenothiazines, increased antimuscarinic effects such as dry mouth and blurred vision can occur and most antipsychotic drugs increase the sedative effect of alcohol. The SSRI antidepressants fluvoxamine, fluoxetine and paroxetine interact with clozapine, resulting in increases in clozapine plasma concentration.

Therapeutic drug monitoring

Therapeutic drug monitoring is only of value if there is a reliable laboratory assay and a correlation exists between the concentration of the drug in any particular body compartment, usually

blood/plasma, and its clinical effectiveness. Unfortunately, this is not the case for most antipsychotic drugs and the measurement of drug concentrations is not a part of routine clinical practice. In recent years, however, it has become common to measure clozapine levels although even with this drug there is only a weak correlation between plasma levels and clinical effect. The general guidance is that individuals who have not adequately responded to clozapine and have a plasma level below 350–500 µcg/L may benefit from a dose increase and those who suffer side effects and have a plasma level above this range may benefit from a dose reduction. Those with a plasma level above 1000 µcg/L are more likely to suffer seizures and cover using sodium valproate should be considered.

Adverse effects and antipsychotic medicines

There are a large number of adverse effects associated with antipsychotic medicines. Some of these effects, such as sedation, antilibido effects and weight gain may be considered to be of value with particular patients, but the susceptibility to such adverse effects is often a major factor in determining drug choice. Prescribing guidelines are available (Bazire, 2009; Taylor et al., 2009) which provide details of the relative likelihood of side effects with the various antipsychotic drugs. The major side effects are set out below.

Sedation

Although sedation is most commonly associated with chlorpromazine and clozapine, it is primarily related to dosage with other antipsychotics. Products claiming to be less sedating can often only substantiate this when used at low doses.

Weight gain and diabetes

Weight gain was a common feature of the first phenothiazine antipsychotics. It was originally thought this side effect was caused by a direct effect on metabolism. This side effect has also become a feature of some of the newer atypical antipsychotic medicines, particularly olanzapine and clozapine. This re-emergence of an old side effect with the new drugs has rekindled interest in the cause, which is now thought to be more associated with loss of control of food intake, rather than a direct effect on food metabolism. In addition to weight gain, these two atypical antipsychotic drugs have also been associated with increased incidence of diabetes. Controversy remains about whether there is a link between the weight gain and onset of diabetes, and whether the development of diabetes is more associated with the illness of schizophrenia than the drugs. Whatever the link, the controversy has led to the acceptance that people with schizophrenia often suffer poor physical health in addition to poor mental health and require regular monitoring of physical health risk factors. Increased concern about the physical and metabolic side effects of the antipsychotic medicines has led to increased requirements to monitor urea and electrolytes, blood lipids, full blood count, plasma glucose and blood pressure.

QT prolongation and cardiac risk

Some antipsychotic drugs are associated with changes to the QT interval measured on the elecrocardiogram (ECG) and, if given in high doses, may increase the risk of sudden cardiac death. Although, overall, the risk is low, monitoring the ECG has become part of normal practice, especially if high doses are used.

Anticholinergic side effects

Side effects such as dry mouth, constipation and blurred vision are particularly associated with piperidine phenothiazines.

Extrapyramidal side effects

Side effects such as akathisia, dystonia and parkinsonian effects are associated with typical antipsychotic drugs and occur frequently, particularly with depot antipsychotics, piperazine phenothiazines such as trifluoperazine and fluphenazine, and butyrophenones such as haloperidol. These side effects are reversible by using anticholinergic drugs or by dosage reduction. The common extrapyramidal effects include akathisia, dystonia and parkinson-like side effects (see the previous section)

Hormonal effects and sexual dysfunction

These side effects are primarily influenced by the effect on prolactin. This may result in galactorrhoea, missed menstrual periods and loss of libido. Some studies have suggested very high levels of sexual dysfunction with some antipsychotic drugs such as typical antipsychotic drugs and the atypical antipsychotics risperidone and amisulpride. However, in many of these studies the background level of such dysfunction is unclear. In addition, there has been a debate about the extent to which the long-term elevation of prolactin, particularly in the young, may be a cause of osteoporosis. What remains controversial though is at what point an elevated prolactin level should result in a discussion about choosing an alternative antipsychotic.

Postural hypotension and photosensitivity

Postural hypotension and photosensitivity are particularly associated with the aliphatic phenothiazines such as chlorpromazine.

Neuroleptic malignant syndrome (NMS)

The NMS is a rare but serious complication of antipsychotic drug treatment. The primary symptoms are rigidity, fever, diaphoresis, confusion and fluctuating consciousness. Confirmation can be sought through detection of elevated levels of creatinine kinase. The onset is particularly associated with high-potency typical drugs such as haloperidol, recent and rapid changes to dose and abrupt withdrawal of anticholinergic drugs. Treatment usually requires admission to a medical ward and withdrawal of all antipsychotic drugs.

Case studies

Case 30.1

Lee is a 20-year-old man. His childhood was disrupted by constant changes to family membership. From an early age his behaviour was difficult but despite such changes by the age of 16 he was achieving well at school. Aged 17, he became involved with the illicit drug culture and increasingly lost interest in his studies. His parents became concerned as he appeared to undergo a change of personality, communicating with them very little. He eventually dropped out of school and took various short-term jobs. He was unable to sustain any long-term employment. He moved into a flat and seemed to live a twilight existence involving illicit drugs and all-night raves. Police were called to his flat following a violent disturbance. They found Lee living in squalor. He was surrounded by pieces of paper containing incomprehensible messages and was incoherent. He sat with a fixed stare, appearing quite inaccessible. He kept laughing and responding to imaginary people. He was very resistant to hospital admission, and had to be admitted under a section of the Mental Health Act 2007. On the ward he has remained quiet but appears to be in conversation with people who are not there.

Questions

1. Outline the drug(s) of choice for Lee and the rationale for selection.
2. What factors would influence the likely prognosis?
3. Outline the drug(s) of choice if there is the need to control aggressive behaviour.

Answers

1. The first need is to ascertain whether the patient's behaviour results from abuse of illicit substances or the onset of a schizophrenic illness. If the former, he would be expected to recover within a few days with little or no drug treatment. If, however, this is the first presentation of a schizophrenic illness, the symptoms are likely to persist and it would be appropriate to prescribe an antipsychotic drug. The choice of antipsychotic drug for first-illness psychosis may partly depend on the formulation acceptable to the situation but would usually be an atypical antipsychotic drug. If oral medicines were refused the intramuscular formulation of olanzapine may be the drug of choice. If there were concerns that he may not swallow the drug, aripiprazole, olanzapine and risperidone are formulated as orodispersible formulations.
2. A number of factors in Lee's history indicate a poor prognosis:
   - there has been a deterioration in function
   - his age, which is typical for a first breakdown
   - his poor work record
   - grossly disorganised behaviour
   - a number of positive symptoms such as hallucinations
3. If Lee becomes aggressive and there was a need to use medicines to control the aggression a decision would have to be made about whether to use antipsychotic drugs or benzodiazepines. In the past, sedative antipsychotic drugs such as chlorpromazine, haloperidol or zuclopenthixol were favoured, but increasing concern about sudden death has led to a move to use benzodiazepines such as lorazepam or diazepam. However, the introduction of intramuscular olanzapine has resulted in some swing back to using antipsychotic drugs for the control of violent and aggressive behaviour.

Case 30.2

Gordon has relapsed for the third time this year, the pattern for the last two relapses being the same. His positive symptoms responded rapidly on both previous occasions. On the first he suffered severe extrapyramidal side effects with 30 mg daily of haloperidol and was subsequently stabilised and discharged on sulpiride 400 mg twice daily and procyclidine 5 mg twice daily. He almost immediately stopped taking the sulpiride, claiming not to be ill. During his second relapse he was successfully treated with risperidone 4 mg daily but again stopped the medicine.

Questions

1. Was Gordon's drug treatment appropriate?
2. What strategies could be adopted to maintain Gordon in treatment?

Answers

1. Gordon's initial treatment was not according to current guidelines. The initial treatment with a large dose of haloperidol in a drug-naive patient would now be regarded as excessive. The initial choice of a low-dose typical antipsychotic followed by a second choice of an atypical after the patient suffered extrapyramidal side effects was common practice prior to the publication of national guidance (National Institute for Health and Clinical Excellence, 2009). An atypical antipsychotic would be regarded as the drug of choice for first illness.
2. Gordon has no insight into his illness or the need for continuing treatment. This could be for a number of reasons:
   - It is part of the illness, and his failure to gain insight is symptomatic of incomplete recovery.
   - He lacks a supportive environment to ensure that he takes medicines.
   - He is suffering from side effects that deter him from taking the medicines.

   In most cases, the use of a depot antipsychotic injection would be the easiest way to ensure adherence, although if Gordon is determined to avoid drug treatment this strategy is unlikely to be successful. In his case, the history of good response to oral risperidone and severe extrapyramidal side effects with a typical antipsychotic drug would indicate that the long-acting intramuscular formulation of risperidone may be a good choice.

Case 30.3

Sharon, aged 25, has a 3-year history of schizophrenia with many admissions to hospital. Throughout the period of her illness she has received a range of different oral antipsychotic drugs including chlorpromazine, haloperidol, sulpiride, risperidone and olanzapine, as well as the depot formulations of haloperidol and zuclopenthixol. For most of this time she has had a fixed belief that she is involved with a range of mythical beasts that sexually assault her. When she is ill these beings torment her. She currently receives zuclopenthixol decanoate 500 mg by intramuscular injection every week, olanzapine 10 mg at night, carbamazepine 200 mg three times daily, haloperidol 10 mg four times daily, and procyclidine 10 mg three times daily. She has remained on the ward for the last 4 months with no sign of improvement. She has greatly increased in weight, now approaching 20 stone. The team wishes to consider clozapine for Sharon.

Questions

1. Comment on the current drug therapy Sharon is receiving.
2. What action is required before Sharon can receive clozapine?

Answers

1. Although it is not uncommon for polypharmacy to occur when there has been poor response, the practice is frowned upon. Additional medicines are often added in a crisis or in the hope of achieving a greater degree of response. As in this case, the strategy is often unsuccessful. The particular issues of note with this patient's drug regimen are

   - The combination of a typical and an atypical antipsychotic drug reduces the potential benefit of using a drug with a low incidence of extrapyramidal side effects because the patient still suffers extrapyramidal side effects, requires procyclidine, and is at risk of developing tardive dyskinesia.
   - The very large total dose she is receiving from the combination of antipsychotic drugs.
   - The dose of anticholinergic drug (procyclidine) is high and likely to result in its own side effects.
   - The need for such frequent dosing of the intramuscular depot might not be necessary; administration at 2-week intervals would normally be appropriate.
   - There is little evidence to support the value of carbamazepine, either for schizophrenia or as an adjunctive treatment.
   - She is suffering severe weight gain.
   - The interaction between carbamazepine and the antipsychotic drugs may be reducing their potential efficacy.

2. The preparation for treatment with clozapine involves a number of steps. These include

   - registration with the clozapine monitoring scheme
   - background blood tests to ensure that the patient is not already suffering from neutropenia or another blood disorder
   - stopping the depot antipsychotic drug; this would usually occur some weeks before starting clozapine
   - stopping carbamazepine as this interacts with clozapine
   - slowly reducing haloperidol
   - gradually stopping procyclidine

   Ideally all other treatments would be stopped and clozapine prescribed alone. Sometimes the final step of withdrawing other medicines may occur during the initiation phase with clozapine.

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31 Epilepsy

J. W. Sander and S. Dhillon

Key points

- An epileptic seizure is a transient paroxysm of uncontrolled discharges of neurones causing an event which is discernible by the person experiencing the seizure and/or an observer.
- The incidence of epileptic seizures is around 50 cases per 100,000 of the population.
- About 70–80% of all those who develop epilepsy will become seizure free on treatment and about 50% will eventually withdraw their medication successfully.
- Generalised seizures result in impairment of consciousness from the onset; they include tonic clonic convulsions, absence attacks and myoclonic seizures.
- Focal seizures include simple partial seizures, complex partial seizures and secondarily generalised seizures.
- Treatment of epilepsy is usually for at least 3 years and, depending on circumstances, sometimes for life.
- Treatment aims to control seizures using one drug without causing side effects and minimising the use of polypharmacy.
- Management of epilepsy requires empowering patients to understand their condition and medication and helping them develop effective partnerships with health professionals.

An epileptic seizure is a transient paroxysm of uncontrolled discharges of neurones causing an event that is discernible by the person experiencing the seizure and/or by an observer. The tendency to have recurrent attacks is known as epilepsy; by definition, a single attack does not usually constitute epilepsy. Epileptic seizures or attacks are a symptom of many different diseases, and the term epilepsy is loosely applied to a number of conditions that have in common a tendency to have recurrent epileptic attacks. A patient with epilepsy will show recurrent epileptic seizures that occur unexpectedly and stop spontaneously.

Epidemiology

There are problems in establishing precise epidemiological information for a heterogeneous condition such as epilepsy. Unlike most ailments, epilepsy is episodic; between seizures, patients may be perfectly normal and have normal investigations. Thus, the diagnosis is essentially clinical, relying heavily on eyewitness descriptions of the attacks. In addition, there are a number of other conditions in which consciousness may be transiently impaired and which may be confused with epilepsy. Another problem area is that of case identification. Sometimes the person may be unaware of the nature of the attacks and so may not seek medical help. People with milder epilepsy may also not be receiving ongoing medical care and so may be missed in epidemiological surveys. Furthermore, since there is some degree of stigma attached to epilepsy, people may sometimes be reluctant to admit their condition. Indeed, epilepsy is still one of the world's most stigmatised conditions. In today's society, in both developed and developing countries, fear, misunderstanding, discrimination and social stigma still exist and these affect the quality of life for people with the disorder and their families.

Epilepsy does impact on an individual's human rights, for example, access to health and life insurance is affected. A person who suffers from epilepsy may not be able to obtain a driving licence and it has an impact on the choice of career. In addition, legislation can impact on the life of individuals with epilepsy, for example, in some countries epilepsy may deter marriages. Legislation based on internationally accepted human rights standards can prevent discrimination and rights violations, improve access to health care services and raise quality of life (WHO, 2009). A global campaign has been established to raise awareness about epilepsy, provide information and highlight the need to improve care and reduce the disorder's impact through public and private collaboration. This is supported through a partnership established between WHO, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).

Epilepsy is recognised as a priority in effective health care delivery and there are still a number of issues that health professionals should consider:

- Epilepsy is a chronic neurological disorder that affects people of all ages.
- Around 50 million people worldwide have epilepsy.
- Nearly 90% of the people with epilepsy are found in developing regions.
- Epilepsy responds to treatment 70% of the time. Despite this, approximately 75% of affected people in developing countries do not get the treatment they need.
- People with epilepsy and their families suffer from stigma and discrimination in many parts of the world.

Incidence and prevalence

Epileptic seizures are common. The incidence (number of new cases per given population per year) has been estimated at between 20 and 70 cases per 100,000 persons, and the cumulative incidence (the risk of having the condition at some point in life) at 2–5%. The incidence is higher in the first two decades of life but falls over the next few decades, only to increase again in late life, due mainly to cerebrovascular diseases. Currently, the elderly are the group in the populations with the highest incidence of epilepsy. Most studies of the prevalence of active epilepsy (the number of cases in the population at any given time) in developed countries cite figures of 4–10 per 1000 with a rate of 5 per 1000 population most commonly quoted. In developed countries, annual new cases are between 0.4 and 0.7 per 1000 general population.

In developing countries, the prevalence of epilepsy is higher with rates of 6–10 per 1000 population cited and reported annual new cases twice those seen in developed countries, presumably due to the higher risk of experiencing conditions that can lead to permanent brain damage. Overall, nearly 90% of epilepsy cases worldwide are found in developing regions.

Prognosis

Up to 5% of people will suffer at least one seizure in their lifetime. The prevalence of active epilepsy is, however, much lower and most patients who develop seizures have a very good prognosis. About 70–80% of all people developing epilepsy will eventually become seizure free, and about half will successfully withdraw their medication. Once a substantial period of remission has been achieved, the risk of further seizures is greatly reduced. A minority of people (20–30%) will develop chronic epilepsy and in such cases, treatment is more difficult. People with symptomatic epilepsy, more than one seizure type, associated learning disabilities or neurological or psychiatric disorders are more likely to have a poor outcome. Of people with chronic epilepsy, fewer than 5% will be unable to live in the community or will depend on others for their day-to-day needs. Most people with epilepsy are entirely normal between seizures but a small minority of patients with severe epilepsy may suffer physical and intellectual deterioration.

Mortality

People with epilepsy, especially younger patients and those with severe epilepsy are at an increased risk of premature death. Most studies have given overall standardised mortality ratios between two and three times that of the general population. Common causes of death in people with epilepsy include accidents such as drowning, head injury, road traffic accidents, status epilepticus, tumours, cerebrovascular disease, pneumonia and suicide. Sudden unexpected death, an entity which remains unexplained, is common in chronic epilepsy, particularly among the young who have convulsive forms of epilepsy.

Aetiology

Epileptic seizures are produced by abnormal discharges of neurones that may be caused by any pathological process which affects the cortical layer of the brain. The idiopathic epilepsies are those in which there is a clear genetic component, and they probably account for a third of all new cases of epilepsy. In a significant proportion of cases, however, no cause can be determined and these are known as the cryptogenic epilepsies. Possible explanations for cryptogenic epilepsy include as yet unexplained metabolic or biochemical abnormalities and microscopic lesions in the brain resulting from brain malformation or trauma during birth or other injury. The term ‘symptomatic epilepsy’ indicates that a probable cause has been identified.

The likely aetiology of epilepsy depends upon the age of the patient and the type of seizure. The commonest causes in young infants are hypoxia or birth asphyxia, intracranial trauma during birth, metabolic disturbances and congenital malformations of the brain or infection. In young children and adolescents, idiopathic seizures account for the majority of the epilepsies, although trauma and infection also play a role. In this age group, particularly in children aged between 6 months and 5 years, seizures may occur in association with febrile illness. These are usually short, generalised tonic clonic convulsions that occur during the early phase of a febrile disease. They must be distinguished from seizures that are triggered by central nervous system infections which produce fever, for example, meningitis or encephalitis. Unless febrile seizures are prolonged, focal, recurrent or there is a background of neurological handicap, the prognosis is excellent and it is unlikely that the child will develop epilepsy.

The range of causes of adult-onset epilepsy is very wide. Both idiopathic epilepsy and epilepsy due to birth trauma may also begin in early adulthood. Other important causes are head injury, alcohol abuse, cortical dysplasias, brain tumours and cerebrovascular diseases. Brain tumours are responsible for the development of epilepsy in up to a third of patients between the ages of 30 and 50 years. Over the age of 50 years, cerebrovascular disease is the commonest cause of epilepsy, and may be present in up to half of patients.

Pathophysiology

Epilepsy differs from most neurological conditions as it has no pathognomonic lesion. A variety of different electrical or chemical stimuli can easily give rise to a seizure in any normal brain. The hallmark of epilepsy is a rather rhythmic and repetitive hyper-synchronous discharge of neurones, either localised in an area of the cerebral cortex or generalised throughout the cortex, which can be observed on an electroencephalogram (EEG).

Neurones are interconnected in a complex network in which each individual neurone is linked through synapses with hundreds of others. A small electrical current is discharged by neurones to release neurotransmitters at synaptic levels to

permit communication with each other. Neurotransmitters fall into two basic categories: inhibitory or excitatory. Therefore, a neurone discharging can either excite or inhibit neurones connected to it. An excited neurone will activate the next neurone whereas an inhibited neurone will not. In this manner, information is conveyed, transmitted and processed throughout the central nervous system.

A normal neurone discharges repetitively at a low baseline frequency, and it is the integrated electrical activity generated by the neurones of the superficial layers of the cortex that is recorded in a normal EEG. If neurones are damaged, injured or suffer a chemical or metabolic insult, a change in the discharge pattern may develop. In the case of epilepsy, regular low-frequency discharges are replaced by bursts of high-frequency discharges usually followed by periods of inactivity. A single neurone discharging in an abnormal manner usually has no clinical significance. It is only when a whole population of neurones discharge synchronously in an abnormal way that an epileptic seizure may be triggered. This abnormal discharge may remain localised or it may spread to adjacent areas, recruiting more neurones as it expands. It may also generalise throughout the brain via cortical and subcortical routes, including collosal and thalamocortical pathways. The area from which the abnormal discharge originates is known as the epileptic focus. An EEG recording carried out during one of these abnormal discharges may show a variety of atypical signs, depending on which area of the brain is involved, its progression and how the discharging areas project to the superficial cortex.

Clinical manifestations

The clinical manifestation of a seizure will depend on the location of the focus and the pathways involved in its spread. An international seizure classification scheme based on the clinical features of seizures combined with EEG data is widely used to describe seizures. It divides seizures into two main groups according to the area of the brain in which the abnormal discharge originates. If it involves initial activation of both hemispheres of the brain simultaneously, the seizures are termed 'generalised'. If a discharge starts in a localised area of the brain, the seizure is termed 'partial' or 'focal'.

Generalised seizures

Generalised seizures result in impairment of consciousness from the onset. There are various types of generalised seizures.

Tonic clonic convulsions

Often called 'grand mal' attacks, these are the commonest of all epileptic seizures. Without warning, the patient suddenly goes stiff, falls and convulses, with laboured breathing and salivation. Cyanosis, incontinence and tongue biting may occur. The convulsion ceases after a few minutes and may often be followed by a period of drowsiness, confusion, headache and sleep.

Absence attacks

Often called 'petit mal', these are a much rarer form of generalised seizure. They happen almost exclusively in childhood and early adolescence. The child goes blank and stares; fluttering of the eyelids and flopping of the head may occur. The attacks last only a few seconds and often go unrecognised even by the child experiencing them.

Myoclonic seizures

These are abrupt, very brief involuntary shock-like jerks, which may involve the whole body, or the arms or the head. They usually happen in the morning, shortly after waking. They may sometimes cause the person to fall, but recovery is immediate. It should be noted that there are forms of non-epileptic myoclonic jerks that occur in a variety of other neurological diseases and may also occur in healthy people, particularly when they are just going off to sleep.

Atonic seizures

These comprise a sudden loss of muscle tone, causing the person to collapse to the ground. Recovery afterwards is quick. They are rare, accounting for less than 1% of the epileptic seizures seen in the general population, but much commoner in patients with severe epilepsy starting in infancy.

Partial or focal seizures

Simple partial seizures

In these seizures, the discharge remains localised and consciousness is fully preserved. Simple partial attacks on their own are rare and they usually progress to the other forms of partial seizure. What actually happens during a simple partial seizure depends on the area of the discharge and may vary widely from person to person but will always be stereotyped in one person. Localised jerking of a limb or the face, stiffness or twitching of one part of the body, numbness or abnormal sensations are examples of what may occur during a simple partial seizure. If the seizure progresses with impairment of consciousness, it is termed a complex partial seizure. If it develops further and a convulsive seizure occurs, it is then called a partial seizure with secondary generalisation. In attacks which progress, the early part of the seizure, in which consciousness is preserved, may manifest as a sensation or abnormal feeling and is called the aura or warning.

Complex partial seizures

The person may present with altered or 'automatic' behaviour: plucking his or her clothes, fiddling with various objects and acting in a confused manner. Lip smacking or chewing movements, grimacing, undressing, performing aimless activities,

and wandering around in a drunken fashion may occur on their own or in different combinations during complex partial seizures. Most of these seizures originate in the frontal or temporal lobes of the brain and can sometimes progress to secondarily generalised seizures.

Secondarily generalised seizures

These are partial seizures, either simple or complex, in which the discharge spreads to the entire brain. The person may have a warning, but this is not always the case. The spread of the discharge can occur so quickly that no feature of the localised onset is apparent to the person or an observer, and only an EEG can demonstrate the partial nature of the seizure. The involvement of the entire brain leads to a convulsive attack with the same characteristics as a generalised tonic clonic convulsion.

There have been recent proposals to revise the concepts, terminology and approaches for classifying seizures and forms of epilepsy (Berg et al., 2010). In this proposal, the so-called natural classes, for example, specific underlying cause, age at onset, associated seizure type; or pragmatic groupings, for example, epileptic encephalopathies, self-limited electroclinical syndromes, serve as the basis for classification.

Diagnosis

Diagnosing epilepsy can be difficult as it is first necessary to demonstrate a tendency to recurrent epileptic seizures. The one feature that distinguishes epilepsy from all other conditions is its unpredictability and transient nature. The diagnosis of epilepsy is clinical and depends on a reliable account of what happened during the attacks, if possible both from the patient and from an eyewitness. Investigations may help and the EEG is usually one of them. These investigations, however, cannot conclusively confirm or refute the diagnosis of epilepsy.

There are other conditions that may cause impairment or loss of consciousness and which can be misdiagnosed as epilepsy; these include syncope, breath-holding attacks, transient ischaemic attacks, psychogenic attacks, etc. In addition, people may present with acute symptomatic seizures or provoked seizures as a result of other problems such as drug intake, metabolic dysfunction, infection, head trauma or flashing lights (photosensitive seizures). These conditions have to be clearly ruled out before a diagnosis of epilepsy is made. Epilepsy must only be diagnosed when seizures occur spontaneously and are recurrent. The diagnosis must be accurate since the label ‘suffering with epilepsy’ carries a social stigma that has tremendous implications for the person.

The EEG is often the only examination required, particularly in generalised epilepsies, and it aims to record abnormal neuronal discharges. EEGs have, however, limitations that should be clearly understood. Up to 5% of people without epilepsy may have non-specific abnormalities in their EEG recording, while up to 40% of people with epilepsy may have a normal EEG recording between seizures. Therefore, the diagnosis of epilepsy should be strongly supported by a bona fide history of epileptic attacks. Nevertheless, the EEG is invaluable in classifying seizures.

The chance of recording the discharges of an actual seizure during a routine EEG, which usually takes 20–30 min, is slight and because of this, ambulatory EEG monitoring and EEG video-telemetry are sometimes required. Ambulatory EEG allows recording in day-to-day circumstances using a small cassette recorder. EEG video-telemetry is useful in the assessment of difficult cases, particularly if surgery is considered. The person is usually admitted to hospital and remains under continuous monitoring. This is only helpful in a very few cases, and it is best suited for people who have frequent seizures.

Neuroimaging with magnetic resonance imaging (MRI) is the most valuable investigation when structural abnormalities such as stroke, tumour, congenital abnormalities or hydrochephalus are suspected. MRI should be carried out in anyone presenting with partial seizures or where a structural lesion on the brain may be responsible for seizures.

Treatment

National Institute for Health and Clinical Excellence (2004a) issued guidance on the diagnosis and treatment of the epilepsies in adults and children in primary and secondary care. The guidance covered issues such as when a person with epilepsy should be referred to a specialist centre, the special considerations concerning the care and treatment of women with epilepsy and the management of people with learning disabilities. The key points of the guidance are summarised in Box 31.1.

Box 31.1 Key points on the diagnosis and management of epilepsy (National Institute for Health and Clinical Excellence, 2004a)

- Diagnosis to be made urgently by a specialist with an interest in epilepsy
- EEG to be used to support diagnosis
- MRI to be used in people who develop epilepsy as adults, in whom focal onset is suspected, or in whom seizures persist
- Seizure type(s) and epilepsy syndrome, aetiology and co-morbidity to be determined
- Initiation of appropriate treatment to be recommended by a specialist
- Treatment individualised according to seizure type, epilepsy syndrome, co-medication and co-morbidity, the individual's lifestyle and personal preferences
- The individual with epilepsy, and their family and/or carers, to participate in all decisions about care, taking into account any specific need
- Comprehensive care plans to be agreed
- Comprehensive provision of information about all aspects of condition
- Regular structured review at least once a year
- Patient to be referred back to secondary or tertiary care if:
  - Epilepsy inadequately controlled
  - Pregnancy considered or pregnant
  - Antiepileptic drug withdrawal considered
- MRI, magnetic resonance imaging; EEG, electroencephalogram.

Treatment during seizures

Convulsive seizures may look frightening but the person is not in pain, will usually have no recollection of the event afterwards and is usually not seriously injured. Emergency treatment is seldom necessary. People should, however, be made as comfortable as possible, preferably lying down (ease to the floor if sitting), cushioning the head and loosening any tight clothing or neckwear. During seizures, people should not be moved unless they are in a dangerous place, for example, in a road, by a fire or hot radiator, at the top of stairs or by the edge of water. No attempt should be made to open the person's mouth or force anything between the teeth. This usually results in damage, and broken teeth may be inhaled, causing secondary lung damage. When the seizure stops, people should be turned over into the recovery position and the airway checked for any blockage.

Partial attacks are usually less dramatic. During automatisms, people may behave in a confused fashion and should generally be left undisturbed. Gentle restraint may be necessary if the automatism leads to dangerous wandering. Attempts at firm restraint, however, may increase agitation and confusion. No drinks should be given after an attack, nor should extra antiepileptic drugs (AEDs) be administered. It is commonly felt that seizures may be life-threatening, but this is seldom the case. After a seizure, it is important to stay with the person and offer reassurance until the confused period has completely subsided and the person has recovered fully.

If a seizure persists for more than 10 min, if a series of seizures occur or if the seizure is particularly severe, then intravenous or rectal administration of 10–20 mg diazepam for adults, with lower doses being used in children, is advisable.

Status epilepticus

Initial management of status epilepticus is supportive and may include:

- positioning the person to avoid injury
- supporting respiration
- maintaining blood pressure
- correcting hypoglycaemia

Drugs used include intravenous lorazepam or diazepam. Alternative medicines include midazolam in cases where the person has not responded to first-line drugs. Alternatively, buccal midazolam has been advocated and is increasingly being used, although it is not licensed in the UK. In severe cases, phenytoin, clonazepam or phenobarbital sodium may be required.

Febrile convulsions

Convulsions associated with fever are termed febrile convulsions and may occur in the young. Brief febrile convulsions are managed conservatively with the primary aim of reducing the temperature of the child. Tepid sponging and use of paracetamol is usual. Prolonged febrile convulsions lasting 10–15 min or longer or in a child with risk factors require active management to avoid brain damage. The drug of choice is diazepam by intravenous or rectal (rectal solution) administration. Prophylactic management of febrile convulsions may be required in some children, such as those with pre-existing risk factors or a history of previous prolonged seizures.

Long-term treatment

In most cases, epilepsy can only be treated by long-term, regular drug therapy. The objective of therapy is to suppress epileptic discharges and prevent the development of epileptic seizures. In the majority of cases, full seizure control can be obtained, and in other patients drugs may reduce the frequency or severity of seizures.

Initiating treatment with an AED is a major event in the life of a person, and the diagnosis should be unequivocal. Treatment options must be considered with careful evaluation of all relevant factors, including the number and frequency of attacks, the presence of precipitating factors such as alcohol, drugs or flashing lights, and the presence of other medical conditions (Feely, 1999). Single seizures do not require treatment unless they are associated with a structural abnormality in the brain, a progressive brain disorder or there is a clearly abnormal EEG recording. If there are long intervals between seizures (over 2 years), there is a case for not starting treatment. If there are more than two attacks that are clearly associated with a precipitating factor, fever or alcohol for instance, then treatment may not be necessary.

Therapy is long-term, usually for at least 3 years and, depending on circumstances, sometimes for life. A full explanation of all the implications must be given to the person and they must be involved in all stages of the treatment plan. It is vital that the person understands the implications of treatment and agrees with the treatment goals. Empowerment of the person with epilepsy to be actively involved in the decision-making process will encourage adherence and is essential for effective clinical management. Support for people so that they understand the implications of the condition and why drug therapy is so important is crucial to ensure effective clinical management.

Health professionals have a key role in supporting people with epilepsy to ensure they are able to manage their medicines appropriately. AED treatment will fail unless the patient fully understands the importance of regular therapy and the objectives of treatment. Poor adherence is still a major factor which results in hospital admissions and poor seizure control and leads to the clinical use of multiple AEDs.

General principles of treatment

Therapy aims to control seizures using one drug, with the lowest possible dose that causes the fewest side effects possible. The established AEDs, carbamazepine, ethosuximide and sodium valproate, are still important parts of the antiepileptic armamentarium. Acetazolamide, clobazam, clonazepam, phenobarbital phenytoin and primidone are also still used. In the last two decades, new AEDs such as vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine,

levetiracetam, pregabalin, zonisamide, lacosamide and eslicarbazepine acetate have been introduced. The choice of drugs depends largely on the seizure type, and so correct diagnosis and classification are essential. Table 31.1 lists the main indications for the more commonly used AEDs, and Table 31.2 summarises the clinical use of the newer AEDs.

Initiation of therapy in newly diagnosed patients

The first-line AED most suitable for the person's seizure type should be introduced slowly, starting with a small dose. This is because too rapid an introduction may induce side effects that will lose the person's confidence. For most drugs, this gradual introduction will produce a therapeutic effect just as fast as a rapid introduction, and the person should be reassured about this.

Maintenance dosage

There is no single optimum dose of any AED that suits all patients. The required dose varies from person to person, and from drug to drug. Drugs should be introduced slowly and then increased incrementally to an initial maintenance dosage. Seizure control should then be assessed, and the dose of drug changed if necessary. For most AEDs, dosage increments are constant over a wide range. More care is, however, needed with phenytoin as the serum level–dose relationship is not linear, and small dose changes may result in considerable serum level changes. Generic prescribing for epilepsy remains controversial. Most specialists would prefer people to remain on the same brand of medication, and this is also preferred by the majority of people with epilepsy. This is obviously important in those people in whom the dosage has been carefully titrated to achieve optimal control.

Table 31.1 Antiepileptic drugs for different seizure types

Seizure type	First-line treatment	Second-line treatment
Partial seizures		
	Carbamazepine Lamotrigine Oxcarbazepine Levetiracetam	Topiramate Valproate Clobazam Zonisamide Pregabalin Phenytoin Gabapentin Lacosamide Eslicarbazepine
Generalised seizures		
Tonic clonic	Valproate sodium	Lamotrigine
Tonic	Carbamazepine	Clobazam
Clonic	Lamotrigine	Phenobarbital
Absence	Ethosuximide Sodium valproate	Clonazepam Lamotrigine
Atypical absences	Sodium valproate	
Atonic	Clonazepam Clobazam	Lamotrigine Carbamazepine Phenytoin Acetazolamide Topiramate
Myoclonic	Sodium valproate Clonazepam	Levetiracetam Acetazolamide Topiramate

Altering drug regimens

If the maximal tolerated dose of a drug does not control seizures, or if side effects develop, the first drug can be replaced with another first-line AED. To do this, the second drug should be added gradually to the first. Once a good dose of the new drug is established, the first drug should then slowly be withdrawn.

Withdrawal of drugs

AEDs should not be withdrawn abruptly. With barbiturates and benzodiazepines, in particular, rebound seizures may occur. Withdrawal of individual AEDs should be carried out in a slow stepwise fashion to avoid the precipitation of withdrawal seizures (e.g. over 2–3 months). This risk is particularly great with barbiturates, for example, phenobarbital and primidone, and benzodiazepines, for example, clobazam and clonazepam. If a drug needs to be withdrawn rapidly, for example, if there are life-threatening side effects, then diazepam or another benzodiazepine can be used to cover the withdrawal phase.

Examples of withdrawal regimens are given below.

- Carbamazepine
  100–200 mg every 2 weeks (as part of a drug change)
  100–200 mg every 4 weeks (total withdrawal)
- Phenobarbital
  15–30 mg every 2 weeks (as part of a drug change)
  15–30 mg every 4 weeks (total withdrawal)
- Phenytoin
  50 mg every 2 weeks (as part of a drug change)
  50 mg every 4 weeks (total withdrawal)
- Sodium valproate
  200–400 mg every 2 weeks (as part of a drug change)
  200–400 mg every 4 weeks (total withdrawal)
- Ethosuximide
  125–250 mg every 2 weeks (as part of a drug change)
  125–250 mg every 4 weeks (total withdrawal)

Variations in the above regimens may be used in different settings. People must be monitored closely for any change in seizure frequency. The pace of withdrawal may be slower if the person is within the higher end of the quoted dose range. The pace of withdrawal may be faster if the person is an inpatient.

When to make dose changes

Some AEDs have long half-lives and it may, therefore, take some time, normally five half-lives, before a change in dose results in a stable blood level. For example, phenobarbital has a half-life of up to 6 days and will take more than 4 weeks to

Table 31.2 Summary of newer antiepileptic agents

Antiepileptic drugs	Clinical use	Available formulation	Side effect profile
Lamotrigine	Monotherapy and adjunctive treatment of partial seizures, primary and secondary generalised tonic clonic seizure, Lennox–Gastaut syndrome	Tablets: 25, 50, 100, 200 mg Dispersible tablets: 5, 25, 100 mg	Dizziness, headache, diplopia, ataxia, nausea, somnolence, vomiting, rash. Rare: Stevens–Johnson syndrome, hematological
Vigabatrin	Adjunctive treatment of partial seizures with or without secondary generalisation, monotherapy for West's syndrome	Tablets: 500 mg Powder: 500 mg/sachet	Drowsiness, fatigue, dizziness, visual field defects nystagmus, abnormal vision, agitation, amnesia, depression, psychosis, increased weight, withdrawal seizures
Gabapentin	Adjunctive treatment of partial seizures with or without secondary generalisation, neuropathic pain	Capsules: 100, 300, 400 mg Tablets: 600, 800 mg	Somnolence, dizziness, ataxia, headache, fatigue, nystagmus, tremor, nausea, vomiting, increased weight
Tiagabine	Adjunctive treatment of partial seizures with or without secondary generalisation	Tablets: 5, 10, 15 mg	Dizziness, asthenia, nervousness, tremor, diarrhoea, depression, emotional liability, confusion, abnormal thinking, decreased weight
Topiramate	Adjunctive treatment of partial seizures with or without secondary generalisation, Lennox–Gastaut syndrome, primary generalised tonic clonic seizures	Tablets: 25, 50, 100, 200 mg Sprinkle capsules: 15, 25 mg	Dizziness, abnormal thinking, somnolence, ataxia, fatigue, confusion, impaired concentration, paresthesia, decreased weight, nephrolithiasis (1.5%)
Zonisamide	Adjunctive therapy in treatment of partial seizures with or without secondary generalisation	Capsule: 25, 50, 100 mg	Somnolence, anorexia, dizziness, headache, nausea, agitation/irritability, confusional state, depression
Lacosamide	Adjunctive for partial epilepsy with or without secondary generalisation	Tablets: 50, 100, 150, 200 mg Syrup: 15 mg/mL	Dizziness, headache, depression, diplopia nystagmus, impaired co-ordination, impaired memory, drowsiness, tremor, fatigue, pruritus

produce a stable blood level. For this reason an assessment of the effectiveness of any dose change should be undertaken several weeks after the dose change has been made and be informed by knowledge of the half-life of the drug.

Newer AEDs

The newer AEDs are generally used as second-line drugs when treatment with established first-line drugs has failed. Exceptions to this are lamotrigine, levetiracetam, topiramate and oxcarbazepine, which have indications for first-line use in the UK. Lamotrigine is considered the first-line option in women of child-bearing potential who have idiopathic generalised epilepsy because of the teratogenic profile of sodium valproate, otherwise the first-line drug for this indication. Oxcarbazepine has the same indications as carbamazepine, although the latter is probably more cost-effective.

There is no evidence that the newer AEDs are more effective than the established drugs, although it could be argued that they might be better tolerated. The chronic side effect profile of the new AEDs has not yet been fully established and this is the main reason why use should be reserved for those cases where benefit outweighs risk. Guidance has been issued that covers the use of the newer AEDs in adults (National Institute for Health and Clinical Excellence, 2004b):

- Newer drugs, for example, lamotrigine, oxcarbazepine and topiramate, suitable for the type of epilepsy to be treated can be used in patients where older drugs, for example, sodium valproate or carbamazepine, do not provide effective clinical control or cause untolerable side effects.
- Gabapentin, levetiracetam, tiagabine and vigabatrin are generally used in combination with another drug.
- Newer drugs can be used where older drugs are unsuitable for the person, for example, liver disease, or where unwanted effects cannot be tolerated.
- The aim should be to treat people with just one AED where possible.

The guidance for adults was followed up by advice for use of the newer AEDs in children (National Institute for Health

and Clinical Excellence, 2004c). This advice reflected that issued for adults and included:

- Lamotrigine, oxcarbazepine or topiramate can be given to children as sole treatment for epilepsy.
- Gabapentin, tiagabine and vigabatrin are generally used as combination therapy with another drug.
- Vigabatrin is suitable for first-line treatment of young children with a rare type of infantile spasm called West's syndrome.
- Newer drugs are indicated if older drugs are unsuitable, for example, in liver disease, or if patients cannot tolerate unwanted effects.
- Children should be treated with just one AED where possible.

A third set of national guidance was issued on the diagnoses and management of the epilepsies in adults and children in primary and secondary care (National Institute for Health and Clinical Excellence, 2004a). A recent report on the implementation of this guidance (National Institute for Health and Clinical Excellence, 2009) revealed:

- No major change was noticed in the rate of increase for prescriptions for newer AEDs.
- Use of the newer AEDs had increased at a faster rate than the older drugs.
- Over 70% of patients received mono-therapy for their epilepsy during the period monitored. Of these patients, 60% received an 'old' epilepsy drug. Of newly diagnosed patients, 80% received mono-therapy as their treatment.
- 68% of adults received a medication review within 12 months of being prescribed a drug for their epilepsy.

Follow-up and monitoring of treatment

It is essential to follow up patients in whom AED treatment has been started. The reason for this is essentially to monitor the efficacy and side effects of treatment, upon which drug dosage will depend, but also to encourage good adherence to the treatment. This follow-up is particularly important in the early stages of treatment, when an effective maintenance dose may not have been fully established, when the importance of regular adherence may not have been recognised by the person, and when the psychological adjustment to regular treatment may not be resolved.

Chronic epilepsy

The drug treatment of people with established epilepsy that is uncontrolled despite initial attempts is much more difficult than that of newly diagnosed patients. Prognosis is worse, drug resistance may have developed, and there may be additional neurological, psychological or social problems.

Assessment. The diagnosis of epilepsy should be reassessed before assuming seizures are intractable. A significant proportion of patients may have been incorrectly diagnosed. The aetiology of the epilepsy should also be considered, and the question of a progressive neurological condition addressed. A treatment history should be obtained and note made of previous drugs used which were helpful, unhelpful or of uncertain benefit. Serum level measurements should be obtained where appropriate and drugs not previously tried should be identified.

Choice of drug and dosage. Treatment should always be started with one AED appropriate for seizure type and suitable for the individual. Only when attempts at monotherapy fail should a combination of two AEDs be tried. In the majority of patients, there is no place for therapy with more than two drugs. The choice of drugs should be made according to seizure type and previous treatment history. Drugs that were helpful in the past or found to be of uncertain benefit, or which have not been used before, should be tried if appropriate to seizure type. The use of sedative AEDs should be minimised where possible.

Intractable epilepsy. It is important to realise that there are limits to AED treatment and that in some people, albeit a small group, seizure control is not possible with the drugs currently available. In such cases, the goal of drug treatment changes, and the objectives are to reduce medication to minimise toxicity while providing partial control. The sedative drugs, for example, barbiturates or benzodiazepines, should be used only where absolutely necessary. In these persons, surgical treatment or the use of experimental antiepileptic agents may be considered. However, only a relatively small number of people with partial epilepsy are suitable for curative surgical treatment.

Stopping treatment

Withdrawing therapy should be considered in people who have been seizure free for a considerable period of time. In no individual case, however, can the safety of drug withdrawal be guaranteed, and the risk of relapse on withdrawal of medication in a person who has been seizure free for more than 2 years is about 40%. The longer the person has been free of seizures, the lower the risk of seizure recurrence when drugs are withdrawn. If a person has a learning disability, partial seizures or symptomatic epilepsy, neurological signs or other evidence of cerebral damage, this risk is much higher and in such cases it may be best to continue drug treatment indefinitely. Drug withdrawal should be carried out only very slowly in staged decrements, and only one drug at a time should be withdrawn.

The risks of drug withdrawal should be clearly explained to the person, and the possible medical and social implications taken into account. There may be serious social or domestic consequences should seizures recur, and the attacks may be subsequently difficult to control, even if the original AED regimen is re-established. In the final analysis, the decision to withdraw therapy is an individual one, and the person should be made aware of the risks and benefits of withdrawal.

Monitoring antiepileptic therapy

Therapeutic drug monitoring (TDM) involves the measurement of serum drug levels and their pharmacokinetic interpretation. It is an integral component in the management of

people taking phenytoin and carbamazepine but is less useful in people receiving other AEDs. Indeed, TDM has a very limited use for new AEDs except in people who are acutely unwell, pregnant or elderly. It is also very useful to document AED side effects and in managing drug interactions. Adherence may also be a problem in these patients and hence TDM may be useful to establish adherence with the treatment.

TDM is indicated:

- at the onset of therapy
- if seizure control is poor or sudden changes in seizure control occur
- if toxicity is suspected
- if poor or non-adherence is suspected
- to monitor the time-scale of drug interactions
- when changing AED therapy or making changes to other aspects of a person's drug regimen that may interact with the AED.

The frequency of undertaking TDM varies. Stabilised patients may require their serum levels to be checked only once or twice a year. TDM may be used more often in some people, for one or more of the above indications. A number of the newer AEDs do not require routine TDM. However, since most are used as adjuvant therapy, it is useful to establish baseline levels of existing drugs before the new agent is introduced. Clinical effects should be monitored and TDM, where appropriate, carried out at 6–12 month intervals.

Drug development and action

The older, more established AEDs were developed in animal models in which the potential drugs were assessed in terms of their ability to raise seizure threshold or prevent spread of seizure discharge. The animals involved in these tests would not have epilepsy but would have seizures induced by, for instance, maximal electroshock or subcutaneous pentylenetetrazole. As a consequence the relevance of these models to epilepsy can be questioned.

Established AEDs such as phenytoin, phenobarbital, sodium valproate, carbamazepine, ethosuximide, clonazepam and diazepam are effective but have poor side effect profiles, are involved in many interactions and have complex pharmacokinetics. Over the past 10–15 years, there has been renewed interest in the development of new AEDs, based on a better understanding of excitatory and inhibitory pathways in the brain. The main mechanisms of current drugs are thought to involve enhancement of the inhibitory GABA-ergic system, for example, benzodiazepines, barbiturates, tiagabine, vigabatrin or use-dependent blockers of sodium channels, for example, carbamazepine, oxcarbazepine, lamotrigine and phenytoin (Fig. 31.1).

New drugs include lamotrigine, pregabalin, levetiracetam, topiramate, felbamate, lacosamide, oxcarbazepine, eslicarbazepine and zonisamide. Unlike most of the older agents, vigabatrin, lamotrigine, levetiracetam, lacosamide, gabapentin, pregabalin and zonisamide are devoid of clinically significant enzyme-inhibiting or enzyme-inducing properties. Oral contraceptives may increase the metabolism of lamotrigine and topiramate, and oxcarbazepine may induce cytochrome P450 CYP3A4 which is responsible for the metabolism of oral contraceptives (Sabers and Gram, 2000).

AED profiles

The maintenance doses for the more widely used AEDs are given in Table 31.3, while their pharmacokinetic profile is presented in Table 31.4. Drug interactions are summarised in Table 31.5, and common side effects in Table 31.6.

Acetazolamide

Acetazolamide is occasionally used as an AED. It can be prescribed as a second-line drug for most types of seizures, but particularly for partial seizures, absence seizures and myoclonic seizures. Its intermittent use in catamenial seizures has also been suggested. Acetazolamide has only limited use as long-term therapy because of the development of tolerance in the majority of patients. Side effects include skin rashes, weight loss, paraesthesia, drowsiness and depression. Routine TDM is not available for this drug.

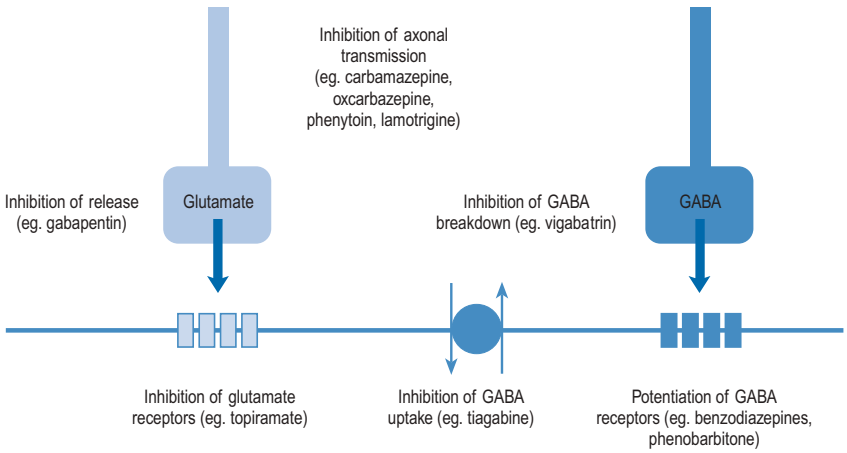

Fig. 31.1 Action of antiepileptic drugs (from Duncan et al., 2006).

Table 31.3 Commonly used starting and maintenance doses of antiepileptic drugs for adults

Antiepileptic drug	Starting dose (mg)	Average maintenance	Doses/day (total mg/day)
Acetazolamide	250	500–1500	2
Carbamazepine	100	600–2400	2–4 (retard 2)
Clobazam	10	10–30	1–2
Clonazepam	0.5	0.5–3	1–2
Ethosuximide	250	500–1500	1–2
Gabapentin	300	900–1200	3
Lacosamide	50	200–400	2
Lamotrigine	50[a]	100–500[a]	2
Levetiracetam	1000	2000–3000	2
Oxcarbazepine	300	900–1800	2–3
Phenobarbital	60	60–180	1
Phenytoin	200–300	200–400	1–2
Sodium valproate	500	2000–2500	1–2
Tiagabine	5[b]	30–45	3
Vigabatrin	500	2000–4000	1–2
Zonisamide	50	300–500 or 200–300[c]	2

[a]Reduce by 50% if on sodium valproate.
[b]If taking enzyme inducer.
[c]If taking enzyme inducer or have impaired renal or liver function.

Carbamazepine

Carbamazepine is a drug of first choice in tonic clonic and partial seizures, and may be of benefit in all other seizure types except generalised absence seizures and myoclonic seizures. Tolerance to its beneficial effect does not usually develop. Adverse events may occur in up to a third of patients treated with carbamazepine but only about 5% of these events will require drug withdrawal, usually due to skin rash, gastro-intestinal disturbances or hyponatraemia. Dose-related adverse reactions including ataxia, dizziness, blurred vision and diplopia are common. Serious adverse events including hepatic failure and bone marrow depression are extremely uncommon.

Carbamazepine exhibits autoinduction, that is, induces its own metabolism as well as inducing the metabolism of other drugs. It should, therefore, be introduced at low dosage and this should be steadily increased over a period of a month. The target serum concentration therapeutic range is 4–12 µcg/mL. In addition, a number of clinically important pharmacokinetic interactions may occur, and caution should be exercised when co-medication is instituted (see Table 31.5). For patients requiring higher doses, the slow-release preparation of carbamazepine has distinct advantages, allowing twice-daily ingestion and avoiding high peak serum concentrations. A 'chewtab' formulation is also available and pharmacokinetic studies have shown that it performs well even if inadvertently swallowed whole. Carbamazepine retard offers paediatric patients in particular a dosage form that reduces fluctuations in the peak to trough serum levels and hence allows a twice-daily regimen, which can assist compliance.

Clobazam

Clobazam is a 1,5-benzodiazepine that is said to be less sedative than 1,4-benzodiazepine drugs such as clonazepam and diazepam. Although the development of tolerance is common, clobazam is used as an adjunctive therapy for patients

Table 31.4 Pharmacokinetic data of antiepileptic drugs

	Absorption			Protein binding	Elimination		
Drug	*F* (%)	T_{peak} (h)	V_d (L/kg)	(% bound)	$T_{½}$ (h)	Renal excretion (%)	Active metabolite
Carbamazepine	75–85	1–5 (chronic dose)	0.8–1.6	70–78	24–45 (single), 8–24 (chronic)	<1	Yes
Diazepam	90	1–2	1–2	96	20–95	2	Yes
Clonazepam	80–90	1–2	2.1–4.3	80–90	19–40	2	–
Gabapentin	51–59	2–3	57.7	0	5–7	100	No
Lamotrigine	100	2–3	0.92–1.22	55	24–35 (induces its own metabolism)	<10	No
Ethosuximide	90–95	3–7	0.6–0.9	0	20–60	10–20	No
Phenobarbital	95–100	1–3	0.6	40–50	50–144	20–40	No

Table 31.4 Pharmacokinetic data of antiepileptic drugs—cont'd

Drug	Absorption			Protein binding (% bound)	Elimination		
	F (%)	T_{peak} (h)	V_d (L/kg)		$T_{½}$ (h)	Renal excretion (%)	Active metabolite
Phenytoin	85–95	4–7	0.5–0.7	90–95	9–40 (non-linear kinetics)	<5	No
Primidone	90–100	1–3	0.4–1.1	20–30	3–19	40	Yes
Sodium valproate	100	0.5–1.0	0.1–0.5	88–92	7–17	<5	No
Vigabatrin	60–80	2	0.6–1.0	0	5–7	100	No
Zonisamide	100	2–4	1.1–1.7	40	52–69	30	Yes

F, bioavailability; T_{peak}, time to peak; V_d, volume of distribution.

Table 31.5 Examples of drug interactions involving antiepileptic drugs

Drug affected	Effect on serum level	Drug implicated	Possible mechanism
Carbamazepine	Increase	Valproate sodium Cimetidine Dextropropoxyphene Erythromycin Isoniazid Troleandomycin Danazol	Enzyme inhibition
	Decrease	Phenytoin, phenobarbital	Enzyme induction
Ethosuximide	Increase	Valproate sodium	Enzyme inhibition
	Decrease	Carbamazepine	Enzyme induction
Lamotrigine	Increase	Valproate sodium	Enzyme inhibition
	Decrease	Phenytoin, carbamazepine	Enzyme induction
Phenobarbital	Increase	Valproate sodium	Enzyme inhibition
	Decrease	Rifampicin	Enzyme induction
Phenytoin	Increase	Valproate sodium Chloramphenicol Isoniazid Disulfiram Fluconazole Flu vaccine	Enzyme inhibition
		Amiodarone Fluoxetine	Mechanism unclear
	Decrease	Phenobarbital Rifampicin Carbamazepine	Enzyme induction
		Furosemide Acetazolamide	Decreased responsiveness of renal tubules. Increased osteomalacia
Sodium valproate	Increase	Salicylates	Displacement from protein binding sites and possible enzyme inhibition
Topiramate	Decrease	Phenytoin, carbamazepine	Enzyme induction
	Decrease	Potential enzyme inducers	Enzyme induction
Zonisamide	Decrease	Carbamazepine, phenytoin, phenobarbital and primidone	Enzyme induction

Table 31.6 Side effect profile of antiepileptic drugs

Drug	Dose related (predictable)	Non-dose related (idiosyncratic)
Carbamazepine	Diplopia, drowsiness, headache, nausea, orofacial dyskinesia, arrhythmias	Photosensitivity, Stevens–Johnson syndrome, agranulocytosis, aplastic anaemia, hepatotoxicity
Clonazepam	Fatigue, drowsiness, ataxia	Rash, thrombocytopenia
Ethosuximide	Nausea, vomiting, drowsiness, headache, lethargy	Rash, erythema multiforme, Stevens–Johnson syndrome
Gabapentin	Drowsiness, diplopia, ataxia, headache	Not reported
Lacosamide	Nausea, vomiting, dizziness, headache, drowsiness, depression, diplopia (double vision), impaired memory, impaired coordination, tremor, fatigue (tiredness), asthenia (muscle weakness), pruritus (itching).	Not reported
Lamotrigine	Headaches, drowsiness, diplopia, ataxia	Liver failure, disseminated intravascular coagulation
Levetiracetam	Dizziness, drowsiness, irritability, behavioural problems, insomnia, ataxia (unsteadiness), tremor, headache, nausea	Not reported
Oxcarbazepine	Diplopia (double vision), ataxia (unsteadiness), headache, nausea, confusion and vomiting	Skin rash
Phenobarbital	Fatigue, listlessness, depression, poor memory, impotence	Maculopapular rash, exfoliation, hepatotoxicity hypocalcaemia, osteomalacia, folate deficiency
Phenytoin	Ataxia, nystagmus, drowsiness, gingival hyperplasia, hirsutism, diplopia, asterixis, orofacial dyskinesia, folate deficiency	Blood dyscrasias, rash, Dupuytren's contracture, hepatotoxicity
Sodium valproate	Dyspepsia, nausea, vomiting, hair loss, anorexia, drowsiness	Acute pancreatitis, aplastic anaemia, thrombocytopenia, hepatotoxicity
Tigabine		Dizziness, fatigue (tiredness), nervousness, tremor, concentration difficulties, depression of mood, agitation
Topiramate	Dizziness, drowsiness, nervousness, fatigue, weight loss	Not reported
Vigabatrin	Drowsiness, dizziness, weight gain	Behavioural disturbances, severe psychosis
Zonisamide	Ataxia, dizziness, somnolence, anorexia	Hypersensitivity, weight decrease, rash, gastro-intestinal problems

with partial or generalised seizures who have proved unresponsive to other antiepileptic medication. Its intermittent use in catamenial epilepsy has also been suggested. Clobazam may produce less sedation than other benzodiazepines, but otherwise its adverse effects are similar, including dizziness, behavioural disturbances and dry mouth. Withdrawal may be difficult.

Clonazepam

Clonazepam, a 1,4-benzodiazepine, is a second-line drug for generalised tonic clonic seizures, absences, myoclonic seizures and as adjunctive therapy for partial seizures but, as with clobazam, effectiveness often wears off with time as tolerance develops. Parenteral clonazepam is useful in status epilepticus. It has an adverse effect profile similar to that of clobazam, but may be more sedating.

Diazepam

Diazepam is used mainly in the treatment of status epilepticus, intravenously or in the acute management of febrile convulsions as a rectal solution. Absorption from suppositories or following intramuscular injection is slow and erratic. The rectal solution may also be useful in status epilepticus if it is not possible to give the drug intravenously.

Eslicarbazepine acetate

Eslicarbazepine acetate is a drug which is similar to oxcarbazepine and which is licensed as a second-line treatment for partial seizures. As with oxcarbazepine, its mode of action is thought to be by interacting with voltage-gated sodium channels. Currently it is only available in a 800-mg tablet. It has a long half-life and can be used once per day. Its pharmacokinetics profile and side effects are also similar to those of oxcarbazepine.

Ethosuximide

Ethosuximide is a drug of first choice for generalised absence seizures, and has no useful effect against any other seizure type. Tolerance does not seem to be a problem. The most commonly encountered adverse effects are gastro-intestinal symptoms, which occur frequently at the beginning of therapy. Behaviour disorders, anorexia, fatigue, sleep disturbances and headaches may also occur. The therapeutic range commonly quoted is 40–100 μcg/mL, but some patients may require higher concentrations, sometimes as high as 150 μcg/mL. The absorption of ethosuximide is complete, the bioavailability of the syrup and capsule formulations being equivalent. An increase in daily dose may lead to disproportionately higher increases in average serum concentrations; therefore, careful monitoring is indicated at high doses.

Felbamate

Felbamate may be used as a drug of last resort in people with intractable epilepsy. It is licensed in the USA and most countries of the European Union but not in the UK. Its mechanism of action is unknown. The usual dose is between 1200 and 3600 mg/day. Felbamate exhibits significant pharmacokinetic interactions with phenytoin, carbamazepine and valproic acid. Side effects of felbamate include diplopia, insomnia, dizziness, headache, ataxia, anorexia, nausea and vomiting. A major limiting problem is its potential to cause aplastic anaemia and liver failure, affecting up to 1 in 4000 patients exposed to the drug. It, therefore, seems prudent to limit use to specialist centres and severe intractable cases.

Gabapentin

Gabapentin is occasionally used as a second-line treatment of partial seizures. Although initially developed as an AED, its main use currently is for the treatment of neuropathic pain. In view of its pharmacokinetic profile, a three times daily dosage must be used. To date, no clinically significant interactions with other AEDs, or other drugs, have been reported. The most frequently reported side effects are drowsiness, dizziness, diplopia, ataxia and headache.

Lacosamide

Lacosamide, a functionalised amino acid, is a second-line drug for partial epilepsy in patients over the age of 16 years. Its putative mode of action is not shared with any other currently available AEDs. It is said to enhance the slow inactivation of sodium channels and to modulate collapsing response mediator protein-2 (CRMP-2), although it is not known how this contributes to its antiepileptic action. The recommended doses are between 200 and 400 mg/day divided in two doses. It should be started at 50–100 mg/day and increased by 50 mg/day every 1 or 2 weeks. No drug–drug interactions are known. Its commonest side effects are dizziness, headaches, nausea and diplopia. No idiosyncratic side effects have yet been associated with this drug. The drug should be used with caution in patients with a history of cardiac conduction problems as it is know to increase the PR interval in some patients.

Lamotrigine

Lamotrigine may be used as a first-line drug in patients with partial seizures, with or without secondary generalisation, and in tonic clonic convulsions. The recommended starting dose is 50 mg when used as monotherapy, and 25 mg when used as an add-on therapy; the latter dose is given on alternate days in patients receiving concomitant sodium valproate and daily in patients receiving other AEDs, with a maximum recommended dose of 400 mg/day in two divided doses. It should be slowly titrated as too rapid a titration may be associated with an increased incidence of skin rash. Lamotrigine does not seem to interact with other concomitantly administered AEDs. However, hepatic enzyme inducers increase the metabolism of lamotrigine, reducing its half-life. Therefore, higher doses of lamotrigine need to be administered if it is used in conjunction with enzyme inducers such as phenytoin and carbamazepine. Inhibitors of hepatic enzymes such as sodium valproate block the metabolism of lamotrigine and reduced doses of lamotrigine need to be used if both drugs are given in combination.

Headaches, drowsiness, ataxia and diplopia, usually transient, are the most commonly reported acute adverse effects, particularly during dose escalation. A skin rash is the commonest idiosyncratic side effect of lamotrigine and affects up to 3% of patients.

Levetiracetam

Levetiracetam is indicated for the treatment of refractory partial epilepsy. Placebo-controlled trials in refractory partial epilepsy have shown a 50% seizure reduction in up to 40% of patients. In these trials, 8% of participants became seizure free compared to none on placebo. The usual dose is between 1500 and 3000 mg a day. It is usually started at 500 mg a day and the dose titrated upwards in incremental steps of 500 mg every 1 or 2 weeks. It is well tolerated and the most frequent central nervous system adverse events are dizziness, irritability, asthenia and somnolence. No idiosyncratic adverse events have yet been reported.

Oxcarbazepine

Oxcarbazepine is an analogue of carbamazepine. It is an inactive pro-drug that is converted in the liver to the active 10-hydroxy metabolite and bypasses the 10,11-epoxide, the

primary metabolite of carbamazepine. The usual dose is between 900 and 2400 mg/day. The spectrum of efficacy and side effects is broadly comparable to carbamazepine. The principal advantage of oxcarbazepine over carbamazepine is the lack of induction of hepatic enzymes, with the consequence that there is no auto-induction of the metabolism of the drug and fewer pharmacokinetic interactions. In addition, two-thirds of patients who are allergic to carbamazepine can tolerate oxcarbazepine.

Phenobarbital

Phenobarbital, a barbiturate, may be used for the treatment of tonic clonic, tonic and partial seizures. It may also be used in other seizure types. Its antiepileptic efficacy is similar to that of phenytoin or carbamazepine. Adverse effects on cognitive function, the propensity to produce tolerance and the risk of serious seizure exacerbation on withdrawal make it an unattractive option, and it should be used only as a last resort. In addition to cognitive effects, barbiturates may cause skin rashes, ataxia, folate deficiency, osteomalacia, behavioural disturbances (particularly in children) and an increased risk of connective tissue disorders such as Dupuytren's contracture and frozen shoulder. Phenobarbital is a potent enzyme inducer and is implicated in several clinically important drug interactions (see Table 31.5).

Phenytoin

In current practice, phenytoin is now a second-line drug for partial seizures, tonic clonic seizures as well atonic seizures and atypical absences. It is not effective in typical generalised absences and myoclonic seizures. Tolerance to its antiepileptic action does not usually occur. Phenytoin has non-linear kinetics and a low therapeutic index, and in some patients frequent drug serum level measurements may be necessary. Drug interactions (see Table 31.5) are common as phenytoin metabolism is very susceptible to inhibition by some drugs, while it may enhance the metabolism of others. Caution should be exercised when other medication is introduced or withdrawn.

Adverse events may occur in up to a half of patients treated with phenytoin, but only about 10% will necessitate drug withdrawal, most commonly due to skin rash. Dose-related adverse reactions including nystagmus, ataxia and lethargy are common. Cosmetic effects such as gum hypertrophy, hirsutism and acne are well-recognised adverse effects, and should be taken into account when prescribing for children and young women. Chronic adverse effects include folate deficiency, osteomalacia, Dupuytren's contractures and cerebellar atrophy. Serious idiosyncratic adverse events, including hepatic failure and bone marrow depression, are extremely uncommon.

Pregabalin

This drug has been licensed for the adjunctive treatment of refractory partial epilepsy. It is closely related to gabapentin and a structural analogue of the neurotransmitter GABA but does not seem to affect transmitter response. It modulates calcium channels by binding to a subunit of Ca^{2+} and this action is thought to be the basis of its antiepileptic mechanism. The recommended doses for pregabalin are between 150 and 600 mg divided into two doses, although some people may respond to doses outside this range. Pregabalin would normally be started at 50 or 75 mg twice daily and increased in incremental steps of 50 mg every 2 weeks up to 600 mg according to clinical need. Pregabalin is available in 25, 50, 75, 100, 150, 200 and 300 mg tablets.

Overall, pregabalin is well tolerated and so far no idiosyncratic side effects have been described. Dizziness, drowsiness, ataxia, tremor and diplopia are the most common side effects. Weight gain, particularly with higher doses, seems to be a chronic side effect of this medication. No pharmacokinetic interactions have yet been identified. In addition to its use in epilepsy, pregabalin has also been indicated for neuropathic pain and there are studies to suggest that it might be useful in generalised anxiety disorders.

Primidone

Primidone is principally metabolised to phenobarbital *in vivo* and has similar effects but a more severe side effect profile than phenobarbital. There is nothing to recommend primidone as an AED over phenobarbital.

Rufinamide

Rufinamide is licensed as an orphan drug for the adjunctive treatment of seizures in Lennox-Gastaut syndrome. It is a triazole derivative and is structurally unrelated to any other AED. Its mode of action is unknown. A serious hypersensitivity syndrome that may include rash, fever, lymphadenopathy, hepatic dysfunction, haematuria and multi-organ dysfunction has been reported upon initiation of therapy. Individuals should be warned to seek immediate medical assistance if signs or symptoms of hypersensitivity develop.

Sodium valproate

Sodium valproate is a drug of first choice for the treatment of generalised absence seizures, myoclonic seizures and generalised tonic clonic seizures, especially if these occur as part of the syndrome of primary generalised epilepsy. Tolerance to its anti-epileptic action does not usually occur. Drug interactions with other AEDs may be problematic. Phenobarbital levels increase following co-medication with valproate, and a combination of these two drugs may result in severe sedation. Sodium valproate may also inhibit the metabolism of lamotrigine, phenytoin and carbamazepine. Enzyme-inducing drugs enhance the metabolism of sodium valproate, so caution should be exercised when other AEDs are introduced or withdrawn.

Up to a third of patients may experience adverse effects, but fewer than 5% will require the drug to be stopped. Adverse effects include anorexia, nausea, diarrhoea, weight gain, alopecia, skin rash and thrombocytopenia. Confusion, stupor,

tremor and hyper-ammonaemia are usually dose related. Serious adverse events, including fatal pancreatic and hepatic failure, are extremely uncommon. In children under 2 years, on other AEDs and with pre-existing neurological deficit, the risk of this is 1/500. In adults on valproate monotherapy, the risk is 1/37,000.

The usual therapeutic range quoted is 50–100 µcg/mL, although because of the lack of a good correlation between total valproate concentrations and effect, serum level monitoring of the drug has limited use. TDM should only be performed in cases of suspected toxicity, deterioration in seizure control, to check adherence or to monitor drug interactions. Routine monitoring of this drug is not necessary. Sodium valproate is more teratogenic than other commonly used AEDs and should be used cautiously in women of child-bearing age.

Stiripentol

Stiripentol is licensed as an orphan drug for severe myoclonic epilepsy of infancy (SMEI) when used in conjunction with sodium valproate and clobazam. It is an aromatic alcohol and is unrelated to any other AED. Its mode of action is unknown.

Tiagabine

Tiagabine is a drug with mild efficacy in seizure control. It is used as a second-line drug in partial seizures with or without secondary generalisation. The usual dose is between 30 and 45 mg a day, and it is normally started at 10 mg/day in two divided doses, with incremental steps of 5 mg every 2 weeks. The most common adverse events are on the central nervous system and consist of sedation, tremor, headache, mental slowing, tiredness and dizziness. Confusion, irritability and depression may occur. Increases in seizure frequency and episodes of non-convulsive status have also been reported.

So far, no life-threatening idiosyncratic reactions have been reported. Use in pregnancy is not recommended, although no teratogenicity has been reported in humans.

Topiramate

Topiramate is chemically unrelated to other AEDs and is used as a second-line drug for patients with partial seizures. Usual doses are between 200 and 600 mg/day. It has to be titrated slowly, and the recommended starting dose is 25 mg once daily, titrating upwards in 25 mg/day increments every 2 weeks up to 200 mg/day in two divided doses. After that the dose should be increased by 50 mg every 2 weeks until seizure control is achieved or side effects develop. It has no clinically significant interactions with other AEDs, although hepatic enzyme inducers accelerate its metabolism and topiramate doses need to be adjusted downwards if patients are coming off carbamazepine or phenytoin.

Side effects of topiramate include dizziness, drowsiness, nervousness, impaired concentration, paraesthesias, nephrolithiasis and fatigue. Patients starting topiramate should increase their fluid intake to reduce the risk of kidney stones. Weight loss is seen in up to 30% of patients receiving topiramate.

Vigabatrin

Vigabatrin is an inhibitor of GABA transaminase but because of a poor safety profile, it is a last resort drug for partial seizures. Vigabatrin may also be useful in West's syndrome, particularly if associated with tuberous sclerosis. Vigabatrin does not interact with other drugs apart from decreasing phenytoin levels, probably by blocking its absorption. The most common adverse events associated with vigabatrin are behavioural disturbances, ranging from agitation and confusion to frank psychosis and visual field defects. Other known adverse effects include drowsiness, headaches, ataxia, weight gain, depression and tremor. Careful monitoring for side effects, particularly ophthalmological, on initiation of therapy is essential. Routine TDM is not available for this drug.

Zonisamide

Zonisamide, a sulphonamide analogue which inhibits carbonic anhydrase, is a potent blocker of the spread of epileptic discharges. This effect is believed to be mediated through action at voltage-sensitive sodium channels.

It is used as a second-line drug for patients with partial seizures with or without secondary generalisation. Anecdotal reports of its efficacy in other seizure types, particularly myoclonic seizures, need to be formally tested. Recommended doses are between 200 and 500 mg/day, although some patients may derive benefit from doses outside this range. The recommended starting dose for most patients is 100 mg once daily, titrating upwards every 2 weeks in 100 mg/day increments until seizure control is achieved or side effects develop. Its long elimination half-life allows once-daily dosing.

Zonisamide does not affect levels of carbamazepine, barbiturates or valproate, but may increase the serum concentration of phenytoin by about 10–15%. Zonisamide metabolism is, however, induced by carbamazepine, barbiturates and phenytoin and higher zonisamide doses may be necessary during co-administration with these AEDs.

Side effects of zonisamide include dizziness, drowsiness, headaches, hyporexia, nausea and vomiting, weight loss, skin rashes, irritability, impaired concentration and fatigue. These are mostly transient and seem to be related to the dose and rate of titration. Nephrolithiasis has also been reported, particularly in caucasians. It is not recommended for women of child-bearing age as there are issues about its teratogenic potential (Table 31.7).

Evidence for clinical use of newer drugs

The evidence for the efficacy, tolerability, and safety of seven new AEDs (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide) in the treatment

Table 31.7 Common therapeutic problems in epilepsy

Problem	Comment
Hepatic enzyme induction	Enzyme induction occurs with carbamazepine, phenytoin, phenobarbital, primidone and topiramate Interactions occur with a large number of drugs including oral contraceptives
Use of progesterone-only contraceptives with enzyme-inducing antiepileptic drug	Best avoided. If no acceptable alternative, patient should take at least double usual dose of progesterone-only pill
Use of combined oral contraceptive with enzyme-inducing antiepileptic drug	Preparations containing 50 µcg of oestrogen should be used
Continuation of antiepileptic drug during pregnancy	Ideally review before attempting pregnancy to determine if reducing or discontinuing treatment is possible
Use of phenytoin as monotherapy	Less frequently considered first-line monotherapy due to poor side effect profile, narrow therapeutic index and saturation pharmacokinetics
Prescribing of branded antiepileptic drugs	Debate continues about whether significant differences exist between generic and branded antiepileptic drugs

of children and adults with refractory partial and generalised epilepsies was assessed by French et al. (2004). All drugs demonstrated efficacy as add-on therapy in patients with refractory partial epilepsy. The relative efficacy of the various agents could not, however, be determined due to the differing populations and dose ranges employed in the various studies. The analysis did, however, show that for all drugs, efficacy and side effects increased with increasing dose. A slower titration of dosage improved tolerability and hence the guidance remains to start with a low dose and increase slowly until side effects occur. For efficacy it appears useful to push to maximal tolerated dose.

Wilby et al. (2005) evaluated the clinical effectiveness, tolerability and cost-effectiveness of gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin for epilepsy in adults. They included randomised controlled trials (RCTs) and systematic reviews for the newer AEDs when used in the treatment of adults with newly diagnosed or refractory epilepsy and relevant comparator studies which employed older AEDs, other newer AEDs and placebo. The overall findings revealed the following:

- Minimal good-quality evidence exists to support the use of newer AEDs as part of monotherapy or adjunctive therapy over older AEDs, or to support the use of one new AED in preference to another.
- Data relating to clinical effectiveness, safety and tolerability failed to demonstrate consistent and statistically significant differences between the newer and older drugs. The exception being comparisons between newer adjunctive AEDs and placebo, where a significant difference favoured use of the newer AEDs.
- Newer AEDs used as monotherapy may be cost-effective for the treatment of patients who have experienced adverse events with older AEDs, who have failed to respond to the older drugs, or where such drugs are contraindicated.
- An integrated economic analysis suggested that newer AEDs used as adjunctive therapy were cost-effective when compared with continuing current treatment alone.

Case studies

Case 31.1

JB is a 31-year-old woman with a history of early morning myoclonic jerks starting at the age of 16. When she was 18 years old she had her first generalised tonic clonic convulsive seizure. A diagnosis of juvenile myoclonic epilepsy was made and she was started on sodium valproate 1200 mg a day which controlled her seizures.

At the age of 21 the patient had a healthy baby and experienced no problems with epilepsy control. Aged 22, she had her second pregnancy and delivered a healthy baby girl. Three weeks after delivery early morning myoclonic seizures returned. The dose of sodium valproate was increased to 1500 mg to control jerks. However, 6 months later she experienced a recurrence of her convulsive attacks with no clear precipitating factor. Sodium valproate was increased to 2000 mg a day. Early morning myoclonic seizures crept back and she had further convulsive seizures. Lamotrigine was started at 200 mg daily. She has been completely seizure-free for the last 2 years and is now driving again.

JB wants to discuss her medication with you and would like to stop treatment. She has no plans to increase her family.

Question

What advice would you give JB?

Answers

JB should be advised to continue on medication. She has juvenile myoclonic epilepsy, which tends to recur when medication is withdrawn. The patient has no intention of having further children and, therefore, pregnancy need not be a consideration in the choice of her continued drug therapy. She is generally well and hence it would be sensible to advise her to continue with the

present regimen, as sodium valproate and lamotrigine have a synergistic effect in juvenile myoclonic epilepsy. If, however, she wants to reduce medication, then a slow decrease of valproate with optimisation of treatment with lamotrigine should be considered.

Case 31.2

Mr OB is a 44-year-old man who suffers from partial epilepsy. An MRI scan shows a choroid cyst on the right temporal lobe, bilateral hippocampal sclerosis and cerebral atrophy. Seizures take the form of complex partial attacks and at night secondary generalisations occur. He has had trials of treatment with every single drug in the book and almost every combination.

Six months ago, he was taking 225 mg of topiramate (could not tolerate more), 400 mg of phenytoin and 10 mg of clobazam each day. At this point levetiracetam was added and titrated up to 2000 mg a day. This led to a significant improvement in seizure control. Indeed, seizures have almost completely been abolished and he is only having occasional nocturnal events. He is, however, complaining of drowsiness and periods of unsteadiness.

Question

What treatment is appropriate for this patient?

Answer

Mr OB needs his drug regimen optimising. The decision should be made to reduce either the dose of topiramate or that of phenytoin. The consensus view is that phenytoin should probably be reduced first. However, this patient had a bad experience in the past when an attempt was made to discontinue phenytoin, at which time he had a significant increase in seizure frequency. It would, therefore, be more appropriate to discontinue topiramate in Mr OB. This was done and his improvement has been maintained.

Case 31.3

Ms GD is a 28-year-old woman with a history of early morning myoclonic jerks since age 14 years. At 16 years of age she presented with her first generalised tonic clonic convulsive seizure and was referred to a hospital specialist who diagnosed juvenile myoclonic epilepsy. At that time Ms GD was started on sodium valproate 1200 mg a day and within a few weeks her seizures were totally controlled. Ms GD has since remained on the same medication and has been well controlled. However, she now wishes to start a family and is concerned about the effects of the valproate on her baby.

Question

What advice would you give Ms GD?

Answer

The available evidence indicates sodium valproate is teratogenic, with the most common malformation reported being neural tube defects. Ms GD has had no seizures for over 5 years and it must, therefore, be determined whether she still needs medication. The risk of recurrence is low since she has been fit free for well over 5 years. An important consideration is whether or not she is a driver since if she is taken off medication and has a seizure, she will be unable to hold a licence. The other issue is the effect of pregnancy on her seizure threshold as there is some evidence that up to 20% of women may experience an increase in fits during pregnancy. The options that need to be considered include change of medication. The following medicines need to be reviewed: lamotrigine, topiramate and levetiracetam.

Case 31.4

TD is a 41-year-old patient who has cryptogenic partial epilepsy. He experienced his first seizure at age 14 and this was diagnosed as a secondary generalised attack, although discussing his history revealed he might have had complex partial seizures. Two years ago TD was referred for assessment but it was felt that he was not a candidate for surgery. TD was taking carbamazepine 1200 mg a day and could not tolerate higher doses. Previous trials of valproate, phenytoin, phenobarbital, vigabatrin, lamotrigine, oxcarbazepine and topiramate had demonstrated little benefit. Levetiracetam was started and increased to 2500 mg. Improvement in seizure control has been noted over the past 2 years with only two nocturnal complex partial seizures recorded. His current medication is levetiracetam 2500 mg/day and carbamazepine 1200 mg/day.

Question

What should be done next? Should TD's therapy be reduced to levetiracetam monotherapy?

Answer

There is a need to discuss with TD whether he wishes to continue with his medication. Issues of relevance include a long history of epilepsy, the diagnosis and the range of drugs previously tried. It also needs to be clear whether he wishes to drive or not. If patients have been seizure free for 2 years, it is usual to review therapy.

Case 31.5

Mr FD is a 23-year-old student who was involved in a road traffic accident and admitted to hospital with a head trauma. He was stabilised but during his admission had a seizure and was then discharged on no medication. At 3 months he attends an out-patient hospital follow-up appointment and has had no further seizures.

Question

With regard to his clinical management was this appropriate; is there a role for prophylactic anticonvulsant medication?

Answer

Mr FD requires a full neurological review. The long-term use of antiepileptics following head injury is not indicated unless the patient has a history of seizures and Mr FD has had no seizures post-discharge.

Case 31.6

RA is a 75-year-old retired teacher who lives alone. He has long-standing epilepsy and his current medication includes phenytoin 300 mg daily. RA is in general good health but suffered a recent fall and was rushed to hospital with a suspected fractured neck of femur. On admission he was stabilised and found not to have sustained a fracture. His other medication included furosemide 40 mg mane and enalapril 5 mg twice daily. Routine blood levels of the anticonvulsants revealed a toxic level of phenytoin of 40 mg/L (normal therapeutic range 10–20 mg/L).

Question

How long will it take for the toxic levels of phenytoin to fall within the therapeutic range?

Answer

Phenytoin exhibits non-linear pharmacokinetics. Usual management will involve withholding phenytoin and monitoring serum levels each day. One assumption that can be made is that if the hepatic enzymes are fully saturated with phenytoin then at maximum metabolic capacity, approximately 10 mg/L of the drug will be eliminated each day. Initially, however, the drug will redistribute into serum so for the first few days phenytoin levels will fall slowly. It is usual for the levels to take 6–7 days to fall within the therapeutic range. Therapy will then need to be reviewed. On further investigation it was revealed the patient had a severe chest infection and was prescribed ciprofloxacin. His antibiotic regimen was completed 5 days ago. He was suffering from phenytoin toxicity which may have resulted in ataxia and contributed to his fall.

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Parkinson's disease 32

D. J. Burn

Key points

- Parkinson's disease is the second most common neurodegenerative disease, affecting 1% of the population over the age of 65.
- Parkinson's disease is characterised by bradykinesia, rest tremor, rigidity and, later in the disease course, postural instability.
- Neuronal loss in the brainstem (substantia nigra) leads to a profound dopamine deficiency in the striatum. This provides the rationale for dopaminergic replacement therapies.
- Depression is common in Parkinson's disease. It is the major determinant of quality of life and is often missed. The depression of Parkinson's disease can be readily treated.
- Levodopa, coupled with a dopa-decarboxylase inhibitor, remains the most potent oral treatment for Parkinson's disease. There is debate as to whether levodopa should be deferred in biologically young patients, in an attempt to delay the onset of motor complications.
- Several other drug treatments are available for the management of Parkinson's disease. When given as adjunctive therapy to levodopa, the primary aim of these agents is to smooth out motor fluctuations.
- End-of-dose deterioration and the on–off phenomenon are motor complications synonymous with the use of levodopa, usually after a number of years. Despite advances in oral pharmacotherapy, the on–off phenomenon remains difficult to treat effectively.
- Surgical treatments of Parkinson's disease, using deep brain stimulation, are effective in highly selected cases.
- Advanced Parkinson's disease is difficult to manage, particularly dementia and neuropsychiatric problems. Reduction of dopaminergic therapy may be the best compromise. Rivastigmine may be useful for dementia associated with Parkinson's disease.

Parkinson's disease is the most common cause of Parkinsonism and is the second most common neurodegenerative disease, after Alzheimer's disease. Although descriptions of the condition appeared before the nineteenth century, it was James Parkinson's eloquent account in 1817 that fully documented the clinical features of the illness now bearing his name. The identification of dopamine deficiency in the brains of people with Parkinson's disease and the subsequent introduction of replacement therapy with levodopa represent a considerable success story in the treatment of neurodegenerative illness in general. There remain, however, a number of significant management problems in Parkinson's disease, particularly in the advanced stages of the condition.

Epidemiology

Parkinson's disease affects 1% of the population over 65 years of age, rising to 2% over the age of 80. One in 20 patients is, however, diagnosed before their 40th year. It is estimated that 110,000 people have Parkinson's disease in the UK. The condition is found worldwide, with variability in prevalence estimates most likely reflecting study methodology, rather than real differences. Most epidemiological studies have indicated a small male-to-female predominance.

Other causes of Parkinsonism include neurodegenerative conditions, multiple system atrophy and progressive supranuclear palsy. The prevalence for these conditions is approximately 5.0 per 100,000. Drug-induced Parkinsonism is a common form of so-called symptomatic Parkinsonism. It affects 10–15% of individuals exposed to dopamine receptor-blocking agents including neuroleptics and some labyrinthine sedatives.

Aetiology

Both genetic and environmental factors have been implicated as a cause of Parkinson's disease. While opinions were initially polarised, it now seems probable that in the majority of cases there is an admixture of influences, with environmental factors precipitating the onset of Parkinson's disease in a genetically susceptible individual.

Environmental factors became pre-eminent in the 1980s, when drug addicts attempting to manufacture pethidine accidently produced a toxin called MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Ingestion or inhalation of MPTP rapidly produced a severe Parkinsonian state, indistinguishable from advanced Parkinson's disease. Notably, not all individuals exposed to MPTP developed Parkinsonism, either acutely or on subsequent follow-up, suggesting inter-individual susceptibility to the toxic effects. MPTP is a relatively simple compound and is quite similar to paraquat. The more recent demonstration that chronic systemic exposure to the pesticide rotenone can reproduce the clinical and pathological features of Parkinson's disease in rats has generated considerable interest.

In a small number of patients, genetic factors are dominant. The discovery of a mutation in the gene coding for a synaptic protein called α-synuclein has provided tremendous

impetus for further research. Such mutations have been described in fewer than 10 families worldwide. Nevertheless, because α-synuclein is a major component of the pathological hallmark of Parkinson's disease, the Lewy body (see below), the challenge is to discover how a mutation in this protein in a tiny minority can relate to the formation of Lewy bodies in the vast majority. In recent years, eight genetic loci and a further four genes (*parkin, DJ-1*, *PINK1* and *LRRK-2*) have been identified (Healy et al., 2004). The intriguing thing is that the protein products of these genes are involved in a cellular system called the ubiquitin-proteasome system, which plays a crucial role in removing and recycling abnormal or damaged proteins. Current thinking is that abnormalities in the way in which the cell handles mutated or abnormal proteins may ultimately lead to its death, through increased oxidative stress and/or reduced mitochondrial energy production. The Lewy body may actually represent a defence mechanism by the cell to 'parcel up' potentially damaging proteinaceous material (Olanow et al., 2004).

More recently, cell-to-cell transfer of α-synuclein has been demonstrated *in vitro* and also in engrafted stem cell tissue. This suggests that the pathology of Parkinson's disease may be propagated between neurones and could have major implications for the spread of Lewy body pathology within the brain, as well as its treatment (Olanow and Prusiner, 2009) (Fig. 32.1).

Pathophysiology

The characteristic pathological features of Parkinson's disease are neuronal loss in pigmented brainstem nuclei, together with the presence of eosinophilic inclusion bodies, called Lewy bodies, in surviving cells. The pars compacta of the substantia nigra in the midbrain is particularly affected. Dopaminergic neurones within this nucleus project to the striatum, which is, therefore, deprived of the neurotransmitter dopamine. In Parkinson's disease, there is a loss of over 80% of nigral neurones before symptoms appear. The 'Braak hypothesis' has been proposed to account for spread of pathology within the Parkinsonian brain and suggests that α-synuclein may first accumulate in the lower brainstem and then gradually ascend rostrally to affect critical brain regions including the substantia nigra and ultimately the cerebral cortex (Braak et al., 2003).

Dopaminergic neurones are not the only cells to die within the brainstem, and a plethora of other nuclei and neurotransmitter systems are also involved. For example, cholinergic neurones within the pedunculopontine nucleus degenerate, providing potential clinicopathological correlates with postural instability, swallowing difficulty (dysphagia) and sleep disturbance (REM sleep behavioural disturbance). The involvement of this nucleus in Parkinson's disease may explain why dopaminergic therapy is relatively ineffective in treating these particular clinical problems. Within the striatum, changes occur within γ-aminobutyric acid-containing neurones, as a consequence of nigrostriatal dopaminergic deficiency and also non-physiological dopaminergic replacement. These changes are thought to play a key role in mediating the development of involuntary movements (dyskinesias) which develop after a number of years of levodopa treatment. The loss of noradrenergic and serotonergic neurones within the locus coeruleus and the raphé nucleus, respectively, may provide a pathophysiological basis for depression, which is common in Parkinson's disease.

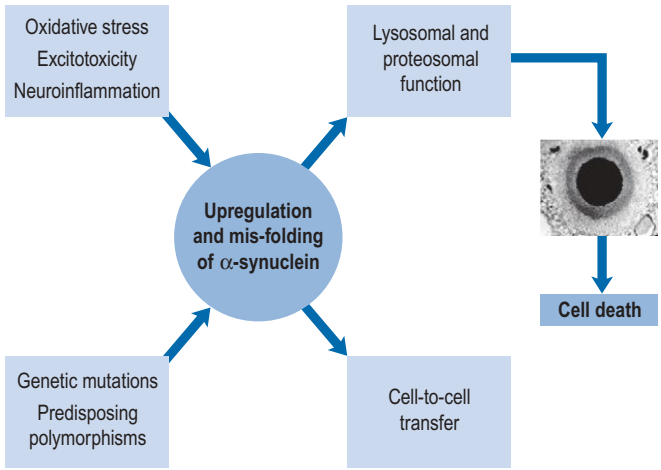

Fig. 32.1 Summary of pathophysiological processes believed to be central to Parkinson's disease.

Clinical features

Motor features

Bradykinesia is a sine qua non for Parkinsonism in general. If a person does not have slowness of movement, they cannot have either Parkinsonism or Parkinson's disease. Rest tremor, extrapyramidal rigidity (so-called lead pipe and/or cog-wheel) and postural instability comprise the remaining classic tetrad of clinical features for Parkinson's disease. Asymmetry of signs at disease onset is very common. The rest tremor is a rhythmic movement with a frequency of 4–6 Hz (cycles/s), typically noticed with the patient at rest. It is sometimes described as 'pill-rolling' in nature, from the movement of the thumb across the fingers. However, 15–20% of patients do not develop a tremor. Further, up to 60% of people with Parkinson's disease may have a dominant postural tremor, worse with the arms held outstretched, which can cause diagnostic confusion with essential tremor (see below). Postural instability is a late feature of Parkinson's disease and comprises an impairment of righting reflexes with a tendency to fall. There may be a flexed truncal posture and loss of arm swing when walking. There is reduced blink frequency and facial expression, which, together with rather reduced volume (hypophonic) and monotonous speech, may lead to significant difficulties in communication. Writing becomes small (micrographia) and barely legible.

Non-motor features

Autonomic dysfunction may occur in Parkinson's disease. The patient may drool and have greasy skin (seborrhoea). Urogenital difficulties, with erectile dysfunction in males and urinary urgency in both sexes, are commonly encountered. Frank incontinence is, however, rare. Constipation is invariable and is multifactorial in origin. Falling blood pressure on standing (postural hypotension) may contribute to falls later in the disease course. Depression affects approximately 40% of people with Parkinson's disease and is a major determinant of both carer stress and nursing home placement. It can be a very early feature, and may precede the onset, of Parkinson's disease. Recent studies have demonstrated that depression, above any other factor, is the most significant determinant of quality of life in the person with Parkinson's disease, yet it is generally underdiagnosed. The occurrence of dementia in Parkinson's disease is related predominantly to the age of the patient. Longitudinal community-based studies indicate that dementia may ultimately develop in 80% of people with Parkinson's disease. The cognitive impairment may be accompanied by hallucinations that are often visual, delusional misinterpretation, including paranoid ideation, and rapid fluctuations in attention.

Differential diagnosis

It is important to remember that, while Parkinson's disease is a common form of Parkinsonism, there are numerous other degenerative and symptomatic causes. Further, 'all that shakes is not Parkinson's disease'. Table 32.1 gives a differential diagnosis for causes of Parkinsonism. These are separated into degenerative and symptomatic categories. The list is not exhaustive and excludes, for instance, rare Parkinsonian manifestations in uncommon diseases. A detailed description of these different causes of Parkinsonism is beyond the scope of this chapter, but a few points should be highlighted. Essential tremor is not included in Table 32.1, as this common condition does not cause bradykinesia. Nevertheless, it may be very difficult to differentiate from tremor-dominant Parkinson's disease. A positive family history and good response to alcohol may provide vital clues towards the diagnosis of essential tremor, although in practice these are not always reliable.

Several clinical and clinicopathological series have confirmed our fallibility in not making a correct diagnosis of Parkinson's disease. If clinical criteria, such as those produced by the UK Parkinson's Disease Brain Bank, are not applied, then the error rate (false-negative diagnosis) may be as high as 25–30%. These criteria are listed in Box 32.1. Degenerative conditions commonly masquerading as Parkinson's disease include progressive supranuclear palsy, multiple system atrophy and Alzheimer's disease.

Box 32.1 Clinical criteria for diagnosis of Parkinson's disease

Step 1 Diagnosis of Parkinsonian syndrome
The patient has bradykinesia, plus one or more of the following:
(a) classic rest tremor
(b) muscular rigidity
(c) postural instability, without other explanation

Step 2 Exclusion criteria for Parkinson's disease
(a) history of repeated strokes
(b) history of repeated head injury
(c) history of definite encephalitis
(d) oculogyric crises
(e) dopamine receptor blocking agent exposure at onset of symptoms
(f) more than one affected relative
(g) sustained remission
(h) strictly unilateral features after 3 years
(i) supranuclear gaze palsy
(j) cerebellar signs
(k) early severe autonomic involvement
(l) early severe dementia
(m) extensor plantar
(n) cerebral tumour or hydrocephalus on CT
(o) negative response to large doses of levodopa
(p) MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease (three or more required for diagnosis of definite Parkinson's disease)
(a) unilateral onset
(b) rest tremor present
(c) progressive disorder
(d) progressive persistent asymmetry
(e) an excellent (>70%) response to levodopa
(f) a sustained (>5 years) response to levodopa
(g) severe levodopa-induced dyskinesias
(h) clinical course >10 years

CT, computed tomography.

Drug-Induced Parkinsonism

Perhaps the most important differential diagnosis to consider when a patient presents with Parkinsonism is whether their symptoms and signs may be drug induced. This is because drug-induced Parkinsonism is potentially reversible upon cessation of the offending agent. Reports linking drug-induced Parkinsonism with the neuroleptic chlorpromazine were first published in the 1950s. Since then, numerous other agents have been associated with drug-induced Parkinsonism. Many of these are widely recognised, although others are not (Box 32.2). Compound antidepressants were a problem in the past because they contained neuroleptic drugs. For example, fluphenazine was found with nortriptyline in Motival® (discontinued in the UK in 2006) and often overlooked as a potential culprit. Repeat prescription of vestibular sedatives and anti-emetics

Table 32.1 Differential diagnosis of Parkinsonism

Degenerative causes	Symptomatic causes
Parkinson's disease	Dopamine receptor blocking agents

Box 32.2 Examples of non-neuroleptic drugs associated with drug-induced Parkinsonism

Sodium valproate
Tetrabenazine
Calcium channel blockers (e.g. cinnarizine)
Amiodarone
Lithium[a]
Phenelzine[b]
Amphotericin B[c]
5-Fluorouracil[b]
Vincristine–adriamycin[b]
Pethidine[b]

[a]Lithium causes postural tremor. Reports of Parkinsonism occurring with lithium have usually been in the context of prior exposure to neuroleptics.
[b]Only single case reports of drug-induced Parkinsonism with these drugs.
[c]One case report of drug-induced Parkinsonism in a child after bone marrow transplantation and a second in association with cytosine arabinoside therapy.

such as prochlorperazine and cinnarizine are other commonly encountered causes of drug-induced Parkinsonism. The pathogenesis of drug-induced Parkinsonism is unlikely to be only due to dopamine receptor blockade. If this were the case, the incidence and severity should correlate with the drug dosage and length of exposure, and this is not clearly observed. Sodium valproate is also now recognised to cause an encephalopathy dominated by Parkinsonism and cognitive impairment which is reversible upon drug cessation. Again, there is considerable idiosyncrasy in who develops this encephalopathy when exposed to valproate.

Drug-induced Parkinsonism is more common in the elderly and in women. The clinical features can be indistinguishable from Parkinson's disease, although the signs in drug-induced Parkinsonism are more likely to be bilateral at the onset. Withdrawal of the offending agent will lead to improvement and resolution of symptoms and signs in approximately 80% of patients within 8 weeks of discontinuation. Drug-induced Parkinsonism may, however, take up to 18 months to fully resolve in some cases. Further, in other patients, the Parkinsonism may improve after stopping the drug, only to then deteriorate. In this situation, the drug may have unmasked previously latent Parkinson's disease. This contention is supported by a study which noted an increased risk of Parkinson's disease in subjects who had experienced a previous reversible episode of drug-induced Parkinsonism.

Investigations

The diagnosis of Parkinson's disease is a clinical one and should be based, preferably, upon validated criteria. In young-onset or clinically atypical Parkinson's disease, a number of investigations may be appropriate. These include copper studies and DNA testing to exclude Wilson's disease and Huntington's disease, respectively. Brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI) may be necessary to exclude hydrocephalus, cerebrovascular disease or basal ganglia abnormalities suggestive of an underlying metabolic cause. When there is difficulty in distinguishing Parkinson's disease from essential tremor, a form of functional imaging called FP-CIT SPECT (also known as *DaTSCAN*) may be useful, as this technique can sensitively identify loss of nigrostriatal dopaminergic terminals in the striatum (Fig. 32.2). Thus, in essential tremor, the SPECT scan is normal, whereas in Parkinson's disease, reduced tracer uptake is seen (Jennings et al., 2004).

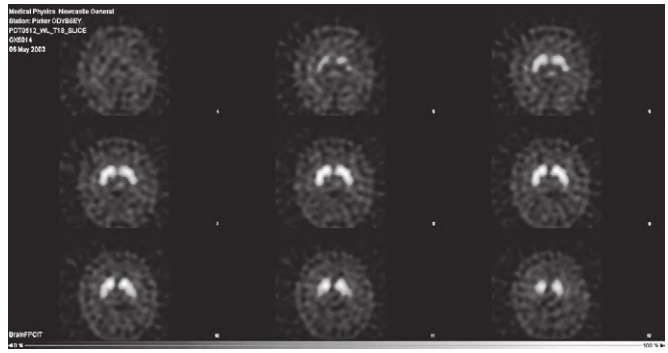

Fig. 32.2 A normal FP-CIT SPECT scan image, showing symmetric tracer uptake in both striata (mirror image commas). In Parkinson's disease, the tail of the comma is lost at an early stage, with the most severe loss being contralateral to the side most affected clinically.

Differentiating Parkinson's disease from multiple system atrophy and progressive supranuclear palsy is a not uncommon clinical problem and may be very difficult, particularly in the early disease stages. FP-CIT SPECT cannot differentiate Parkinson's disease from these other forms of degenerative Parkinsonism. MRI brain scanning, anal sphincter electromyography, tilt table testing for orthostatic hypotension and eye movement recordings may all be of some help, although they are rarely diagnostic in their own right.

Treatment

General approach

When treatment becomes necessary, it is impossible to generalise about which drug should be commenced. All currently available drugs for Parkinson's disease are symptomatic, as no agent has yet been shown, beyond reasonable doubt, to have disease-modifying or neuroprotective properties. There is no accepted algorithm for the treatment of Parkinson's disease, although a clinical management guideline has been produced (NICE, 2006).

A number of factors, including patient preference, age, severity and type of disease (tremor-dominant versus bradykinesia-dominant) and co-morbidity, need to be taken into account. The efficacy and tolerability of levodopa in Parkinson's disease was first described 1967, when the drug was started in low doses and gradually increased thereafter (Cotzias et al., 1967).

Unfortunately, despite dramatic initial benefits, the limitations of levodopa treatment were quickly realised and a phenomenon termed the 'long-term levodopa syndrome' was recognised. This syndrome comprises premature wearing off of the anti-Parkinsonian effects of levodopa, and response fluctuations. The wearing-off effect is the time before a patient is due their next dose of medication, during which they become increasingly bradykinetic. Response fluctuations can include dramatic swings between gross involuntary movements (dyskinesias) and a frozen, immobile state. The rapid and sudden switching between the dyskinetic state and profound akinesia is also termed the 'on–off' phenomenon. If this occurs rapidly and repeatedly, the term 'yo-yo-ing' is sometimes used. These problems emerge at a rate of approximately 10% per year, so that by 10 years into their illness all Parkinson's disease patients can expect to experience such unpredictable responses. Notably, however, levodopa-induced dyskinesias and fluctuations develop earlier in younger Parkinson's disease patients than in older patients. On–off episodes may be extremely disabling and remain a major therapeutic challenge in the management of Parkinson's disease.

Current management trends have, therefore, shifted towards either later administration of levodopa, provided alternative treatments can give adequate symptomatic control, or the use of combination therapies, in an effort to reduce the cumulative dose of levodopa given. The benefit for such 'levodopa-sparing' strategies beyond 5 years into the illness remains a matter of debate.

Drug treatment

Levodopa preparations

Immediate-release levodopa. Irrespective of the debate regarding early or late levodopa therapy, there is no doubt that levodopa remains the most effective oral symptomatic treatment for Parkinson's disease. It is administered with the peripheral dopa-decarboxylase inhibitors carbidopa or benserazide, where carbidopa plus levodopa is known as co-careldopa (Sinemet®) and benserazide plus levodopa is co-beneldopa (Madopar®). The decarboxylase inhibitor blocks the peripheral conversion of levodopa to dopamine and thereby allows a lower dose of levodopa to be administered. Levodopa readily crosses the blood–brain barrier and is converted by endogenous aromatic amino acid decarboxylase to dopamine and then stored in surviving nigrostriatal nerve terminals.

Immediate-release levodopa is usually commenced in a dose of 50 mg/day, increasing every 3–4 days until a dose of 50 mg three times daily is reached. The patient should be instructed in the early stage of the illness to take the drug with food to minimise nausea. Paradoxically, in more advanced Parkinson's disease, it may be beneficial to take levodopa 30 min or so before food, as dietary protein can critically interfere with the absorption of the drug. If there is little or no response to 50 mg three times daily, the unit dose may be doubled to 100 mg. Should the patient's levodopa dose escalate to 600 mg/day with no significant response, the diagnosis of Parkinson's disease should be reviewed. Levodopa, commenced in the above way, is usually well tolerated. Nausea, vomiting and orthostatic hypotension are the most commonly encountered side effects. These adverse events may be circumvented by increasing the levodopa dose even more slowly, or co-prescribing domperidone 10 or 20 mg three times daily. Later in the illness, and in common with all anti-Parkinsonian drugs, levodopa may cause vivid dreams, nightmares or even a toxic confusional state.

Clinically relevant drug interactions with levodopa include hypertensive crises with monoamine oxidase type A inhibitors. Levodopa should, therefore, be avoided for at least 2 weeks after stopping the inhibitor. Levodopa can also enhance the hypotensive effects of antihypertensive agents and may antagonise the action of antipsychotics. The absorption of levodopa may be reduced by concomitant administration of oral iron preparations.

Controlled-release levodopa. Both Sinemet® and Madopar® are available as controlled-release (CR) preparations. The nomenclature for Sinemet CR® is confusing, as the drug is marketed as Sinemet CR® (carbidopa/levodopa 50/200) and also as Half Sinemet CR® (carbidopa/levodopa 25/100). Trying to prescribe Half Sinemet CR® unambiguously can be difficult. If the instruction is misinterpreted and a tablet of Sinemet CR® is halved, the slow-release mechanism is actually disrupted.

Levodopa in controlled release preparations has a bioavailability of 60–70%, which is less than the 90–100% obtained from immediate-release formulations. Controlled release preparations have a response duration of 2–4 h, compared with 1–3 h for immediate release.

Two large studies in early Parkinson's disease over 5 years have not shown any benefit for controlled release use over immediate-release levodopa in terms of dyskinesias and response fluctuation frequency. However, controlled release preparations may be of help in simplifying drug regimens, in relieving nocturnal akinesia, and in co-prescribing with immediate-release levodopa during the day to relieve end-of-dose deterioration.

Two commonly encountered problems with controlled release preparations are, first, changing the patient from all immediate release to all controlled release levodopa. This is poorly tolerated, as controlled release levodopa has a longer latency than immediate-release levodopa to turn the patient 'on' (typically 60–90 vs. 30–50 min), and the patient's perception is that the quality of their 'on' period is poorer. Second, controlled release preparations should not be prescribed more than four times a day, as the levodopa may accumulate, causing unpredictable motor fluctuations.

Co-careldopa intestinal gel. An intestinal gel preparation of levodopa and carbidopa (Duodopa®) is available that is administered directly into the small bowel (specifically, the jejunum) via a percutaneous route, using a portable electronic pump. Through continuous delivery in this way, motor fluctuations may be significantly reduced. Although effective, this treatment modality requires careful patient selection. The endoscopic insertion of a percutaneous jejunostomy carries a definite morbidity and mortality. The treatment is also very expensive while mechanical problems with tube detachment and blockage have been reported.

Dopamine agonists

In theory, dopamine agonists, which stimulate dopamine receptors both post- and presynaptically, would seem to be a very attractive therapeutic option in Parkinson's disease, as they may bypass the degenerating nigrostriatal dopaminergic neurones. Unfortunately, experience to date with the oral agents available has usually shown them to be less potent than levodopa and less well tolerated. One drug in this class, apomorphine, is used in a parenteral form. It is particularly potent and is described in detail below.

Dopamine agonists differ in their affinity for a number of receptors, including the dopamine receptor family. It is not known whether these differences are clinically significant, but experience to date would suggest not. Cabergoline is an ergot dopamine agonist with a much longer plasma half-life of 63–68 h than other agents in this class. This means that once-daily dosing is possible. Ropinirole and pramipexole are non-ergot derivatives that originally had to be administered three times daily. Slow release preparations of ropinirole (XL) and pramipexole (PR) are now available for once-daily dosing. A transdermally administered non-ergot dopamine agonist, rotigotine, is also available as a 24-h adhesive patch.

Four double-blind, randomised and controlled studies of up to 5 years duration have compared the use of a dopamine agonist (cabergoline, ropinirole, pramipexole and pergolide) with levodopa in the treatment of early Parkinson's disease. Although the studies differed in a number of ways, such as levodopa supplementation not being permitted in the pergolide study, the results produced a consistent message that use of dopamine agonists in early Parkinson's disease is associated with a lower incidence of dyskinesias when compared with levodopa. Supplementary levodopa was, however, required in a significant number of patients in the cabergoline (65% of patients initially randomised to cabergoline), ropinirole (66% of patients initially randomised to ropinirole) and pramipexole (53% of patients initially randomised to pramipexole) studies, suggesting that only a subgroup of patients derive adequate benefit from agonist monotherapy alone. Follow-up studies suggest that the addition of levodopa is required in the vast majority of patients and that any initial benefits in terms of lower dyskinesia incidence on agonist alone may be lost when levodopa is then introduced.

There have been very few comparative studies performed between the dopamine agonists, so it is not possible to be definitive as to which drug should be recommended. In practice, it is often worth changing from one agonist to another if side effects are a problem, since there is variability in a given patient's tolerance to the different drugs.

Dopamine agonist side effects. The principal side effect of the dopamine agonists are nausea and vomiting, postural hypotension, hallucinations and confusion, and exacerbation of dyskinesias. Ergot derivatives run the risk of causing pleuropulmonary fibrosis, which occurs in 2–6% of patients on long-term bromocriptine treatment. Annual monitoring with chest X-ray and erythrocyte sedimentation rate (ESR) has been suggested for patients taking ergot derivative agonists, although the utility and cost-effectiveness of this recommendation have not been established. More recently, concern has been expressed over the high frequency of cardiac valvulopathy, notably of the tricuspid valve, found in patients exposed to the ergot derivatives pergolide and cabergoline. Neither drug should be used as first-line agonists in Parkinson's disease. If prescribed, regular echocardiographic monitoring should be undertaken. There is also an increased risk of toxicity when erythromycin is co-prescribed with a dopamine agonist.

Ropinirole and pramipexole were previously implicated in causing 'sleep attacks', with sudden onset of drowsiness, leading to driving accidents in some cases. The term 'sleep attack' is almost certainly a misnomer, however, as patients do have warning of impending sleepiness, although they may subsequently be amnesic for up to several minutes while in this state. Excessive sleepiness attributable to anti-Parkinsonian drugs is actually not a new phenomenon and is almost certainly a 'class effect' of all dopaminergic therapies. It is essential to advise patients taking all anti-Parkinsonian agents that they may be prone to excessive drowsiness. This may be compounded by the use of other sedative drugs and alcohol.

Dopamine agonists have also been associated with impulse control disorders (ICDs). These disorders include pathological gambling, hypersexuality and excessive shopping. The onset may relate to dopamine D2/3 receptor stimulation in predisposed individuals. The patient and their carer should be warned about these potential problems before the drug is prescribed and regularly screened for abnormal behaviours while taking the agonist.

Catechol-*O*-methyl transferase inhibitors

Inhibitors of the enzyme catechol-*O*-methyl transferase (COMT) represent a novel addition to the range of therapies available for Parkinson's disease (Schrag, 2005). Use of the first agent in this class, tolcapone, was originally suspended in Europe because of fears over hepatotoxicity, although the drug became available again in 2005, accompanied by strict prescribing and monitoring guidelines. Entacapone is also available and studies have not shown derangement of liver function with this drug.

COMT itself is a ubiquitous enzyme, found in gut, liver, kidney and brain among other sites. In theory, COMT inhibition may occur both centrally, where the degradation of dopamine to homovanillic acid is inhibited, and peripherally, where conversion of levodopa to the inert 3-*O*-methyldopa is inhibited, to benefit the patient with Parkinson's disease. In practice, both tolcapone and entacapone act primarily as peripheral COMT inhibitors.

Placebo-controlled studies in patients with fluctuating Parkinson's disease have confirmed the efficacy of entacapone in decreasing 'off' time and permitting a concomitant reduction in levodopa dose. A 20% reduction in 'off' time is reported, translating into nearly 1.5 h less immobility per day. This reduction tends to occur towards the end of the day, a time when many Parkinson's disease patients are at their worst in terms of motor function. A comparison of entacapone and tolcapone

suggested that tolcapone may be the more potent COMT inhibitor, achieving up to an extra 1.5 h of 'on' time per day.

When entacapone is prescribed, a 200 mg dose is used with each dose of levodopa administered, up to a frequency of 10 doses/day. Because of increased dyskinesias, an overall reduction of 10–30% in the daily dose of levodopa may be anticipated. Entacapone can be employed with any other anti-Parkinsonian drug, although caution may be needed with apomorphine. More recently, entacapone has been marketed as a compound tablet with levodopa and carbidopa (Stalevo®). Although each tablet contains 200 mg of the COMT inhibitor, there are six different doses of levodopa available (50, 75, 100, 125, 150 and 200 mg), to provide flexibility. The compound tablet may help adherence by significantly reducing the total daily number of tablets a patient needs to take.

Tolcapone is prescribed as a fixed 100 mg three times a day regimen, increasing if necessary to 200 mg three times a day. It may only be used after the patient has tried and failed entacapone and where provision for 2-weekly monitoring of liver function tests for the first 12 months, reducing in frequency thereafter, is available. Again, a concomitant reduction in levodopa may be necessary to offset an increase in dyskinesias.

The optimal way to use COMT inhibition is unknown. A patient experiencing end-of-dose deterioration, or generally underdosed, would seem to be the ideal candidate. However, there are few comparative studies of COMT inhibitors versus dopamine agonists available to provide guidance as to which class of drug is best to use, and when. The STRIDE-PD study (Stocchi et al., 2010) assessed the potential benefit of combined treatment with levodopa and entacapone in *de novo* Parkinson's disease patients to address whether this combined treatment was associated with a lower incidence of dyskinesias. Unfortunately, the opposite was actually found, with a higher incidence of dyskinesias in patients randomised to levodopa and entacapone compared with levodopa alone.

Other than exacerbation of dyskinesias, COMT inhibitors may also cause diarrhoea, abdominal pain and dryness of the mouth. Urine discolouration is reported in approximately 8% of patients taking entacapone.

It is best to avoid non-selective monoamine oxidase inhibitors or a daily dose of selegiline in excess of 10 mg when using entacapone. In addition, the co-prescribing of venlafaxine and other noradrenaline (norepinephrine) reuptake inhibitors is best avoided. Entacapone may potentiate the action of apomorphine. Patients taking iron preparations should be advised to separate this medication and entacapone by at least 2 h.

Monoamine oxidase type B inhibitors

The propargylamines selegiline and rasagiline are inhibitors of monoamine oxidase type B. Inhibition of this enzyme slows the breakdown of dopamine in the striatum. These agents effectively have a 'levodopa-sparing' effect and may delay the onset of, or reduce existing, motor complications. Both drugs may also have an antiapoptotic effect (apoptosis is a form of programmed cell death thought to be important in several neurodegenerative conditions, including Parkinson's disease). Whether or not the drugs have a neuroprotective effect by this or some other means remains controversial. A recent study suggested that 1 mg of rasagiline may have a disease-modifying benefit in early Parkinson's disease, although this study was difficult to interpret since the same effect was not seen with the 2 mg dose (Olanow et al., 2009). Further, the magnitude of effect was very modest and of uncertain clinical relevance. The findings, therefore, need to be interpreted with caution but do offer some cause for optimism.

A single daily dose of 5 or 10 mg of selegiline is prescribed. Higher doses are associated with only minimal additional inhibition of monoamine oxidase. Selegiline may also be administered as a lyophilised freeze-dried buccal preparation. The dose of rasagiline is 1 mg daily.

Both selegiline and rasagiline may be used as *de novo* or adjunctive treatments in Parkinson's disease, although trial data for the latter indication are strongest for rasagiline and buccal selegiline.

Following publication of a study (Lees, 1995) which showed excess mortality in a group of patients taking selegiline, it was suggested that the drug was best avoided in patients with falls, confusion and postural hypotension. A subsequent meta-analysis, including nine trials of selegiline, did not, however, identify any excess mortality in patients taking selegiline (Ives et al., 2004). Selegiline can cause hallucinations and confusion, particularly in moderate-to-advanced disease. The withdrawal of selegiline may then be associated with significant deterioration in motor function. Unlike selegiline, rasagiline is not metabolised to amfetamine-like products, so neuropsychiatric side effects are less frequent. Selegiline should not be co-prescribed with selective serotonin reuptake inhibitors, as a serotonin syndrome, including hypertension and neuropsychiatric features, has been reported in a small minority of cases. Caution is also required for rasagiline when co-prescribing with a selective serotonin reuptake inhibitor.

Amantadine

Amantadine was introduced as an anti-Parkinsonian treatment in the late 1960s. It has a number of possible modes of action, including facilitation of presynaptic dopamine release, blocking dopamine reuptake, an anticholinergic effect, and also as a *N*-methyl-D-aspartate (NMDA) receptor antagonist. Initially employed in the early stages of treatment, where its effects are mild and relatively short-lived, interest has focused more recently upon the use of amantadine as an antidyskinetic agent in advanced disease (Blanchet et al., 2003).

Daily doses of 100–300 mg amantadine may be used. Some recommend even higher doses for improved antidyskinetic effect, although side effects become much more frequent at higher doses. These side effects include a toxic confusional state, peripheral oedema and livedo reticularis (a persistent patchy reddish-blue mottling of the legs, and occasionally the arms). There may be significant rebound worsening of Parkinsonism when amantadine is withdrawn. The mechanism for this is unknown.

Anticholinergic drugs

The availability of anticholinergic drugs such as trihexyphenidyl and orphenadrine predated the introduction of levodopa by nearly 90 years. Anticholinergic drugs have a moderate effect in reducing tremor but do not have any significant benefit upon bradykinesia.

The use of anticholinergic agents has declined because of troublesome side effects, including constipation, urinary retention, cognitive impairment and toxic confusional states. In selected younger patients, an anticholinergic drug may still be helpful but close monitoring is advised. Postmortem studies have suggested that long-term anticholinergic use may have adverse disease-modifying effects in Parkinson's disease, by increasing cortical levels of Alzheimer-type pathology (Perry et al., 2003).

Tricyclic antidepressants have anticholinergic properties, normally regarded as a disadvantage in the treatment of depression. These drugs are generally longer acting than other anticholinergic agents and may have a potential benefit in Parkinson's disease, both for their anticholinergic effects and also their effect in inhibiting monoamine reuptake at adrenergic nerve endings. A low dose of a tricyclic antidepressant, for example, amitriptyline 10–25 mg, at night is sometimes useful in alleviating nocturnal akinesia, improving sleep and improving performance early in the morning.

Apomorphine

Apomorphine is a specialised, but almost certainly underused, drug in the treatment of Parkinson's disease. It is the most potent dopamine agonist available and is administered either by bolus subcutaneous injection or by continuous subcutaneous infusion. The drug is acidic and is generally difficult to administer in a stable form which does not lead to irritation of skin or mucosal surfaces. Alternative methods of administration, including transdermal and intranasal routes and the use of an implantable copolymer-based apomorphine matrix, are being evaluated.

The drug produces a reliable 'on' effect with short latency of action. A single bolus lasts for up to 60 min, depending upon the dose given. Continuous subcutaneous apomorphine may significantly improve dyskinesias in advanced Parkinson's disease, as well as lessening akinesia and rigidity. This may allow oral anti-Parkinsonian medications to be reduced.

Apomorphine causes profound nausea, vomiting and orthostatic hypotension. These problems are counteracted by predosing for 2–3 days with domperidone 20 mg three times daily. Neuropsychiatric disturbance, probably at a lower frequency than with oral agonists, and skin reactions, including nodule formation, are other potential side effects. Apomorphine, in conjunction with levodopa, may cause a Coomb's positive haemolytic anaemia, which is reversible. It is recommended that patients be screened before beginning treatment and at 6-monthly intervals thereafter.

Surgical treatment

There has been renewed interest in the use of neurosurgical techniques for the treatment of Parkinson's disease (Walter and Vitek, 2004). This has resulted not only from recognition of the shortcomings of medical treatment currently available but also from an improved understanding of basal ganglia circuitry and better neuroimaging methods. Table 32.2. summarises techniques currently being employed and evaluated. The functional effects of lesioning (-otomy) and the use of deep brain stimulation are similar, in that the high frequency used in stimulation is believed to act by blocking, or 'jamming' neurones. Deep brain stimulation has the advantage of being reversible but is costly, and programming the stimulator may be very time consuming.

The subthalamic nucleus target is the current target of choice in most centres and the number of published patient-years experience with this surgical approach has increased rapidly over the past decade. Several randomised controlled studies have confirmed the benefits that may be gained from deep brain stimulation of the subthalamic nucleus, in terms of impairment, activities of daily living, and quality of life. Careful case selection is essential for all forms of surgical intervention for Parkinson's disease: older and less biologically fit patients, those with active cognitive and/or neuropsychiatric problems, and patients with a suboptimal levodopa response are generally regarded as poor surgical candidates.

Surgery may also play a role in neurorestorative treatments. Such approaches include stem cell and fetal cell transplantation, and also gene transfer using viral vectors. To date, there have been conflicting results regarding the efficacy of fetal cell

Table 32.2 Summary of anatomical targets for surgical treatment of Parkinson's disease

Target	Bradykinesia	Tremor	Dyskinesia	Comments
Thalamus	–	+++	–	Bilateral thalamotomy is not recommended because of a high incidence of bulbar dysfunction
Globus pallidus	++	++	+++	10–15% incidence of persistent adverse events with unilateral pallidotomy; no reliable data for bilateral procedures
Subthalamic nucleus	+++	+++	++	Weight gain, contralateral dyskinesia, involuntary eyelid closure and speech disturbance reported

+ to +++ refers to the relative efficacy of the procedure for the clinical feature; – refers no benefit for the procedure for the clinical feature.
For each of the three targets listed, both ablation and stimulation procedures have been evaluated.

transplants. These differences may well reflect transplantation technique, the nature of the tissue being implanted, whether immunosuppression is prescribed, and how patients are selected and assessed. Despite the negative results from two double-blind studies of embryonic cell implantation, researchers continue to explore the potential benefits from this approach.

Patient care

Common therapeutic solutions to problems encountered in the management of people with Parkinson's disease are presented in Table 32.3. After diagnosis, the provision of an explanation of the condition, education and support are essential. The Parkinson's Disease Society (www.parkinsons.org.uk) produces an excellent range of literature to help the newly diagnosed patient come to terms with the condition. In accordance with advice given by the Society itself, patients who drive are advised to inform their insurance company and also the Driver and Vehicle Licensing Agency.

A doctor will record impairments in the clinic, while the patient is more concerned with their disability and handicap. Thus, a patient can be noted to have seemingly marked impairment and yet may not complain about significant disability. The converse may also be true. Not all patients, therefore, require immediate treatment. Further, concomitant depression may distort the patient's perception of their disability, leading to inappropriate prescribing of anti-Parkinsonian therapy. In this situation, the use of an antidepressant may be more helpful. There is no good evidence base for which antidepressant should be used, and both the tricyclic agents and selective serotonin reuptake inhibitors have their advocates.

Accurate adherence with the timing of therapy may be particularly important in patients who are beginning to develop long-term treatment complications. It can be helpful for patients to keep diary cards when they begin to experience problems with either bradykinesia or dyskinesia, so that these symptoms can be related to drug and food intake. Careful changes in timing of drug therapy or meals may initially be sufficient to reduce variation in performance. Some patients experience troublesome early morning bradykinesia. It may then be beneficial to prescribe an initial dose of a rapidly acting agent, such as dispersible oral co-beneldopa, to take on first wakening so that the patient can then get up and dress. A combination of levodopa with dopamine agonists, which are more slow acting, may be useful in the patient with motor fluctuations. A combination of levodopa and a COMT inhibitor may be more appropriate in a patient with end-of-dose deterioration.

Other factors that need to be considered in patients with Parkinson's disease are the benefits of adequate sleep and rest at night, which may be made more difficult if they have urinary frequency or problems with nocturnal bradykinesia. Judicious use of hypnotic therapy may be appropriate, while a tricyclic antidepressant may offer the dual benefit of sedation with anti-cholinergic effect. Low friction sheets to assist turning in bed and encouragement of mobility through physiotherapy may also be helpful. The treatment of the patient with severe disease remains one of the greatest challenges in the management of Parkinson's disease. On–off fluctuations may be refractory to oral dopaminergic therapies. Sudden freezing episodes compound failing postural stability, leading

Table 32.3 Common therapeutic solutions in the management of Parkinson's disease

Problem	Cause	Possible Solution
Early-onset dyskinesias in young Parkinson's disease patient	Exposure to levodopa? Biological factors?	Delay introduction of levodopa, or use lowest possible dose, or use alternative agent (e.g. agonist, MAOB inhibitor)
One dose of levodopa does not last until the next (wearing off)	Advanced disease (pre- and post-synaptic changes)	More frequent, smaller doses of levodopa, COMT inhibitor, dopamine agonist or MAOB-inhibitor
Pain and immobility during the night	Evening dose of levodopa not lasting long enough	Use slow release levodopa preparation or dopamine agonist
Freezing episodes and/or unpredictable motor fluctuations	Advanced disease (pre- and post-synaptic changes)	Apomorphine, duodopa or surgery Physiotherapy helpful for freezing
Mismatch between patient's symptoms and signs	Underlying depression?	Consider antidepressant
Confusion and hallucinations with preserved cognition	Toxic (drug-related) psychosis	Exclude intercurrent infection or other medical problem Review and reduce anti-Parkinsonian therapy Consider atypical anti-psychotic agent
Confusion and hallucinations with impaired cognition	Underlying brain pathology, and cholinergic deficit	Reduce anti-Parkinsonian therapy Cholinesterase inhibitor

to increasing falls and injuries. In select patients, the use of apomorphine, either as bolus injection (via a 'Penject' device) or as a continuous subcutaneous infusion, may be helpful.

The presence of reduced dexterity in virtually all people with Parkinson's disease means that thought needs to be given to the way in which medication is dispensed and stored. If the patient is taking a complex regimen of drugs or has early cognitive problems, the use of pre-packaged therapies may improve adherence.

Patients' relatives also need emotional and social support through what can be a very demanding period. The loss of physical mobility, together with a personality change, can be very difficult for relatives to cope with. The involvement of occupational therapists, social workers and specialists in palliative care in this situation is important.

Psychosis and dementia

When cognitive impairment is problematic, the use of conventional antipsychotic medication is inappropriate because such drugs can precipitate a catastrophic worsening of Parkinsonism. Behavioural disturbances require discussion with carers and, if possible, with the patient him- or herself. A graded withdrawal of anti-Parkinsonian drugs is often indicated, aiming to simplify the regimen to levodopa monotherapy. In rare cases, it may be necessary to reduce the dose or even completely withdraw levodopa therapy in order to control aggressive, sexually demanding or psychotic features. When reduction in dopaminergic therapy is ineffective or not tolerated because of unacceptable immobility, an atypical antipsychotic drug may be considered. In practice, the choice narrows down to quetiapine or clozapine, since risperidone and olanzepine are associated with worsening Parkinsonism, even in low doses. Further, both risperidone and olanzepine should not be used in cognitively impaired elderly people because of an increased risk of stroke. Clozapine is difficult to use for Parkinson's disease-associated psychosis because of the need to register the patient with a blood-monitoring programme. When quetiapine is used, it should be commenced in a low dose of 25 or 50 mg at night and increased slowly. The sedative effects may be helpful in promoting sleep.

Cholinesterase inhibitors have shown promise in treating the neuropsychiatric features of Parkinson's disease and may also have modest cognitive-enhancing benefits. Visual hallucinations, delusions, apathy and depression seem to be particularly responsive to these agents. These effects have been demonstrated for rivastigmine in dementia associated with Parkinson's disease in a large, multicentre, double-blind, placebo-controlled study (Emre et al., 2004). A randomised controlled trial of memantine in dementia associated with Parkinson's disease (and also patients with the closely related dementia with Lewy bodies) showed a modest benefit for memantine in the primary end-point, the Clinician's Global Impression of Change (Aarsland et al., 2009).

Autonomic problems

Other complications that may need attention include disorders of gut motility, which present as constipation or difficulty with swallowing, disturbances of micturition, sometimes presenting as nocturia, and postural hypotension. Constipation can be managed in the usual way with bulking agents and, if necessary, stimulant laxatives and stool-softening agents. The management of postural hypotension includes assessment of the patient's autonomic function in order to establish whether this is primarily drug related or associated with autonomic neuropathy. If the patient is dizzy on standing, simple measures such as advice on rising slowly may be adequate. The use of elastic stockings, to reduce pooling of the blood in the lower limbs, is sometimes helpful. Pharmacological approaches include the use of fludrocortisone or occasionally midodrine (a selective α_1-adrenergic agonist). It is also important to consider other therapies the patient is receiving that might contribute to such symptoms, for example, diuretics, and to stop these if possible.

Case studies

Case 32.1

A 48-year-old man, Mr V, has a 2-year history of Parkinson's disease. He is still working in an office. His wife confides in the Parkinson's Disease Nurse Specialist that she is concerned about his gambling. Whilst never a problem before his diagnosis, he is now spending huge sums of money on on-line casinos. They are getting into financial difficulties on account of this habit. She is upset and desperate for help.

Questions

1. What might be responsible for this gentleman's behaviour?
2. What would be the most appropriate management?

Answers

1. The most likely cause of Mr V's pathological gambling (so-called because of the adverse effect this is having on his family and life in general) relates to his medication. He was, in fact, taking the dopamine agonist pramipexole, as well as rasagiline to control his Parkinsonian symptoms. Dopamine agonists have been associated with impulse control disorders.
2. Mr V's dopamine agonist should be withdrawn as quickly as possible, via down-titration of the dose over a few weeks. This will, of course, worsen his motor symptoms. In Mr V's case, he required the use of co-careldopa to regain adequate control of his Parkinsonism, but off the agonist his gambling habit ceased completely. His wife was delighted. Had the patient and his wife been warned of this possible problem prior to starting the agonist the situation may not have got to such a near-disastrous social level. It is, therefore, essential to warn all patients starting dopamine agonists about the risk of impulse control disorders and to document this in writing in the medical records.

Case 32.2

A 70-year-old man, Mr W, was diagnosed as having mild Parkinson's disease 6 months ago. This did not require any treatment. He has no past medical history of note. He returns to clinic and it is clear that both his impairment and disability have worsened.

Questions

1. What initial treatment options should be considered for Mr W?
2. What considerations should be given to the initial drug choice?

Answers

1. There is no evidence to suggest that Mr W is depressed; a masked depression should always be considered when there is a 'mismatch' between impairment and reported disability. This was not the case here. A number of first-line anti-Parkinsonian drugs might, therefore, be considered, including immediate-release levodopa preparations, dopamine agonists and monoamine oxidase type B inhibitors.
2. Co-morbid illness or a life-shortening problem, such as cancer, usually mean that levodopa would be first choice, simply because it is most potent, with a good risk:benefit ratio. If the patient is biologically fit, then either a dopamine agonist or a monoamine oxidase type B inhibitor might be appropriate, so long as the disability is not too severe and there are no other contraindications. Dopamine agonists and selegiline, in particular, have the potential to cause or exacerbate neuropsychiatric problems and the patient and their family should be warned of such side effects. In particular, the patient and their family should be informed of the risk of impulse control disorders, generally associated with dopamine agonists, and this warning recorded in the medical records. By using these 'levodopa-sparing' agents, the onset of dyskinesias may be delayed by several years.

Case 32.3

A 59-year-old gentleman, Mr X, has had Parkinson's disease for 8 years. This was initially treated with selegiline and ropinirole. Due to progressive functional disability and his wish to keep working, levodopa was introduced 5 years previously. He is now experiencing severe motor fluctuations during the day, with periods of marked dyskinesia and also increasingly unpredictable 'off' periods, during which he is stiff, immobile and anxious. Unsuccessful attempts to smooth out these fluctuations have been made by manipulating his levodopa unit dose and frequency, the use of entacapone, and changing his dopamine agonist.

Questions

1. What therapeutic options could be considered in Mr X's case?
2. What factors would influence the choice of treatment?

Answers

1. A relatively simple option that has not yet been considered is amantadine. This agent may have useful antidyskinetic effects in advanced Parkinson's disease. It is usually administered as 100 mg daily initially, increasing gradually to two or three times daily. The dose of levodopa therapy is left unchanged, to avoid worsening 'off' periods. Neuropsychiatric problems and/or a livedinous rash may complicate the use of amantadine, although younger patients are often able to tolerate the drug better. An alternative approach which may well be required is the use of continuous subcutaneous apomorphine with or without amantadine, as this may have a significant antidyskinetic effect and also effectively manage freezing episodes. Duodopa® therapy, administered via a percutaneous jejunostomy, may also be a consideration. Finally, deep brain stimulation of the subthalamic nucleus may be appropriate for Mr X.
2. Patient choice, after being given the relevant options, is clearly important, as the treatments involved are potentially invasive and associated with morbidity. A previous history of neuropsychiatric problems, active psychosis or severe depression, or cognitive impairment would be relative contraindications to surgery. Severe needle phobia or the lack of an appropriately experienced and committed local nurse specialist would compromise the effective administration of apomorphine.

Case 32.4

A 63-year-old lady, Mrs Y, is referred by a colleague because of suspected Parkinson's disease. There is also evidence of some cognitive decline in the past 12 months. She has a background history of epilepsy which was quiescent until three years ago. At that stage, she presented to the neurology department, and her anticonvulsant regimen adjusted to good effect. Examination confirms a mini-mental state examination (MMSE) score of 22/30, symmetric bradykinesia and some rigidity.

Questions

1. Which question might give additional diagnostic help in this lady's history?
2. What would be the best management?

Answers

1. Given this lady's history of epilepsy, and the subsequent evolution of Parkinsonism and cognitive decline, one would be suspicious of the change in her anticonvulsant medication. A drug history confirmed that she had been switched from phenytoin to sodium valproate, raising the possibility of a 'valproate encephalopathy'.
2. Discontinuation of the valproate is definitely worth attempting and converting to an alternative anticonvulsant. If there is doubt over the diagnosis, an FP-CIT SPECT scan can be helpful; in Parkinson's disease, the scan is abnormal, whereas in drug-induced Parkinsonism, because the problem is caused by postsynaptic blockade of dopamine receptors, tracer uptake will be normal. In this case, Mrs Y's Parkinsonism resolved completely and on repeat testing 6 months later her MMSE had risen to 29/30. She was taking lamotrigine to control her seizures at review.

Case 32.5

Mr Z has an 8-year history of Parkinson's disease. He is 77 years old. His motor symptoms are well controlled on a combination of one tablet of co-careldopa (25/100), three times a day and selegiline 10 mg daily. His wife comes to clinic with him and reports that he has recently been confused at night. Further, he has been hallucinating, seeing his long-dead mother at the bottom of the bed.

Question

What should be done?

Answer

The problem here is to what extent the features of Mr Z's psychosis relates to his drugs or to the underlying disease process. Dementia associated with Parkinson's disease is more common in the older patient with long-standing disease.

An MMSE to assess cognitive function in more detail would be appropriate (although note that this scale is relatively insensitive in detecting dementia associated with Parkinson's disease). Intercurrent infection and metabolic derangements, for example, hypothyroidism, should also be excluded.

Selegiline is best avoided in cases like this and should be discontinued. This may lead to an improvement in Mr Z's psychotic features, without any other action being necessary. The use of a typical antipsychotic agent for Mr Z is absolutely contraindicated, as it will only serve to worsen his Parkinson's disease. If cognitive function is well preserved and discontinuing selegiline fails to improve the situation, then a low dose of the atypical antipsychotic quetiapine could be considered. If there is evidence of dementia, a cholinesterase inhibitor would be a better therapeutic choice.

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Pain 33

R. D. Knaggs and G. J. Hobbs

Key points

- Pain is multifactorial in its aetiology.
- Treatment often requires use of a combination of drugs with different mechanisms of action.
- For cancer pain, the World Health Organization (WHO) analgesic ladder forms the basis for the use of analgesic drugs. Some clinicians prefer to omit weak opioids and start strong opioid therapy earlier.
- Opioids are not effective for all types of pain. Adjuvant drugs, such as tricyclic antidepressants or anti-epileptic drugs, should be considered.
- Breakthrough pain is treated with doses of immediate-release opioids, usually prescribed in addition to modified release opioids.
- Antiemetics and laxatives may need to be prescribed for patients taking opioids.
- Cancer pain may vary as the disease progresses. Drug therapy should be reviewed regularly to ensure that the most appropriate agent is being used for the type, site and intensity of pain.
- Most drugs exist in a range of different formulations but, whenever possible, the oral route should be used.

Pain can be defined as:

'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.

Acute pain may be thought of as a physiological process having a biological function, allowing the patient to avoid or minimise injury. Persistent pain, on the other hand, may be described more as a disease than a symptom (Woolf, 2004).

Aetiology and neurophysiology

Neuroanatomy of pain transmission

The majority of tissues and organs are innervated by special sensory receptors (nociceptors) connected to primary afferent nerve fibres of differing diameters. Small myelinated Aδ fibres and unmyelinated C fibres are responsible for the transmission of painful stimuli to the spinal cord where these afferent primary fibres terminate in the dorsal horn.

Pain transmission further within the Central Nervous System (CNS) is far more complex and understood less well. The most important parts of this process are the wide dynamic range cells in the spinothalamic tract that project to the thalamus and to the somatosensory cortex beyond. Modulation or inhibition of these neurones within the spinal cord result in less activity in the pain pathway. This modulatory action can be activated by stress or certain analgesic drugs such as morphine and is an important component of the gate theory of pain (Fig. 33.1). The gate control theory recognises the pivotal role the spinal cord plays in the continual modulation of neuronal activity by the relative activity of large (Aβ) and small (Aδ and C) fibres and by descending messages from the brain. Conversely, other influences can lead to an increased sensitivity to noxious stimuli. The most important of these is pain itself and further painful stimuli can lead to increased pain from relatively trivial insults. This occurs through neurochemical and anatomical changes within the CNS that have been termed central sensitisation.

Neurotransmitters and pain

Various neurotransmitters in the dorsal horn of the spinal cord are involved in pain modulation. These include amino acids such as glutamate and γ-aminobutyric acid (GABA), monoamines such as noradrenaline and 5-hydroxytryptamine (5-HT, serotonin) and peptide molecules, of which the opioid peptides are the most important. Opioid receptors are found in both the CNS and the periphery; in the CNS they are found in high concentrations in the limbic system, the brainstem and the spinal cord. The natural ligands (molecules that bind to

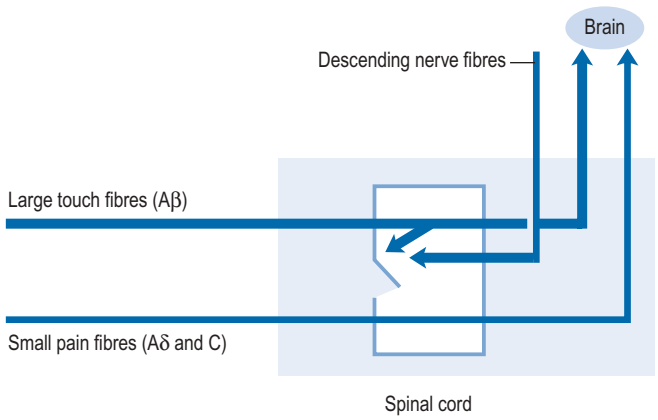

Fig. 33.1 Gate control theory of pain.

the receptor) at opioid receptors are a group of neuropeptides including the endorphins. Opioid analgesics mimic the actions of these natural ligands and exert their effect through the μ, δ and, to a lesser extent, the κ receptors. These receptors mediate the analgesic effect of morphine-like drugs.

Assessment of pain

Evaluation of pain should include a detailed description of the pain and an assessment of its consequences. There should be a full history, psychosocial assessment, medication history and assessment of previous pain problems, paying attention to factors that influence the pain. Diagnostic laboratory tests, imaging, including plain radiography, computer tomography (CT) and magnetic resonance imaging (MRI), and diagnostic nerve blocks may aid confirmation of the diagnosis.

Pain is a subjective phenomenon and quantitative assessment is difficult (Breivik et al., 2008). The most commonly used instruments are visual analogue and verbal rating scales. Visual analogue scales are 10 cm long lines labelled with an extreme at each end; usually 'no pain at all' and 'worst pain imaginable'. The patient is required to mark the severity of the pain between the two extremes of the scale. Verbal rating scales use descriptors such as 'none', 'mild', 'moderate' and 'excruciating'. More elaborate questionnaires such as the Brief Pain Inventory and the McGill Pain Questionnaire help to describe other aspects of the pain, and pain diaries record the influence of activity and medication on pain.

Management

Acute pain usually results from noxious stimulation as a result of tissue damage or injury. It can be managed effectively using analgesic drugs and is often self-limiting.

Persistent pain may be considered as pain which continues beyond the usual time required for tissue healing. Treatment may involve specialist pain management services, hospices and a multidisciplinary approach that assesses and manages patients using a biopsychosocial approach. Initial treatment is usually directed at the underlying disease process where possible, for example, medication, surgery or anti-tumour therapy. However, non-medical treatments such as physical therapy and various psychological techniques including cognitive behavioural therapy may also form part of a multimodal treatment programme. Pain can be modulated using non-pharmacological techniques: for example, stimulation-produced analgesia such as transcutaneous electrical nerve stimulation (TENS), acupuncture and massage, or invasive procedures such as neurosurgery or neurolytic nerve blocks.

Analgesic ladder

The World Health Organization (WHO) analgesic ladder (Fig. 33.2) forms the basis of many approaches to the use of analgesic drugs. There are essentially three steps: non-opioid analgesics, weak opioids and strong opioids. The analgesic efficacy of non-opioids, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. aspirin, ibuprofen and diclofenac), is limited by side effects and ceiling effects, that is, beyond a certain dose, no further pharmacological effect is seen. If pain remains uncontrolled, then a weak opioid, such as codeine or dihydrocodeine, may be helpful. There may be additional benefit in combining a weak opioid with a non-opioid drug, although many commercial preparations contain inadequate quantities of both components and are no more effective than a non-opioid alone. Strong opioids, of which morphine is considered the gold standard, have no ceiling effect and therefore increased dosage continues to give increased analgesia but side effects often limit effectiveness. Adjuvant drugs, such as corticosteroids, antidepressants or anti-epileptics, may be considered at any step of the ladder.

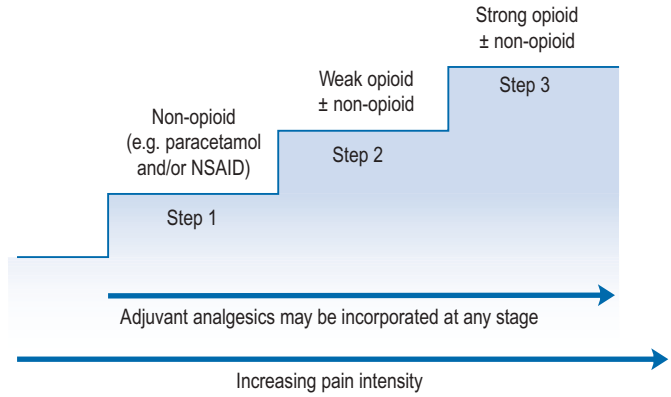

Fig. 33.2 WHO three-step analgesic ladder.

Analgesic drugs

Paracetamol

Despite being used in clinical practice for over 50 years and much investigation, the mechanism by which paracetamol exerts its analgesic effect remains uncertain. Inhibition of prostaglandin synthesis within the CNS has been proposed, although this is probably not the only mechanism. Interaction with the serotonin (Tjolsen et al., 1991) and endocannabinoid (Högestätt et al., 2005) neurotransmitter systems have been demonstrated in animal models.

Following oral administration the bioavailability of paracetamol is around 60%, but if given by the rectal route it is much lower and much more variable. A formulation for intravenous infusion has been promoted over the last few years and this has largely replaced the rectal route of administration. Therapeutic plasma levels are reached within 30 min of oral administration. The elimination half-life of paracetamol is relatively short ($t_{½}$ = 2–4 h); hence, frequent dosing is required to maintain its analgesic effect.

With normal doses, the majority of paracetamols are metabolised and inactivated in the liver, undergoing a phase II conjugation reaction with glucuronic acid (Fig. 33.3). A small

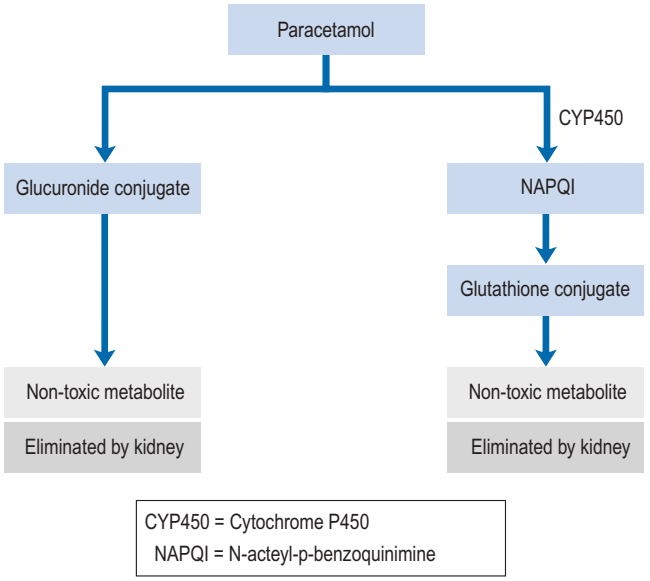

Fig. 33.3 Paracetamol metabolism in humans.

proportion of a dose is metabolised using a cytochrome P450 mediated reaction that forms a reactive intermediate, *N*-acteyl-*p*-benzoquinimine (NAPQI). Usually, NAPQI can be deactivated by conjugation with glutathione in the liver. However, following ingestion of a large amount of paracetamol the hepatic stores of both glucuronic acid and glutathione become depleted leaving free NAPQI, which causes liver damage.

The usual therapeutic dose for adults is paracetamol 1 g taken four times daily. It is very important that this dose is not exceeded, otherwise hepatotoxicity is more common. This may be particularly problematic for malnourished adults with low body weight (Claridge et al., 2010). A reduced maximum daily infusion dose (3 g/24 hours) is recommended for patients with hepatocellular insufficiency, chronic alcoholism or dehydration. Paracetamol is also available as an over-the-counter (OTC) medicine and is a component of many cold and influenza remedies. Compared with other analgesics, paracetamol is not as potent; however, when taken in combination with a NSAID or opioid, there is an additive analgesic effect.

Non-steroidal anti-inflammatory drugs

Mode of action

NSAIDs exert their analgesic and anti-inflammatory effects through inhibition of the enzyme cyclo-oxygenase. NSAIDs are used widely to relieve pain, with or without inflammation, in people with acute and persistent musculoskeletal disorders. In single doses, NSAIDs have superior analgesic activity compared to paracetamol (Hyllested et al., 2002). In regular higher dosages, they have both analgesic and anti-inflammatory effects, which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. NSAIDs have been shown to be suitable for the relief of pain in dysmenorrhoea, toothache and some headaches and to treat pain caused by secondary bone tumours, which result from lysis of bone and release of prostaglandins.

Clinical considerations

Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual patient response as well as the incidence and type of side effects. About 60% of patients will respond to any NSAID. Of the remaining patients, those who do not respond to one NSAID may well respond to another. An analgesic effect should normally be seen within a week, whereas an anti-inflammatory effect may not be achieved or assessable clinically for up to 3 weeks.

The potential treatment benefits of an NSAID must be weighed against the risks. NSAIDs are contraindicated in patients with known active peptic ulceration and should be used with caution in the elderly and in those with renal impairment or asthma.

COX-2 selective drugs

Cyclo-oxygenase exists in two forms: cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2). COX-1 is a constitutive enzyme that is expressed under normal conditions in a variety of tissues, including the gastro-intestinal tract and kidney, where it catalyses the formation of prostaglandins required for homeostatic functions. It does not have a role in nociception or inflammation. COX-2 is an inducible enzyme that appears in damaged tissues shortly after injury and leads to the formation of inflammatory prostaglandins within these tissues. COX-2 selective NSAIDs should, theoretically, inhibit the formation of inflammatory prostaglandins without affecting the activity of COX-1 in areas such as the gut. In practice, use of COX-2 specific drugs is associated with reduced risks of gastro-intestinal side effects when compared with non-selective drugs. However, their use has also been linked with adverse effects including ischaemic cardiac events and this now limits their use.

Guidance on NSAID use

The lowest effective dose of NSAID or COX-2 selective inhibitor should be prescribed for the shortest time necessary. The need for long-term treatment should be reviewed periodically. Prescribing should be based on the safety profiles of individual NSAIDs or COX-2 selective inhibitors, on individual patient risk profiles, for example, gastro-intestinal and cardiovascular. Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient's individual risk factors, as well as the patient's preference (Medicines and Healthcare Regulatory Agency, 2006).

Concomitant aspirin, and possibly other antiplatelet drugs, greatly increases the gastro-intestinal risks of NSAIDs and severely reduces any gastro-intestinal safety advantages of COX-2 selective inhibitors. Aspirin should only be co-prescribed if absolutely necessary.

Weak opioids

Weak opioids are prescribed frequently, either alone or in combination with other analgesics, for a wide variety of painful disorders. There are three major drugs in this group,

codeine, dihydrocodeine and dextropropoxyphene, which are recommended as step 2 of the WHO analgesic ladder for pain that has not responded to non-opioid analgesics. Despite this recommendation, there is little data which demonstrates that weak opioids are of any benefit in the relief of persistent pain, and it may be more beneficial to use a smaller dose of a strong opioid.

Co-proxamol, a combination of dextropropoxyphene and paracetamol, was withdrawn in the UK in 2007 following safety concerns, particularly toxicity in overdose. An unlicensed product remains available for patients who find it difficult to change to alternative treatment.

Codeine

Codeine is the prototypical drug in this group. It is structurally similar to morphine and about 10% of the codeine is demethylated to form morphine, and the analgesic effect may be due to this, at least in part. It is a powerful cough suppressant as well as being very constipating. In combination with NSAIDs, the analgesic effects are usually additive but the variability in response is considerable. A degree of genetic polymorphism occurs within the population such that the hepatic microsomal enzyme CYP2D6 that is responsible for the conversion of codeine to morphine does not catalyse this conversion in approximately 8% of the Caucasian population. The duration of analgesic action is about 3 h.

Dihydrocodeine

Dihydrocodeine is only available in a few countries and is chemically similar to codeine. It has similar properties to codeine when used at the same dosage and may be slightly more potent.

Dextropropoxyphene

Historically, dextropropoxyphene was prescribed in combination with other analgesics such as paracetamol (co-proxamol). There are few data on its therapeutic value, and at least one review concluded that analgesic efficacy is less than aspirin and barely more than placebo. At best, dextropropoxyphene failed to show any superiority over paracetamol (Li Wan Po and Zhang, 1997). At worst, it is a dangerous drug which has the potential for steadily developing toxicity. Patients with hepatic dysfunction and poor renal function are particularly at risk. It is associated with problems in overdose, notably a non-naloxone reversible depression of the cardiac conducting system. Dextropropoxyphene interacts unpredictably with a number of drugs, including carbamazepine and warfarin. In 2005, the Medicines and Healthcare products Regulatory Agency (MHRA) announced concerns about the safety and effectiveness of co-proxamol and directed that it should be withdrawn from clinical use in the UK; however, it still remains available as an unlicensed medicine for the small number of patients who do not obtain analgesia with other analgesic medicines.

Strong opioids

Morphine

Morphine is the 'gold standard' strong opioid analgesic. It is available for administration by a range of administration routes, including oral, rectal and injectable formulations and has a duration of action of about 4 h after oral administration. There is no ceiling effect when the dose is increased. A general protocol for morphine use to obtain rapid relief from acute pain is to use intravenous bolus doses of 2–5 mg titrated until pain relief is achieved. In the initial management of persistent non-cancer pain or cancer pain, an oral regimen is more appropriate using an immediate-release formulation. A usual starting dose is 5–10 mg every 4 h, and the patient should be advised to take the same dose as often as is necessary for breakthrough pain. It may be necessary to double the dose every 24 h until pain relief is achieved, although a slower dose escalation will often suffice. After control is achieved, it is usual to change to an oral modified release formulation, which allows less frequent dosing, either daily or twice-daily. There is no ceiling dose for the analgesic effect of morphine; daily doses of up to 1 or 2 g of morphine may be required for some cancer patients, but relatively few require more than about 200 mg daily. Morphine is metabolised in the liver and one metabolite, morphine 6-glucuronide, is pharmacologically active and this should be taken into consideration in patients who have renal failure.

Other strong opioids

Opioids such as pethidine and dextromoramide offer little advantage over morphine in that they are generally weaker in action with a relatively short duration of action (2 h). Dipipanone is only available in a preparation which contains an antiemetic (cyclizine), and increasing doses lead to sedation and the risk of developing a tardive dyskinesia with long-term use. Methadone has a long elimination half-life of 15–25 h, and accumulation occurs in the early stages of use. It has minimal side effects with long-term use and some patients who experience serious adverse effects with morphine may tolerate methadone.

Hydromorphone and oxycodone are synthetic opioids that have been used for many years in North America and more recently in Europe. They are available in both immediate and modified release preparations. Some patients appear to tolerate hydromorphone or oxycodone better than morphine but there is no evidence to suggest which patients achieve the best effect with either of these drugs.

Fentanyl is available as a transdermal formulation for long-term use. The patch is designed to release the drug continuously over 3 days. When starting the drug, alternative analgesic therapy should be continued for at least the first 12 h until therapeutic levels are achieved, and an immediate acting opioid should be available for breakthrough pain. Patches are replaced every 72 h.

The relative potencies of the commonly used opioids are summarised in Table 33.1.

Table 33.1 Relative potencies of opioid drugs

Drug	Potency (morphine = 1)
Codeine	0.1
Dihydrocodeine	0.1
Tramadol	0.2
Pethidine	0.1
Morphine	1
Diamorphine	2.5
Hydromorphone	7
Methadone	2–10 (with repeat dosing)
Fentanyl (transdermal)	150

Clinical considerations

Use of opioids is almost universally accepted in cancer pain but many patients with persistent non-cancer pain can find considerable relief with strong opioids; however, barriers to their use in this context appear to be based more on ignorance and political fashions than clinical evidence (Ballantyne and Mao, 2003). As a general rule, strong opioids effective in the management of neuropathic and musculoskeletal pain, including osteoarthritis, are less effective for sympathetically maintained pain.

Agonist-antagonist and partial agonists

Most of the drugs in this category are either competitive antagonists at the μ opioid receptor, where they can bind to the site but exert no action, or they exert only limited actions; that is, they are partial agonists. Those that are antagonists at the μ opioid receptor can provoke a withdrawal syndrome in patients receiving concomitant opioid agonists such as morphine. These properties make it difficult to use these agents in the control of persistent pain, and the process of conversion from one group of drugs to another can be complex.

Buprenorphine

Buprenorphine is a semi-synthetic, highly lipophilic opioid that is a partial agonist at the μ opioid receptor and an antagonist at both the δ and κ receptors. It undergoes extensive metabolism when administered orally and to avoid this effect, it is given sublingually. It has high receptor affinity and, through this property, a duration of action of 6 h.

A long duration of action and high bioavailability would suggest a role for buprenorphine in the management of persistent pain. Relatively recently, buprenorphine has been marketed as a transdermal formulation and may be an effective alternative to other strong opioids for persistent non-cancer pain. There is limited evidence of efficacy in osteoarthritis and low back pain. Following sublingual or intravenous administration the incidence of nausea and vomiting appears to be substantially higher than with morphine; however, respiratory depression and constipation are less frequent.

Pentazocine

Pentazocine, a benzomorphan derivative, is an agonist and at the same time a very weak antagonist at the μ opioid receptor. This drug became popular in the 1960s, when it was thought it would have little or no abuse potential. This is now known to be untrue, although its abuse potential is less than that of the conventional agonists such as morphine. It produces analgesia that is clearly different from morphine and is probably due to agonist actions at the κ-receptor. There are no detailed studies of its use in persistent pain, but its short duration of action (about 3 h) and the high incidence of psychomimetic side effects make it a totally unsuitable drug for such use.

Tramadol

Tramadol is a centrally acting analgesic that has opioid agonist activity and also has potent monoamine reuptake properties similar to many antidepressants. Indeed, tramadol appears to have intrinsic antidepressant activity. It is not as potent as morphine and efficacy is limited by side effects, including an unfavourably high risk of drowsiness and nausea and vomiting. Its monoaminergic activity appears to be valuable in the management of neuropathic pain and hence may be an acceptable alternative to a weak opioid.

Adverse effects of opioids

The adverse effects of opioids are nearly all dose related, and tolerance develops to the majority with long-term use.

Respiratory depression

Respiratory depression is potentially dangerous in patients with impaired respiratory function, but tolerance develops rapidly with regular dosing. It can be reversed by naloxone.

Sedation

Sedation is usually mild and self-limiting. Smaller doses, given more frequently, may counteract the problem. Rarely, dexamfetamine or methylphenidate has been used to counteract this effect.

Nausea and vomiting

Antiemetics should be co-prescribed routinely with opioids for the first 10 days. Choice of antiemetic will depend upon the cause, and a single drug will be sufficient in two-thirds of patients. Where nausea is persistent, additional causes should be sought and prescribing reviewed. If another antiemetic is used, it should have a different mode of action.

Constipation

Opioids reduce intestinal secretions and peristalsis, causing a dry stool and constipation. Unlike other adverse effects constipation tends not to improve with long-term use, and when opioids are used on a long-term basis most patients need a stool softener (e.g. docusate sodium) and a stimulant laxative (e.g. senna) regularly. Dosage should be titrated to give a comfortable stool. High-fibre diets and bulking agents do not work very well in preventing constipation in patients on opioids. Co-danthrusate (dantron + docusate sodium) and co-danthramer (dantron + poloxamer 188) are alternatives; however, because of the potential carcinogenicity and genotoxicity of dantron, they are only indicated for use in terminal care.

Tolerance, dependence and addition

Persistent treatment with opioids often causes tolerance to the analgesic effect, although the mechanism remains unclear (Holden et al., 2005). When this occurs the dosage should be increased or, alternatively, another opioid can be substituted, since cross-tolerance is not usually complete. Addiction is very rare when opioids are prescribed for pain relief.

Smooth muscle spasm

Opioids cause spasm of the sphincter of Oddi in the biliary tract and may cause biliary colic, as well as urinary sphincter spasm and urinary retention. Thus, in biliary or renal colic, it may be preferable to use another drug without these effects. Pethidine was believed to be the most effective in these circumstances but the evidence for this has been questioned (Thompson, 2001).

There is increasing evidence that long-term use of potent opioids may cause clinically significant adverse effects on the endocrine system, namely testosterone deficiency. Effects on the immune system are also under scrutiny.

Special techniques of opioid drug delivery

Patient-controlled analgesia (PCA)

PCA is a system which allows the patient to titrate the dose of opioid to suit their individual analgesic requirements. The drug is delivered using a syringe attached to an electronic or elastomeric pump, which delivers a preset dose when activated by the patient depressing a button. A lock-out period, during which the machine is programmed not to respond, ensures that a second dose is not delivered before the previous one has had an effect. Some devices allow an additional background infusion of drug to be delivered continuously. A maximum dose facility ensures that the machine does not deliver more than a preset dose over a given time. PCA is a useful technique for the management of pain after surgery. The system is convenient and enjoys a high degree of patient acceptability.

The traditional intermittent intramuscular injection of opioids can be effective but is less versatile than titrated intravenous administration. The subcutaneous route is subject to most of the problems associated with intramuscular administration but tends to be less painful.

Opioid use via any route is associated with nausea, and antiemetics should be prescribed routinely. Administration of compound preparations containing both opioids and antiemetics is not recommended as few preparations contain drugs with similar pharmacokinetic profiles and accumulation, usually of the antiemetic, may occur.

Epidural analgesia

Epidural injections and infusions may be effective in relieving pain arising from both malignant causes and non-cancer diseases and are very effective in postoperative and labour pain. Various combinations of local anaesthetics, opioids or steroids can be administered into the epidural space near to the spinal level of the pain.

Epidural opioids

Effective analgesia can be obtained by administering small doses of opioids to the epidural space. As there are opioid receptors in the spinal cord, smaller doses than administered by other parenteral routes are required and may be given with and without long acting local anaesthetic drugs. However, severe respiratory depression, nausea and vomiting, urinary retention and pruritus can occur after their use. Life threatening respiratory depression can occur when additional opioids are given by other routes to patients already receiving epidural opioids, and this practice should be actively discouraged. Respiratory depression which occurs soon after administration, due to intravascular absorption, is relatively common and simple to detect and treat. However, respiratory depression can also occur many hours after opioid administration. This is most common with morphine, probably because of its lower lipophilicity compared with fentanyl and diamorphine. Fentanyl has much greater stability than diamorphine and it can be prepared with bupivacaine in a terminally sterilised formulation which minimises the risk of adding the incorrect dose to an infusion fluid in a clinical environment and maintains sterility.

Local anaesthetics

Local anaesthetic drugs, such as lidocaine and bupivacaine, produce reversible blockade of neural transmission in automonic, sensory and motor nerve fibres by binding to sodium channels in the axon membrane from within, preventing sodium ion entry during depolarisation. The threshold potential is not reached, and consequently the action potential is not propagated. The concentration of local anaesthetic and dose used determine the onset, density and duration of the block. There are marked differences in the recommended maximum safe doses of different local anaesthetic agents. If the maximum dose is exceeded, serious cardiovascular (arrhythymias) and CNS effects (convulsions) may be observed.

Local anaesthetic drugs injected close to a sensory nerve or plexus will block the conduction of nerve impulses, including

pain from sensory fibres and provide excellent analgesia. Some local anaesthetics are given with adrenaline (epinephrine) to reduce systemic toxicity and increase the duration of action.

Local anaesthetics can be applied directly to wounds or by local infiltration to produce postoperative analgesia; however, these approaches will not normally block pain arising from deep internal organs. Local anaesthetic techniques are particularly useful in day-stay surgery and children. Continuous infusions via a catheter will allow prolonged analgesia. More permanent neural blockade for the control of cancer pain may be achieved by using a neurolytic agent such as absolute alcohol or phenol.

A topical formulation of lidocaine has been marketed for the management of neuropathic pain caused by post-herpetic neuralgia. Up to three plasters may be worn for a 12-h period each day.

Epidural local anaesthetics

Long acting local anaesthetic drugs such as bupivacaine are most effective in relieving pain after major surgery. They work by blocking nerves in the spinal canal serving both superficial and deep tissues, and thus analgesia can be obtained in deep internal organs. Sensory and sympathetic nerves that maintain smooth muscle tone in blood vessels are blocked. As a result, vasodilation can occur, which may result in significant hypotension. Epidural catheters allow continuous infusions and long-term therapy by this route. Adverse effects may include muscle weakness in the area supplied by the nerve and, rarely, infection and haematomas.

Non-opioid analgesics

The pharmacological actions and use of the conventional non-opioids such as paracetamol, aspirin and NSAIDs are well known and will not be discussed further here.

Nefopam is a drug which is chemically related to orphenadrine and diphenhydramine, however, it is neither an opioid, anti-inflammatory drug nor an antihistamine. The mechanism of analgesic action remains unclear. As a non-opioid, it is not associated with the problems of dependence and respiratory depression. The drug has a very high number of dose-related side effects in clinical use that may be linked to its anti-cholinergic actions. Nefopam may be useful in asthmatic patients and in those who are intolerant of NSAIDs.

Adjuvant medication

To be an analgesic, a drug must relieve pain in animal models and give demonstrable and reliable pain relief in patients. Drugs such as the opioids and the NSAIDs clearly are analgesics. In some types of pain, such as cancer pain or neuropathic pain, the addition of non-analgesic drugs to analgesic therapy can enhance pain relief. A list of some adjuvant drugs is given in Table 33.2. It should be remembered that some drugs such as tricyclic antidepressants (TCAs) have intrinsic analgesic activity, perhaps related to their ability to affect 5-HT and noradrenergic neurotransmission.

Table 33.2 Adjuvant drugs used in the treatment of pain

Drug class	Type of pain	Example
Anti-epileptics	Neuropathic pain Migraine Cluster headache	Carbamazepine Sodium valproate Gabapentin Pregabalin Lamotrigine
Antidepressants	Neuropathic pain Musculoskeletal pain	Amitriptyline Imipramine Venlafaxine Duloxetine
Intravenous anaesthetic agents	Neuropathic pain Burn pain Cancer pain	Ketamine
Skeletal muscle relaxants	Muscle spasm Spasticity	Baclofen Dantrolene Botulinum toxin (type A)
Steroids	Raised intracranial pressure Nerve compression	Dexamethasone Prednisolone
Antibiotics	Infection	As indicated by culture and sensitivity
Antispasmodics	Colic Smooth muscle spasm	Hyoscine butylbromide Loperamide
Hormones/ hormonal analogues	Malignant bone pain Spinal stenosis Intestinal obstruction	Calcitonin Octreotide
Bisphosphonates	Bone pain (caused by cancer or osteoporosis)	Pamidronate (for cancer pain) Alendronate

Antidepressants

Persistent pain is accompanied frequently by anxiety and depression. Thus, it is not surprising that the use of antidepressants and other psychoactive drugs is a routine component of pain management. There is evidence that some of these drugs have analgesic properties independent of their psychotropic effects.

The TCAs are frequently used for the treatment of persistent pain conditions with and without the anti-epileptics, and there is a substantial body of literature about their analgesic action (McQuay et al., 1996).

The biochemical activity of the TCAs suggests that their main effect is on serotonergic and noradrenergic neurones. The TCAs inhibit the reuptake of the monoamines, 5-HT and/or

noradrenaline in neurones found within in the brain and spinal cord. Through a rather complex mechanism, this causes an initial fall in the release of these transmitters followed by a sustained rise in the concentration of neurotransmitter at synapses in the pain neural pathways. This rise usually takes 2–3 weeks to develop. Tricyclic antidepressants are effective analgesics in headache, facial pain, low back pain, arthritis, and, to a lesser degree, cancer pain.

Clinical use of antidepressants in persistent pain

When used in pain management, it is usual to start with a very low TCA dose, for example, amitriptyline 10–25 mg at night and to titrate upwards according to response and adverse effects. Within clinical trials TCA doses have varied considerably but most are lower than used in psychiatry, in the order of amitriptyline 50–75 mg/day. Under specialist supervision higher doses, for example, amitriptyline 150–200 mg/day may be appropriate.

Tricyclic antidepressants have a wide range of adverse effects due to interaction with histamine and muscarinic acetylcholine receptors and these may cause a marked reduction in patient adherence. Newer antidepressant drugs have generally been disappointing from the analgesic perspective. However, much of the research has looked at the selective serotonin reuptake inhibitors (SSRIs). Scientific (Sindrup and Jensen, 1999) and clinical evidence (Sindrup et al., 2005) suggest that a combination of noradrenergic and serotonergic transmission both need to be enhanced for an analgesic effect to be seen. The serotonin/noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine have effects on both monoamines and appear to possess analgesic activity in neuropathic pain models. A number of antidepressant compounds, including trazodone and mirtazepine, do not act via monoamine reuptake inhibition and do not appear to possess intrinsic analgesic activity. They are effective antidepressants and may have a place in the treatment of coexisting depression but analgesia should be treated separately.

Anti-epileptics

The usefulness of this group of drugs is well established for the treatment of neuropathic pain (McQuay et al., 1995). Conditions which may respond to anti-epileptics include trigeminal neuralgia, glossopharyngeal neuralgia, various neuropathies, lancinating pain arising from conditions such as postherpetic neuralgia and multiple sclerosis and similar pains that may follow amputation or surgery. Several classes of drugs show anti-epileptic activity and these can be broadly classed as sodium channel blockers (carbamazepine, phenytoin), glutamate inhibitors (lamotrigine), voltage gated calcium channel ligands (gabapentin, pregabalin), GABA potentiators (sodium valproate, tiagabine) or drugs showing a mixture of these effects (topiramate). Failure to respond to one particular drug does not indicate that anti-epileptics as a broad class will be ineffective. A drug with a different mechanism of action or combination therapy could be considered.

Anti-epileptics are surprisingly effective in the prophylaxis of migraine and cluster headache. Their mode of action is unclear but both of these conditions are associated with abnormal excitability of certain groups of neurones and the neuronal depression caused by anti-epileptics is probably important.

Ketamine

Ketamine is an intravenous anaesthetic agent with a variety of actions within the CNS. Many of its effects are related to its activity at central glutamate receptors, although it also has actions at certain voltage-gated ion channels and opioid receptors. Low doses of ketamine (0.1–0.3 mg/kg/h via the intravenous route) can produce profound analgesia, even in situations where opioids have been ineffective, such as neuropathic pain. Despite its variable oral availability, oral administration of ketamine can be surprisingly effective (Annetta et al., 2005; Mercadante, 1996). Its usefulness is limited by troublesome psychotropic side effects, although the simultaneous administration of benzodiazepines or antipsychotics can reduce these problems.

Anxiolytics

Benzodiazepines may be used for short-term pain relief in conditions associated with acute muscle spasm and are sometimes prescribed to reduce the anxiety and muscle tension associated with persistent pain conditions. Many authorities believe that they reduce pain tolerance and there is good evidence that they can reduce the effectiveness of opioid analgesics, although the mechanism by which this occurs is unclear. Clonazepam has been used in the management of neuropathic pain. Diazepam can be used to control painful spasticity, due to acute or spinal cord injury, but sedation may be troublesome and baclofen (see below) is probably a more suitable choice.

Antihistamines

These agents were introduced into the management of persistent pain because of their sedative muscle relaxant properties. These actions are non-specific and it is not clear whether the clinical effect is mediated centrally or peripherally. Most clinical studies have been carried out with hydroxyzine, which has shown benefit in acute pain, tension headache and cancer pain, but is not commonly used in current clinical practice.

Skeletal muscle relaxants

Drugs described in this section are used for the relief of muscle spasm or spasticity. It is essential that the underlying cause of the spasticity and any aggravating factors such as pressure sores or infections are treated. Skeletal muscle relaxants usually help spasticity but this may be at the cost of decreased muscle tone elsewhere, which may lead to a decrease in patient mobility, which may make matters worse.

The drug of first choice is probably baclofen, which has a peripheral site of action, working directly on skeletal muscle. Baclofen is a derivative of the inhibitory neurotransmitter GABA and appears to be an agonist at the $GABA_B$ receptor. It is used commonly in the treatment of spasticity caused by multiple sclerosis or other diseases of the spinal cord, especially traumatic lesions.

Dantrolene is an alternative that is effective orally and which may have fewer, but potentially more serious, adverse effects. Its effect is due to a direct action on skeletal muscle and takes several weeks to develop.

The α_2-adrenergic agonist tizanidine has potent muscle relaxant activity and is an alternative to baclofen. It may also have some direct analgesic effects.

Botulinum toxin

The bacterium *Clostridium botulinum* produces a potent toxin that interferes directly with neuromuscular transmission. Purified preparations of the type A toxin produce long-lasting relaxation of skeletal muscle. The effect often lasts in excess of 3 months and avoids the systemic side effects of agents such as baclofen. Great care must be taken in administering this drug as spread may occur to adjacent muscle groups, producing excessive weakness. Overdosage, with systemic absorption, may lead to generalised muscle weakness and even respiratory failure.

Clonidine

The α-adrenergic agonist clonidine has been shown to produce analgesia, and there is evidence that both morphine and clonidine produce a dose-dependent inhibition of spinal nociceptive transmission that is mediated through different receptors for each drug. This may explain why clonidine has been shown to work synergistically with morphine when given by the intrathecal or epidural routes. Clonidine also appears to be effective when given by other routes or even topically, but may cause severe hypotension by any route.

Cannabinoids

Cannabis has been used as an analgesic for hundreds of years. Problems concerning the legal status of cannabis in most countries have hindered scientific investigation of its analgesic properties. The active ingredient in preparations made from the hemp plant, *Cannabis sativa,* is δ-9 tetrahydrocannabinol. This compound has analgesic activity in animal models of experimental pain as well as in the clinical situation (Burns and Ineck, 2006). Overall, analgesic activity appears relatively weak and it has not been possible to separate the analgesic activity from the potent psychotropic effects characteristic of these drugs but a commercial preparation is now licensed for the management of spasticity in multiple sclerosis. There may be a clearer analgesic effect in neuropathic pain but the evidence for this remains anecdotal.

Stimulation-produced analgesia

Stimulation-produced analgesia can be used for trauma, postoperative pain, labour pain and various persistent pains.

TENS and acupuncture

TENS machines are portable battery-powered devices that generate a small current to electrodes applied to the skin. The electrodes are placed at the painful site or close to the course of the peripheral nerve innervating the painful area, and the current is increased until paraesthesia is felt at the site of the pain. The current stimulates the large, rapidly conducting (Aβ) fibres which close the gating mechanism in the dorsal horn cells, and this inhibits the small, slowly conducting (Aδ and C) fibres. TENS, in particular, offers the patient a simple, non-invasive, self-controlled method of pain relief with relatively few adverse effects.

Acupuncture also works using a similar manner, although additional mechanisms, including stimulation of endogenous opioid release, may be involved. Acupuncture has been recommended for the treatment of low back pain (National Institute for Health and Clinical Excellence, 2009).

Treatment of selected pain syndromes

Postoperative pain

The majority of patients experience pain following surgery. The site and nature of surgery influences the severity of pain, although individual variation between patients does not allow prediction of the severity of pain by the type of operation.

Apart from the obvious humanitarian benefit of relieving suffering, pain relief is desirable for a number of physiological reasons after surgery or any form of major tissue injury. For example, poor-quality analgesia reduces respiratory function, increases heart rate and blood pressure, and amplifies the stress response to surgery. The use of intermittent and patient-controlled intermittent intravenous opioids injections has been described earlier in this chapter. However, opioids themselves may delay recovery and are associated with adverse events in the postoperative period (Kehlet et al., 1996). It is now common to treat postoperative pain using a 'multimodal approach', consisting of paracetamol, NSAIDs, opioids and local anaesthetic blocks or wound infiltration. NSAIDs such as diclofenac and ketorolac are used frequently, but must be used with caution in the postoperative period where there is a possibility of renal stress, such as blood loss, and the normal protective effect of prostaglandins on the kidney will be lost, culminating in acute renal failure. There is no evidence to support the pre-emptive use of either NSAIDs or local anaesthetic techniques, although there is some theoretical and clinical evidence suggesting that opioids given prior to surgery may be more effective than when given postoperatively.

Cancer pain

Cancer and pain are not synonymous. One-third of patients with cancer do not experience severe pain. Of the remaining two-thirds that do, about 88% can be controlled using basic principles of pain management (Scottish Intercollegiate Guidelines Network, 2008). Pain associated with cancer may arise from many different sources, and may exhibit the characteristics of both acute and persistent pain. The mechanisms and sources of cancer pain may change with time and regular assessment is required. Cancer occurs more frequently in the elderly, who may have a larger proportion of painful conditions than the general population. Pain may be arising from these sources too, and these require treatment at the same time.

Cancer pain can be treated both with drugs and other interventional techniques, such as radiotherapy and nerve blocks. Usually, drug treatment is based on the WHO analgesic ladder together with the use of adjuvant analgesics. Opioids are the mainstay for the treatment of cancer pain, although increasingly some clinicians progress from non-opioid drugs to a strong opioid such as morphine, omitting the middle step of the analgesic ladder.

Although this chapter is concerned only with the management of pain, care of the patient with a terminal illness requires management of all aspects of the patient. The Liverpool Care Pathway (LCP) is a resource recommended to promote high-quality care in the last days of life (Ellershaw and Wilkinson, 2003). At a basic level, the LCP is a way of acknowledging that death is imminent and ensuring the patient's comfort by omitting long-term non-essential medication and anticipatory prescribing in case the patient experiences pain, delirium, vomiting or breathlessness.

Opioid use in cancer pain

Morphine is the first-line opioid used for the management of cancer pain and may be given in immediate or modified release oral formulations. If not tolerated, alternatives such as oxycodone or hydromorphone, both having relatively long half-lives, may be considered. Optimal dosage is determined on an individual basis for each patient by titration against the pain. Patients requiring long-term modified release opioids should have additional oral doses of rapidly acting opioid to act as an 'escape' medicine for incident or breakthrough pain. The British National Formulary recommends that the standard dose of a strong opioid for breakthrough pain is one-tenth to one-sixth of the regular 24 hour total daily dose. Methadone should not be used as first-line treatment of cancer pain, but may be useful when alternatives have failed or the patient has experienced intolerable adverse effects.

When the oral route is unavailable, other routes of administration such as the buccal, rectal, transdermal or parenteral (subcutaneous, intravenous) or spinal (epidural or intrathecal) routes may be considered. Syringe drivers or implanted pumps may be used to provide analgesia in cases where conventional opioid delivery is ineffective. Morphine and oxycodone are available for parenteral administration and in the UK, diamorphine is also suitable and readily available. Diamorphine hydrochloride has the advantage of being very water soluble, so a high dose may be given in a small volume, which reduces the frequency of changes of syringes and refills necessary to provide adequate pain relief. The proportion of patients who need an implanted pump for intrathecal drug delivery is extremely small and is confined largely to those who are persistently troubled with unacceptable adverse effects. Such patients may achieve pain relief with lower equivalent opioid doses and have few problems with side effects. Long-term maintenance of indwelling lines and catheters requires training for the patient and specialist expertise from physicians and nursing teams, but excellent long-term results are possible.

Use of adjuvant drugs and treatments for cancer pain

Neuropathic pain is common in cancer. As many as 40% of cancer patients may have a neuropathic component to their pain. Tricyclic antidepressants and anti-epileptic drugs should be introduced early but where these are ineffective, ketamine may have an important role.

Levomepromazine, a phenothiazine with analgesic activity, is a useful alternative when opioids cannot be tolerated. It causes neither constipation nor respiratory depression and has antiemetic and anxiolytic activity. It is sedative, which may be either a virtue or a problem in palliative care.

Corticosteroids are useful in managing certain aspects of acute and persistent cancer pain. They are particularly useful for raised intracranial pressure and for relieving pressure caused by tumours on the spinal cord or peripheral nerves. Dexamethasone is the most commonly used steroid to ameliorate raised intracranial pressure in patients with brain tumours. High steroid doses given for 1 or 2 weeks do not require a reducing-dosage regimen. Also, they may produce a feeling of well-being, increased appetite and weight gain, all beneficial for cancer patients, although these effects are usually transient.

It is essential that underlying causes of pain be treated; therefore, it is appropriate to use antibiotics to treat infections, radiotherapy to reduce tumour bulk or control bone pain, or surgery to achieve fracture fixation or to relieve bowel obstruction in conjunction with antispasmodics such as hyoscine butylbromide.

Specific cancer pain syndromes

Three types of malignant pain are briefly outlined below to indicate various therapeutic approaches.

Cancer of the pancreas. Pain is caused by infiltration of the tumour into the pancreas as well as by obstruction of the bowel and biliary tracts and metastases in the liver. Patients may experience anorexia, nausea, vomiting and diarrhoea, and also are often depressed. Surgery, radiotherapy and chemotherapy may relieve pain for long periods, as does neurolytic blockade of the coeliac plexus. Opioid analgesics

are useful and may be administered intravenously or epidurally by either bolus injection or continuous infusion.

Mesothelioma of the lung. Mesothelioma causes pain when the tumour penetrates surrounding tissues such as the pleura, chest wall and nerve plexuses. The WHO analgesic ladder should be used first, but it should be remembered that a NSAID may be beneficial as inflammation is often a component of the chest wall involvement. Adjuvants such as TCAs or steroids may be helpful. As the tumour progresses, nerve blocks or neurosurgery may be necessary, and invasion of the vertebrae can lead to nerve root or spinal cord compression. In the latter case, high dose steroids such as dexamethasone may be given intravenously, but radiotherapy is also useful in reducing the size of the tumour.

Metastatic bone pain. Metastatic bone pain is usually treated with courses of chemotherapy and radiotherapy, but analgesics may also be beneficial. A prostaglandin-like substance has been isolated from bone metastases and therefore NSAIDs and, more recently, bisphosphonates are often used in bone pain. Steroids also interfere with prostaglandin formation and dexamethasone, therefore, has a role, especially where there is nerve root or spinal cord compression.

Neuropathic pain

Neuropathic pain may be defined as 'pain arising as a direct consequence of a disease or lesion affecting the somatosensory system' and may occur as a result of pathological damage to nerve fibres in a peripheral nerve or in the CNS (see Table 33.3). Neuropathic pain may be spontaneous in nature (continuous or paroxysmal) or evoked by sensory stimuli. As the underlying aetiology is different to inflammatory types of pain, patients typically present with disturbances in sensory function often describing their pain as tingling, shooting or electric shocks. It is possible for patients to present with pain in the context of sensory loss. Unlike inflammatory pain, neuropathic pain serves no biological advantage and can be described as an illness in its own right.

Typically, neuropathic pain does not respond as well to conventional analgesics, such as paracetamol and NSAIDs. Guidelines for the pharmacological management of neuropathic pain in the non-specialist setting have been published (National Institute for Health and Clinical Excellence, 2010).

Table 33.3 Examples of causes of neuropathic pain

Cause of neuropathy	Examples
Trauma	Phantom limb Peripheral nerve injury Spinal cord injury Surgical
Infection/inflammation	Post-herpetic neuralgia HIV
Compression	Trigeminal neuralgia Sciatica
Cancer	Invasion/compression of nerve tissue by tumour
Ischaemia	Post-stroke pain Metabolic neuropathies (e.g. diabetic peripheral neuropathy)
Demyelination	Multiple sclerosis
Drugs	Vinca alkaloids Ethanol Taxols Anti-bacterials for TB and HIV

Specific neuropathic pain syndromes

Postherpetic neuralgia. The pain associated with herpes zoster infection is severe, continuous and often described as burning and lancinating. Antiviral therapy, such as aciclovir, initiated at the first sign of the rash can reduce the duration of the pain, particularly postherpetic pain, which follows the disappearance of the rash. Tricyclic antidepressants such as amitriptyline are the mainstay of treatment, commencing with low doses (e.g. amitriptyline 10–25 mg at night) and gradually increased according to pain relief (usual dose amitriptyline 50–75 mg at night). This may be combined with anti-epileptic drugs if the response is poor or incomplete. Carbamazepine is historically important but newer anti-epileptic drugs, such as gabapentin and pregabalin, are considered first-line therapy and may be better tolerated. One study has demonstrated a significant difference in the incidence, and to a lesser extent the intensity, of pain in patients who received a single epidural methylprednisolone and bupivacaine injection, compared with those who received antiviral therapy and analgesia as 'standard care' (van Wijck et al., 2006). However, given the modest clinical effects on acute pain and no effect on the incidence of postherpetic neuralgia, the routine use of epidural local anaesthetic and steroid injection is not widely supported.

Diabetic peripheral polyneuropathy. Nerve damage and neuropathy is one of the long-term complications of diabetes mellitus (see Chapter 44) and is most prevalent in elderly patients with type II diabetes. Often patients describe numbness but also experience a burning sensation on their feet. The sensory loss can result in painless foot ulcers. Tricyclic antidepressants or serotonin noradrenaline reuptake inhibitors (duloxetine or venlafaxine), and anti-epileptics, such as gabapentin and pregabalin, have been demonstrated to be beneficial.

Trigeminal neuralgia. Trigeminal neuralgia presents as abrupt, intense bursts of severe, lancinating pain, provoked by touching sensitive trigger areas on one side of the face. The disorder may spontaneously remit for periods of several weeks or months. Anti-epileptic drugs, particularly carbamazepine, have been used successfully. If drug therapy is ineffective, neurosurgical techniques such as decompression of the fifth cranial nerve may be considered. If surgery is successful, anti-epileptics should be withdrawn gradually afterwards.

Peripheral nerve injury and neuropathy. Damage to, or entrapment of, nerves can cause pain, unpleasant sensations and paraesthesiae. Tricyclic antidepressants and anti-epileptic drugs, such as gabapentin, have been used with some success to treat neuropathic pain (Moore et al., 2011). A neuroma occurs when damaged or severed nerve fibres sprout new small fibres in an attempt to regenerate. Pain develops several weeks after the nerve injury, and is often due to the neuroma growing into scar tissue, causing pain as it is stretched or mobilised. Treatment of neuroma is very difficult and few treatments are successful. Options include surgery and injections of steroid and local anaesthetic agents.

Complex regional pain syndromes

These are an important group of painful conditions that may follow trauma or damage to nerves and are characterised by neuropathic pain, trophic changes and motor dysfunction. The key elements of successful treatment are effective multi-modal analgesia, including drugs with efficacy for neuropathic pain, and aggressive physiotherapy to facilitate a return to normal function. Sympathetic blockade using local anaesthetics may have a therapeutic role.

Back and neck pain

Back pain is one of the commonest reasons for presentation to a medical practitioner. Despite this, the problem is poorly understood. The most practical classification is based on the duration of symptoms (BenDebba et al., 1997). Acute low pain is generally defined as pain that lasts for a few days or weeks. The majority of these problems tend to be self-limiting and resolve spontaneously. Typical treatments include rest, adequate analgesia with paracetamol, combined with a NSAID and/or a weak opioid, and physiotherapy.

Persistent back pain lasts for much longer and progressively leads to a chronic state associated with pain, depression, anxiety and disability. Early intervention is necessary to ensure good functional and vocational outcomes. If a patient is off work for as much as 6 months, then there is a less than 50% chance of them ever returning to work. The likelihood of returning to work falls to less than 25% after 1 year and is almost zero after 2 years. Although pharmacological therapies may aid rehabilitation, other treatment strategies have a greater role to play in the management of persistent back pain. Guidelines for the management of non-specific persistent low back pain have been developed (National Institute for Health and Clinical Excellence, 2009). It is essential for the patient to develop self-management skills, and current recommendations emphasise the importance of using a biopsychosocial approach to manage this problem. Other treatment options include exercise programmes, manual therapy and acupuncture.

Osteoarthritis and rheumatoid arthritis

Pain often is a presenting symptom in osteoarthritis or the inflammatory arthritidies, which include rheumatoid arthritis. The pathophysiology and management of osteoarthritis and rheumatoid arthritis is covered in Chapter 53.

Myofascial pain

Myofascial pain is pain arising from muscles and is associated with stiffness and neuropathic symptoms such as tingling and paraesthesiae. It may occur spontaneously or following trauma, such as whiplash injury. Myofascial pain syndrome is sometimes also termed myositis, fibrositis, myalgia and myofasciitis. Acute muscle injury can be treated using first aid techniques with the application of a cooling spray or ice to reduce inflammation and spasm, followed by passive stretching of the muscle to restore its full range of motion. Injection therapy with local anaesthetic or saline may be used to disrupt sensitive muscle trigger points. Local injections of botulinum toxin have also been shown to be effective where muscle spasm is prolonged and severe. TENS and acupuncture have an important role to play in reducing pain and muscle spasm. Treatment of persistent myofascial syndromes should always include a programme of physical therapy.

Postamputation and phantom limb pain

The majority of amputees suffer significant stump or phantom limb pain for at least a few weeks each year. Pain will be present in the immediate postoperative period in the stump, and this may be caused by muscle spasm, nerve injury and sensitivity of the wound and surrounding skin. As the wound heals, the pain generally subsides. If it does not, the reason may be vascular insufficiency or infection. Pain occurring some number of years after amputation may be caused by changes in the structure of the bones or skin in the stump. Reduction in the thickness of overlying tissue with age may expose nerve endings to increased stimuli or ischaemia. Usually, conventional analgesics are beneficial for stump pain, although sometimes relatively high doses may be required. Tricyclic antidepressants may also be helpful for stump pain, and surgery may be necessary to restore the vascular supply or reduce trauma to nerve endings.

Phantom pain is a referred pain which produces a burning or throbbing sensation, felt in the absent limb. Cramping sensations are caused by muscular spasm in the stump. The patient with phantom limb pain is often anxious, depressed and frightened, all of which exacerbate the pain. Conventional analgesic drugs alone are generally not adequate for phantom pain, but TCAs and anti-epileptic drugs are useful adjuvants. Other therapy which can be effective includes TENS and sympathetic blockade. These patients frequently require management at specialist pain centres.

Headache

Everybody experiences the occasional tension headaches. They are caused by muscle contraction over the neck and scalp. Often they respond to simple analgesics available over-the-counter, such as paracetamol and NSAIDs. They may also respond to TCA drugs given as a single dose at night as well as non-pharmacological treatments, such as TENS. NSAIDs may be indicated if the headache is associated with cervical spondylosis or neck injury.

Migraine

Most migraine attacks respond to simple analgesics such as aspirin or paracetamol. Soluble preparations are best, as gut motility is reduced during a migraine attack and absorption of oral medication may be delayed. Migraine treatment has improved markedly with the development of the triptan drugs such as almotriptan, eletriptan, rizatriptan, sumatriptan, naratriptan and zolmitriptan (Goadsby, 2005). These are $5HT_{1B/1D}$-agonists that will often abort an attack, especially when given by the subcutaneous route. Their vasoconstrictor activity precludes their use in patients with angina or cerebrovascular disease but side effects are less serious than with the ergot derivatives they have replaced.

Prophylactic drug treatment of migraine includes α-adrenergic blockers, anti-epileptics and TCAs. Persistent treatment is undesirable.

Cluster headache

Cluster headache is a disabling condition characterised by severe unilateral head pain occurring in clusters of attacks varying from minutes to hours. It shares some pathological features with migraine and treatment is similar, although high-resolution MRI studies have shown specific anatomical differences in the brains of people with cluster headache. Triptans are effective in acute attacks, as is inhalation of 100% oxygen. Prophylaxis is similar to that of migraine.

Dysmenorrhoea

Dysmenorrhoea is a common cause of pelvic pain in women. NSAIDs are effective as first-line therapy due to their effect on cyclo-oxygenase inhibition but it can be helped also by the prescription of oral contraceptives, since pain is absent in anovulatory cycles. Dysmenorrhoea due to endometriosis may require therapy with androgenic drugs such as danazol or regulators of the gonadotrophins such as norethisterone.

Burn pain

Patients with burns may require a series of painful procedures such as physiotherapy, debridement or skin grafting. Premedication with a strong opioid before the procedure and the use of Entonox® (premixed 50% nitrous oxide and 50% oxygen) may be necessary to control the pain. Regular opioid administration may be useful to prevent the pain induced by movement or touch in the affected area. The anaesthetic drug ketamine (see above) has potent analgesic activity when used in subhypnotic doses. Its short duration of action may be beneficial to reduce the pain of dressing changes or other forms of incident pain. Even with low doses, a significant proportion of patients will experience side effects of dysphoria or hallucinations. These can be treated with benzodiazepines or antipsychotic compounds, such as haloperidol.

A summary of medicine indications and common therapeutic problems associated with analgesic use are presented in Table 33.4.

Table 33.4 Common therapeutic problems

Problem	Solution	Example
Neuropathic pain	Anti-epileptics	Carbamazepine Sodium valproate Gabapentin Lamotrigine
	Antidepressants	Amitriptyline Imipramine
	Intravenous anaesthetic agents	Ketamine
Malignant bone pain	Bisphosphonates	Pamidronate Calcitonin
Muscle spasm/ spasticity	Skeletal muscle relaxants	Baclofen Dantrolene Botulinum toxin (type A)
Raised intracranial pressure	Corticosteroids	Dexamethasone Prednisolone
Nausea with morphine	Antiemetic	Cyclizne Droperidol Ondansetron
	Use an alternative route of administration	Topical or subcutaneous
Constipation	Determine if drug induced, for example, opioids or tricyclic antidepressant	Co-prescribe laxatives (e.g. docusate sodium and senna)
Antidepressants in patients with ischaemic heart disease	Use a less cardiotoxic antidepressant	Duloxetine, venlafaxine
Drug interactions with carbamazepine	Use an anti-epileptic which does not affect hepatic enzymes	Gabapentin
Renal failure	Morphine accumulates; use lower dose Use a drug which is not eliminated by kidney	Fentanyl Buprenorphine
Sedation/ impaired cognition	Identify any drug-related causes and adjust dose or stop drug	

Case studies

Case 33.1

Mrs NP is a 55-year-old care home assistant who has type 2 diabetes. Her current prescription is for metformin 500 mg three times a day and amitriptyline 50 mg. When collecting her

repeat prescription she mentions that she 'Can't get on with the new tablets' because they make her very drowsy in the mornings. You invite Mrs NP to attend to review her medication. During the consultation Mrs NP explains that for some time she has suffered from constant tingling and occasional shooting pain in her legs and feet and 3 months ago amitriptyline 10 mg daily was prescribed. About 1 month ago the dose of amitriptyline was increased to 50 mg daily. She takes the dose at night, as advised by her primary care doctor. When she works an early shift (about three times a week) she usually omits the dose of amitriptyline to be sure that she wakes up in time to get to work. Mrs NP says that she takes the metformin regularly and has no associated problems. She is keen to be fit enough to work because she is supporting her youngest son who is studying to be a doctor.

Question

What advice should you give to this patient?

Answer

Mrs NP has developed diabetic peripheral neuropathy, a type of neuropathic pain. She is experiencing intolerable side effects from the increased dose of amitriptyline and therefore does not take it regularly. There are several options to improve tolerability. Firstly, Mrs NP should consider increasing the dose of amitriptyline more slowly. She may also benefit from taking her amitriptyline dose earlier in the evening, approximately 60–90 min before retiring to bed, so that it results in less hangover effect the following day. If neither of these strategies is beneficial, she should consult her primary care doctor about switching to an alternative drug to manage her neuropathic symptoms. Recent guidance (National Institute for Health and Clinical Excellence, 2010) recommends either pregabalin or duloxetine as alternatives to a tricyclic anti-depressant as first-line therapy for neuropathic pain in the non-specialist setting.

Case 33.2

A 55-year-old lady with metastatic abdominal cancer from a probable primary in the pelvis presents with an abdominal mass. Her pain is uncontrolled despite regular prescription of oral opioids, and she has been sick for a week. Subacute bowel obstruction is present.

Question

How should this lady be managed?

Answer

Management should begin with admission and rehydration. She may be dehydrated and have marked electrolyte abnormalities which would need to be corrected. The oral route is unavailable for the delivery of adequate analgesia, and thus consideration should be given to the use of parenteral administration, either by the subcutaneous route or using patient-controlled analgesia. The sickness should be treated, and an underlying cause sought. This may be subacute obstruction which, in turn, may be due to constipation caused by the opioids or by the disease process. Abdominal masses that indent on palpation are faeces (not tumour). Abdominal radiographs would show fluid levels if there was obstruction rather than constipation. Other possible causes of vomiting are recent anticancer therapy, anxiety, dyspepsia from NSAIDs, raised intracranial pressure and vertigo.

Surgery may be needed to relieve the obstruction, but the need may be avoided by use of hyoscine butylbromide, which may control colic with little additional sedation. If the problem is one of constipation, rectal measures may be necessary to re-establish function. These may include suppositories, enemas or digital disimpaction. Once control of pain has been achieved and bowel function has returned to normal, she must receive regular combination laxative therapy, ideally a stimulant laxative such as senna, and a faecal softener, such as docusate sodium. A high fluid intake and increased dietary fibre should be encouraged, as this will help prevent stool from becoming hard.

There has been interest in the use of peripheral opioid receptor antagonists to reduce opioid-induced constipation. As they have higher affinity for the opioid receptor than the agonist, they bind preferentially to opioid receptors in the gastro-intestinal tract, allowing the agonist to continue to have its desired effect in the CNS. A combination of prolonged-release oxycodone and prolonged release naloxone (Targinact®) may be an alternative if maximal laxative therapy does not help this patient.

Attention should be paid to Mrs NP's emotional and spiritual needs at all times.

Case 33.3

A 28-year-old man had a crush fracture of his ankle after falling from a roof. Fixation 9 months ago was described as satisfactory, but his leg is now very painful to even small stimuli and he cannot use it or bear weight. The lower leg has muscle wasting and is much colder than the opposite limb. The skin is very sensitive to touch, shiny and has a poor circulation.

Question

What is this condition and how should this pain be treated?

Answer

The patient presents with a complex regional pain syndrome. Management should be aggressive and directed towards functional restoration. Use of effective multi-modal analgesia using pharmacological and non-pharmacological treatments is required. The aim is to facilitate aggressive physiotherapy and occupational therapy. There may be a burning component to the pain, which may respond to low doses of TCAs such as amitriptyline (10–25 mg at night initially, increased in small increments to 50–75 mg at night).

Aggressive treatment early in the course of the disease can reduce the length of time that patients have this problem, and early referral to seek specialised help is recommended. A small percentage of patients continue to have problems whatever treatment is given.

Case 33.4

An 85-year-old man is admitted to hospital after falling down a flight of stairs and landing heavily on his right side. On admission, he is in severe pain and finds breathing, and especially coughing, unbearably painful. A chest X-ray reveals that he has fractures of the 5th to 8th ribs on the right side.

Question

How should his pain be managed and what are the risks of under treatment?

Answer

Multiple rib fractures are potentially very serious and good analgesia can prevent potentially dangerous complications. Initial analgesia should include both potent opioids and NSAIDs (unless contraindicated). Opioids should be administered parenterally in the first instance and subsequent use of patient-controlled analgesia would allow the patient to titrate their own analgesic requirements. The chest injury may well result in damage to the underlying lung and it is essential to administer unrestricted high-flow oxygen to the patient as the combination of lung injury and ventilatory suppression secondary to either pain or the effects of opioids could lead to dangerous hypoxia. TENS may also prove helpful.

Arterial oxygen saturation (and preferably arterial blood gases) should be monitored. If pain remains poorly controlled or the patient's oxygenation deteriorates, thoracic epidural analgesia using a mixture of local anaesthetic and opioid may be considered.

Failure to treat pain adequately in this situation may lead to a reduction in the patient's ability to cough and clear secretions from the chest. This can lead to respiratory failure and even death. Analgesia should be sufficient to allow regular physiotherapy in order to minimise the risk of such complications.

Case 33.5

A 45-year-old woman presents to her primary care doctor with a 2-day history of back pain following a lifting injury at work. The pain is constant and aching in character with radiation into the posterior aspect of both thighs as far as the knee. Physical examination shows her to be maintaining a very rigid posture with some spasm of the large muscles of the back. Her range of movement is very poor but there are no neurological signs in the legs.

Question

Which drugs may help this lady's pain? What other advice should be given?

Answer

Acute back pain is very common and is rarely associated with serious spinal pathology. The absence of neurological signs is reassuring and indicates that early activity, possibly aided by a short course of analgesics, is the best way forward. Regular paracetamol every 6 h should be first-line treatment. This may be combined with NSAIDs, if tolerated. A muscle relaxant such as baclofen 20–40 mg/day in divided doses may be beneficial for short-term use only. The role of opioids is less clear. Short-term (7–14 days) use of a weak opioid such as codeine or tramadol is probably safe. Longer term use is less satisfactory as there is no clear evidence of their efficacy and sedative side effects may reduce the patient's capacity and motivation to remain active.

The patient should be advised to remain active and accept that some pain is likely during the recovery phase. Failure to remain active and, in particular, excessive bed rest are both associated with worse outcomes.

Case 33.6

A 50-year-old man is admitted to hospital with an acute onset of severe mid-thoracic spinal pain. He is found to be anaemic and investigations show that he has multiple myeloma with widespread bony lesions, including fresh spinal fractures.

Question

Which drugs may help this man's pain? What particular hazards may occur in this condition?

Answer

This patient is extremely ill and even with aggressive chemotherapy, he is unlikely to survive more than a few months. Most of his pain will be related to the destruction of bone and the aim should be to provide pain relief via a 'central' mechanism through the use of opioids as well as reducing the rate of bone destruction and associated inflammatory responses. A potent opioid will be required and oral morphine would usually be the drug of first choice. In this situation, a combination of a modified release preparation together with liberal 'as required' dosing would be appropriate. The correct dose is the dose required to produce adequate pain relief without producing excessive sedation. Inflammatory pain may be improved by the use of NSAIDs and these should be given regularly, although they may be contraindicated in this condition (see below). High dose corticosteroids may achieve a similar effect and may also reduce the hypercalcaemia that is often seen in myeloma. Bone destruction and its associated pain may be reduced by the use of bisphosphonate compounds. In this case, intravenous pamidronate should be given.

Renal failure is common in myeloma. This may be due to obstruction of renal tubules by myeloma proteins or the effects of some chemotherapeutic agents. If renal impairment occurs, opioids should be used with caution so as to avoid problems with accumulation. Transdermal fentanyl may be a more appropriate drug. NSAIDs can precipitate acute renal failure in the presence of reduced renal blood flow. Finally, platelet function is often poor in patients with myeloma. This can be due to direct effects of myeloma proteins on platelets, bone marrow replacement by myeloma or the effects of chemotherapy. Use of NSAIDs may be associated with increased risk of gastro-intestinal haemorrhage.

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Useful websites

The Radar Approach to Pain,
http://www.painradar.co.uk/acute-pain-management-consensus.aspx.
Oxford Pain Internet site,
http://www.medicine.ox.ac.uk/bandolier/booth/painpag/index.html.
Change Pain,
http://www.change-pain.co.uk/
PalliativeDrugs.com,
http://www.palliativedrugs.com/
The British Pain Society,
http://www.britishpainsociety.org.

34 Nausea and vomiting

E. Mason and P. A. Routledge

Key points

- Patients must be assessed carefully, and often reassessed frequently, to identify the primary underlying cause of their nausea and/or vomiting.
- Antiemetics are symptomatic treatments only and do not treat the underlying cause.
- Drug choice is based on an understanding of the likely pathophysiology, the receptors involved, the available route of administration and drug side effects.
- In certain situations, prophylactic regimens are beneficial, for example, motion sickness, post-operative nausea and vomiting, chemotherapy-induced nausea and vomiting.
- Simple regimens are used where possible to prevent postoperative nausea and vomiting, such as parenteral cyclizine or prochlorperazine administered at induction. These and other antiemetics can be used for rescue therapy if vomiting occurs post-operatively.
- The choice of antiemetic to use in conjunction with cytotoxic chemotherapy depends on the emetogenicity of the cytotoxic drugs used. The $5HT_3$ antagonists such as ondansetron are very effective antiemetic drugs when highly emetogenic chemotherapy is used. The addition of dexametasone may provide further benefit.
- Anticipatory emesis associated with chemotherapy can be treated with benzodiazepine and dexametasone is useful in alleviating delayed emesis.

Nausea and vomiting are commonly (but not universally) associated symptoms. The word nausea is derived from the Greek *nautia*, meaning sea-sickness, while vomiting is derived from the Latin *vomere*, meaning to discharge. Nausea is a subjective sensation whereas vomiting is the reflex physical act of expulsion of gastric contents. Retching is defined as 'spasmodic respiratory movements' against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, that is, 'dry heaves' (American Gastroenterological Association, 2001). It is important to differentiate vomiting from regurgitation, rumination and bulimia. Regurgitation is the return of oesophageal or gastric contents into the hypopharynx with little effort. Rumination is the passive regurgitation of recently ingested food into the mouth followed by re-chewing, re-swallowing or spitting out. It is not preceded by nausea and does not include the various physical phenomena associated with vomiting. Bulimia involves overeating followed by self-induced vomiting.

Epidemiology

Nausea and vomiting from all causes have significant associated social and economic costs in terms of loss of productivity and extra medical care. In the community, nausea (with or without vomiting) is most likely to be associated with infection, particularly gastro-intestinal infection. Vestibular disorders may cause vomiting as can motion sickness. Nausea and vomiting may be associated with pain, for example, migraine and severe cardiac pain. Many medicines also cause nausea and occasionally vomiting as a common dose-related (Type A) adverse effect. This is particularly common with opioid use in palliative care. Nausea and vomiting also occur post-operatively or in association with cytotoxic chemotherapy, or radiotherapy. These and other causes of nausea and vomiting are listed in Table 34.1.

Pathophysiology

Complex interactions between central and peripheral pathways occur in the production of the clinical features of nausea and vomiting. The most important areas involved peripherally are the gastric mucosa and smooth muscle (the enteric brain) and the afferent pathways of the vagus and sympathetic nerves. Centrally the significant areas involved are the area postrema, the chemoreceptor trigger zone (CTZ), the nucleus tractus solitarus (NTS) and the vomiting centre.

From a pharmacotherapeutic point of view, the most important aspect of this complex pathophysiology is the variety of receptors involved, including histaminergic (H_1), cholinergic (muscarinic M_1), dopaminergic (D2), serotonergic ($5HT_3$) and neurokinin-1 (NK_1) receptors. In the clinical situation, these become targets for various drugs directed at controlling the symptoms.

There are 10^8 neurons in the intestine and a complex interaction occurs between these, the mucosa, the smooth muscle in the intestine, the parasympathetic (vagus nerve) and sympathetic nerves and the higher centres in the spinal cord and brain to result in normal gastro-intestinal peristaltic activity. The enteric brain and the vagus nerve monitor stimuli from mucosal irritation and smooth muscle stretch which may result in nausea and/or vomiting.

The area postrema in the floor of the fourth ventricle contains the CTZ and is a special sensory organ rich in

Table 34.1 Selected causes of nausea and vomiting (adapted from Quigley et al., 2001)

Central	
i. Intracranial	Migraine Raised intracranial pressure (tumour, infection, haemorrhage, hydocephalus, etc.)
ii. Labyrinthine	Labyrinthitis, motion sickness, Ménière's disease, otitis media
Iatrogenic	Cancer chemotherapy Many other medicines (e.g. opioids) Radiotherapy Post-operative
Endocrine/ metabolic	Pregnancy, uraemia, diabetic ketoacidosis, hyperthyroidism, hyperparathyroidism, hypoparathyroidism, Addison's disease, acute intermittent porpyhria
Infectious	Gastroenteritis (viral or bacterial) Other infections elsewhere
Gastro-intestinal disorders	Mechanical obstruction (gastric outlet or small bowel) Organic gastro-intestinal disorders (e.g. cholecystitis, pancreatitis, hepatitis, etc.) Functional gastro-intestinal disorders (e.g. non-ulcer dyspepsia, irritable bowel syndrome, etc.)
Psychogenic disorders	Psychogenic vomiting, anxiety, depression
Pain related	Myocardial infarction

dopaminergic, serotonergic, histaminergic and muscarinic receptors. It is located outside the blood–brain barrier (BBB) and it is likely that chemicals, toxins, peptides, drugs and neurotransmitters in the cerebrospinal fluid (CSF) and bloodstream interact with this area to cause nausea and vomiting. However, the precise mechanism is not known.

The vomiting centre is situated in the dorsolateral reticular formation close to the respiratory centre and receives impulses from higher centres, visceral efferents, the eighth (auditory) nerve (the latter two through the nucleus tractus solitarius) and from the CTZ (Fig. 34.1). It includes a number of brainstem nuclei required to integrate the responses of the gastro-intestinal tract, pharyngeal muscles, respiratory muscles and somatic muscles to result in a vomiting episode. The vomiting centre may be stimulated in association with, or in isolation from, the nausea process.

The vomiting reflex can be elicited either directly via afferent neuronal connections, especially from the gastro-intestinal tract and is probably dependent on the integrity of the nucleus tractus solitarius, or from humoral factors dependent on the integrity of the area postrema. The sequence of muscle excitation and inhibition necessary for the act of vomiting is probably controlled by a central pattern generator located in the nucleus tractus solitarius, and information from the CTZ and vagus nerve converges at this point.

The central causes of nausea and vomiting include increased intracranial pressure, dilation of cerebral arteries during migraine and stimulation of the labyrinthine mechanism or of the senses of sight, smell and taste.

The peripheral causes of nausea and vomiting include motion sickness, delayed gastric emptying and gastric mucosal irritation (ulceration, NSAIDs). These mechanisms are all mediated through the vagal afferent neurons. The vomiting associated with distension or obstruction of the gastro-intestinal tract is mediated through both the sympathetic and vagal afferent neurons.

Patient management

Management of the patient with nausea and vomiting is approached in three steps.

1. Recognise and correct any complications. This includes correction of dehydration, hypokalaemia and metabolic alkalosis in the acute situation with symptoms of less than 4 weeks duration. Weight loss and malnutrition are features of chronic nausea/vomiting, that is, when symptoms have been present for 4 weeks or longer.
2. Where possible, identify the underlying cause (see Table 34.1) and institute appropriate treatment. Here it is important to be aware that metabolic or endocrine conditions such as hypercalcaemia, hyponatraemia and hyperthyroidism can result in vomiting.
3. Implement therapeutic strategies to suppress or eliminate symptoms (these depend on the severity and clinical context). Ideally, antiemetic drugs are prescribed only when the cause of the nausea and/or vomiting is known, since by suppressing symptoms, they may otherwise delay diagnosis. This is especially true in children. However, they may sometimes be necessary temporarily in situations when directly addressing the underlying cause will not bring symptom relief sufficiently rapidly.

Some scenarios illustrating common therapeutic problems in the management of nausea and vomiting are outlined in Table 34.2.

Antiemetic drugs

Several classes of antiemetic drugs are available that antagonise the neurotransmitter receptors involved in the pathophysiology of nausea and vomiting. These classes of drugs are generally distinguished from each other by the identity of their main target receptor, although some act at more than one receptor.

Antihistamines

This group of medicines includes cinnarizine, cyclizine, diphenhydramine, diphenhydrinate and promethazine. They have some efficacy in nausea and vomiting caused by a wide

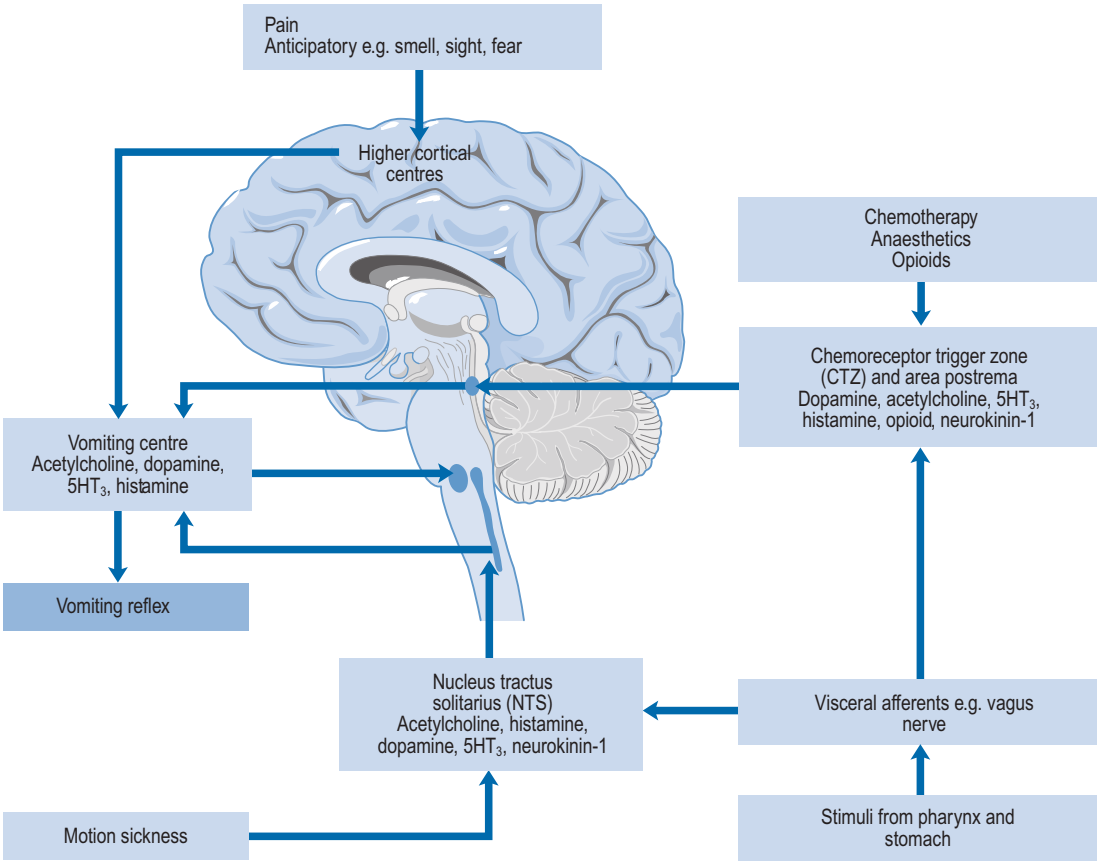

Fig. 34.1 Schematic representation of pathways involved in nausea and vomiting.

Table 34.2 Common therapeutic problems in managing patients with nausea and vomiting

Problem	Possible cause/solution
Persistent nausea and vomiting despite treatment	Is the cause correctly diagnosed? Review the antiemetic agent and the dose: if both correct, change to or add a second agent
Patient with PONV is vomiting despite suitable antiemetic regimen	Check analgesia: pain may be causing nausea and vomiting, or patient-controlled analgesia may require adjustment downwards to reduce analgesic dose
Patient with bowel obstruction is passing flatus	Prokinetic drug is first-choice antiemetic. $5HT_3$ antagonists may also be effective
Patient with bowel obstruction is not passing flatus	Spasmolytic drug is first choice. Prokinetic drugs are contraindicated. Similarly, bulk-forming, osmotic and stimulant laxatives are inappropriate; phosphate enemas and faecal softeners are better
A terminally ill patient receiving diamorphine is vomiting, despite use of haloperidol	Levomepromazine given as a 24-h subcutaneous infusion can be very effective
A patient with renal failure (uraemia) is vomiting	Consider a $5HT_3$ antagonist
A patient develops an acute dystonic reaction to metoclopramide	Give an intramuscular injection of an antihistamine. Such extrapyramidal reactions to metoclopramide are more common in young adults (especially females) and this agent is best avoided in this group

PONV, post-operative nausea and vomiting.

range of conditions, including motion sickness and post-operative nausea and vomiting (PONV). They are thought to block H_1 receptors in the CTZ and possibly elsewhere. However, several of these agents also have potent anticholinergic (M_1) receptor antagonist activity, which may contribute significantly to their efficacy as well as their adverse effect profile (see Section 'Anticholinergics'). The sedative effects of some antihistamines may also contribute to antiemetic activity, although this property appears not to be essential and it can be a particular problem when skilled tasks, such as driving, need to be performed. Nevertheless, the newer non-sedating antihistamines, for example, fexofenadine, are of limited value in nausea and vomiting.

Anticholinergics

This is one of the oldest classes of antiemetics, of which many members are potent inhibitors of muscarinic receptor (M_1) activity both peripherally and centrally. Anticholinergic drugs such as atropine, hyoscine and glycopyrronium have been used preoperatively to inhibit salivation and excessive respiratory secretions during anaesthesia. Anticholinergics act by inhibiting cholinergic transmission from the vestibular nuclei to higher centres within the cerebral cortex, thereby explaining their predominant use in the treatment of motion sickness. Hyoscine hydrobromide (scopolamine hydrobromide) is the most widely used agent and it can be given orally, by subcutaneous or intramuscular injection, or transdermally for motion sickness. Inhibition of peripheral muscarinic receptors can cause drowsiness, dry mouth, dilated pupils and blurred vision, decreased sweating, gastro-intestinal motility and gastro-intestinal secretions and difficulty with micturition. Anticholinergic agents may also precipitate closed-angle glaucoma in susceptible individuals.

Antidopaminergics

Phenothiazines and butyrophenones

Phenothiazines (e.g. prochlorperazine, perphenazine, and trifluoperazine) and butyrophenones (e.g. haloperidol and droperidol) act as antagonists at dopamine (D2) receptors in the CTZ, but may also have cholinergic (M_1) and histaminergic (H_1) receptor antagonist activity. As a consequence they share several adverse effects with antihistamines and anticholinergics, including drowsiness. In addition, the dopamine-blocking effects may be associated with acute dystonia (especially in children), and tardive dyskinesias or parkinsonism when used for prolonged periods. Prochlorperazine is less sedating and available as a buccal tablet and suppository for use when vomiting precludes oral administration. Phenothiazines are sometimes used for drug-associated emesis, including chemotherapy-induced nausea and vomiting (CINV), but like the butyrophenones, have in many situations been superseded by more specific agents such as metoclopramide and the selective $5HT_3$ antagonists. Levomepromazine is sometimes used to relieve nausea and vomiting in terminal care.

Metoclopramide

At lower doses, metoclopramide acts as a selective D2 antagonist at the CTZ and its effects mirror those of the phenothiazines and butyrophenones. However, it also exerts peripheral D2 antagonism at these doses, and stimulates cholinergic receptors in gastric smooth muscle, thus stimulating gastric emptying. It may, therefore, be more effective than phenothiazines and butyrophenones when nausea is related to gastro-intestinal or biliary disease. At higher doses, it may exert some $5HT_3$-receptor antagonism but at these doses, the incidence of acute dystonic reactions, particularly in young women and the elderly, may limit its usefulness in CINV.

Domperidone

Although domperidone does not readily cross the BBB, it is a selective antagonist of D2 receptors at the CTZ, which lies outside the BBB in the area postrema. It may also have peripheral effects that result in increased gastro-intestinal motility and faster gastric emptying. It is used in drug-associated vomiting, including CINV, and is relatively non-sedating. It can be given orally or by suppository. Acute dystonic reactions occur less frequently than with metoclopramide. It prevents nausea and vomiting during treatment with apomorphine and other dopamine agonists in Parkinson's disease and is also used to treat vomiting associated with emergency hormonal contraception.

Selective $5HT_3$-receptor antagonists

Serotonin or 5-hydroxytryptamine (5HT) plays an important role in nausea and vomiting. The subtype $5HT_3$-receptors, which mediate the vomiting pathway, are located peripherally on vagal nerve endings in the gastro-intestinal tract and centrally in the brain, with high concentrations found in the area postrema and nucleus tractus solitarius. Highly emetogenic agents such as cisplastin are thought to disrupt gastric mucosa and initiate the release of 5HT from enterochromaffin cells, which stimulate the $5HT_3$-receptors on afferent vagal nerve endings and thus trigger the emetic reflex. Selective $5HT_3$-receptor antagonists that act centrally and peripherally are now commonly used to treat or prevent CINV (with drugs of moderate to high emetogenic potential) and PONV. They are also effective in radiotherapy-induced nausea and vomiting. Selective $5HT_3$ antagonists are generally well tolerated, with the most common adverse effects being constipation, headache, dizziness and sensation of warmth or flushing. Some available agents include granisetron, ondansetron and palonosetron. They are all more expensive than antihistamines, phenothiazines, anticholinergics or dopamine antagonists.

Neurokinin-1 (NK_1) receptor antagonists

Substance P is a bioactive peptide that shares a common amino acid sequence with other bioactive peptides known as tachykinins. It appears to play an important role as a neurotransmitter in emesis as well as in pain and a number of

other inflammatory processes. Substance P binds to the subtype neurokinin-1, or NK_1 receptors, which are found in the area postrema and nucleus tractus solitarius. Selective NK_1 receptor antagonists, aprepitant and fosaprepitant (a prodrug of aprepitant), are now available for use as an adjunct to dexametasone and a $5HT_3$ antagonist in preventing, but not treating, nausea and vomiting associated with moderately and highly emetogenic chemotherapy. They appear to be well tolerated but it is an inhibitor (and sometimes inducer) of cytochrome P450 (CYP3A4) and inducer of CYP2C9 and glucuronidation, so potential drug interactions with chemotherapeutic agents as well as other concomitantly administered agents, for example, possibly warfarin, may occur.

Cannabinoids

It is likely that the antiemetic activity of cannabinoids is related to stimulation of central and peripheral cannabinoid (CB1) receptors. Cannabinoids have modest antiemetic activity that is of similar magnitude to prochlorperazine in CINV, but they can cause a range of central nervous adverse effects, including drowsiness and sometimes behavioural disturbances, which may at times be severe. Thus, while the synthetic cannabinoid nabilone is indicated for nausea and vomiting caused by cytotoxic chemotherapy unresponsive to conventional antiemetics, it is recommended that patients are made aware of possible changes in their mood and other unwanted effects on their behaviour. In addition, nabilone should be used under close supervision, preferably in a hospital setting.

Corticosteroids

Corticosteroids are known to have antiemetic effects. Their mechanism of action is unclear but steroid receptors are thought to exist in the area postrema. As single agents, they appear to be at least as effective as prochlorperazine in preventing nausea and vomiting associated with mild to moderately emetogenic cytotoxic chemotherapy. Dexametasone, the most widely used corticosteroid in this context, improves the antiemetic activity of prochlorperazine and metoclopramide and may reduce some of the side effects associated with the latter. When combined with $5HT_3$ antagonists, corticosteroids are particularly effective in CINV associated with moderately emetogenic chemotherapy, or when used in delayed emesis. The same combination of dexametasone and a $5HT_3$ antagonist, and sometimes with aprepitant, may also be effective in CINV associated with highly emetogenic chemotherapy regimens.

Complementary and alternative medicines

Systematic reviews support the use of stimulating wrist acupuncture point P6 for preventing PONV in combination with, or as an alternative to, conventional antiemetics (Lee and Done, 2004). A systematic review of randomised trials has also demonstrated the efficacy of ginger (at least 1 g preoperatively) in PONV. Ginger has also been claimed to be beneficial in motion sickness and pregnancy-associated nausea, but the evidence for each is limited to single randomised trials (Ernst and Pittler, 2000).

Drug treatment in selected circumstances

Post-operative nausea and vomiting

Around 25% of patients experience PONV within 24 h of surgery (Gan et al., 2003). The aetiology is complex and multifactorial and includes patient-, medical-, surgical- and anaesthetic-related factors. Management is multimodal and involves strategies to reduce baseline risk such as using less emetogenic induction agents, anaesthetic agents and analgesics, consideration of the use of regional rather than general anaesthesia, adequate hydration and intraoperative supplemental oxygen use and avoidance of high-dose neostigmine.

Many antiemetic agents have some efficacy in post-operative nausea and vomiting but combination therapy with drugs from different classes may be needed in patients at high risk, such as those with a previous history of post-operative nausea and vomiting or motion sickness, or after high-risk procedures, for example, prolonged operations. Prophylactic treatments include dexametasone before induction or $5HT_3$ antagonists, antihistamines or phenothiazines at the end of surgery. Metoclopramide and cannabinoids appear to be of limited value in the management of post-operative nausea and vomiting.

Premedication with opioids increases the incidence of post-operative nausea and vomiting and this may be reduced by concurrent administration of either atropine or hyoscine, which are primarily used as anti-secretory drugs at premedication.

Risk scores

Prophylaxis is preferable to treatment and this can often be achieved not only by use of antiemetic drugs but also by suitable planning. For example, not all patients undergoing surgery will experience post-operative nausea and vomiting and universal prophylaxis is not cost-effective (Habib and Gan, 2004). A simple risk scoring system has been devised in which the score increases relative to the presence or absence of four factors:

- female gender
- history of motion sickness or PONV
- non-smoker
- opioid use during operation.

The incidence of post-operative nausea and vomiting with the presence of none, one, two, three or all four of these risk factors has been shown to be 10%, 20%, 40%, 60% and 80%, respectively (Apfel et al., 1999). Use of risk scores based on these criteria helps to appropriately tailor antiemetic use and can significantly reduce the incidence of nausea and vomiting in clinical practice (Apfel et al., 2002; Pierre et al., 2004).

Chemotherapy-induced nausea and vomiting

Three different types of CINV have been identified: acute, delayed and anticipatory. Acute emesis begins within 1 or 2 h of treatment and peaks in the first 4–6 h. Delayed emesis occurs more than 24 h after treatment, peaks at 48–72 h and then subsides over 2–3 days. It occurs characteristically after high-dose cisplatin but may also occur after the related agent carboplatin, as well as cyclophosphamide or an anthracycline. Anticipatory emesis occurs in patients who have developed significant CINV during previous cycles of therapy. Acute CINV is often associated with an increase in plasma serotonin concentrations for the most emetogenic agents, while delayed and anticipatory vomiting seem to be mediated by serotonin-independent pathways.

Management of CINV depends on the emetogenicity of the chemotherapy regimen and the use of combinations of antiemetic drugs based on their varying target receptors. Chemotherapy agents are divided into four emetogenic levels (Table 34.3) defined by expected frequency of emesis (Kris et al., 2006).

In high-level acute emesis, a single dose of a $5HT_3$ antagonist given before chemotherapy is therapeutically equivalent to a multidose regimen with these agents. Odansetron and granisetron appear to be equally effective in CINV and only one study suggests palonosetron is superior to granisetron when given in combination with dexametasone (Billio et al., 2010). Oral formulations of antiemetics are often as effective as intravenous ones. In lower level acute emesis, the cost of the $5HT_3$ antagonists is prohibitive and metoclopramide or prochlorperazine are commonly used and are sufficiently effective.

Dexametasone is the most extensively evaluated steroid in the management of CINV. Used alone, it is not sufficiently potent in CINV. However, it enhances the effect of other agents such as $5HT_3$ antagonists in high-risk situations and, together with metoclopramide, it also appears to be useful in treating delayed emesis.

The best management for anticipatory emesis is the avoidance of acute and delayed emesis during previous cycles. However, when anticipatory nausea and vomiting are a problem, a low dose of a benzodiazepine such as lorazepam is often effective.

When apparently appropriate antiemesis regimens fail, consideration should be given to the possibility of other underlying disease- and medication-related issues (Box 34.1).

Table 34.3 Relative emetogenicity of chemotherapy drugs (from Kris et al., 2006)

Emetic risk (incidence of emesis without antiemetics)	Agent
High (>90%)	Cisplatin Mechlorethamine Streptozotocin Cyclophosphamide ≥1500 mg/m^2 Carmustine Dacarbazine Dactinomycin
Moderate (30–90%)	Oxaliplatin Cytarabine >1000 mg/m^2 Carboplatin Ifosfamide Cyclophosphamide <1500 mg/m^2 Doxorubicin Daunorubicin Epirubicin Idarubicin Irinotecan
Low (10–30%)	Paclitaxel Docetaxel Mitoxantrone Topotecan Etoposide Pemetrexed Methotrexate Mitomycin Gemcitabine Cytarabine ≤1000 mg/m^2 Flurouracil Bortezomib Cetuximab Trastuzumab
Minimal (<10%)	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Fludarabine Rituximab Vinblastine Vincristine Vinrelbine

Pregnancy-associated nausea and vomiting

Pregnancy-associated nausea and/or vomiting occurs in about 70% of women during the first trimester. Risk factors for vomiting include a personal history of previous pregnancy-associated nausea/vomiting or motion sickness or migraine-associated nausea/vomiting, a family history of hyperemesis gravidarum or a large placental mass, for example, due to multiple pregnancy. Symptoms usually begin 4 weeks after the last menses and in 80% of cases end at 12 weeks, having peaked at 9 weeks. In some women, the problem may persist

Box 34.1 Factors that cause nausea and vomiting in their own right and may contribute to the failure of apparently appropriate prophylactic regimens for chemotherapy-induced nausea and vomiting (CINV)

Hypercalcaemia or other metabolic or endocrine disturbance
CNS metastases
Antibiotics such as erythromycin/clarithromycin
Gastro-intestinal obstruction
Radiotherapy enteropathy

until 16–20 weeks. First-trimester nausea and vomiting are not usually harmful to either the fetus or the mother and is not generally associated with a poor pregnancy outcome.

In contrast, hyperemesis gravidarum is a condition of intractable vomiting complicating between 1% and 5% of pregnancies and sometimes resulting in serious fluid and electrolyte disturbance and nutritional deficits.

In first-trimester nausea and vomiting, simple measures such as small frequent carbohydrate-rich meals and reassurance are sufficient to control symptoms. Ginger and P6 acupressure have also been advocated, although the evidence base is equivocal in early pregnancy (Jewell and Young, 2003). More recent studies on the use of acupuncture in pregnancy-associated nausea and vomiting remain unclear (King and Murphy, 2009). It is important to avoid antiemetic drugs when possible, but promethazine has been recommended in severe vomiting, with prochorperazine or metoclopramide as second line agents. In Canada and the USA, a combination of pyridoxine (vitamin B_6) and an antihistamine (doxylamine) is approved for the treatment of nausea in pregnancy but this combination treatment appears to be less effective for controlling vomiting.

In the serious condition of hyperemesis gravidarum, drug therapy may be used, although no trials have shown clear benefit (Jewell and Young, 2003). Fluid and electrolyte replacement, rest and if necessary postpyloric or parenteral feeding to provide nutritional support and vitamins (e.g. thiamine to reduce the risk of Wernicke's encephalopathy) supplementation should be considered. There are few safety or efficacy data on which to select the most appropriate treatments so the agents recommended for vomiting of pregnancy mentioned above are generally used in the first instance in the UK.

Migraine

Migraine is a paroxysmal disorder with attacks of headaches, nausea, vomiting, photophobia and malaise. Treatment is directed at:

- prophylaxis: avoid triggers, try β-blockers, pizotifen and in severe cases a $5HT_{1B/D}$-receptor agonist such as sumatriptan
- analgesia, including aspirin, paracetamol, opioids, NSAIDs
- antiemetics.

Nausea and vomiting in migraine are associated with headache intensity, and the concomitant gastric stasis aggravates the nausea and vomiting and may also delay absorption of oral analgesics. Metoclopramide and domperidone attenuate the autonomic dysfunction and promote gastric emptying but the risk of acute dystonic crisis, especially with metoclopramide therapy should be borne in mind, especially in young women and children, but also in the elderly.

Labyrinthitis

Labyrinthine dysfunction results in vertigo, nausea and vomiting. Episodes may last a few hours or days. Causes include labyrinth viral infections, tumours and Ménière's disease. The onset of episodes is often unpredictable and disabling. Betahistine sometimes has some benefit. The anticholinergics, antihistamines, phenothiazines or benzodiazepines can be used to suppress the vestibular system. Usually hyoscine is sufficient but if there is severe vomiting, prochlorperazine or metoclopramide may be of value.

Motion sickness

Motion sickness is a syndrome, a collection of symptoms without an identifiable cause. It is brought on by chronic repetitive movements which stimulate afferent pathways to the vestibular nuclei and lead to activation of the brainstem nuclei. Histaminergic and muscarinic pathways are involved. The symptoms include vague epigastric discomfort, headache, cold sweating and nausea which may culminate in vomiting. This is often followed by marked fatigue which can last hours or days. Onset of symptoms may be abrupt or gradual.

The anticholinergic agent hyoscine is the prophylactic drug of choice, although there is no evidence of its benefit once motion sickness is established (Spinks et al., 2004). Antihistamine drugs may also be effective. The less sedating antihistamines cinnarizine or cyclizine are used. Promethazine, an antihistamine with sedative effects, is also effective but phenothiazines, domperidone, metoclopramide and $5HT_3$-receptor antagonists appear to be ineffective in this situation. Treatment should be started before travel; for long journeys, promethazine or transdermal hyoscine may be preferred for their longer duration (24 h and 3 days, respectively). Otherwise, repeated doses will be needed.

The most important adverse effect of many drugs used is sedation, whilst for anticholinergic drugs it is blurred vision, urinary retention and constipation. In laboratory studies, the degree to which these effects impair performance, for example, driving a car, is highly variable but subjects who take antimotion sickness drugs should normally be deemed unfit for such tasks. These drugs also potentiate the effects of alcohol.

Many non-drug treatments have been advocated for alleviation of motion sickness, including wristbands, which act on acupuncture points, variously positioned pieces of coloured paper or card, as well as plant extracts such as ginger. The evidence base for these interventions remains very limited.

Drug-associated nausea and vomiting

As well as chemotherapeutic agents, many commonly used medications for other disorders can cause nausea and vomiting (Quigley et al., 2001). Opioids are perhaps the most important group clinically, but dopamine agonists (used in Parkinson's disease), theophylline, digoxin and macrolide antibiotics such as erythromycin can all cause nausea and/or vomiting, often in a dose-related manner (Type A toxicity). High-dose oestrogen, used in postcoital contraception, can produce these symptoms. Consideration should be given to altering the dose of the offending agent when possible, and administering the medication with food. With some agents, tolerance may develop. Thus, tolerance to the emetic effects of opioids often develops within 5–10 days and, therefore, antiemetic therapy is not generally needed for long-term opioid use.

Palliative care-associated nausea and vomiting

Nausea and vomiting are common and distressing symptoms in cancer patients. In most cases, the causes of nausea and vomiting are due to multiple factors such as the tumour itself, concurrent infection, drugs and metabolic disturbances such as renal failure.

It is important to determine the predominant underlying cause for patients' symptoms by taking a careful history, examination and appropriate investigations so that potentially reversible causes of nausea and vomiting can be treated (Box 34.2) and the most suitable antiemetic prescribed.

Oral antiemetic therapy is effective for treatment of nausea in patients with advanced cancer but the subcutaneous route is preferred for those with severe persistent vomiting, either as a single dose injection or a continuous infusion via a syringe driver. When patients' symptoms improve, switching from subcutaneous injection to oral route might be preferable. Non-pharmacological interventions such as avoidance of certain food smells or unpleasant odours, relaxation techniques and use of acupuncture should be considered.

CINV is described in detail elsewhere in the chapter. Strong opioids such as morphine, diamorphine, oxycodone and fentanyl cause nausea and/or vomiting in up to one-third of patients following initiation of treatment but the incidence is lower for weaker opioids such as codeine. Metoclopramide, cyclizine or haloperidol are often given for the relief of the nausea and vomiting induced by opioids.

Gastroduodenal or intestinal obstructions in advanced malignancy are usually caused by occlusion to the lumen (intrinsically and/or extrinsically) or by absence of normal peristaltic propulsion. Surgery remains the definitive treatment for luminal occlusion due to cancer but this is often inappropriate for patients who are frail or with advanced malignancy. The main aim of pharmacological interventions is symptom control. A prokinetic dopamine (D2) antagonist such as metoclopramide or domperidone should be used for patients with nausea and vomiting associated with functional gastric or intestinal stasis. Prokinetics are also used in patients with partial gastric outlet obstruction but can worsen patients' symptoms of abdominal pain in complete gastric outlet obstruction. As prokinetics can exacerbate abdominal colicky pain associated with intestinal obstruction, their use should be avoided in that situation and antiemetics such as cyclizine or haloperidol should be used for symptom control.

Box 34.2 Potentially treatable causes of nausea and vomiting in palliative care

Hypercalcaemia
Constipation
Renal failure
Raised intracranial pressure
Infection
Bowel obstruction
Peptic ulcer disease
Drugs
Anxiety

Dexametasone has also been used for control of symptoms in malignant intestinal obstruction, not only for any antiemetic effect but also to reduce inflammatory tumour oedema around the obstructive lesion. Anticholinergics such as hyoscine butylbromide and somatostatin analogues such as octreotide have been used for symptom relief in intestinal obstruction by reducing gastro-intestinal secretion and motility and thus reducing the frequency and volume of vomitus.

Biochemical disturbances such as hypercalcaemia and renal failure can be a cause of nausea and vomiting in patients with advanced malignancy. However, aggressive treatment with bisphosphonates or insertion of nephrostomy tubes, respectively, would not be appropriate for those who are in the terminal stages of their disease. Haloperidol and cyclizine appear to be effective for biochemical causes of nausea and vomiting. Levomepromazine has antidopaminergic, antihistaminergic, antimuscarinic and antiserotonergic activity. It is effective for most causes of nausea and vomiting and may help alleviate restlessness. It can also be given intramuscularly, intravenously or subcutaneously, including by continuous subcutaneous infusion. It may be considered if first line antiemetics are insufficiently effective. Unfortunately, sedation and postural hypotension can be a problem in association with this agent.

Conclusion

Nausea and vomiting are symptoms caused by a variety of underlying causes. Thorough clinical assessment and appropriate investigations should be undertaken when prescribing a therapeutic trial of an antiemetic. The choice of agent(s) should be based upon the likely cause and severity of the symptoms, the possible underlying pathophysiology, and the recommendations of evidence-based guidelines which take into account clinical effectiveness and cost-effectiveness.

Case studies

Case 34.1

A 30-year-old man presents seeking a remedy for vomiting which had an acute onset, 12 h previously.

Question

What questions should be asked to determine the nature, cause and seriousness of these symptoms?

Answer

The cause of vomiting needs to be determined where possible to allow appropriate treatment to be initiated. The following questions should be asked.

- Are there symptoms or signs of infection, such as diarrhoea, sore throat, dysuria, photophobia, fever? (Infection, often of the gastro-intestinal tract, is one of the commonest causes of vomiting.)

- Is there headache? (Raised intracranial pressure and meningitis can present with vomiting as an early symptom, usually without any nausea.)
- Is there abdominal pain? (Abdominal pain before vomiting usually means an organic gastro-intestinal cause. Pain after vomiting may be due to muscle tenderness.)
- Has the patient started any new drugs (opioids, chemotherapeutic agents, digoxin, nicotine, NSAIDs, oral hypoglycaemics and some antibiotics are common causes) or drunk excess alcohol?
- Is there vertigo? (If present, this is suggestive of a labyrinthine cause.)

Case 34.2

A 19-year-old girl who is 12 weeks pregnant presents to hospital with intractable nausea and vomiting which has not responded to home therapy and which has resulted in hypotension and dehydration.

Question

List, in order of importance, the therapeutic strategies for this problem.

Answer

Treatment would normally involve:

- intravenous rehydration and electrolyte replacement
- bed rest
- antiemetics, such as promethazine; these are likely to be effective and there is little evidence to suggest that they have teratogenic effects
- postpyloric feeding
- steroids
- parenteral nutrition.

Case 34.3

A 45-year-old woman presents with ovarian carcinoma for which she is due to receive a course of cancer chemotherapy.

Question

What drugs might be appropriate, when should they be given, and what advice should be given to the patient regarding monitoring of symptoms after treatment with the chemotherapy?

Answer

This woman is likely to receive repeated cycles of emetic chemotherapy with carboplatin (moderate emetic risk) or cisplatin (high emetic risk) and, therefore, should be given prophylactic antiemetics before the start of chemotherapy. The choice of drug lies between metoclopramide combined with dexamethasone for some moderate emetic risk situations, and one of the $5HT_3$-receptor antagonists (granisetron, ondansetron, or palonosetron) for high-risk situations, with dexamethasone to provide additional benefit. The monitoring of emesis and nausea both within and outside hospital for up to 5 days after treatment is a useful exercise in deciding which patients may need other therapies. It is also important to remember that patients should be given appropriate doses of antiemetics as rescue therapy to cover delayed-onset nausea.

Case 34.4

A hospital with a large number of surgical specialties, including major inpatient thoraco-abdominal and day care procedures, wishes to update its PONV programme.

Question

What principles for a PONV programme should be taken into account?

Answer

The programme should contain a PONV risk score which can be used in preoperation assessment. A simplified score has been devised, adding one point for each of the following: female gender, non-smoking status, history of PONV, and opioid use. In low-risk individuals scoring 0 or 1 (<10% risk), prophylactic antiemetic therapy is unnecessary. Moderate-risk subjects (score 1, risk 10–30%) may require single-agent antiemetic prophylaxis, while in high-risk subjects (score 3, risk 30–60%) two agents (one of them often dexamethasone) may be needed if intravenous anaesthesia is not possible. In very high-risk subjects (score 4, risk > 60%), intravenous anaesthesia should be considered when possible and dexamethasone and another antiemetic agent administered. PONV rescue therapy should be chosen depending on the post-operative clinical situation.

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35 Respiratory infections

A. Robb and A. W. Berrington

Key points

- Oral cephalosporins have better clinical efficacy than penicillins in the treatment of streptococcal pharyngitis.
- There is controversy about whether otitis media should be treated with antibiotics or allowed to run its course.
- Viral respiratory tract infections are usually mild and self-limiting, but influenza and severe acute respiratory syndrome (SARS) can have severe consequences for individuals, for public health and for economic activity.
- Exacerbations of chronic bronchitis are not always infective in origin; antibiotics are used where appropriate but other therapeutic modalities are also valuable.
- *Streptococcus pneumoniae* remains the single most common cause of community-acquired pneumonia (CAP). Reduced susceptibility to penicillin can complicate the management of serious pneumococcal infections, but more significant degrees of resistance are currently not widespread among UK strains.
- CAP can be caused by a variety of pathogens, and this is reflected in the antimicrobial regimens recommended for initial treatment.
- There are many potential causes of hospital-acquired (nosocomial) pneumonia and each unit with patients at risk will have its own resident bacterial flora. This will strongly influence the choice of antibiotics for empiric therapy.
- *Pseudomonas aeruginosa* remains the most important respiratory pathogen in infections complicating cystic fibrosis; antibiotic treatment is targeted at this organism.
- Immunocompromised patients are at risk from a variety of opportunistic respiratory infections, for example, pneumocystis pneumonia in AIDS and invasive aspergillosis in neutropenic states.
- Health care-associated infections such as meticillin-resistant *Staphylococcus aureus* (MRSA) infection and *Clostridium difficile* infection (CDI) remain prevalent and should always be considered when choosing antibiotics.

Respiratory tract infections are the most common group of infections seen in the UK. Most are viral, for which (with some exceptions) only symptomatic therapy is available. In contrast, bacterial infections are a major cause of treatable respiratory illness.

The respiratory tract is divided into upper and lower parts: the upper respiratory tract consists of the sinuses, middle ear, pharynx, epiglottis and larynx, while the lower respiratory tract consists of the structures below the larynx, the bronchi, bronchioles and alveoli. Although there are anatomical and functional divisions both within and between these regions, infections do not always respect such boundaries. Nevertheless, it is clinically and bacteriologically convenient to retain a distinction between upper respiratory tract infections (URTIs) and lower respiratory tract infections (LRTIs).

Upper respiratory tract infections

Colds and flu

Viral URTIs causing coryzal symptoms, rhinitis, pharyngitis and laryngitis, and associated with varying degrees of systemic symptoms, are extremely common. These infections are usually caused by viruses from the rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, influenza virus and adenovirus families, although new viruses continue to be identified. For instance, in 2001, a novel respiratory pathogen was described that has become known as human *metapneumovirus* (hMPV). This causes a spectrum of respiratory illnesses particularly in young children, the elderly and the immunocompromised (Van Den Hoogen et al., 2001).

Colloquially, milder infections are called ‘colds’, while more severe infections may be known as ‘flu’. This term should be distinguished from true influenza, reserved for infection caused by the influenza virus. In general, the management of these infections is symptomatic and consists of rest, adequate hydration, simple analgesics and antipyretics. Apart from one or two exceptional situations, antiviral drugs are not indicated and in most cases are not active. Antibacterial drugs have no activity against viral infections, although in the past they were widely prescribed, sometimes with spurious rationale such as prophylaxis against bacterial superinfection, sometimes simply because patients demanded them. In recent years, heightened awareness of the adverse consequences of antibiotic overuse has led to national campaigns aimed at discouraging the public from seeking antibiotic treatment for viral infections.

Influenza

True influenza is caused by one of the influenza viruses (influenza A, B or rarely C). It can be a serious condition characterised by severe malaise and myalgia and potentially complicated by life-threatening secondary bacterial infections such as staphylococcal pneumonia. Coryzal symptoms are not usually a feature of influenza, but the patient may have

a cough. Influenza tends to occur during the winter months, providing an opportunity to offer preventive vaccination in the autumn. In the UK, influenza vaccine is normally targeted at three groups:

- those at risk of severe infection, for example, people aged 65 years and over, and younger patients in special disease risk groups
- those living in long-stay care facilities in which the infection might spread particularly rapidly, and
- those in whom infection would be problematic for other reasons, such as carers and health care workers.

Unfortunately, the virus mutates so rapidly that the circulating strains tend to change from season to season, necessitating annual revaccination against the prevailing virus.

Influenza A and B infections are amenable to both prevention and treatment with neuraminidase inhibitors (NAIs) and include agents such as zanamivir and oseltamivir, although there is controversy about whether the benefits justify the costs involved. Zanamivir is administered by dry powder inhalation, whereas oseltamivir is given orally. Clinical trials on parenteral administration for use in individuals with life-threatening infections are underway.

National guidelines for the UK recommend NAIs should only be used when influenza is circulating in the community (which is carefully defined), and in patients who are both at risk of developing complications and can commence treatment within a defined time window of onset or exposure (NICE, 2008, 2009). Individuals at risk and eligible for treatment include those:

- with chronic lung disease including asthma and chronic obstructive pulmonary disease (COPD)
- with heart disease (excluding uncomplicated hypertension)
- with chronic kidney disease
- with diabetes mellitus
- with chronic liver disease
- with chronic neurological disease
- who might be immunosuppressed
- aged 65 years or older
- in long-term residential or nursing homes during local outbreaks.

The anti-Parkinsonian drug amantadine, which has activity against influenza A virus, is not recommended for the treatment or prophylaxis of influenza due to emergence of resistance and the high incidence of adverse effects.

Pandemics (or global epidemics) of influenza A occur around every 25 years and affect huge numbers of people. The 1918 'Spanish flu' pandemic is estimated to have killed 20 million people. Further pandemics have taken place in 1957–1958 (Asian flu), 1968–1969 (Hong Kong flu) and 1977 (Russian flu). An avian strain, H5N1, emerged in South East Asia in 2003 and is now considered endemic in many parts of South East Asia and remains a concern for public health (WHO, 2010).

The World Health Organisation declared a worldwide influenza pandemic in June 2009 following the emergence of a novel H1N1 strain of swine lineage. In the UK, NICE guidance was superseded during the pandemic and NAIs were given to all individuals with flu-like illness. A vaccine was also developed. Pandemic planning had been in operation for many years with plans for rapid vaccine development and stockpiling of antivirals. However, in retrospect, infections caused by the pandemic strain were generally associated with much milder disease than seen in previous pandemics, and some authorities have been accused of over-reaction.

The widespread use of NAIs during the 2009 pandemic brought its own problems. Resistance to oseltamavir emerged (Gulland, 2009), and some argued that the cure was worse than the disease (Strong et al., 2009). Further, a Cochrane review (Jefferson et al., 2009) found no good evidence that oseltamivir prevents secondary complications such as pneumonia, one of the main justifications for its widespread use in pandemic influenza. However, the relatively benign course of the 2009 pandemic should not provide false reassurance as to the risks associated with future pandemics.

Sore throat (pharyngitis)

Causative organisms

Pharyngitis is a common condition. In most cases, it never comes to medical attention and is treated with simple therapy directed at symptom relief. Many cases are not due to infection at all but are caused by other factors such as smoking. Where infection is the cause, most cases are viral and form part of the cold-and-flu spectrum. Epstein–Barr virus (EBV), which causes glandular fever (infectious mononucleosis), is a less common but important cause of sore throat since it may be confused with streptococcal infection.

The only common bacterial cause of sore throat is *Streptococcus pyogenes*, the Lancefield group A β-haemolytic streptococcus. Infrequent causes include β-haemolytic streptococci of groups C and G, *Arcanobacterium haemolyticum, Neisseria gonorrhoeae* and mycoplasmas. *Corynebacterium diphtheriae*, the cause of diphtheria, is rare in the UK but should be borne in mind when investigating travellers returning from parts of the world where diphtheria is common. *C. ulcerans* is as common a cause of clinical diphtheria in the UK as *C. diphtheriae* but usually runs a more benign course.

Clinical features

The presenting complaint is sore throat, often associated with fever and the usual symptoms of the common cold. It is standard teaching that sore throats of different aetiology cannot be distinguished clinically. Nevertheless, more severe cases are more likely to be caused by EBV or *S. pyogenes,* and in these patients, there may be marked inflammation of the pharynx with a whitish exudate on the tonsils, plus enlarged and tender cervical lymph nodes.

Group A streptococcal infection has a number of potential complications. Pharyngeal infection may occasionally give rise to disseminated infection elsewhere, but this is rare. More frequent accompaniments are otitis media, peritonsillar abscess and sinusitis. These should be distinguished from the non-suppurative complications of streptococcal infection,

rheumatic fever and glomerulonephritis, which are mediated immunologically. Occasional cases are still seen in the UK and remain important causes of renal and cardiac disease in developing countries. Scarlet fever, a toxin-mediated manifestation of streptococcal infection, is associated with a macular rash and sometimes considerable systemic illness.

In the UK, there has been a recent increase in rates of group A streptococcal infection. This includes invasive group A streptococcal infection (iGAS), associated with infection in normally sterile sites such as blood or tissue. The most common serotypes seen in England and Wales are *emm* 1, 3, and 89; *emm* 3 infections are associated with higher case fatality rates. The cause of the upsurge is unknown but may represent a natural periodic increase or alternatively excess transmission associated with high rates of influenza in 2008 (Lamagni et al., 2009).

Diagnosis

In most cases of pharyngitis, a bacteriological diagnosis cannot be made and thereby these are presumed to be viral in origin. The aim of any diagnostic procedure is to distinguish the streptococcal sore throat, which is amenable to antibiotic treatment, from viral infections, which are not. If a definite bacterial diagnosis is required, a throat swab should be taken for culture and, unless the details of a particular case prompt a search for more unusual organisms, culture techniques are directed towards detecting β-haemolytic streptococci. If bacterial culture is negative and glandular fever is suspected, blood should be taken for serological confirmation using either the non-specific 'monospot test' for atypical lymphocytes or specific tests for antibodies to EBV. Other viruses may be diagnosed by viral culture or serology, but this does not usually contribute to management. Rapid bedside tests are available that detect group A streptococcal antigens in the throat, but there are concerns about their sensitivity and specificity and they have not been widely introduced in the UK.

Treatment

Treatment of viral sore throat is directed at symptomatic relief, for example with rest, antipyretics and aspirin gargles. Streptococcal sore throat is usually treated with antibiotics although the extent to which they shorten the duration of symptoms and reduce the incidence of suppurative complications is modest (Del Mar et al., 2004). Antibiotic treatment also reduces the incidence of non-suppurative complications so is likely to be of greater benefit where these are common. There is also an argument that treating to eradicate streptococcal carriage might reduce the risk of relapse or later streptococcal infection at other sites.

Broadly, there are three treatment strategies:

1. give antibiotics to all patients with suspected streptococcal infection and do not investigate unless symptoms persist
2. give antibiotics to all patients with suspected streptococcal infection but stop them if a throat swab is negative, or
3. wait for throat swab culture results before starting antibiotics.

There is no correct approach and each has its advocates, although the problem of resistance has led to increasing pressure on prescribers to restrict empirical antibiotic use particularly for conditions such as pharyngitis that are frequently viral. The prevailing view is that antibiotics should not be routinely prescribed except where there is a high risk of severe infection, for instance, in immunocompromised patients (NICE, 2010).

Antibiotics effective against *S. pyogenes* include penicillins, cephalosporins and macrolides. Resistance to penicillins and cephalosporins has not (yet) been described in group A streptococci, although about 4% of isolates are resistant to erythromycin. Even against sensitive strains, macrolides such as erythromycin are demonstrably less effective than β-lactams.

Penicillins such as benzylpenicillin (penicillin G) or phenoxymethylpenicillin (penicillin V) have traditionally been regarded as the treatment of choice for streptococcal sore throat, but there is now convincing evidence that cephalosporins are more effective in terms of both clinical response and eradication of the organism from the oropharynx. This was summarised in a large meta-analysis of 40 studies in which 10-day courses of oral cephalosporins and penicillins were compared in the management of children with streptococcal pharyngitis (Casey and Pichichero, 2004). Bacteriological and clinical cure significantly favoured cephalosporins over penicillins, perhaps because penicillins are hydrolysed by β-lactamases produced by organisms such as anaerobes naturally resident in the oropharynx, whereas cephalosporins are not. The 10-day course length became accepted following earlier studies that compared the effect of different durations of penicillin treatment on bacteriological colonisation, but a recent systematic review (Atamimi et al., 2009) found comparable efficacy with shorter courses of newer antibiotics such as azithromycin.

However, despite the therapeutic superiority, it remains debatable whether the extra expense of cephalosporins is justified. Cefalexin is the preferred cephalosporin. Penicillin or amoxicillin is the preferred penicillin, with the proviso that amoxicillin and other aminopenicillins should not be used unless EBV infection is unlikely, since for reasons that are not understood, these drugs often cause skin rashes if used in this condition.

Acute epiglottitis

Acute epiglottitis is a rapidly progressive cellulitis of the epiglottis and adjacent structures. Local swelling has the potential to cause rapid-onset airway obstruction, so the condition is a medical emergency. Previously, almost all childhood cases and a high proportion of adult cases were caused by *Haemophilus influenzae* type b (Hib), with the rest being caused by other organisms such as pneumococci, streptococci and staphylococci. With the advent of routine vaccination against *H. influenzae* type b in October 1992, this disease has become uncommon.

The typical patient is a child between 2 and 4 years old with fever and difficulty speaking and breathing. The patient may

drool because of impaired swallowing. The diagnosis is made clinically and the initial management is concentrated upon establishing or maintaining an airway. This takes priority over all other diagnostic and therapeutic manoeuvres. Thereafter, the diagnosis may be confirmed by visualisation of the epiglottis, typically described as 'cherry-red'. Microbiological confirmation may be obtained by culturing the epiglottis and the blood, but not until the airway is secure.

In view of the high prevalence of amoxicillin resistance among encapsulated *H. influenzae*, the treatment of choice is a cephalosporin. It is customary to use a third-generation cephalosporin such as cefotaxime or ceftriaxone, but there is no reason why the infection should not respond to a second-generation agent such as cefuroxime. If a sensitive organism is recovered, high-dose parenteral amoxicillin may be substituted.

Otitis media

Causative organisms

Inflammation of the middle ear (otitis media) is a common condition seen most frequently in children under 3 years of age. Most cases are due to bacteria, although viruses such as influenza virus and rhinoviruses have been implicated in a sizeable minority. *S. pneumoniae* and *H. influenzae* are the two most commonly encountered bacterial pathogens. *Moraxella catarrhalis* and *S. pyogenes* account for a smaller proportion of cases, perhaps 10%, and other bacteria are seen only rarely.

Clinical features

Classically, otitis media presents with ear pain, which may be severe. If the drum perforates, the pain is relieved and a purulent discharge may follow. There may be a degree of hearing impairment plus non-specific symptoms such as fever or vomiting. Complications include mastoiditis (which is now rare), meningitis and, particularly in the case of *H. influenzae* infection, septicaemia and disseminated infection. With the advent of routine vaccination against *H. influenzae* type b, these complications have become uncommon.

Diagnosis

The diagnosis of otitis media is essentially made clinically and laboratory investigations have little role to play. Unless the drum is perforated, there is little sense in sending a swab of the external auditory canal, the results of which are likely to be unhelpful or misleading. For this reason, a causative organism is rarely isolated and treatment has to be given empirically.

Treatment

There has been much debate about whether or not antibiotics should be used for the initial treatment of acute otitis media. A meta-analysis combined seven clinical trials involving 2202 children and concluded that, although antibiotics confer a modest reduction in pain at 2–7 days, they do not reduce the incidence of short-term complications such as hearing problems and they do cause side effects (Glasziou et al., 2004). The benefit of antibiotic treatment may be greater in children under two than in older children (Damoiseaux et al., 2000), but in any case about 80% of cases treated without antibiotics will resolve spontaneously within 3 days. If antibiotic treatment is to be given, it should be effective against the three main bacterial pathogens: *S. pneumoniae*, *H. influenzae* and *S. pyogenes*. The streptococci are usually sensitive to penicillins, but these are much less active against *H. influenzae*, so the broader spectrum agents amoxicillin or ampicillin are preferred. These drugs have identical antibacterial activity, but amoxicillin is recommended for oral treatment since it is better absorbed from the gastro-intestinal tract. Patients with penicillin allergy may be treated with a later-generation cephalosporin (see later).

About 20% of *H. influenzae* strains are resistant to amoxicillin due to production of β-lactamase, so if there is no response to amoxicillin, an alternative agent should be chosen. Both erythromycin and the earlier oral cephalosporins such as cefalexin are insufficiently active against *H. influenzae* and should not be used. Alternatives include co-amoxiclav (a combination of amoxicillin and the β-lactamase inhibitor clavulanic acid) or an orally active later-generation cephalosporin such as cefixime. Cefuroxime axetil, while active *in vitro*, is poorly absorbed and often causes diarrhoea.

Pneumococcal conjugate vaccines, which are currently given routinely in the childhood vaccination schedule, may reduce the incidence of acute otitis media, although a recent review (Jansen et al., 2009) found only modest benefit. No benefit was found for influenza vaccination (Hoberman et al., 2003). Long-term antibiotic prophylaxis might have a role in some children (Leach and Morris, 2006), but any benefit has to be balanced against the risks.

Acute sinusitis

Causative organisms

Normally, the paranasal sinuses are sterile but they can become infected following damage to the mucous membrane which lines them. This usually occurs following a viral URTI but is sometimes associated with the presence of dental disease. Acute sinusitis is usually caused by the same organisms which cause otitis media, but occasionally other organisms such as *S. aureus*, viridans streptococci (a term used to describe α-haemolytic streptococci other than *S. pneumoniae*) and anaerobes may be found. Viruses are occasionally found in conjunction with the bacteria.

Clinical features

The main feature of acute sinusitis is facial pain and tenderness, often accompanied by headache and a purulent nasal discharge. Complications include frontal bone osteomyelitis, meningitis and brain abscess. The condition may become chronic with persistent low-grade pain and nasal discharge, sometimes with acute exacerbations.

Diagnosis

As with otitis media, this is a clinical diagnosis and obtaining specimens for bacteriological examination is not usually practicable. In patients with chronic sinusitis, therapeutic sinus washouts may yield specimens for microbiological culture.

Treatment

Since the causative organisms are the same as those found in otitis media, the same recommendations for treatment apply. Proximity to the mouth means that anaerobes are implicated quite frequently in acute sinusitis, particularly if associated with dental disease, and in such cases, the addition of metronidazole may be worthwhile. Amoxicillin/clavulanate (co-amoxiclav) has also demonstrated effectiveness. Doxycycline has proved popular due to its broad spectrum of activity and once-daily dosage.

Lower respiratory infections

Acute bronchitis and acute exacerbations of COPD

Bronchitis means inflammation of the bronchi. It is important to distinguish between acute bronchitis, which is usually, if not always, infective, and chronic bronchitis, which is a chronic inflammatory condition characterised by thickened, oedematous bronchial mucosa with mucus gland hypertrophy and usually caused by smoking. Chronic bronchitis often co-exists with emphysema, both of which lead to airflow limitation and the clinical syndrome of COPD.

The importance of chronic bronchitis is that it renders the patient more susceptible to acute infections and more likely to suffer respiratory compromise as a result. These acute exacerbations of COPD are a frequent cause of morbidity and admission to hospital. An exacerbation is defined as 'a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset' (NICE, 2004). Common symptoms include worsening breathlessness, cough, increased sputum production and change in sputum colour. It is important to remember that not all acute exacerbations of COPD have an infective aetiology since atmospheric pollutants are sometimes implicated.

Causative organisms

In otherwise healthy patients, the causes of acute bronchitis include viruses such as rhinovirus, coronavirus, adenovirus and influenza virus, and bacteria such as *Bordetella pertussis*, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (formerly *Chlamydia pneumoniae*). The role of bacteria such as *S. pneumoniae* and *H. influenzae* is uncertain because these organisms are nasopharyngeal commensals and their isolation can be misleading, but there is a presumption that they account for at least a proportion of infections.

In patients with acute exacerbations of chronic bronchitis, sputum culture frequently yields potential pathogens such as *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. However, these organisms are also found in the sputum at much the same frequencies between exacerbations, so it is unclear to what extent (if at all) they play a pathogenic role. A considerable proportion of acute exacerbations is associated with viral infections such as colds or influenza, or might even be non-infective.

Clinical features

The characteristic feature of acute bronchitis is a cough productive of purulent sputum, that is, phlegm that is yellow or green, the colour reflecting the presence of pus cells, sometimes with wheezing and breathlessness. In patients with pre-existing lung disease, the lack of reserve may lead to respiratory compromise, which in turn may exacerbate, or be exacerbated by, cardiac failure. Sometimes, the condition progresses to frank bronchopneumonia (see later), although the dividing line between a severe exacerbation of COPD and bronchopneumonia is often unclear.

Diagnosis

The diagnosis of acute bronchitis or acute exacerbation of COPD is made clinically and does not depend on the results of investigations. If antibiotics are to be given, a sputum sample should be sent for bacteriology, as this will allow antibiotic sensitivity tests to be performed on potential pathogens. However, the decision to treat should not be based on the results of sputum culture alone.

Treatment

Younger patients without pre-existing respiratory disease are likely to recover rapidly and might not require specific treatment. For more severe cases, including exacerbations of COPD, the two main arms of treatment are airflow optimisation and antibiotic therapy. Airflow optimisation consists of physiotherapy to aid expectoration of secretions, adjunctive oxygen if appropriate, bronchodilators and sometimes short-course corticosteroids. In severe cases, a period of artificial ventilation may be required, an intervention which has become more common with the advent of non-invasive ventilation techniques.

Despite the reservation that many cases are non-infective, current guidelines recommend that antibiotics are prescribed when an exacerbation is associated with more purulent sputum (NICE, 2004). There is no unequivocal evidence that one antibiotic is better than another, so recommendations for empiric treatment are based generally upon spectrum, side effects and cost. Most authorities favour either a tetracycline such as doxycycline or an aminopenicillin such as amoxicillin, since these agents cover most strains of *S. pneumoniae* and *H. influenzae*. Some people argue in favour of co-amoxiclav, which covers β-lactamase producing strains of *H. influenzae*

and *M. catarrhalis* that are therefore resistant to amoxicillin, but this agent is more expensive and has a greater incidence of side effects. For penicillin-allergic patients for whom tetracyclines are contraindicated, neither the macrolide erythromycin nor the earlier oral cephalosporins such as cefalexin or cefradine are sufficiently active against *H. influenzae* for empiric use. However, both clarithromycin and newer oral cephalosporins such as cefixime are active against haemophili while retaining activity against pneumococci.

The following recommendations can be made for the empiric antibiotic treatment of acute bronchitis and exacerbations of COPD. If a plausible pathogen is isolated, treatment can be modified accordingly.

First-line agents

- Doxycycline
- Amoxicillin

Second-line agents

- Co-amoxiclav
- Clarithromycin
- Cefixime

A number of other drugs are promoted for the treatment of COPD exacerbations. Of these, azithromycin is not recommended, as it is less active than clarithromycin against *S. pneumoniae*. The activity of ciprofloxacin against *S. pneumoniae* is insufficient to justify its use as monotherapy against pneumococcal infections (although it has useful activity against *H. influenzae* and *M. catarrhalis*), and levofloxacin (which is the active isomer of ofloxacin) does not seem to offer any great microbiological advantage. Moxifloxacin is a quinolone that retains activity against Gram-negative organisms such as *Haemophilus* and *Moraxella* but has greater activity against Gram-positives such as *S. pneumoniae*. It has been favourably compared to standard treatment in exacerbations of COPD (Wilson et al., 2004). However, its use has been limited by the high incidence of *Clostridium difficile* infection (CDI) associated with quinolone use, and rarely the development of life-threatening hepatic toxicity.

Bronchiolitis

Bronchiolitis is characterised by inflammatory changes in the small bronchi and bronchioles, but not by consolidation. It is particularly recognised as a disease of infants in the first year of life, in whom a small degree of airway narrowing can have a dramatic effect on airflow, but the causal organisms are equally capable of infecting adults, who may then act as reservoirs of infection. Most cases are caused by respiratory syncytial virus (RSV), which occurs in annual winter epidemics, but hMPV, parainfluenzaviruses, rhinoviruses, adenoviruses and occasionally *M. pneumoniae* have also been implicated.

Bronchiolitis is characterised by a prodrome of fever and coryzal symptoms which progresses to wheezing, respiratory distress and hypoxia of varying degrees. Aetiological confirmation may be made by immunofluorescence and/or viral culture of respiratory secretions, although increasingly the diagnosis of respiratory syncytial virus is made using rapid antigen detection tests.

The treatment of bronchiolitis is mainly supportive and consists of oxygen, adequate hydration and ventilatory assistance if required. Severe cases of respiratory syncytial virus disease may be treated with ribavirin, a synthetic nucleoside administered by nebuliser. There is limited evidence for its efficacy and it is currently only recommended for use in immunocompromised patients to reduce the duration of viral shedding (Yanney and Vyas, 2008).

Babies born earlier than 35 weeks of gestation or those less than 6 months of age at the onset of the respiratory syncytial virus season are at high risk of the disease. Likewise, infants under two years of age with chronic lung disease or severe immunodeficiency, or under 6 months of age with congenital heart disease are similarly at high risk, and all are candidates for prophylactic treatment with palivizumab. This is a humanised monoclonal antibody used for passive immunisation against respiratory syncytial virus (JCVI, 2005). There is currently no vaccine against RSV.

Pneumonia

Pneumonia is defined as inflammation of the lung parenchyma, that is, of the alveoli rather than the bronchi or bronchioles, of infective origin and characterised by consolidation. Consolidation is a pathological process in which the alveoli are filled with a mixture of inflammatory exudate, bacteria and white blood cells that on chest X-ray appear as an opaque shadow in the normally clear lungs.

A wide range of organisms can cause pneumonia, so it is useful to apply some kind of classification system, at least until the aetiology of a particular case has been determined. Pneumonia is often classified clinically into lobar pneumonia, bronchopneumonia or atypical pneumonia, but this does not correlate entirely with the bacteriological cause and in any case the distinctions are often blurred. It is more practical to classify pneumonia according to the nature of its acquisition, the usual terms being community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP).

Community-acquired pneumonia

Causative organisms. The causes of CAP are summarised in Table 35.1. The most common vegetative bacterial causes are *S. pneumoniae*, the pneumococcus, which can cause both lobar and bronchopneumonia, and non-capsulate strains of *H. influenzae* which usually give rise to bronchopneumonia.

The so-called atypical pneumonias are a heterogeneous group of diseases which nevertheless have several clinical features in common and which are clinically distinct from the classic picture of pneumococcal pneumonia. Aetiological agents include *Legionella pneumophila, M. pneumoniae, C. pneumoniae, Chlamydophila psittaci, Coxiella burnetii* and viruses. *L. pneumophila* is the cause of Legionnaire's disease which occurs sporadically and in outbreaks often associated with contaminated air-conditioning or water systems. From 2002 to 2008, there were 300–600 new cases a year reported in England and Wales.

Table 35.1 Causes of community-acquired pneumonia

Organism	Comments
Streptococcus pneumoniae	Classically causes lobar pneumonia, bronchopneumonia now common
Haemophilus influenzae	Cause of bronchopneumonia, usually non-capsulate strains
Staphylococcus aureus	Severe pneumonia with abscess formation, typically following influenza
Klebsiella pneumoniae	Friedlander's bacillus, causing an uncommon but severe necrotising pneumonia
Legionella pneumophila	Particularly serogroup 1; causes Legionnaire's disease, usually acquired from aquatic environmental sources
Mycoplasma pneumoniae	Cause of acute pneumonia in young people, respiratory symptoms often overshadowed by systemic upset
Chlamydophila pneumoniae	Mild but prolonged illness usually seen in older people, respiratory symptoms often overshadowed by systemic upset
Chlamydophila psittaci	Causes psittacosis, a respiratory and multisystem disease acquired from infected birds
Coxiella burnetii	Causes Q fever, a respiratory and multisystem disease acquired from animals such as sheep
Viruses	Several viruses can cause pneumonia in adults, including influenza, parainfluenza and varicella zoster viruses

Legionnaire's disease may be rapidly progressive with very extensive consolidation and consequent respiratory failure.

Viral infections should not be forgotten as causes of pneumonia, although in practice it is unusual to make a definitive early diagnosis, so most cases are treated with antibacterials. Influenza can cause a primary viral pneumonia as well as be complicated by secondary bacterial (particularly staphylococcal) pneumonia, chickenpox can be complicated by primary varicella pneumonia particularly in adults, and cytomegalovirus is capable of causing a variety of infections, including pneumonia, in patients with compromised cell-mediated immunity.

Clinical features. Pneumococcal lobar pneumonia presents with a cough, initially dry but later producing purulent or blood-stained, rust-coloured sputum, together with dyspnoea, fever and pleuritic chest pain. The peripheral white blood cell count is usually raised and the patient may be bacteraemic. The chest X-ray shows consolidation confined to one or more lobes (or segments of lobes) of the lungs. This classic picture is now quite rare perhaps because the early use of antibiotics modifies the natural history of the disease. Bronchopneumonia presents more non-specifically with productive cough and breathlessness, and patchy consolidation on the chest X-ray usually in the bases of both lungs. This disease is very common and is typically seen in patients with severe COPD or in those who are frail and terminally ill. In fact, pneumonia has been described as the old man's friend because it is a relatively painless cause of death.

The atypical pneumonias are characterised clinically by fever, systemic symptoms and a dry cough, radiologically by widespread patchy consolidation in both lungs and biochemically by abnormalities in liver enzymes and perhaps evidence of inappropriate antidiuretic hormone secretion, evident as a low plasma sodium.

Despite the differences described, clinical features alone are not usually sufficient to make a confident bacteriological diagnosis, a fact that has major implications for the empirical treatment of pneumonia.

Diagnosis. Sputum culture is the mainstay of diagnosis for pneumonia caused by pneumococci and *H. influenzae*. Sputum microscopy is unreliable because oropharyngeal contaminants are often indistinguishable from pathogens. The success of sputum culture is very dependent upon the quality of the specimen, which may be inadequate either because the patient is unable to expectorate or because the nature of the disease is such that sputum production is not a major feature. A more sensitive (although more invasive) technique is to perform bronchoscopy and bronchoalveolar lavage. Lavage fluid, being uncontaminated by mouth flora, is suitable for microscopy as well as culture.

In pneumococcal disease, blood cultures are frequently positive and national guidance (Lim et al., 2009) suggests that laboratories should also offer plasma and urine testing for pneumococcal antigen. *Legionella* infection may be diagnosed by culture (if appropriate media are used) or by urinary antigen testing, but culture of *Mycoplasma* and *Chlamydophila* species is beyond the scope of most routine diagnostic laboratories. Viruses may be detected by immunofluorescence, by viral culture or by polymerase chain reaction (PCR), but timely diagnosis requires a good specimen such as bronchoalveolar lavage fluid. In practice, the aetiology of atypical pneumonia is usually determined serologically (for instance, by acute and convalescent antibody testing), if at all.

Targeted treatment. The treatment of choice for pneumococcal pneumonia is benzylpenicillin or amoxicillin. Erythromycin monotherapy may be used in penicillin-allergic patients, but resistance rates are rising, macrolides are bacteriostatic rather than bactericidal and the comparative efficacy of this approach is not known. There is retrospective evidence that combination therapy using both a β-lactam and a macrolide can reduce mortality in patients whose pneumonia is complicated by pneumococcal bacteraemia (Martinez et al., 2003).

Pneumococci with reduced susceptibility to penicillin are becoming increasingly common, particularly in continental Europe and the USA. In the UK, about 5–10% of strains express 'intermediate susceptibility' (minimum inhibitory concentration; MIC 0.1–1 mg/L), but high-level resistance (MIC >1 mg/L) remains uncommon. Intermediate susceptibility may result in treatment failure in conditions such as

otitis media or meningitis, infections at sites where antibiotic penetration is reduced, but antibiotic penetration into the lungs is sufficiently good that penicillin and amoxicillin remain effective for pneumonia. Strains expressing high-level resistance are unlikely to respond to penicillins, however. Such strains are often co-resistant to macrolides and other first-line agents, and may require treatment with a later-generation cephalosporin or a glycopeptide.

The sensitivity of *H. influenzae* to antibiotics has been discussed above. Amoxicillin is the agent of choice, with co-amoxiclav, parenteral cefuroxime, cefixime or ciprofloxacin as alternatives. Erythromycin is poorly active, but the newer macrolide clarithromycin and the azalide azithromycin possess more activity.

M. pneumoniae does not possess a cell wall and is therefore not susceptible to β-lactam agents. A tetracycline or a macrolide are suitable alternatives. Tetracyclines are also effective against *C. pneumoniae, C. psittaci* and *C. burnetii*, but erythromycin is probably less effective. Quinolones are also highly active against these organisms.

Staphylococcal pneumonia is usually treated with flucloxacillin plus a second agent such as rifampicin or fusidic acid, although there is no good clinical evidence that combination treatment is better than a single agent. MRSA (meticillin-resistant *S. aureus*) pneumonia is being seen more commonly in the community as well as in hospital. Strains of *S. aureus* expressing Panton-Valentine Leukocidin, an exotoxin, are capable of causing a severe necrotising pneumonia and if clinically suspected should warrant urgent critical care and specialist microbiological input.

Treatment recommendations for Legionnaire's disease are based on a retrospective review of the famous Philadelphia outbreak of 1976 (Fraser et al., 1977), in which two deaths occurred among the 18 patients who were given erythromycin, compared to 16 deaths in 71 patients treated with penicillin or amoxicillin. This observation accords with the facts that *Legionella* is an intracellular pathogen and that macrolides penetrate more efficiently than β-lactams into cells. Azithromycin is probably the most effective of the macrolide/azalide derivatives, but clinical evidence to confirm this is lacking. Other agents with proven clinical efficacy and good intracellular activity against *Legionella* include rifampicin and quinolones. There have been no randomised controlled clinical trials, nor are there likely to be. Guidance, based on observation studies, suggests non-severe cases should be treated with an oral fluoroquinolone (with a macrolide as an alternative), and severe cases treated with a combination of a fluoroquinolone plus either a macrolide or rifampicin, de-escalating to a fluoroquinolone as the sole agent after the first few days (Lim et al., 2009). Treatment is not recommended for the non-pneumonic form of legionellosis (Pontiac fever) which presents as a self-limiting flu-like illness.

Empiric treatment. All of the foregoing recommendations presuppose that the infecting organism is known before treatment is commenced. In practice, this is rarely the case and therapy will initially be empirical or best-guess in nature (Table 35.2). The most authoritative recommendations for the initial treatment of CAP are those produced by the British Thoracic Society (Lim et al., 2009). For mild disease, these recommend treatment with amoxicillin, providing activity against pneumococci and most strains of *H. influenzae,* with doxycycline or clarithromycin being the preferred alternatives in penicillin-allergic patients. However, for moderate or severe disease requiring admission to hospital, they take the view that, until the aetiology is known, treatment should cover both 'typical' causes (such as *S. pneumoniae* and *H. influenza*) and atypical causes (such as *M. pneumoniae*, *Chlamydophila* species and *Legionella*). For patients with moderate or severe CAP, the guidelines therefore recommend a combination of a β-lactam drug plus a macrolide, the exact choice of agent and route being decided according to the clinical severity of the infection. In practice, this is usually interpreted as amoxicillin plus a macrolide for less severe disease, and co-amoxiclav plus a macrolide (or cefuroxime plus a macrolide) for more severe disease. Severity is assessed according to clinical parameters and outcome predicted by use of one of a number of assessment tools such as CURB-65, based on the onset of *C*onfusion, the serum *U*rea, the *R*espiratory rate, the *B*lood pressure and age >65 years.

Moxifloxacin, a newer fluoroquinolone, is licensed in the UK for treatment of non-severe pneumonia where other antibiotics cannot be used. Currently, it is licensed only in oral form.

Pressure to treat pneumonia (much of which is pneumococcal and would respond to penicillin) with broad-spectrum empiric regimens, in particular, with cephalosporins and fluoroquinolones, has been cited as a factor in the rising incidence of *Clostridium difficile* and MRSA infections. The treatment of pneumonia illustrates many of the dilemmas and conflicting priorities of modern antimicrobial prescribing.

Prevention. Pneumococcal 23-valent polysaccharide vaccine and influenza vaccine should be offered to all those at risk of infection. For pneumococcal infection, this includes patients who fulfil the following criteria:

- asplenia or dysfunction of the spleen
- chronic respiratory disease
- chronic heart disease
- chronic renal disease
- chronic liver disease
- diabetes
- immunosuppressed
- aged 65 years or older
- cochlear implants
- cerebrospinal fluid leaks.

Hospital-acquired (nosocomial) pneumonia

Causative organisms. The most frequent causes of HAP are Gram-negative bacilli (Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp.) and *S. aureus*, including MRSA (Box 35.1). However, it is important to remember that pneumococcal pneumonia may develop in hospitalised patients and also that hospital water supplies have been implicated in outbreaks and sporadic cases of *Legionella* infection. Further, it must be recognised that the common Gram-negative causes of nosocomial pneumonia will vary between

Table 35.2 Treatment of community-acquired pneumonia

Scenario	Typical regimen	Comments
Mild to moderate pneumonia, organism unknown	Amoxicillin plus a macrolide	Amoxicillin covers *S. pneumoniae* and most *H. influenzae* while macrolide provides cover against atypical pathogens. It is debatable whether clinical outcomes are improved by using antibiotics active against atypical pathogens in all-cause non-severe community-acquired pneumonia
Severe pneumonia, organism unknown	Co-amoxiclav plus a macrolide Cefuroxime plus a macrolide in penicillin allergy	Co-amoxiclav and cefuroxime provide cover against *S. aureus*, coliforms and β-lactamase producing haemophili while retaining the pneumococcal cover of amoxicillin
Pneumococcal pneumonia	Penicillin or amoxicillin or a macrolide	High-level penicillin resistance remains uncommon in the UK.
H. influenzae	Non-β-lactamase producing: amoxicillin β-lactamase producing: cefuroxime or co-amoxiclav	Also sensitive to quinolones
Staphylococcal pneumonia	Non-MRSA: flucloxacillin +/– a second agent such as rifampicin or fusidic acid MRSA: requires microbiology input, options include linezolid or glycopeptides	Isolation of *S. aureus* from sputum may reflect contamination with oropharyngeal commensals and should be interpreted cautiously. MRSA pneumonia may also be treated with linezolid
Mycoplasma pneumoniae	Macrolide or tetracycline	Treat for 14 days
Chlamydophila spp.	Tetracycline preferred	Treat for 14 days
Legionella spp.	A fluoroquinolone such as ciprofloxacin. A macrolide such as clarithromycin is an alternative if intolerant.	Addition of a macrolide or rifampicin in severe cases

Box 35.1 Causes of hospital-acquired pneumonia

Common organisms

1. Gram-negative bacteria:
   Pseudomonas aeruginosa
   E. coli
   Klebsiella spp.
2. Gram-positive bacteria:
   S. pneumoniae
   S. aureus including MRSA

Less common organisms

1. Other 'coliforms' such as *Enterobacter* spp., *Serratia marcescens*, *Citrobacter* spp., etc.
   Acinetobacter spp.
   Other *Pseudomonas* and related species, such as
   S. maltophilia
   L. pneumophila (and other species)
2. Anaerobic bacteria
3. Fungi:
   Candida albicans (and other species)
   Aspergillus fumigatus (particularly following prolonged episodes of neutropenia)
4. Viruses:
   Cytomegalovirus
   Herpes simplex virus

hospitals and even between different units within the same hospital. This is especially true of ventilator-associated pneumonia, which for obvious reasons is usually acquired on intensive care units where broad-spectrum antibiotics are frequently used, and where there may be a particular 'resident flora' with an established antibiotic resistance pattern.

Clinical features. Nosocomial pneumonia accounts for 10–15% of all hospital-acquired infections, usually presenting with sepsis and/or respiratory failure. Up to 50% of cases are acquired on intensive care units. Predisposing features include stroke, mechanical ventilation, chronic lung disease, recent surgery and previous antibiotic exposure.

Diagnosis. Sputum is commonly sent for culture but is sometimes unhelpful as it may be contaminated by mouth flora. If the patient has received antibiotics, the normal mouth flora is often replaced by resistant organisms such as staphylococci or Gram-negative bacilli, making the interpretation of culture results difficult. Bronchoalveolar lavage is often more helpful. Blood cultures may be positive.

Treatment. The range of organisms causing nosocomial pneumonia is very large, so broad-spectrum empiric therapy is indicated. The choice of antibiotics will be influenced by preceding antibiotic therapy, the duration of hospital admission and above all by the individual unit's

Table 35.3 Treatment regimens for hospital-acquired pneumonia (HAP)

Regimen	Comments
Co-amoxiclav	Good activity against community-associated pathogens, many Enterobacteriaceae and *S. aureus*. Recommended for early-onset HAP (within 5 days of admission) in antibiotic naïve patients without other risk factors
Ureidopenicillin plus aminoglycoside (e.g. piperacillin plus gentamicin)	Good activity against Gram-negative bacilli such as *P. aeruginosa* and also against pneumococci. Combination of piperacillin with the β-lactamase inhibitor tazobactam, currently the only ureidopenicillin product marketed in the UK, extends the spectrum to include *S. aureus* (not MRSA), anaerobes and some strains of *E. coli, Klebsiella*, etc. that are resistant to piperacillin alone. Piperacillin-tazobactam can also be used reliably as monotherapy
Cephalosporin plus an aminoglycoside (e.g. cefuroxime plus gentamicin)	Good activity against Gram-negative bacilli such as *E. coli, Klebsiella*, and Gram-positive organisms, but poor against *P. aeruginosa* and anaerobes
Clindamycin plus aminoglycoside	Good activity against Gram-positive organisms and anaerobes but much less so against Gram-negatives. Favoured in the USA where metronidazole is unpopular for the treatment of anaerobic infections
Ciprofloxacin plus glycopeptide (vancomycin or teicoplanin)	Ciprofloxacin provides good activity against most Gram-negative bacilli including *P. aeruginosa*. Glycopeptide provides activity against *S. aureus* (including MRSA) and pneumococci, although its penetration into the respiratory tract is relatively poor
Meropenem (monotherapy)	Broad-spectrum agent including activity against Extended Spectrum Beta Lactamase (ESBL) producing Enterobacteriaceae. Not active against MRSA. Ertapenem does not cover *Pseudomonas* spp. or *Acinetobacter* spp. so is unsuitable
Linezolid combinations	It is increasingly necessary to cover MRSA in empiric or targeted treatment of hospital-acquired pneumonia. Traditional options include glycopeptides and, where the prevailing strains are sensitive, aminoglycosides, but there are concerns about penetration into the lung. Linezolid, an oxazolidinone, provides reliable activity
Aztreonam combinations	Good activity against gram-negative bacilli Including *Pseudomonas* but offers no activity against anaerobic or Gram-positive organisms. Expensive. A β-lactam agent that can be used safely in patients with history of severe penicillin allergy
Temocillin	Excellent activity against Gram-negative organisms including ESBL-producing Enterobacteriaceae. No activity against Gram-positive organisms and *Pseudomonas*
Ceftazidime (monotherapy)	Very active against Gram-negative bacilli including *Pseudomonas* but less so against Gram-positive organisms and anaerobes. Due to the high incidence of *Clostridium difficile* infection and selection of multi-resistant organisms associated with its use, this agent has largely been superseded by other newer agents

experience with hospital bacteria. The combinations shown in Table 35.3 have all been used at some time and all have advantages and disadvantages. Several of the combinations include an aminoglycoside, and this may not be desirable in all patients. Single-agent therapy is attractive for ease of administration, and agents such as piperacillin-tazobactam and meropenem have suitably broad spectra that include activity against *P. aeruginosa*. Currently licensed β-lactam agents are inactive against MRSA infections; in such cases specialist management advice is required.

In all cases, a macrolide would be added if Legionnaire's disease was suspected and, if not already covered by the regimen, metronidazole would be required for suspected anaerobic infection.

Prevention. General strategies for minimising the incidence of HAP include early postoperative mobilisation, analgesia, physiotherapy and promotion of rational antibiotic prescribing. The Department of Health's Saving Lives programme makes specific recommendations for the prevention of ventilator-associated pneumonia (DoH, 2007), including head of bed elevation, sedation holding to reduce the duration of mechanical ventilation and good general hygiene of tubing management and suction.

Another strategy proposed for the prevention of ventilator-associated pneumonia is selective decontamination of the digestive tract (SDD), based on the premise that the infecting organisms initially colonise the patient's oropharynx or intestinal tract (Kallett and Quinn, 2005). By administering non-absorbable antibiotics such as an aminoglycoside or colistin to the gut, and applying a paste containing these agents to the oropharynx, it is proposed that the potential causative organisms will be eradicated and the incidence of pneumonia

thereby reduced. In some centres, an antifungal agent such as amphotericin B is added; others also advocate addition of a systemic broad-spectrum agent such as cefotaxime.

The role of selective decontamination of the digestive tract remains controversial. Recent guidelines (Masterton et al., 2008) recommend its consideration in patients in whom mechanical ventilation is anticipated for more than 48 h. Whether any benefits really outweigh the risks is unclear.

Another suggestion is prophylactic administration of aerosolised antibiotics to ventilated patients (and perhaps other patients at risk). Agents suitable for aerosolised delivery and with the appropriate antimicrobial spectrum include aminoglycosides (particularly tobramycin) and the polymyxin drug colistin. There are no published data available at present and therefore this approach cannot be universally recommended.

Aspiration pneumonia

One further condition which may be seen either in hospital or in the community is aspiration pneumonia, initiated by inhalation of stomach contents contaminated by bacteria from the mouth. Risk factors include alcohol, hypnotic drugs and general anaesthesia, all of these being factors that may make a patient vomit while unconscious. Gastric acid is very destructive to lung tissue and leads to severe tissue necrosis. Damaged tissue is then prone to secondary infection often with abscess formation. Anaerobic bacteria are particularly implicated, but these are often accompanied by aerobic organisms such as viridans streptococci. Treatment with metronidazole plus amoxicillin is usually adequate, but broader spectrum drugs may be used if there are reasons to suspect Gram-negative involvement, for instance, if the patient has been in hospital or previously exposed to antibiotics.

Severe acute respiratory syndrome

Severe acute respiratory syndrome (SARS) is caused by a coronavirus (SARS-associated coronavirus or SARS CoV). Clinically it causes pneumonitis, presenting with a flu-like prodrome and progressing to dyspnoea, dry cough and often adult respiratory distress syndrome, requiring ventilatory support. Treatment is largely supportive. It was first described in 2003 (Drosten et al., 2003) after a large outbreak originating in China spread throughout the Americas, Europe and Asia. The outbreak terminated in that year, with only small numbers of cases occurring since. Many experts predict that SARS will re-emerge.

Cystic fibrosis

Cystic fibrosis (CF) is an inherited, autosomal recessive disease which at the cellular level is due to a defect in the transport of ions in and out of cells. This leads to changes in the consistency and chemical composition of exocrine secretions, which in the lungs is manifest by the production of very sticky, tenacious mucus which is difficult to clear by mucociliary action. The production of such mucus leads to airway obstruction with resulting infection. Repeated episodes of infection lead eventually to bronchiectasis and permanent lung damage, which in turn predisposes the patient to further infection.

Infecting organisms

In infants and young children, *S. aureus* is the most common pathogen. *H. influenzae* is sometimes encountered, but from the age of about 5 years onwards *P. aeruginosa* is seen with increasing frequency until, by the age of 18, most patients are chronically infected with this organism, which once present is never completely eradicated. An important feature of those *P. aeruginosa* strains which infect patients with cystic fibrosis is their production of large amounts of alginate, a polymer of mannuronic and glucuronic acid. This seems to be a virulence factor for the organism in that it inhibits opsonisation and phagocytosis and enables the bacteria to adhere to the bronchial epithelium, thus inhibiting clearance. It does not confer additional antibiotic resistance. Strains which produce large amounts of alginate have a wet, slimy appearance on laboratory culture media and are termed 'mucoid' strains.

Occasionally, other Gram-negative bacteria are seen, such as *Escherichia coli*, which interestingly may also produce alginate in these patients, a characteristic which is otherwise very rare, or *Stenotrophomonas maltophilia*. Many centres worldwide have also experienced problems with members of the *Burkholderia cepacia* complex, which previously were known as plant pathogens. The most frequent culprits are *B. cenocepacia* (formerly *B. cepacia* genomovar III) and *B. multivorans* (formerly *B. cepacia* genomovar II). These organisms are often exceptionally resistant to antibiotics, and their acquisition may be associated with rapidly progressive respiratory failure. Patients colonised with *P. aeruginosa* and *B. cepacia* complex should be isolated to prevent transmission to other CF patients.

Clinical features

CF is characterised by persistent cough and copious sputum production. Many patients are chronically breathless. At times, acute exacerbations occur in which there is fever, increased cough with purulent sputum and increased dyspnoea. Systemic sepsis, however, is very rare. Eventually, chronic pulmonary infection leads to respiratory insufficiency, cardiac failure and death.

Treatment

Although this section will concentrate on antibiotic therapy, it should not be forgotten that other means of treatment such as physiotherapy play a vital part, while lung transplantation can be life saving. Even regarding antibiotics, there are fundamental questions that remain to be addressed; for instance, it is not known whether it is best to give antibiotics according to a planned, regular schedule or in response to exacerbations, and practice varies.

The treatment of infection in a child with cystic fibrosis will probably be directed against staphylococci, for which the usual anti-staphylococcal antibiotics such as flucloxacillin or erythromycin can be used. Once the patient is colonised by *P. aeruginosa*, treatment depends on early and vigorous therapy with antipseudomonal antibiotics (see Table 35.4). At first isolation of *P. aeruginosa*, eradication is attempted with oral ciprofloxacin and a nebulised antibiotic such as colistin.

Table 35.4 Antipseudomonal antibiotics

Antibiotic	Comment
Ticarcillin	One of the first β-lactam agents effective against *Pseudomonas* but now considered insufficiently active. In combination with the β-lactamase inhibitor clavulanic acid, it may be active against some otherwise resistant strains
Ureidopenicillins	Piperacillin, formulated in combination with the β-lactamase inhibitor tazobactam, is the only one of these agents now available in the UK
Monobactams	Aztreonam offers good activity against Gram-negative organisms but no activity against Gram-positive organisms
Cephalosporins	Ceftazidime is the most active antipseudomonal cephalosporin and is very active against other Gram-negative bacilli. It has rather lower activity against Gram-positive bacteria. *Pseudomonas* may develop resistance during treatment
Aminoglycosides	Gentamicin and tobramycin have very similar activity against *Pseudomonas*; tobramycin is perhaps slightly more active. Netilmicin is less active, while amikacin may be active against some gentamicin-resistant strains
Quinolones	Ciprofloxacin can be given orally and parenterally but as with ceftazidime, resistance can develop while the patient is on treatment. Other quinolones such as ofloxacin, its L-isomer levofloxacin, and moxifloxacin have better Gram-positive spectrum but concomitantly less activity against *Pseudomonas*
Polymyxins	These peptide antibiotics are considered too toxic for systemic use in all but the most desperate cases, but colistin (polymyxin E) can be given by inhalation
Carbapenems	Broad-spectrum agents with good Gram-negative activity. Imipenem was the first of these drugs, but CNS toxicity and its requirement for combination with the renal dipeptidase inhibitor cilastatin have largely led to its replacement by meropenem. Doripenem is a newer carbapenem with similar activity to meropenem. Ertapenem has poor activity against *P. aeruginosa*

For chronically colonised patients, regular prophylactic intravenous treatment is given with a β-lactam/aminoglycoside combination such as ceftazidime plus tobramycin. Agents such as meropenem or a quinolone are usually reserved for treatment failures or when resistant organisms are encountered. The prolonged use of ceftazidime or ciprofloxacin alone should be avoided if possible since strains of *P. aeruginosa* and some other Gram-negative bacilli may become resistant to these agents while the patient is receiving treatment. Other treatment modalities are emerging: in a multi-centre, randomised controlled trial, long-term low-dose azithromycin was associated with improvements in lung function in patients chronically infected with *P. aeruginosa* (Saiman et al., 2003).

Interestingly, patients with cystic fibrosis have a more rapid clearance of some antibiotics than other patients. This is particularly noticeable with the aminoglycosides and larger doses are often required to achieve satisfactory plasma levels.

Children with cystic fibrosis are admitted to hospital very frequently, sometimes for long periods of time, and it is not surprising that some of these children develop an intense dislike of hospitals. This has encouraged the use of long-term indwelling central venous cannulae to allow administration of intravenous antibiotics at home by the parents. Ciprofloxacin can be given orally and offers the possibility of treatment for less severe exacerbations at home, perhaps after a brief time in hospital for parenteral therapy.

B. cepacia is often very difficult to treat and strains may be resistant to all available antibiotics. Under these circumstances, combination therapy is often used.

There is some evidence that *in vitro* resistance in some Gram-negative organisms such as *P. aeruginosa* and *B. cepacia* complex does not correlate with treatment failure in the patient.

The use of inhaled (usually nebulised) antibiotics as an adjunct to parenteral therapy has attracted attention, both for treatment of acute exacerbations and for longer-term use in an attempt to reduce the *Pseudomonas* load. Agents which have been administered in this way include colistin, tobramycin and other aminoglycosides, carbenicillin and ceftazidime. The best evidence that long-term administration can be beneficial comes from a large multi-centre trial of nebulised tobramycin (Moss, 2001) in which 520 patients were randomised to receive once-daily nebulised tobramycin or placebo in on–off cycles for 24 weeks, followed by open-label tobramycin to complete 2 years of study. Nebulised tobramycin was safe and well tolerated and was associated with a reduction in hospitalisation and improvements in lung function. This was at the expense of a degree of tobramycin resistance, although this did not seem to be clinically significant.

Respiratory infection in the immunocompromised

The increased use of immunosuppressive agents, and to a lesser extent, the spread of HIV infection, has led to increasing numbers of immunocompromised individuals. Respiratory tract infections, in general, and pneumonia, in particular, are

Table 35.5 Basic causes, defects and infections in immunocompromised individuals

Principal defect	Causative illnesses, diseases or agents	Pathogens causing chest problem (defect related)			
		Bacteria	Viruses	Fungi	Others
Phagocytes	Acute leukaemia, bone marrow failure and chronic granulomatous disease	Staphylococci, aerobic Gram-negative bacilli, *Nocardia asteroides*		*Candida* and *Aspergillus* species	
Antibody (B-cell) immunity	X-linked agammaglobulinaemia, multiple myeloma, Waldenstrom's macroglobulinaemia and chronic lymphocytic leukaemia	Encapsulated bacteria such as *S. pneumoniae*, *H. influenzae*, *S. aureus*		*Pneumocystis jiroveci*	
Complement system		Encapsulated bacteria, and *N. meningitidis*			
Cell-mediated (T-cell) immunity	Di George syndrome, lymphoma, hairy cell leukaemia, medications (ciclosporin, steroids), AIDS, CMV and EBV infection	Intracellular micro-organisms, for example, mycobacteria, *Nocardia asteroides*	Varicella zoster virus, herpes simplex virus, cytomegalovirus, EBV	*Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis jiroveci*	*Toxoplasma gondii*
Defects caused by splenectomy or hyposplenism		Encapsulated bacteria such as *S. pneumoniae*, *H. influenzae*, *N. meningitidis* and *Capnocytophaga canimorsus*			

Most agents currently used in mainstay immunosuppression regimens to prevent graft rejection, in organ transplantation, interfere with discrete sites in the T- and B-cell activation cascades.

frequent complications. Morbidity and mortality are high; so rapid recognition, accurate diagnosis and correct treatment are of prime importance. Diagnosis may be complicated by the sheer number of potential pathogens, the problem of distinguishing infection from non-infective conditions such as malignant infiltration or radiation pneumonitis, and non-specific or delayed presentation. The nature, duration and severity of the underlying immune defect, together with specific epidemiologic or environmental factors, influence the risk of infection by different organisms. These are summarised briefly in Table 35.5. Common therapeutic problems are summarised in Table 35.6.

Table 35.6 Common therapeutic problems

Problem	Comments
No pathogens isolated on sputum culture	Possibilities include an inadequate specimen such as saliva, non-infected or sterilised sputum, or a pathogen that cannot be cultured on routine media such as *Chlamydophila pneumoniae* or *Mycobacterium tuberculosis*. Pneumococci are susceptible to autolysis and may fail to grow even from a well-taken specimen, particularly if transport to the laboratory is delayed
Staphylococcus aureus isolated (including MRSA)	*S. aureus* pneumonia is a severe disease with characteristic clinical features, often associated with bacteraemia. However, the organism is frequently isolated from the sputum of patients with bronchitis or bronchopneumonia. In these instances, it usually reflects contamination of the specimen with oropharyngeal commensals although some patients undoubtedly have a clinical infection requiring anti-staphylococcal antibiotics
Candida spp. isolated	Unless there are reasons to suspect *Candida* pneumonia (as a consequence of neutropenia, for example), the isolation of yeasts is likely to reflect oropharyngeal contamination of the specimen. Yeasts can be carried commensally in the mouth, particularly in the presence of dentures, but a search for clinically apparent mucocutaneous candidiasis should be made
Aspergillus spp. isolated	Invasive aspergillosis, allergic bronchopulmonary aspergillosis and aspergilloma should be considered. Alternatively, the finding might reflect inconsequential oropharyngeal carriage

Continued

Table 35.6 Common therapeutic problems—cont'd

Problem	Comments
Penicillin-resistant pneumococci isolated	Respiratory infections caused by strains with low-level resistance (MIC 0.1–1 mg/L) may be treated with penicillins. Strains with high-level resistance should be treated according to their sensitivity profile, for example, using a later-generation cephalosporin or a macrolide
Coliforms isolated	Significance depends on the clinical context: unlikely to be responsible for community-acquired infection unless there is bronchiectasis, but may be relevant to hospital-acquired infections particularly if present in pure culture
Failure of a chest infection to respond to antibiotics	Consider poor compliance, inadequate dosage, viral or otherwise insensitive aetiology. Remember that β-lactam drugs are ineffective against *Chlamydophila*, *Mycoplasma* and *Legionella* infections
Sore throat, no pathogens isolated	Consider viral aetiology, particularly glandular fever in teenagers and young adults
Persistent illness following treatment for pneumococcal pneumonia	Consider the possibility of an empyema (pus in the pleural space), a condition which usually requires surgical drainage

Case studies

Case 35.1

A 40-year-old woman presents to her GP with a 1-week history of sore throat. She is normally fit and well and has had no other symptoms other than some lethargy.

Questions

1. What are the likely causes of the sore throat?
2. Should antibiotics be prescribed?

   The GP decides to prescribe a 10-day course of penicillin V to cover possible streptococcal infection. Two weeks later the patient returns. She is feeling worse and now experiencing difficulty in swallowing. Examination of the throat reveals widespread white plaques.
3. What is the likely diagnosis?
4. What other investigations might be indicated?

Answers

1. A viral aetiology is the most likely cause. These are usually the same viruses that cause colds. Bacterial infection with group A streptococci usually presents with a more severe infection, but where there is doubt a throat swab can establish if bacteria are responsible.
2. Antibiotics are not recommended for routine use. Treatment is directed at symptomatic relief.
3. The likely cause is oral candidiasis. The presence of dysphagia raises the question of oesophageal involvement and hospital admission may be indicated.
4. Underlying immunocompromise must be considered. All patients with oral candidiasis should be offered HIV testing.

Case 35.2

A 61-year-old man is found collapsed at home and taken to hospital. His family report him complaining of a sore throat a few days before admission. On examination, he is pyrexial, hypoxic and tachycardic with reduced air entry to auscultation at the right base. Chest X-ray reveals a right basal pneumonia.

Questions

1. What is the likely diagnosis?
2. What are the possible infecting organisms?
3. What empirical antibiotics would you choose?

   The next day, his sputum yields a growth of beta haemolytic streptococci group A.
4. How should the patient be treated now?

Answers

1. Community-acquired pneumonia.
2. *S. pneumoniae*, *H. influenzae*; sore throat should alert to the possibility of iGAS.
3. Treatment should be guided by the CURB65 score, which assesses severity. Generally, a beta lactam antibiotic and a macrolide are used in combination.
4. There has been no reported resistance of group A streptococci to penicillins, so beta lactam agents should be appropriate. Patients should be isolated until they have received 24 h of treatment. However, this period has often elapsed by the time the diagnosis is made. Blood culture samples should also have been received as invasive infection may often cause an associated bacteraemia.

Case 35.3

A 72-year-old man with a known history of COPD presents to the hospital accident and emergency department with increasing breathlessness. He has a cough productive of cream coloured sputum which is normal for him. He has not noticed an increase in purulence or volume. Chest X-ray showed hyperinflated lungs but no focal consolidation, and a diagnosis of acute exacerbation of COPD was made.

Questions

1. How should this patient be managed?
2. What investigations would inform the diagnosis?

Answers

1. Many exacerbations of COPD are non-infective. Antibiotics should be reserved for where sputum has become more purulent.
2. The diagnosis of exacerbation of COPD is clinical. Sputum cultures should only be performed where antibiotics are being prescribed.

Case 35.4

A 7-year-old girl is seen in the hospital paediatric outpatient clinic. She is known to have cystic fibrosis and has had several exacerbations in the past which have been treated with flucloxacillin. On this visit she is stable, but a report of sputum culture received two days after the clinic shows a growth of *P. aeruginosa*.

Questions

1. What treatment should be started?
2. What other options are available?

   One week later, you receive a telephone call from the parents that she has become unwell and they suspect she has another chest infection.
3. What agents might be appropriate in treating the infection?

Answers

1. Eradication treatment should be commenced, with oral ciprofloxacin plus a nebulised antibiotic such as colistin.
2. In patients with chronic *Pseudomonas* carriage, there are other options to help reduce the frequency of infections. These include regular low-dose azithromycin and nebulised antibiotics such as tobramycin. Non-pharmacological measures such as physiotherapy should also be included.
3. Combination treatment is usually favoured, depending on individual susceptibility results, but might include a beta lactam antibiotic such as ceftazidime or piperacillin-tazobactam in combination with an aminoglycoside such as tobramycin.

Case 35.5

A 70-year-old man who is a lifelong non-smoker presents to his GP with recurrent chest infections. He has been experiencing a cough productive of sputum which is occasionally blood-stained for several months. He also complains of increasing breathlessness. He has had no relief from several courses of antibiotics. Chest examination is unremarkable. The following day the local microbiology laboratory reports the presence of acid-fast bacilli in the sputum.

Questions

1. What is the likely diagnosis?
2. What are the next steps in the management of this patient?

Answers

1. Acid-fast bacilli are consistent with the presence of *Mycobacterium* species in the sputum. This may indicate TB but does not confirm this, as other non-tuberculous mycobacteria may be present. The culture result will confirm the identity.
2. TB is best managed by a specialist in respiratory medicine and this patient should be referred for further investigation. Community infection control teams should be made aware of this result as this patient might have infective TB and may have come into contact with at risk individuals.

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Useful website

Health Protection Agency, http://www.hpa.org.uk/.

36 Urinary tract infections

N. J. B. Carbarns

Key points

- Urinary tract infection (UTI) is one of the most common complaints seen in general practice and accounts for about one-third of hospital-acquired infections.
- UTI is one of the commonest reasons for prescribing antibiotics.
- *Escherichia coli* is the most frequent pathogen, accounting for more than three-quarters of community-acquired urinary tract infections.
- Symptoms are variable; many UTIs are asymptomatic and some present atypically, particularly in children and the elderly.
- The concept of significant bacteriuria (at least 100,000 organisms/mL of urine) is generally used to distinguish between contamination and infection, but lower counts than this can cause symptoms and disease.
- Asymptomatic UTI should be treated in children and pregnant women.
- Catheter-related UTI should be treated only when the patient has systemic evidence of infection.
- Antimicrobial sensitivity patterns are changing. *E. coli* is becoming increasingly resistant to amoxicillin, cephalosporins, trimethoprim and the quinolones.
- A 3-day treatment course is usually sufficient in uncomplicated lower UTI in women. Longer, 7–14-day courses are recommended for men, children and pregnant women.
- While it is not always necessary to send urine samples for laboratory analysis unless empirical treatment fails, they provide local epidemiology and antibiotic resistance data.
- Antibiotic prophylaxis may be beneficial in women with recurrent UTIs and in children with structural or functional abnormalities.

The term urinary tract infection (UTI) usually refers to the presence of organisms in the urinary tract together with symptoms, and sometimes signs, of inflammation. However, it is more precise to use one of the following terms.

- *Significant bacteriuria:* defined as the presence of at least 100,000 bacteria/mL of urine. A quantitative definition such as this is needed because small numbers of bacteria are normally found in the anterior urethra and may be washed out into urine samples. Counts of fewer than 1000 bacteria/mL are normally considered to be urethral contaminants unless there are exceptional clinical circumstances, such as a sick immunosuppressed patient.
- *Asymptomatic bacteriuria:* significant bacteriuria in the absence of symptoms in the patient.
- *Cystitis:* a syndrome of frequency, dysuria and urgency, which usually suggests infection restricted to the lower urinary tract, that is, the bladder and urethra.
- *Urethral syndrome:* a syndrome of frequency and dysuria in the absence of significant bacteriuria with a conventional pathogen.
- *Acute pyelonephritis:* an acute infection of one or both kidneys. Usually, the lower urinary tract is also involved.
- *Chronic pyelonephritis:* a potentially confusing term used in different ways. It can refer to continuous excretion of bacteria from the kidney, to frequent recurring infection of the renal tissue or to a particular type of pathology of the kidney seen microscopically or by radiographic imaging, which may or may not be due to infection. Although chronic infections of renal tissue are relatively rare, they do occur in the presence of kidney stones and in tuberculosis.
- *Relapse and reinfection:* recurrence of urinary infection may be due to either relapse or reinfection. Relapse is recurrence caused by the same organism that caused the original infection. Reinfection is recurrence caused by a different organism, and is therefore a new infection.

Epidemiology

UTIs are among the most common infectious diseases occurring in either the community or health care setting. Uncomplicated UTIs typically occur in healthy adult non-pregnant women, whereas complicated UTIs are found in either sex and at any age, frequently associated with structural or functional urinary tract abnormalities.

Babies and infants

UTI is a problem in all age groups, although its prevalence varies markedly. In infants up to the age of 6 months, symptomatic UTI has a prevalence of about two cases per 1000 and is much more common in boys than in girls. In addition to these cases, asymptomatic UTI is much more common than this, occurring in around 2% of boys in their first few months of life.

Children

In preschool children, UTIs become more common and the sex ratio reverses, such that the prevalence of bacteriuria is 4.5% in girls and 0.5% in boys. In older children, the prevalence of bacteriuria falls to 1.2% among girls and 0.03% among boys. Overall, about 3–5% of girls and 1–2% of boys will experience a symptomatic UTI during childhood. However, in girls, about two-thirds of UTIs are asymptomatic. The occurrence of bacteriuria during childhood appears to correlate with a higher incidence of bacteriuria in adulthood.

Adults

When women reach adulthood, the prevalence of bacteriuria rises to between 3% and 5%. Each year, about a quarter of these bacteriuric women clear their infections spontaneously and are replaced by an equal number of newly infected women, who are often those with a history of previous infections. On average, about one in eight adult women has a symptomatic UTI each year and over half of adult women report that they have had a symptomatic UTI at some time, 20% recurrently, with the peak age incidence in their early 20s. UTI is uncommon in young healthy men, with 0.5% of adult men having bacteriuria. The rate of symptomatic UTI in men rises progressively with age, from 1% annually at age 18 to 4% at age 60.

Elderly

In the elderly of both sexes, the prevalence of bacteriuria rises dramatically, reaching 20% among women and 10% among men. In hospitals, a major predisposing cause of UTI is urinary catheterisation. With time, even with closed drainage systems and scrupulous hygiene, bacteria can be found in almost all catheters and this is a risk for the development of symptomatic infection.

Aetiology and risk factors

In acute uncomplicated UTI acquired in the community, *Escherichia coli* is by far the most common causative bacterium, being responsible for about 80% of infections. The remaining 20% are caused by other Gram-negative enteric bacteria such as *Klebsiella* and *Proteus* species, and by Gram-positive cocci, particularly enterococci and *Staphylococcus saprophyticus*. The latter organism is almost entirely restricted to infections in young, sexually active women.

UTI associated with underlying structural abnormalities, such as congenital anomalies, neurogenic bladder and obstructive uropathy, is often caused by more resistant organisms such as *Pseudomonas aeruginosa*, *Enterobacter* and *Serratia* species. Organisms such as these are also more commonly implicated in hospital-acquired urinary infections, including those in patients with urinary catheters.

Rare causes of urinary infection, nearly always in association with structural abnormalities or catheterisation, include anaerobic bacteria and fungi. Urinary tract tuberculosis is an infrequent but important diagnosis that may be missed through lack of clinical suspicion. A number of viruses are excreted in urine and may be detected by culture or nucleic acid amplification methods, but symptomatic infection is confined to immunocompromised patients, particularly children following bone marrow transplantation, in whom adenoviruses and polyomaviruses such as BK virus are associated with haemorrhagic cystitis.

Pathogenesis

There are three possible routes by which organisms might reach the urinary tract: the ascending, blood-borne and lymphatic routes. There is little evidence for the last route in humans. Blood-borne spread to the kidney can occur in bacteraemic illnesses, most notably *Staphylococcus aureus* septicaemia, but by far the most frequent route is the ascending route.

In women, UTI is preceded by colonisation of the vagina, perineum and periurethral area by the pathogen, which then ascends into the bladder via the urethra. Uropathogens colonise the urethral opening of men and women. That the urethra in women is shorter than in men and the urethral meatus is closer to the anus are probably important factors in explaining the preponderance of UTI in females. Further, sexual intercourse appears to be important in forcing bacteria into the female bladder, and this risk is increased by the use of diaphragms and spermicides, which have both been shown to increase *E. coli* growth in the vagina. Whether circumcision reduces the risk of infection in adult men is not known, but it markedly reduces the risk of UTI in male infants.

Organism

E. coli causes most UTIs and although there are many serotypes of this organism, only a few of these are responsible for a disproportionate number of infections. While there are as yet no molecular markers that uniquely identify uropathogenic *E. coli*, some strains possess certain virulence factors that enhance their ability to cause infection, particularly infections of the upper urinary tract. Recognised factors include bacterial surface structures called P-fimbriae, which mediate adherence to glycolipid receptors on renal epithelial cells, possession of the iron-scavenging aerobactin system, and increased amounts of capsular K antigen, which mediates resistance to phagocytosis.

Host

Although many bacteria can readily grow in urine, and Louis Pasteur used urine as a bacterial culture medium in his early experiments, the high urea concentration and extremes of osmolality and pH inhibit growth. Other defence mechanisms include the flushing mechanism of bladder emptying, since small numbers of bacteria finding their way into the bladder are likely to be eliminated when the bladder is emptied. Moreover, the bladder mucosa, by virtue of a surface

glycosaminoglycan, is intrinsically resistant to bacterial adherence. Presumably, in sufficient numbers, bacteria with strong adhesive properties can overcome this defence. Finally, when the bladder is infected, white blood cells are mobilised to the bladder surface to ingest and destroy invading bacteria. The role of humoral antibody-mediated immunity in defence against infection of the urinary tract remains unclear. Genetic susceptibility of individual patients to UTI has been reviewed (Lichtenberger and Hooton, 2008).

Abnormalities of the urinary tract

Any structural abnormality leading to the obstruction of urinary flow increases the likelihood of infection. Such abnormalities include congenital anomalies of the ureter or urethra, renal stones and, in men, enlargement of the prostate. Renal stones can become infected with bacteria, particularly *Proteus* and *Klebsiella* species, and thereby become a source of 'relapsing' infection. Vesicoureteric reflux (VUR) is a condition caused by failure of physiological valves at the junction of the ureters and the bladder which allows urine to reflux towards the kidneys when the bladder contracts. It is probable that VUR plays an important role in childhood UTIs that lead to chronic renal damage (scarring) and persistence of infection. If there is a diminished ability to empty the bladder such as that due to spinal cord injury, there is an increased risk of bacteriuria.

Clinical manifestations

Most UTIs are asymptomatic. Symptoms, when they do occur, are principally the result of irritation of the bladder and urethral mucosa. However, the clinical features of UTI are extremely variable and to some extent depend on the age of the patient.

Babies and infants

Infections in newborn babies and infants are often overlooked or misdiagnosed because the signs may not be referable to the urinary tract. Common but non-specific presenting symptoms include failure to thrive, vomiting, fever, diarrhoea and apathy. Further, confirmation may be difficult because of problems in obtaining adequate specimens. UTI in infancy and childhood is a major risk factor for the development of renal scarring, which in turn is associated with future complications such as chronic pyelonephritis in adulthood, hypertension and renal failure. It is therefore vital to make the diagnosis early, and any child with a suspected UTI should receive urgent expert assessment.

Children

Above the age of 2, children with UTI are more likely to present with some of the classic symptoms such as frequency, dysuria and haematuria. However, some children present with acute abdominal pain and vomiting, and this may be so marked as to raise suspicions of appendicitis or other intra-abdominal pathology. Again, however, it is extremely important that the diagnosis of UTI is made promptly to pre-empt the potential long-term consequences. National guidance has been published in the UK on paediatric UTIs to promote a more consistent clinical practice by ensuring prompt, accurate diagnosis and appropriate management (NICE, 2007). A key feature of the guidance is that children with unexplained fever should have their urine tested within 24 h and attention is given to avoiding over- or underdiagnosis, appropriate investigation and the prompt start of antibiotic treatment.

Adults

In adults, the typical symptoms of lower UTI include frequency, dysuria, urgency and haematuria. Acute pyelonephritis (upper UTI) usually causes fever, rigors and loin pain in addition to lower tract symptoms. Systemic symptoms may vary from insignificant to extreme malaise. Importantly, untreated cystitis in adults rarely progresses to pyelonephritis, and bacteriuria does not seem to carry the adverse long-term consequences that it does in children.

In about 40% of women with dysuria, urgency and frequency, the urine sample contains fewer than 100,000 bacteria/mL. These patients are said to have the urethral syndrome. Some have a true bacterial infection but with relatively low counts (100–1000 bacteria/mL). Some have urethral infection with *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, mycoplasmas or other 'fastidious' organisms, any of which might give rise to symptoms indistinguishable from those of cystitis. In others, no known cause can be found by conventional laboratory techniques. It is important to consider the possibility of urinary tract tuberculosis, as special methods are necessary for its detection. Sometimes, the symptoms are of non-infectious origin, such as menopausal oestrogen deficiency or allergy. However, most cases of urethral syndrome will respond to standard antibiotic regimens as used for treating confirmed UTI.

Elderly

Although UTI is frequent in the elderly, the great majority of cases are asymptomatic, and even when present, symptoms are not diagnostic because frequency, dysuria, hesitancy and incontinence are fairly common in elderly people without infection. Further, there may be non-specific systemic manifestations such as confusion and falls, or alternatively the infection may be the cause of deterioration in pre-existing conditions such as diabetes mellitus or congestive cardiac failure, whose clinical features might predominate. UTI is one of the most frequent causes of admission to hospital among the elderly.

Investigations

The key to successful laboratory diagnosis of UTI lies in obtaining an uncontaminated urine sample for microscopy and culture. Contaminating bacteria can arise from skin, vaginal flora in women and penile flora in men. Patients therefore

need to be instructed in how to produce a midstream urine sample (MSU). For women, this requires careful cleansing of the perineum and external genitalia with soap and water. Uncircumcised men should retract the foreskin. This is followed by a controlled micturition in which about 20 mL of urine from only the middle portion of the stream is collected, the initial and final components being voided into the toilet or bedpan. Understandably, this is not always possible and many so-called MSUs are in fact clean-catch specimens in which the whole urine volume is collected into a sterile receptacle and an aliquot transferred into a specimen pot for submission to the laboratory. These are more likely to contain urethral contaminants. In very young children, special collection pads for use inside nappies or stick-on bags are useful ways of obtaining a urine sample. Occasionally, in-and-out diagnostic catheterisation or even suprapubic aspiration directly from the bladder is necessary.

For primary care doctors located some distance from a laboratory, transport of specimens is a problem. Specimens must reach the laboratory within 1–2 h or should be refrigerated; otherwise, any bacteria in the specimen will multiply and might give rise to a false-positive result. Methods of overcoming bacterial multiplication in urine include the addition of boric acid to the container and the use of dip-slides, in which an agar-coated paddle is dipped into the urine and submitted directly to the laboratory for incubation. Both of these alternatives have difficulties. For the boric acid technique, it is important that the correct amount of urine is added to the container to achieve the appropriate concentration of boric acid (1.8%, w/v), as the chemical has significant antibacterial activity when more concentrated. When the dip-slide is used, no specimen is available on which to do cell counts.

Concerns about the relative expense and slow turn-around time of urine microscopy and culture have stimulated interest in alternative diagnostic strategies. Some advocate a policy of empirical antimicrobial treatment in the first instance, and reserve investigation only for those cases that do not respond. Others are in favour of using cheaper, more convenient screening tests, for example, urine dipsticks. It is important to be aware that there is no rapid screening test that will reliably detect all UTIs. Urine microscopy and culture remain the standard by which other investigations are measured.

Dipsticks

Dipsticks for rapid near-patient testing for urinary blood, protein, nitrites and leucocyte esterase are usually used, although there are concerns that these are reliable only when applied to fresh urine samples tested at the point of care. Assessment of colour changes on dipsticks can be subjective and automated reading systems have been developed to assist interpretation. Generally, the negative predictive value is better than the positive predictive value, so their preferred use is as screening tests to identify those specimens which are least likely to be infected and which therefore do not require culture. A perfectly valid alternative is just to hold the specimen up to the light: specimens that are visibly clear are very likely to be sterile.

The leucocyte esterase test detects enzyme released from leucocytes in urine and is ~90% sensitive at detecting white blood cell counts of >10 mm^{-3}. It will be positive even if the cells have been destroyed due to delays in transport to a laboratory. However, vitamin C and antibiotics in the urine such as cephalosporins, gentamicin and nitrofurantoin may interfere with the reaction. Although the presence of leucocytes is common in UTIs, it may also occur in other conditions. Particularly in children, white blood cells can be present for many reasons, including fever alone.

The nitrite test (also called the Griess test) detects urinary nitrite made by bacteria that can convert excreted dietary nitrate used as a food preservative to nitrite. Although the coliform bacteria that commonly cause UTI can be detected in this way, some organisms cannot, for example, enterococci, group B streptococci, *Pseudomonas*, because they do not contain the converting enzyme. In addition, the test depends on sufficient nitrate in the diet and on allowing enough time, at least 4 h, for the chemical conversion to occur in the urine. Performance of the dipstick test is generally less diagnostic in infants and younger children than in the older age groups, and this may relate in part to the small capacity and frequent emptying of the infant bladder, resulting in lower numbers of organisms and less pyuria. The use of dipsticks alone for the diagnosis of UTI is not recommended for children under 3 years of age (NICE, 2007). The inability of the test to detect group B streptococci also makes it a relatively inappropriate test for screening for asymptomatic bacteriuria in pregnancy, in which this organism assumes particular importance as a cause of neonatal sepsis.

Although a negative dipstick test for leucocytes and nitrites can quite accurately predict absence of infection, their absence does not necessarily predict non-response to antibiotic treatment and further research is needed on this (Richards et al., 2005). Some experts consider that detection of nitrites in a symptomatic patient should prompt initiation of treatment (Gopal Rao and Patel, 2009). An algorithm for the use of dipstick testing in uncomplicated UTI in adult women is set out in Fig. 36.1.

There are other rapid methods for detecting bacteriuria, such as tests for interleukin-8, and no shortage of data concerning their sensitivity and specificity, but the optimal strategy will always be a compromise between accuracy, speed, convenience and cost, and is likely to be very different for different settings and populations.

Microscopy

Microscopy is the first step in the laboratory diagnosis of UTI and can be readily performed in practice. A drop of uncentrifuged urine is placed on a slide, covered with a coverslip and examined under a 40× objective. Excess white cells are usually seen in the urine of patients with symptomatic UTI, and more than 10 per high-power field is abnormal. It should be noted that there are other methods in common use, and laboratories may report white cell counts per microlitre (cubic millimetre) of urine or per millilitre. Automated machinery for microscopy of urine is increasingly used and

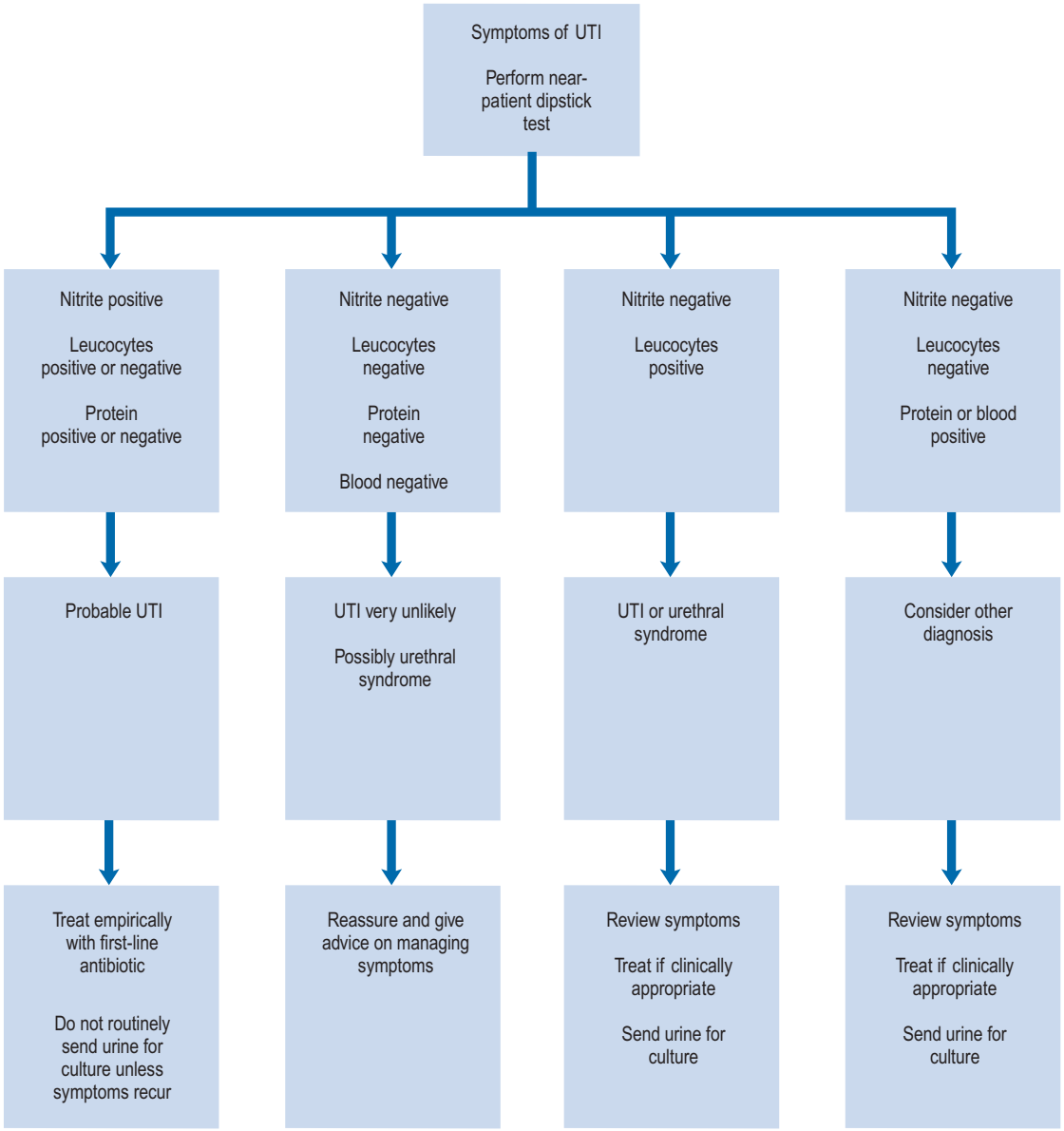

Fig. 36.1 Algorithm for diagnosis of acute uncomplicated urinary tract infection (UTI) in adult women.

offers increased precision and handling capacities of over 100 specimens/h. Although there is a substantial capital cost to such equipment, it is offset by savings in labour and bacterial culture materials. One feature of this equipment is that it is generally much more sensitive in detecting cells, so much so that laboratories using such systems will have a much higher number for significant results (e.g. >50 rather than >10 white cells/mm^3).

It is important not to be too rigid in the interpretation of the white cell count. UTI may occur in the absence of pyuria, particularly at the extremes of age, in pregnancy and in pyelonephritis. Red blood cells may be seen, as may white cell casts, which are suggestive of pyelonephritis. As a rule of thumb, the presence of at least one bacterium per field correlates with 100,000 bacteria/mL.

Culture

Bladder urine is normally sterile, but when passed via the urethra, it is inevitable that some contamination with the urethral bacterial flora will occur. This is why it is important that laboratories quantify the number of bacteria in urine specimens. In work carried out over 40 years ago, it was demonstrated that patients with UTI usually have at least 100,000 bacteria/mL, while in patients without infection, the count is usually below 1000 bacteria/mL. Between these figures lies a grey area, and it should be appreciated that the MSU is not an infallible guide to the presence or absence of urinary infection. True infections may be associated with low counts, particularly when the urine is very dilute because of excessive fluid intake or where the pathogen is slow growing. While the

quantitative criterion for 'significant' bacteriuria is generally taken as >100,000/mL, in some specific groups, it is less: for men, >1000/mL and for women with symptoms of UTI, it is >100/mL (SIGN, 2006).

Most genuine infections are caused by one single bacterial species; mixed cultures usually suggest contamination. If a patient is taking an antibiotic when a urine specimen is obtained for culture, growth of bacteria may be inhibited. The laboratory may perform a test to detect antimicrobial substances in the urine, and this may be useful information to clarify circumstances in which the culture is negative but a significant pyuria is present.

Treatment

Although many, and perhaps most, cases clear spontaneously given time, symptomatic UTI usually merits antibiotic treatment to eradicate both symptoms and pathogen. Asymptomatic bacteriuria may or may not need treatment depending upon the circumstances of the individual case. Bacteriuria in children and in pregnant women requires treatment, as does bacteriuria present when surgical manipulation of the urinary tract is to be undertaken, because of the potential complications. On the other hand, in non-pregnant, asymptomatic bacteriuric adults without any obstructive lesion, screening and treatment are probably unwarranted in most circumstances (Nicolle et al., 2005). Unnecessary treatment will lead to selection of resistant organisms and puts patients at risk of adverse drug effects including bowel infection with *Clostridium difficile*, which has been particularly associated with the use of cephalosporins and quinolones. A number of common management problems are summarised in Table 36.1.

Non-specific treatments

Advising patients with UTI to drink a lot of fluids is common practice on the theoretical basis that more infected urine is removed by frequent bladder emptying. This is plausible, although not evidence based. Some clinicians recommend urinary analgesics such as potassium or sodium citrate, which alkalinise the urine, but these should be used as an adjunct to antibiotics. They should not be used in conjunction with nitrofurantoin, which is active only at acidic pH.

Antimicrobial chemotherapy

The principles of antimicrobial treatment of UTI are the same as those of the treatment of any other infection: from a group of suitable drugs chosen on the basis of efficacy, safety and cost, select the agent with the narrowest possible spectrum and administer it for the shortest possible time. In general, there is no evidence that bactericidal antibiotics are superior to bacteriostatic agents in treating UTI, except perhaps in relapsing infections. Blood levels of antibiotics appear to be unimportant in the treatment of lower UTI; what matters is the concentration in the urine. However, blood levels probably are important in treating pyelonephritis, which may progress to bacteraemia. Drugs suitable for the oral treatment of cystitis include trimethoprim, the β-lactams, particularly amoxicillin, co-amoxiclav and cefalexin, fluoroquinolones such as ciprofloxacin, norfloxacin and ofloxacin, and nitrofurantoin. Where intravenous administration is required, suitable agents include β-lactams such as amoxicillin and cefuroxime, quinolones, and aminoglycosides such as gentamicin.

In renal failure, it may be difficult to achieve adequate therapeutic concentrations of some drugs in the urine, particularly nitrofurantoin and quinolones. Further, accumulation and toxicity may complicate the use of aminoglycosides. Penicillins and cephalosporins attain satisfactory concentrations and are relatively non-toxic, and are therefore the agents of choice for treating UTI in the presence of renal failure.

Antibiotic resistance

Antimicrobial resistance is a major concern worldwide. The susceptibility profile of commonly isolated uropathogens has been constantly changing. Coliform bacteria of many species that produce extended-spectrum β-lactamase (ESBL) enzymes have emerged in recent years, particularly as a cause of UTI in community-based patients. Before 2003, most ESBL-producing bacteria were hospital acquired and occurred in specialist units.

ESBL-producing bacteria are clinically important as they produce enzymes that destroy almost all commonly used β-lactams except the carbapenem class, rendering most penicillins and cephalosporins largely useless in clinical practice. Some ESBL enzymes can be inhibited by clavulanic acid, and combinations of an agent containing it, for example, co-amoxiclav, with other oral broad-spectrum β-lactams, for example, cefixime or cefpodoxime, have been used to treat UTIs caused by ESBL-producing *E. coli* (Livermore et al., 2008). These combinations are unlicensed and their effectiveness is variable.

In addition, many ESBL-producing bacteria are multiresistant to non-β-lactam antibiotics too, such as quinolones, aminoglycosides and trimethoprim, narrowing treatment options. ESBL-*E. coli* is often pathogenic and a high proportion of infections result in bacteraemia with resultant mortality (Tumbarello et al., 2007). Some strains cause outbreaks both in hospitals and in the community. Empirical treatment strategies may need to be reviewed in settings where ESBL-producing strains are prevalent, and it may be considered appropriate to use a carbapenem in seriously ill patients until an infection has been proved not to involve an ESBL producer.

Recently, even more resistant strains have emerged in India and Pakistan, with subsequent transfer to the UK, that carry a gene for a novel New Delhi metallo-β-lactamase-1 that also confers resistance to carbapenems. This $bla_{\text{NDM-1}}$ gene was mostly found among *E. coli* and *Klebsiella*, which were highly resistant to all antibiotics except to colistin and tigecycline, which is not effective for UTI as it is chemically unstable in the urinary tract (Kumarasamy et al., 2010).

Table 36.1 Common management problems with urinary tract infections (UTI)

Problem	Comments
Asymptomatic infection	Asymptomatic bacteriuria should be treated where there is a risk of serious consequences (e.g. in childhood), where there is renal scarring, and in pregnancy. Otherwise, treatment is not usually required
Catheter *in situ*, patient unwell	Systemic symptoms may result from catheter-associated UTI, and should respond to antibiotics although the catheter is likely to remain colonised. Local symptoms such as urgency are more likely to reflect urethral irritation than infection
Catheter *in situ*, urine cloudy or smelly	Unless the patient is systemically unwell, antibiotics are unlikely to achieve much and may give rise to resistance. Interventions of uncertain benefit include bladder wash-outs or a change of catheter
Penicillin allergy	Clarify 'allergy': vomiting or diarrhoea are not allergic phenomena and do not contraindicate penicillins. Penicillin-induced rash is a contraindication to amoxicillin, but cephalosporins are likely to be tolerated. Penicillin-induced anaphylaxis suggests that all β-lactams should be avoided
Symptoms of UTI but no bacteriuria	Exclude urethritis, candidosis, etc. Otherwise likely to be urethral syndrome, which usually responds to conventional antibiotics
Bacteriuria but no pyuria	May suggest contamination. However, pyuria is not invariable in UTI and may be absent particularly in pyelonephritis, pregnancy, neonates, the elderly, and *Proteus* infections
Pyuria but no bacteriuria	Usually, the patient has started antibiotics before taking the specimen. Rarely, a feature of unusual infections (e.g. anaerobes, tuberculosis, etc.)
Urine grows *Candida*	Usually reflects perineal candidosis and contamination. True candiduria is rare, and may reflect renal candidosis or systemic infection with candidaemia
Urine grows two or more organisms	Mixed UTI is unusual – mixed cultures are likely to reflect perineal contamination. A repeat should be sent unless this is impractical (e.g. frail elderly patients), in which case best-guess treatment should be instituted if clinically indicated
Symptoms recur	May represent relapse or reinfection. A repeat urine culture should be performed shortly after treatment

Uncomplicated lower UTI

The problem with empirical treatment is that over 10% of the healthy adult female population would receive an antibiotic each year. The use of antibiotics to this extent in the population has implications for antibiotic resistance, a major focus of public health policy worldwide. This highlights the tension between maximising the benefit for individuals and minimising antibiotic resistance at a population level. Strategies have included diagnostic algorithms to predict more precisely who has a UTI, as well as issuing delayed prescriptions (Mangin, 2010).

Therapeutic decisions should be based on accurate, up-to-date antimicrobial susceptibility patterns. Data have been published from a European multicentre survey that examined the prevalence and antimicrobial susceptibility of community-acquired pathogens causing uncomplicated UTI in women (Kahlmeter, 2003). Among almost 2500 *E. coli* isolates, the resistance rates were 30% for amoxicillin, 15% for trimethoprim, 3.4% for co-amoxiclav, 2.3% for ciprofloxacin, 2.1% for cefadroxil and 1.2% for nitrofurantoin. These figures are lower than most routine laboratory data would suggest, but it should be remembered that the experience of diagnostic laboratories is likely to be biased by the overrepresentation of specimens from patients in whom empirical treatment has already failed. It is important to be aware of local variations in sensitivity pattern and to balance the risk of therapeutic failure against the cost of therapy.

Adults

The preference for best-guess therapy would seem to be a choice between trimethoprim, an oral cephalosporin such as cefalexin, co-amoxiclav or nitrofurantoin, with the proviso that therapy can be refined once sensitivities are available. The quinolones are best reserved for treatment failures and more difficult infections, since overuse of these important agents is likely to lead to an increase in resistance, as has been seen in countries such as Spain and Portugal. These recommendations are summarised in Table 36.2.

Other drugs that have been used for the treatment of UTI include co-trimoxazole, pivmecillinam, fosfomycin and earlier quinolones such as nalidixic acid. Co-trimoxazole is now recognised as a cause of bone marrow suppression and other haematological side effects, and in the UK, its use is greatly restricted. Further, despite superior activity *in vitro*, there is no convincing evidence that it is clinically superior to trimethoprim alone in the treatment of UTI caused by strains susceptible to both. Pivmecillinam is an oral pro-drug that is metabolised

Table 36.2 Oral antibiotics used for lower urinary tract infections

Antibiotic	Dose (adult)	Side effects	Contraindications	Comments
Amoxicillin	250–500 mg three times a day	Nausea, diarrhoea, allergy	Penicillin hypersensitivity	High levels of resistance (>50%) in *E. coli*. Not used empirically
Co-amoxiclav	375–625 mg three times a day	See amoxicillin	See amoxicillin	Amoxicillin and clavulanic acid
Cefalexin	250–500 mg four times a day	Nausea, diarrhoea, allergy	Cephalosporin hypersensitivity, porphyria	
Trimethoprim	200 mg twice a day	Nausea, pruritus, allergy	Pregnancy, neonates, folate deficiency, porphyria	
Nitrofurantoin	50 mg four times a day	Nausea, allergy, rarely pneumonitis, pulmonary fibrosis, neuropathy	Renal failure, neonates, porphyria, G6PD deficiency	Modified-release form may be given twice daily. Inactive against *Proteus*
Ciprofloxacin	100–500 mg twice a day	Rash, pruritus, tendinitis	Pregnancy, children	Reserve for difficult cases

G6PD, glucose-6-phosphate dehydrogenase.

to mecillinam, a β-lactam agent with a particularly high affinity for Gram-negative penicillin-binding protein 2 and a low affinity for commonly encountered β-lactamases, and which therefore has theoretical advantages in the treatment of UTI. Pivmecillinam has been extensively used for cystitis in Scandinavian countries, where it does not seem to have led to the development of resistance, and for this reason, there have been calls for wider recognition of its usefulness, particularly for UTI caused by ESBL-producing strains. Fosfomycin is a broad-spectrum antibiotic with pharmacokinetic and pharmacodynamic properties that favour its use for treatment of cystitis with a single oral dose (Falagas et al., 2010). Finally, older quinolones such as nalidixic acid and cinoxacin were once widely used, but generally these agents have given ground to the more active fluorinated quinolones.

Duration of treatment

The question of duration of treatment has received much attention. Traditionally, a course of 7–10 days has been advocated, and this is still the recommendation for treating men, in whom the possibility of occult prostatitis should be borne in mind. For women, though, there has been particular emphasis on the suitability of short-course regimens such as 3-day or even single-dose therapy. The consensus of an international expert working group was that 3-day regimens are as effective as longer regimens in the cases of trimethoprim and quinolones. β-Lactams have been inadequately investigated on this point but short courses are generally less effective than trimethoprim and quinolones, and nitrofurantoin requires further study before definite conclusions can be drawn. Single-dose therapy, with its advantages of cost, adherence and the minimisation of side effects, has been used successfully in many studies but in general is less effective than when the same agent is used for longer.

In the urethral syndrome, it is worth trying a 3-day course of one of the agents mentioned earlier. If this fails, a 7-day course of tetracycline could be tried to deal with possible chlamydia or mycoplasma infection.

Children

In children, the risk of renal scarring is such that UTI should be diagnosed and treated promptly, even if asymptomatic. The drugs of choice include β-lactams, trimethoprim and nitrofurantoin. Quinolones are relatively contraindicated in children because of the theoretical risk of causing cartilage and joint problems. Children should be treated for 7–10 days.

Renal scarring occurs in 5–15% of children with UTI, who should be identified so that appropriate treatment can be instituted. Unfortunately, the subgroup at high risk cannot be predicted, and for this reason, many clinicians choose to investigate all children with UTI, for example, using ultrasound and radioisotope scanning.

Acute pyelonephritis

Patients with pyelonephritis may be severely ill and, if so, will require admission to hospital and initial treatment with a parenteral antibiotic. Suitable agents with good activity against *E. coli* and other Gram-negative bacilli include cephalosporins such as cefuroxime and ceftazidime, some penicillins such as co-amoxiclav, quinolones, and aminoglycosides such as gentamicin (Table 36.3). A first-choice agent would be parenteral cefuroxime, gentamicin or ciprofloxacin. When the patient is improving, the route of administration may be switched to oral therapy, typically using a quinolone. Conventionally, treatment is continued for 10–14 days.

Patients who are less severely ill at the outset may be treated with an oral antibiotic, and possibly with a shorter course of

Table 36.3 Parenteral antibiotics used for pyelonephritis

Antibiotic	Dose (adult)	Side effects	Contraindications	Comments
Cefuroxime	750 mg three times a day	Nausea, diarrhoea, allergy	Cephalosporin hypersensitivity, porphyria	Implicated in *Clostridium difficile*
Ceftazidime	1 g three times a day	See cefuroxime	See cefuroxime	See cefuroxime
Co-amoxiclav	1.2 g three times a day	Nausea, diarrhoea, allergy	Penicillin hypersensitivity	
Gentamicin	80–120 mg three times a day or 5 mg/kg once daily	Nephrotoxicity, ototoxicity	Pregnancy, myasthenia gravis	Monitor levels
Ciprofloxacin	200–400 mg twice a day	Rash, pruritus, tendinitis	Pregnancy, children	Implicated in *Clostridium difficile*
Piperacillin with tazobactam	4.5 g three times a day	Nausea, allergy	Penicillin hypersensitivity	
Meropenem	500 mg three times a day	Nausea, rash, convulsions		Reserve for multiresistant cases

treatment. The safety of this approach has been demonstrated in a study of adult women with acute uncomplicated pyelonephritis (Talan et al., 2000). Among 113 patients treated with oral ciprofloxacin 500 mg twice daily for 7 days (± an initial intravenous dose), the cure rate was 96%.

In hospital-acquired pyelonephritis, there is a risk that the infecting organism may be resistant to the usual first-line drugs. In such cases, it may be advisable to start a broad-spectrum agent such as ceftazidime, ciprofloxacin or meropenem.

Relapsing UTI

The main causes of persistent relapsing UTI are renal infection, structural abnormalities of the urinary tract and, in men, chronic prostatitis. Patients who fail on a 7–10-day course should be given a 2-week course, and if that fails, a 6-week course can be considered. Structural abnormalities may need surgical correction before cure can be maintained. It is essential that prolonged courses (i.e. more than 4 weeks) are managed under bacteriological control, for example, with monthly cultures. In men with prostate gland infection, it is appropriate to select antibiotics with good tissue penetration such as trimethoprim and the fluoroquinolones.

Catheter-associated infections

In most large hospitals, 10–15% of patients have an indwelling urinary catheter. Even with the very best catheter care, most will have infected urine after 10–14 days of catheterisation, although most of these infections will be asymptomatic. Antibiotic treatment will often appear to eradicate the infecting organism, but as long as the catheter remains in place, the organism, or another more resistant one, will quickly return. The principles of antibiotic therapy for catheter-associated UTI are therefore as follows:

- Do not treat asymptomatic infection.
- If possible, remove the catheter before treating symptomatic infection.

Although it often prompts investigation, cloudy or strong-smelling urine is not *per se* an indication for antimicrobial therapy. In these situations, saline or antiseptic bladder washouts are often performed, but there is little evidence that they make a difference. Similarly, encrusted catheters are often changed on aesthetic grounds, but it is not known whether this reduces the likelihood of future symptoms.

Following catheter removal, bacteriuria may resolve spontaneously but more often it persists (typically for over 2 weeks in over half of patients) and may become symptomatic, though usually it will respond well to short-course treatment.

Antimicrobial catheters

Several different types of novel catheters with anti-infective properties have been developed with the aim of reducing the ability of bacteria to adhere to the material, which should lead to a decreased incidence of bacteriuria and symptomatic infection. Several studies of the effect of incorporating antibiotics such as rifampicin and minocycline or silver-based alloys into the catheter have shown benefit. Although clearly more costly than standard catheters, economic evaluation shows silver alloy catheters to be cost efficient when used in patients needing catheterisation for several days. The effect of these catheters on clinical outcomes such as bacteraemia remains to be determined.

Bacteriuria of pregnancy

The prevalence of asymptomatic bacteriuria of pregnancy is about 5%, and about a third of these women proceed to develop acute pyelonephritis, with its attendant consequences

for the health of both mother and pregnancy. Further, there is evidence that asymptomatic bacteriuria is associated with low birth weight, prematurity, hypertension and pre-eclampsia. For these reasons, it is recommended that screening be carried out, preferably by culture of a properly taken MSU, which should be repeated if positive for confirmation (National Collaborating Centre for Women's and Children's Health, 2003).

Rigorous meta-analysis of published trials has shown that antibiotic treatment of bacteriuria in pregnancy is effective at clearing bacteriuria, reducing the incidence of pyelonephritis and reducing the risk of preterm delivery. The drugs of choice are amoxicillin or cefalexin or nitrofurantoin, depending on the sensitivity profile of the infecting organism. Co-amoxiclav is cautioned in pregnancy because of lack of clinical experience in pregnant women. Trimethoprim is contraindicated (particularly in the first trimester) because of its theoretical risk of causing neural tube defects through folate antagonism. Nitrofurantoin should be avoided close to the time of expected delivery because of a risk of haemolysis in the baby. Ciprofloxacin is contraindicated because it may affect the growing joints. There are insufficient data concerning short-course therapy in pregnancy, and 7 days of treatment remains the standard. Patients should be followed up for the duration of the pregnancy to confirm cure and to ensure that any reinfection is promptly addressed.

Prevention and prophylaxis

There are a number of folklore and naturopathic recommendations for the prevention of UTI. Most of these have not been put to statistical study, but at least are unlikely to cause harm.

Cranberry juice

Cranberry juice (*Vaccinium macrocarpon*) has long been thought to be beneficial in preventing UTI, and this has been studied in a number of clinical trials. Cranberry is thought to inhibit adhesion of bacteria to urinary tract cells on the surface of the bladder. In sexually active women, a daily intake of 750 mL cranberry juice was associated with a 40% reduction in the risk of symptomatic UTI in a double-blinded 12-month trial. Many studies have been criticised for methodological flaws, and currently there is only limited evidence that cranberry juice is effective at preventing recurrent UTI (McMurdo et al., 2009). There have been no randomised controlled trials of the use of cranberry products (juice, tablets or capsules) in the treatment of established infection, or comparing it with established therapies such as antibiotics for preventing infection.

A hypothetical benefit in using cranberry instead of antibiotics for this purpose is a reduced risk of the development of antibiotic-resistant bacteria. A significant hazard is an interaction of cranberry with warfarin, with a risk of bleeding episodes, and available products are not available in standardised formulations. Further, cranberry juice is unpalatable unless sweetened with sugar and therefore carries a risk of tooth decay, although ironically it is reported to prevent dental caries by blocking adherence of plaque bacteria to teeth.

Antibiotic prophylaxis

In some patients, mainly women, reinfections are so frequent that long-term antimicrobial prophylaxis with specific antibiotics is indicated. If the reinfections are clearly related to sexual intercourse, then a single dose of an antibiotic after intercourse is appropriate. In other cases, long-term, low-dose prophylaxis may be beneficial. One dose of trimethoprim (100 mg) or nitrofurantoin (50 mg) at night will suffice. These drugs are unlikely to lead to the emergence of resistant bacteria, although breakthrough infection with strains intrinsically resistant to the chosen prophylactic antibiotic is possible.

Children

In children, recurrence of UTI is common and the complications potentially hazardous, so many clinicians recommend antimicrobial prophylaxis following documented infection. The evidence in favour of this practice is not strong (Le Saux et al., 2000), and although it has been shown to reduce the incidence of bacteriuria, there is no good-quality evidence that prophylactic antibiotics are effective in preventing further symptomatic UTIs and they have not been shown to reduce the incidence of renal scarring complications, which are the most important outcomes for the patient (Mori et al., 2009). Further, important variables remain to be clarified, such as when to begin prophylaxis, which agent to use and when to stop. Recent guidelines have abandoned the time-honoured recommendation for routine antibiotic prophylaxis following a first infection, although it may be considered when there is recurrent UTI (NICE, 2007).

Although evidence is limited for some recommendations, there are many common-sense general measures aimed at reducing the risk of recurrence of infection, particularly in girls. They include advice on regular bladder emptying, cleaning the perineal/anal area from front to back after toilet, treating constipation adequately and avoiding both bubble baths and washing the hair in the bath.

Case studies

Case 36.1

A 70-year-old man has consulted his primary care doctor three times in the past 3 months and seems to have the same *E. coli* infection on each occasion. A short course of antibiotics clears up the symptoms, but a clinical relapse is soon apparent. He is admitted to hospital for transurethral resection of the prostate and 2 days after the operation he becomes unwell with rigors, fever and loin pain. Microscopy of his urine shows over 200 white cells/mm^3. Blood cultures are taken and rapidly become positive, with Gram-negative bacilli seen on microscopy.

Question

Is there any way of predicting which UTIs are likely to go on to cause further problems such as pyelonephritis or prostatitis? What antibiotic therapy is indicated now?

Answer

Progression of a simple UTI is much more common in patients other than young women. Foreign bodies such as catheters and stents, or physiological problems such as neurogenic bladder, increase the risk of a complicated UTI. In men, persistent or recurrent infection with the same organism is highly suggestive of prostatitis and should prompt an extended course of treatment. Pyelonephritis is more difficult to predict. Frequency, dysuria and haematuria indicate lower tract infection. Fever, vomiting, rigors and flank pain are more suggestive of upper renal tract involvement.

The patient should be started on intravenous antibiotic therapy for presumed prostatitis or pyelonephritis and consequent bacteraemia. The antibiotic should cover Gram-negative organisms found in the hospital environment such as *Klebsiella*, *Enterobacter* and *Pseudomonas*. Appropriate agents would be piperacillin-tazobactam, ceftazidime, ciprofloxacin or meropenem. An alternative would be an aminoglycoside such as gentamicin, provided the patient has satisfactory renal function.

Case 36.2

A pregnant woman aged 26 years is found to have bacteriuria at her first antenatal visit. There are no white or red cells seen in her urine. Urine culture demonstrates *E. coli* at a count of more than 100,000 bacteria/mL, sensitive to trimethoprim, nitrofurantoin and cefalexin but resistant to amoxicillin. Other than a degree of urinary frequency, which she ascribes to the pregnancy itself, the patient does not complain of any urinary symptoms.

Question

Does this patient need antibiotic treatment, and if so, which drugs could be safely used?

Answer

The patient may be correct that her urinary frequency is a consequence of pregnancy. However, because of the consequences of untreated infection during pregnancy, even asymptomatic bacteriuria should be treated. A repeat urine specimen should be obtained to confirm the finding, and treatment started with either cefalexin or co-amoxiclav for 7 days. Trimethoprim should be avoided during early pregnancy because of its theoretical risk of teratogenicity, and nitrofurantoin should be avoided in late pregnancy as it may cause neonatal haemolysis. Following treatment, she should be reviewed throughout the pregnancy to ensure eradication of the bacteriuria, and to permit early treatment of any relapse or reinfection.

Case 36.3

A 2-year-old boy is admitted to hospital with vomiting and abdominal pain. His mother reports that he was treated for UTI 6 months previously, but was not investigated further at the time. A clean catch urine sample shows over 50 white cells/mm^3 and bacteria are seen on microscopy.

Question

What action should be taken?

Answer

It seems that this child is suffering from a recurrent UTI. An intravenous antibiotic such as cefuroxime should be started, since the child will not tolerate oral antibiotics at present. If the organism proves to be sensitive to amoxicillin, the treatment could be changed accordingly. Further investigations, for example, ultrasonography and radioisotope scan, may be carried out to determine any underlying cause of the infection and to look for already established renal scarring. The child may require long-term prophylaxis to prevent a further recurrence.

Case 36.4

A 62-year-old lady has been troubled by recurrent symptoms of UTI. She has been taking an oral oestrogen preparation for menopausal symptoms for some years. She is currently on an orthopaedic ward and catheterised because of incontinence. She is afebrile but has been confused since her hip replacement 5 days earlier, and remains on cefuroxime, which was started as prophylaxis at the time of the operation. The urine in her catheter bag is cloudy, has a high white cell count, and grows *Enterococcus faecalis* sensitive to amoxicillin but resistant to cephalosporins.

Question

How should this patient be managed? In older women, is there any association with the use of different types of oestrogen delivery systems and UTIs?

Answer

The patient's confusion may have a number of causes, including her recent surgery, sleep disturbance, drug toxicity, deep venous thrombosis or infection. If, following clinical examination and investigation, which should include blood cultures, her catheter-associated infection is thought to be contributing to her systemic problems, it should be treated with amoxicillin. If possible, the catheter should be removed, even if this is inconvenient for the nursing staff. Unless it has been prescribed for another indication, the cefuroxime is achieving nothing and may be stopped.

In post-menopausal women, there have been trials assessing the merits of topical oestrogen creams. Topical intravaginal oestriol cream has significant benefits in reducing the number of UTIs in those suffering recurrent infections. In a placebo-controlled trial, the rate of UTI was 12-fold less in the group receiving active oestrogen cream. This effect is not seen with oral oestrogens (Perrotta et al., 2008).

Case 36.5

A 45-year-old woman suffers from recurrent episodes of cystitis. Examination is unremarkable. On the occasions when a specimen has been sent, the urine has contained few white cells and no significant growth of organisms.

Question

How should the patient be managed?

Answer

This patient is suffering from the urethral syndrome, in which symptoms of infection are not associated with objective evidence of UTI. It may be felt necessary to investigate her to exclude less common causes of UTI such as herpes simplex virus, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Gardnerella vaginalis*, *Mycoplasma hominis* and *Lactobacilli*. Otherwise, her symptoms are likely to respond to conventional courses of antibiotics. Consider non-infective causes, for example, psychological factors, trauma from intercourse.

Case 36.6

A 23-year-old woman has recurrent symptoms of UTI temporally related to sexual intercourse, despite following advice to empty her bladder as soon as possible after sex.

Question

What do you think of the use of antibiotics such as trimethoprim for women who get recurrent problems after sexual intercourse?

Answer

Post-coital voiding does not have any prospective data to support it, but it is a simple, harmless intervention. Long-term continuous antimicrobial prophylaxis is unquestionably an effective treatment but may be overtreating those in whom UTIs follow intercourse. Post-coital prophylaxis, a single dose within 2 h of intercourse, has the advantage of using less antibiotic overall. One small placebo-controlled double-blind trial assessed the efficacy of post-coital co-trimoxazole in preventing recurrent UTI and found that 12% of the active-treatment patients developed a UTI in 6 months, compared to 82% of the control group. Other studies have shown nitrofurantoin, cefalexin and ciprofloxacin also to be effective.

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Gastro-intestinal infections 37

J.W. Gray

Key points

- There are many different microbial causes of gastro-intestinal infections.
- Gastroenteritis is the most common syndrome of gastro-intestinal infection, but some gastro-intestinal pathogens can cause systemic infections.
- Fluid and electrolyte replacement is the mainstay of management of gastroenteritis.
- Most cases of gastroenteritis that occur in developed countries are mild and self-limiting, and do not require antibiotic therapy.
- Antibiotic therapy should be considered for patients with underlying conditions that predispose to serious or complicated gastroenteritis, or where termination of faecal excretion of pathogens is desirable to prevent further spread of the infection.
- *Clostridium difficile* is a very important cause of diarrhoea in hospitals. Strict control measures are required, and cases should be treated with oral metronidazole or vancomycin.
- Antibiotic therapy is also essential for life-threatening systemic infections, such as enteric fever.
- Where possible, antibiotic therapy should be delayed until a microbiological diagnosis has been established.
- The fluoroquinolones, for example, ciprofloxacin, are currently the most useful antibiotics for treating most bacterial gastro-intestinal infections, but resistance rates are increasing in many pathogens.
- Antibiotic resistance in gastro-intestinal pathogens is an escalating problem.

Gastro-intestinal infections represent a major public health and clinical problem worldwide. Many species of bacteria, viruses and protozoa cause gastro-intestinal infection, resulting in two main clinical syndromes. Gastroenteritis is a non-invasive infection of the small or large bowel that manifests clinically as diarrhoea and vomiting. Other infections are invasive, causing systemic illness, often with few gastro-intestinal symptoms. *Helicobacter pylori*, and its association with gastritis, peptic ulceration and gastric carcinoma, is discussed in Chapter 12.

Epidemiology and aetiology

In Western countries, the average person probably experiences one or two episodes of gastro-intestinal infection each year. Infections are rarely severe and the vast majority of cases never reach medical attention. Nevertheless, they are of considerable economic importance. In the UK, viruses such as rotaviruses, adenoviruses and noroviruses are probably the most common causes of gastroenteritis. *Campylobacter*, followed by non-typhoidal serovars of *Salmonella enterica*, are the most common reported causes of bacterial gastroenteritis. Cryptosporidiosis is the most commonly reported parasitic infection. In developing countries, the incidence of gastro-intestinal infection is at least twice as high and the range of common pathogens is much wider. Infections are more often severe and represent a major cause of mortality, especially in children.

Gastro-intestinal infections can be transmitted by consumption of contaminated food or water or by direct faecal–oral spread. Air-borne spread of viruses that cause gastroenteritis also occurs. The most important causes of gastro-intestinal infection, and their usual modes of spread, are shown in Table 37.1. In developed countries, the majority of gastro-intestinal infections are food borne. Farm animals are often colonised by gastro-intestinal pathogens, especially *Salmonella* and *Campylobacter*. Therefore, raw foods such as poultry, meat, eggs and unpasteurised dairy products are commonly contaminated and must be thoroughly cooked to kill such organisms. Raw foods also represent a potential source of cross-contamination of other foods, through hands, surfaces or utensils that have been inadequately cleaned. Food handlers who are excreting pathogens in their faeces can also contaminate food. This is most likely when diarrhoea is present, but continued excretion of pathogens during convalescence also represents a risk. Food handlers are the usual source of *Staphylococcus aureus* food poisoning, where toxin-producing strains of *S. aureus* carried in the nose or on skin are transferred to foods. Bacterial food poisoning is often associated with inadequate cooking and/or prolonged storage of food at ambient temperature before consumption. Water-borne gastro-intestinal infection is primarily a problem in countries without a sanitary water supply or sewerage system, although outbreaks of water-borne cryptosporidiosis occur from time to time in the UK. Spread of pathogens such as *Shigella* or enteropathogenic *Escherichia coli* by the faecal–oral route is favoured by overcrowding and poor standards of personal hygiene. Such infections in developed countries are most common in children and can cause troublesome outbreaks in paediatric wards, nurseries and residential children's homes.

Treatment with broad-spectrum antibiotics alters the bowel flora, creating conditions that favour superinfection with micro-organisms (principally *Clostridium difficile*) that can cause diarrhoea. *C. difficile* infection (CDI) may be associated

Table 37.1 Important causes of gastro-intestinal infection, their modes of spread and pathogenic mechanisms

Causative agent	Chief mode(s) of spread	Pathogenic mechanisms
Bacteria		
Campylobacter	Food, especially poultry, milk	Mucosal invasion Enterotoxin
Salmonella enterica, non-typhoidal serovars	Food, especially poultry, eggs, meat	Mucosal invasion Enterotoxin
Salmonella enterica serovars Typhi and Paratyphi	Food, water	Systemic invasion
Shigella	Faecal–oral	Mucosal invasion Enterotoxin
Escherichia coli		
Enteropathogenic	Faecal–oral	Mucosal adhesion
Enterotoxigenic	Faecal–oral, water	Enterotoxin
Enteroinvasive	Faecal–oral, food	Mucosal invasion
Verotoxin-producing	Food, especially beef	Verotoxin
Staphylococcus aureus	Food, especially meat, dairy produce	Emetic toxin
Clostridium perfringens	Food, especially meat	Enterotoxin
Bacillus cereus		
Short incubation period	Food, especially rice	Emetic toxin
Long incubation period	Food, especially meat and vegetable dishes	Enterotoxin
Vibrio cholerae O1, O139	Water	Enterotoxin
Vibrio parahaemolyticus	Seafoods	Mucosal invasion Enterotoxin
Clostridium difficile	Faecal–oral (nosocomial)	Cytotoxin Enterotoxin
Clostridium botulinum	Inadequately heat-treated canned/ preserved foods	Neurotoxin
Protozoa		
Giardia lamblia	Water	Mucosal invasion
Cryptosporidium	Water, animal contact	Mucosal invasion
Entamoeba histolytica	Food, water	Mucosal invasion
Viruses	Food, faecal–oral, respiratory secretions	Small intestinal mucosal damage

with any antibiotic but clindamycin, the cephalosporins and the fluoroquinolones are most commonly implicated. CDI is most common in patients with serious underlying disease and in the elderly. Although some sporadic cases are probably due to overgrowth of endogenous organisms, person-to-person transmission also occurs in hospitals and care homes, sometimes resulting in large outbreaks.

Pathophysiology

Development of symptoms after ingestion of gastro-intestinal pathogens depends on two factors. First, sufficient organisms must be ingested and then survive host defence mechanisms, and second, the pathogens must possess one or more virulence mechanisms to cause disease.

Host factors

Healthy individuals possess a number of defence mechanisms that protect against infection by enteropathogens. Therefore, large numbers of many pathogens must be ingested for infection to ensue; for example, the infective dose for *Salmonella* is typically around 10^5 organisms. Other species, however, are better able to survive host defence mechanisms; for example, infection with *Shigella* or verotoxin-producing *E. coli* (VTEC) can result from ingestion of fewer than 100 organisms. VTEC (principally *E. coli* O157) are especially important because

of the risk of a life-threatening complication, haemolytic uraemic syndrome (HUS).

Gastric acidity

Most micro-organisms are rapidly killed at normal gastric pH. Patients whose gastric pH is less acidic, as for example, following treatment with antacids or ulcer-healing drugs, are more susceptible to gastro-intestinal infections. There is a particularly strong association between proton pump inhibitor use and CDI.

Intestinal motility

It is widely held that intestinal motility helps to rid the host of enteric pathogens, and that anti-motility agents are therefore potentially hazardous in patients with infective gastroenteritis. Despite this, self-medication with antidiarrhoeals is commonly practised, and in otherwise healthy individuals is probably safe.

Resident microflora

The resident microflora of the lower gastro-intestinal tract, largely composed of anaerobic bacteria, help to resist colonisation by enteropathogens.

Immune system

Phagocytic, humoral and cell-mediated elements are important in resistance to different pathogens. Individuals with inherited or acquired immunodeficiencies are therefore susceptible to specific gastro-intestinal infections, depending on which components of their immune system are affected.

Organism factors

The first requirement of gastro-intestinal pathogens is that they are able to adhere to the gut wall and colonise the intestine. The symptoms of gastro-intestinal infection can then be mediated by various mechanisms (see Table 37.1).

Toxins

Toxins produced by gastro-intestinal pathogens can be classified as enterotoxins, neurotoxins and cytotoxins. Enterotoxins act on intestinal mucosal cells to cause net loss of fluid and electrolytes. The classic enterotoxin-mediated disease is cholera, the result of infection with toxigenic serotypes of *Vibrio cholerae*. Many other bacteria produce enterotoxins, including enterotoxigenic *E. coli* and *Clostridium perfringens*. The emetic toxins of *S. aureus* and *Bacillus cereus* are neurotoxins that induce vomiting by an action on the central nervous system. The symptoms of botulism are mediated by a neurotoxin that blocks release of acetylcholine at nerve endings. Cytotoxins cause mucosal destruction and inflammation (see later). The pathogenicity of *C. difficile* is mediated by two exotoxins, TcdA and TcdB, both of which are potent cytotoxic enzymes that damage the human colonic mucosa. Verotoxins are potent cytotoxins that cause direct damage to small-vessel endothelial cells, which is exacerbated by stimulation of production of inflammatory mediators by non-endothelial cells. This causes multiorgan microvascular injury, expressed most commonly as haemorrhagic colitis and HUS.

Mucosal damage

Cytotoxins are important in mediating mucosal invasion, but other mechanisms are also involved. Enteropathogenic *E. coli* causes diarrhoea by damaging microvilli when it adheres to the intestinal mucosa. Organisms such as *Shigella* and enteroinvasive *E. coli* express surface proteins that facilitate mucosal invasion. Diarrhoea due to mucosal damage may be due to reduction in the absorptive surface area or the presence of increased numbers of immature enterocytes which are secretory rather than absorptive.

Systemic invasion

The lipopolysaccharide outer membrane and possession of an antiphagocytic outer capsule are important virulence factors in invasive *Salmonella* infections.

Clinical manifestations

Many cases of gastro-intestinal infection are asymptomatic or cause subclinical illness. Gastroenteritis is the most common syndrome of gastro-intestinal infection, presenting with symptoms such as vomiting, diarrhoea and abdominal pain. The term 'dysentery' is sometimes applied to infections with *Shigella* (bacillary dysentery) and *Entamoeba histolytica* (amoebic dysentery), where severe colonic mucosal inflammation causes frequent diarrhoea with blood and pus. Table 37.2 shows the most important causative agents of gastroenteritis together with a brief description of the typical illness that each causes. However, the symptoms experienced by individuals infected with the same organism can differ considerably. This is important because it means that it is rarely possible to diagnose the cause of gastroenteritis on clinical grounds alone.

Gastro-intestinal manifestations of infection with VTEC range from non-bloody diarrhoea to haemorrhagic colitis. In addition, VTEC are the most important cause of HUS, a serious complication which is most common in young children and the elderly. HUS is defined by the triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute renal dysfunction. The mortality is about 5% and up to half the survivors suffer long-term renal damage.

The clinical spectrum of CDI ranges from asymptomatic carriage to life-threatening pseudomembranous colitis (so-called because yellow-white plaques or membranes consisting of fibrin, mucus, leucocytes and necrotic epithelial cells are found adherent to the inflamed colonic mucosa).

Enteric fever, resulting from infection with *S. enterica* serovars Typhi and Paratyphi, presents with symptoms such as headache, malaise and abdominal distension after an incubation

Table 37.2 Characteristic clinical features of various causes of gastroenteritis

Causative agent	Incubation period	Symptoms (syndrome)
Campylobacter	2–5 days	Bloody diarrhoea Abdominal pain Systemic upset
Salmonella	6–72 h	Diarrhoea and vomiting Fever; may be associated bacteraemia
Shigella	1–4 days	Diarrhoea, fever (bacillary dysentery)
Escherichia coli Enteropathogenic Enterotoxigenic Enteroinvasive	 12–72 h 1–3 days 1–3 days	 Infantile diarrhoea Traveller's diarrhoea Similar to Shigella
Verotoxin-producing	1–3 days	Bloody diarrhoea (haemorrhagic colitis) Haemolytic uraemic syndrome
Staphylococcus aureus	4–8 h	Severe nausea and vomiting
Clostridium perfringens	6–24 h	Diarrhoea
Bacillus cereus Short incubation period Long incubation period	 1–6 h 6–18 h	 Vomiting Diarrhoea
Vibrio cholerae O1, O139	1–5 days	Profuse diarrhoea (cholera)
Vibrio parahaemolyticus	12–48 h	Diarrhoea, abdominal pain
Clostridium difficile	Usually occurs during/just after antibiotic therapy	Diarrhoea, abdominal pain, pseudomembranous enterocolitis
Giardia lamblia	1–2 weeks	Watery diarrhoea
Cryptosporidium	2 days–2 weeks	Watery diarrhoea
Entamoeba histolytica	2–4 weeks	Diarrhoea with blood and mucus (amoebic dysentery), liver abscess
Viruses	1–2 days	Vomiting, diarrhoea Systemic upset

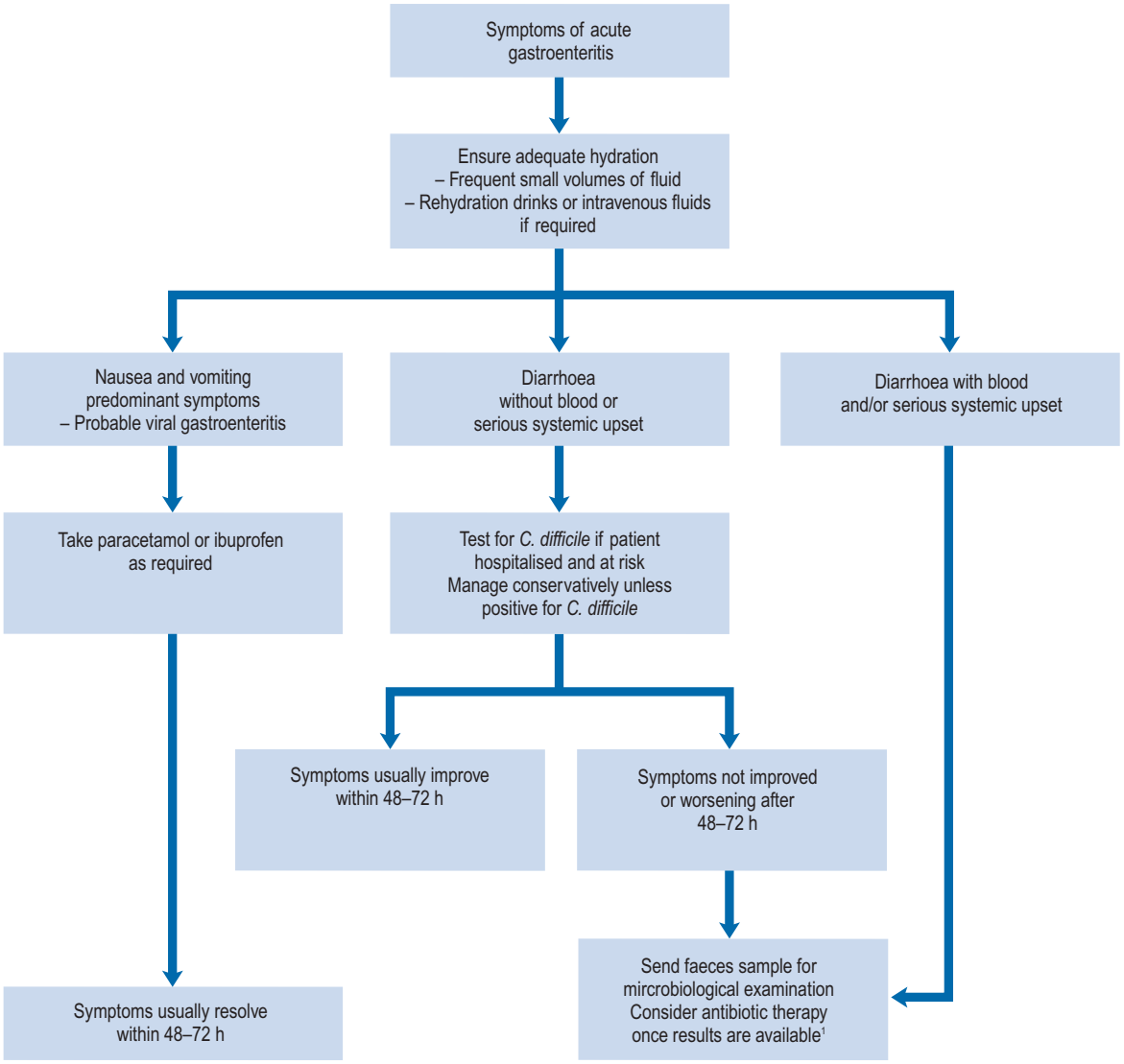
period of 3–21 days. During the first week of the illness, the temperature gradually increases, but the pulse characteristically remains slow. Without treatment, during the second and third weeks, the symptoms become more pronounced. Diarrhoea develops in about half of cases. Examination usually reveals splenomegaly, and a few erythematous macules (rose spots) may be found, usually on the trunk. Serious gastro-intestinal complications such as haemorrhage and perforation are most common during the third week. Symptoms begin to subside slowly during the fourth week. In general, paratyphoid fever is less severe than typhoid fever.

Botulism typically presents with autonomic nervous system effects, including diplopia and dysphagia, followed by symmetrical descending motor paralysis. There is no sensory involvement.

Gastro-intestinal infections are often followed by a period of convalescent carriage of the pathogen. This usually lasts for no more than 4–6 weeks but can be for considerably longer, especially for *Salmonella.*

Investigations

Many cases of gastroenteritis outside hospital are mild and short lived, and microbiological investigation may not be necessary. However, investigations are always recommended where antibiotic therapy is being considered (Fig. 37.1), where there are public health concerns (e.g., if the sufferer works in the food industry) and for gastro-intestinal infections in hospitalised patients.



[1] Antibiotic therapy may have to be commenced empirically if patient has serious systemic upset

Fig. 37.1 Pathway for the investigation and management of patients with symptoms of acute gastroenteritis.

The mainstay of investigation of diarrhoeal illness is examination of faeces. Bacterial infections are usually diagnosed by stool culture. Various selective culture media designed to suppress growth of normal faecal organisms and/or enhance the growth of a particular pathogen are used. When sending specimens to the laboratory, it is important that details of the age of the patient, the clinical presentation and recent foreign travel are provided so that appropriate media for the likely pathogens can be selected. Several tests are available for rapid detection of *C. difficile* toxin, or of toxigenic *C. difficile*, in faeces: early and accurate diagnosis is crucial for the control of *C. difficile* in hospitals. Sigmoidoscopy is used to diagnose pseudomembranous colitis.

Various other procedures are sometimes useful in investigating patients with suspected bacterial gastroenteritis. Blood cultures should be taken from patients with severe systemic upset and are especially important when enteric fever is suspected. In enteric fever, the causative organism may also be cultured from urine or bone marrow. In *S. aureus* and *B. cereus* food poisoning, the pathogen can sometimes be isolated from vomitus. In cases of food poisoning, suspect foods may also be cultured. In general, serological investigations are of little value in the diagnosis of bacterial gastroenteritis. However, demonstration of serum antibodies to *E. coli* O157 can be helpful in confirming the cause of the HUS. Serological tests for typhoid and paratyphoid fever are available, but the results must be interpreted with caution. Botulism is diagnosed by demonstration of toxin in serum.

Parasitic infestations are usually detected by microscopic examination of faeces. Electron microscopy has been largely superseded by immunological and molecular-based detection techniques for detection of enteric viruses.

Treatment

Many gastro-intestinal infections are mild and self-limiting and never reach medical attention. Where treatment is required, there are three main therapeutic considerations. Fluid and electrolyte replacement is the cornerstone of treatment of diarrhoeal disease. Most patients can be managed with oral rehydration regimens, but severely dehydrated patients require rapid volume expansion with intravenous fluids. Symptomatic treatment with antiemetics and antimotility (antidiarrhoeal) agents is sometimes used, especially as self-medication. Antimicrobial agents may be useful both in effecting symptomatic improvement and in eliminating faecal carriage of pathogens and therefore reducing the risk of transmitting infection to others.

Antiemetics and antidiarrhoeal drugs are discussed in Chapters 34 and 14, respectively. This chapter focuses on the place of antibiotic therapy in gastro-intestinal infections.

Antibiotic therapy

The requirement for antibiotic treatment in gastro-intestinal infection depends on the causative agent, the type and severity of symptoms and the presence of underlying disease. Antibiotics are ineffective in some forms of gastroenteritis, including bacterial intoxications and viral infections. For many other infections, such as salmonellosis and campylobacteriosis, effective agents are available, but antimicrobial therapy is often not clinically necessary. Serious infections such as enteric fever always require antibiotic therapy.

Conditions for which antibiotic therapy is not available or not usually required

The symptoms of *S. aureus* and short incubation period *B. cereus* food poisoning and botulism are usually caused by ingestion of preformed toxin, and therefore antibiotic therapy would not influence the illness. Pathogens such as *C. perfringens*, *Vibrio parahaemolyticus* and enteropathogenic *E. coli* usually cause a brief self-limiting illness that does not require specific treatment.

None of the presently available antiviral agents are useful in viral gastroenteritis. While most viral infections are self-limiting, chronic viral gastroenteritis can occur in immunocompromised patients. Where possible, immunosuppression should be reduced. Immunoglobulin-containing preparations, administered orally or directly into the duodenum via a nasogastric tube, have also been reported to be effective in managing chronic viral gastroenteritis in immunocompromised patients. As well as human serum immunoglobulin, antibodies from other species (e.g. immunised bovine colostrum) have been used. Immunotherapy of viral gastroenteritis remains experimental, and dosages and frequency of administration of immunoglobulin preparations cannot be recommended (Mohan and Haque, 2002).

At least one study has found that the risk of HUS in children with diarrhoea due to VTEC was much higher in those who received antibiotics. On that basis, it is advised in the UK that antibiotics are contraindicated in children with VTEC infection (National Collaborating Centre for Women's and Children's Health, 2009).

Conditions for which antimicrobial therapy may be considered

The place for antibiotics in the management of uncomplicated gastroenteritis due to bacteria such as *Salmonella* and *Campylobacter* is not clear cut. Certain antibiotics are reasonably effective in reducing the duration and severity of clinical illness and in eradicating the organisms from faeces. However, many microbiologists are cautious about the widespread use of antibiotics in diarrhoeal illness because of the risk of promoting antibiotic resistance (Sack et al., 1997). Another difficulty with respect to antibiotic prescribing is that it is not usually possible to determine the aetiological agent of diarrhoea on clinical grounds, and stool culture takes at least 48 h. Patients with severe illness, especially systemic symptoms, may require antibiotic therapy before the aetiological agent has been established. In such circumstances, a fluoroquinolone antibiotic such as ciprofloxacin would usually be the most appropriate empiric agent, at least in patients in whom CDI is considered unlikely or has been excluded. Otherwise, it is reasonable to limit antibiotic use to microbiologically proven cases where there is serious underlying disease and/or continuing severe symptoms. Antibiotics may also be used to try to eliminate faecal carriage, for example, in controlling outbreaks in institutions, or in food handlers who may be prevented from returning to work until they are no longer excreting gastro-intestinal pathogens.

Campylobacteriosis. Erythromycin is effective in terminating faecal excretion of *Campylobacter*. Some studies have shown that treatment commenced within the first 72–96 h of illness can also shorten the duration of clinical illness, especially in patients with severe dysenteric symptoms. The recommended dosage for adults is 250–500 mg four times a day orally for 5–7 days, and for children 30–50 mg/kg/day in four divided doses. Clarithromycin 250–500 mg (children under 1 year, 7.5 mg/kg; 1–2 years, twice a day; 3–6 years, 125 mg; 7–9 years, 5–7 days) or azithromycin 500 mg (children 10 mg/kg) once daily for 3 days are also effective. Ciprofloxacin, at a dose of 500 mg twice daily orally for adults, may also be effective in *Campylobacter* enteritis. However, whereas resistance rates to erythromycin have generally remained below 5%, resistance to ciprofloxacin has emerged, exceeding 10% in the UK and 50% in some countries (Dingle et al., 2005).

Salmonellosis. Most cases of *Salmonella* gastroenteritis are self-limiting and antibiotic therapy is unnecessary. However, antimicrobial therapy of salmonellosis is routinely recommended for infants aged under 6 months and immunocompromised patients, who are susceptible to complicated infections. Most antibiotics, even those with good *in vitro* activity, do not alter the course of uncomplicated *Salmonella* gastroenteritis. However, the fluoroquinolones, such as ciprofloxacin, can often shorten both the symptomatic period and the duration of faecal carriage. Ciprofloxacin resistance is now seen in up to 10% of non-typhoidal serovars of *S. enterica* in some

countries but is still uncommon in the UK (Murray et al., 2005). The recommended dose of ciprofloxacin for adults is 500 mg twice daily orally for 1 week. Fluoroquinolones are not licensed for this indication in children, although there is increasing evidence that they can safely be given to children. The recommended dose of ciprofloxacin in childhood is 7.5 mg/kg twice daily orally. Trimethoprim at a dose of 25–100 mg twice daily orally may be used in children if it is preferred not to use a fluoroquinolone.

Ciprofloxacin given orally at a dose of 500–750 mg twice daily in adults (7.5–12.5 mg/kg twice daily in children) or 200 mg intravenously twice daily in adults (5–7.5 mg/kg twice daily in children) is recommended for invasive salmonellosis. Alternative agents include ampicillin or amoxicillin, trimethoprim or chloramphenicol (see under enteric fever). However, resistance to these agents is more common than resistance to ciprofloxacin, and they are not recommended as empiric therapy.

***E. coli* infections.** While most infections with enteropathogenic *E. coli* can be managed conservatively, small trials suggest that trimethoprim may be effective, especially in controlling nursery or hospital outbreaks. On the basis that enteroinvasive *E. coli* are closely related to *Shigella* and cause a similar clinical syndrome, similar therapy may be appropriate. Antibiotic therapy for traveller's diarrhoea caused by enterotoxigenic *E. coli* infection is often unnecessary, but troublesome symptoms will often respond to a single dose of ciprofloxacin or azithromycin, the need for further doses depending on clinical response. Alternatively, a 3–5 day course of trimethoprim may be given, although resistance is becoming increasingly common in some areas. Rifaximin is a new non-absorbable antibiotic that is available in a number of countries. It appears to be as effective as ciprofloxacin in treating *E. coli*-predominant traveller's diarrhoea but is ineffective in patients with inflammatory or invasive enteropathogens (Robins and Wellington, 2005). The dose for adults is 200 mg three times per day for 3 days.

Conditions for which antimicrobial therapy is usually indicated

Shigellosis. *Shigella sonnei*, which accounts for most cases of shigellosis in the UK and most other industrialised countries, usually causes a mild self-limiting illness. Even if not required on clinical grounds, antibiotic therapy for shigellosis is usually recommended in order to eliminate faecal carriage, and therefore prevent person-to-person transmission. In contrast to salmonellosis, a number of antibiotics may be effective in shortening the duration of illness and terminating faecal carriage. This is especially true of strains of *S. sonnei* that are endemic in industrialised countries, whereas in developing countries, *Shigella* species that are multiple antibiotic resistant are an increasing problem. The fluoroquinolones are highly effective in shigellosis and resistance is rare; therefore, they are often considered to be the treatment of choice, especially in adults and/or for treating imported infections. The dose of ciprofloxacin is 500 mg twice daily orally in adults (7.5 mg/kg twice daily in children). Amoxicillin is an alternative first-line drug for *S. sonnei* infections acquired in the UK, where around 90% of isolates are susceptible. The dose of amoxicillin is 250–500 mg three times daily in adults, and 62.5–125 mg three times daily in children. Azithromycin (doses as for campylobacteriosis) is increasingly recommended as an alternative agent for shigellosis, especially in children (Jain et al., 2005). Third-generation cephalosporins such as ceftriaxone are another option for severe shigellosis. Trimethorpim resistance is now common, so this agent can no longer be recommended as empiric therapy. Antibiotic therapy is usually given for a maximum of 5 days.

Enteric fever. Treatment should be commenced as soon as a clinical diagnosis of enteric fever is made. Fluoroquinolones remain widely used as the first-choice treatment for typhoid and paratyphoid fevers. When treating isolates that are fully sensitive, the clinical response is at least as rapid as with the older treatments, there is a lower relapse rate, and convalescent faecal carriage is shortened. However, the proportion of isolates with reduced susceptibility to fluoroquinolones has increased to around 75%. Although most of these isolates have minimum inhibitory concentration (MIC) values below those regarded as fully resistant, treatment failures have been reported. Resistance to other antibiotics that have been commonly used to treat enteric fever, such as co-trimoxazole, chloramphenicol and ampicillin, is now frequent. These agents therefore cannot be recommended as alternatives to fluoroquinolones for empiric treatment of enteric fever, but may be useful in patients with bacterial isolates that are confirmed as sensitive. Doses of ciprofloxacin are as outlined for non-typhoidal salmonellosis. The usual dose of chloramphenicol is 50 mg/kg/day in four divided doses, and for ampicillin 100 mg/kg/day in four divided doses. Two weeks of antibiotic therapy is usually recommended, although shorter courses of ciprofloxacin (7–10 days) may be as effective.

Alternative agents that have been reported to be successful where treatment failure with fluoroquinlones has occurred include intravenous carbapenems or third-generation cephalosporins (e.g. ceftriaxone 75 mg/day; maximum dose 2.5 g/day) or oral azithromycin at a dose of 20 mg/kg/day (maximum 1000 mg) for at least 5 days. Time taken for clearance of bacteraemia may be longer with azithromycin, but the relapse rate appears to be lower than with β-lactam antibiotics such as ceftriaxone. There is some evidence that gatifloxacin, a new-generation fluoroquinolone, may be more effective than ciprofloxacin or ofloxacin in the treatment of infections where isolates have decreased fluoroquinolone susceptibility.

Chronic carriers of Salmonella. Patients may become chronic carriers after *Salmonella* infection, especially in the presence of underlying biliary tract disease. Oral ciprofloxacin 500–750 mg twice daily continued for 2–6 weeks is usually effective in eradicating carriage and has largely superseded the use of oral amoxicillin at a dose of 3 g twice daily.

Cholera. Fluid and electrolyte replacement is the key aspect of the management of cholera. However, antibiotics do shorten the duration of diarrhoea and therefore reduce the overall fluid loss, and also rapidly terminate faecal excretion of the organism. Effective agents include tetracyclines, erythromycin, trimethoprim, ampicillin or amoxicillin,

chloramphenicol, ciprofloxacin and furazolidine. However, antibiotic resistance is being increasingly seen, and in particular, *V. cholerae* O139 is intrinsically resistant to furazolidine and trimethoprim. Choice of antibiotics is therefore governed by knowledge of local resistance patterns, which may vary between outbreaks. Tetracycline 250 mg four times daily, or doxycycline 100 mg once daily by mouth, is probably the most widely used therapy in adults. Ampicillin, amoxicillin or erythromycin are generally the preferred agents for children. Although clinical cure can be achieved after a single dose of antibiotics, treatment is usually given for 3–5 days to ensure eradication of *V. cholerae* from faeces.

***C. difficile* infection.** The first objective is to diagnose CDI as soon as possible so that appropriate treatment and infection control measures can be put in place. Clinicians must consider the diagnosis in any patient where there is no clear alternative diagnosis for their diarrhoea. Stool samples must be sent to the laboratory immediately, and the laboratory must make testing available 7 days per week. Once the diagnosis is confirmed, attention must be paid to the patient's hydration and nutrition, non-essential antibiotic therapy or gastro-intestinal active drugs must be stopped and the patient's condition closely monitored. Although mild cases may resolve without specific therapy, treatment of all hospitalised patients with diarrhoea due to *C. difficile* is recommended, to shorten the duration of illness and to reduce environmental contamination and therefore the risk of nosocomial transmission.

Oral metronidazole 400 mg three times daily for 10 days is the treatment of choice for mild to moderate CDI. For severe CDI, oral vancomycin is recommended at a dose of 125 mg four times daily for 10 days. In patients unable to take oral medication, either drug can be administered via a nasogastric tube. Where there is no response to initial treatment, the dose of vancomycin can be increased to up to 500 mg four times daily, together with intravenous metronidazole 500 mg three times daily. Addition of oral rifampicin (300 mg twice daily) or administration of intravenous immunoglobulin (400 mg/kg) can also be considered.

Recurrence of symptoms occurs in about 20% of patients treated for CDI. Although some recurrences are due to germination of spores that have persisted in the colon since the original infection, it is recognised that some of these cases are due to reinfection, rather than relapse caused by the original strain (Loo et al., 2004). Most recurrences respond to a further 10–14 day course of metronidazole or vancomycin, but a few patients experience repeated recurrences. There is no reliable means of managing these patients. Options include:

- a supervised trial of anti-motility agents alone (if there are no abdominal symptoms or signs of severe CDI)
- tapering or pulse therapy with oral vancomycin given for 4–6 weeks
- a 2-week course of oral vancomycin 125 mg four times daily and oral rifampicin 300 mg twice daily
- intravenous immunoglobulin, especially if the patient's albumin status worsens
- donor stool transplant.

Trial data do not currently support the use of probiotics for the treatment or prevention of CDI (Department of Health and Health Protection Agency, 2009).

Cryptosporidiosis. Cryptosporidiosis in immunocompetent individuals is generally self-limiting. However, in immunosuppressed patients, severe diarrhoea can persist indefinitely and can even contribute to death. HIV-infected patients on highly active antiretroviral therapy (HAART) now have a much lower incidence of cryptosporidiosis due to immune reconstitution, and possibly a direct anti-cryptosporidium effect of protease inhibitors. There is no reliable antimicrobial therapy. Azithromycin, which is readily prescribable, is partially effective at a dose of 500 mg once daily (10 mg/kg once daily in children). Treatment should be continued until *Cryptosporidium* oocysts are no longer detectable in faeces (typically 2 weeks), to minimise the risk of relapse post-treatment. Occasionally, therapy has to be continued indefinitely to prevent relapse. Most other agents that have been recommended for treatment of cryptosporidiosis, for example, nitazoxanide, spiramycin, paromomycin and letrazuril, are not licensed in the UK. These can usually be sourced from special order manufacturing or importing companies (Smith and Corcoran, 2004). Of these agents, nitazoxanide has FDA approval in the USA, and has been shown to be effective in clinical trials at a dose of 500 mg twice daily (adults and children aged 12 years and over) for 3 days (children 1–3 years 100 mg bd; 4–11 years 200 mg bd). However, it is not effective unless the patient is able to mount an appropriate immune response.

Giardiasis. Metronidazole is the treatment of choice for giardiasis. Various oral regimens are effective, for example, 400 mg three times daily (7.5 mg/kg in children) for 5 days, or 2 g/day (children 500 mg to 1 g) for 3 days. Alternative treatments are tinidazole 2 g as a single dose, or mepacrine hydrochloride 100 mg (2 mg/kg in children) three times daily for 5–7 days. Nitazoxanide is a new thiazolide antiparasitic drug (discussed under cryptosporidiosis) that has also been licensed for treatment of giardiasis in some countries, but is not currently available in the UK. A single course of treatment for giardiasis has a failure rate of up to 10%. A further course of the same or another agent is often successful. Sometimes, repeated relapses are due to reinfection from an asymptomatic family member. In such cases, all affected family members should be treated simultaneously.

Amoebiasis. The aim of treatment in amoebiasis is to kill all vegetative amoebae and also to eradicate cysts from the bowel lumen. Metronidazole is highly active against vegetative amoebae and is commonly the treatment of choice for acute amoebic dysentery and amoebic liver abscess. The dose for adults is 800 mg (children 100–400 mg) three times daily for 5–10 days. To eradicate cysts, metronidazole therapy is followed by a 5-day course of diloxanide furoate 500 mg three times daily (20 mg/kg daily in three divided doses for children). Tinidazole has recently been shown to reduce clinical failure and be better tolerated than metronidazole (Gonzales et al., 2009). The dose of tinidazole for adults is 2 g daily for 2–3 days, and for children, 50–60 mg/kg daily for 3 days.

Asymptomatic excretors of cysts living in areas with a high prevalence of *E. histolytica* infection do not merit treatment

because most individuals quickly become reinfected. However, asymptomatic excretors of cysts in Europe or North America are usually treated with diloxanide furoate for 5–10 days: metronidazole and tinidazole are relatively ineffective in this situation.

Patient care

People excreting gastro-intestinal pathogens are potentially infectious to others. Liquid stools are particularly likely to contaminate the hands and the environment. All cases of gastro-intestinal infection should be excluded from work or school at least until the patients are symptom free; hospitalised patients should be isolated in a single room. Patients should be advised on general hygiene, and in particular, on thorough handwashing and drying after visiting the toilet and before handling food.

In most countries, many gastro-intestinal infections are statutorily notifiable. Following notification, the authorities will judge whether the implications for public health merit investigation of the source of infection, contact screening or follow-up clearance stool samples from the original case.

Common therapeutic problems in the management of gastro-intestinal infection are summarised in Table 37.3. Problems associated with specific gastro-intestinal infections are summarised in Table 37.4.

Table 37.3 Practice points: general problems with treatment of gastro-intestinal infections

Problems	Resolution
Difficult or impossible to make a rapid aetiological diagnosis	Hospital laboratories are expected to offer rapid testing for *C. difficile* 7 days per week
New, more accurate, diagnostic tests for viral gastroenteritis are becoming more widely available	Few other recent improvements in the diagnosis of bacterial or parasitic infections
Clinical effectiveness and cost-effectiveness of antibiotic therapy for many bacterial gastro-intestinal infections are not clearly established	Without reliable data showing benefit, antimicrobial therapy is not used in the majority of infections
No specific therapies for viral gastroenteritis	Infections in otherwise healthy individuals are generally self-limiting Various non-evidence-based experimental treatments have been used to manage immunocompromised patients with protracted diarrhoea
Acute illness may be followed by a period of non-infective diarrhoea	Cautious use of antidiarrhoeal medication may be indicated at this stage

Table 37.4 Practice points: problems with treatment of specific gastro-intestinal infections

Infection	Antibiotic	Problems	Resolution
Campylobacteriosis	Erythromycin	Not always effective, especially if commenced >72 h after onset of symptoms	Reserve therapy for cases where symptoms are severe or worsening at time of diagnosis
	Ciprofloxacin[a]	Up to 50% of strains are resistant	Use only as a second-line agent for isolates that have been shown to be sensitive
Salmonellosis	Ciprofloxacin[a]	Not always effective Resistance is increasing	Reserve therapy for cases where symptoms are severe or worsening at time of diagnosis
Enteric fever	Ciprofloxacin[a]	Resistance is increasing	Alternative therapies must be guided by antibiotic sensitivities of the isolate Ciprofloxacin[a] now generally regarded as treatment of choice
	Ampicillin or amoxicillin	Resistance to these agents now common	
	Chloramphenicol	Higher incidence of chronic carriage and relapse than with ciprofloxacin	
Shigellosis	Trimethoprim	Resistance is increasing	Therapy should be guided by antibiotic sensitivities of the isolate. Most trimethoprim-resistant strains are ciprofloxacin sensitive

Continued

Table 37.4 Practice points: problems with treatment of specific gastro-intestinal infections—cont'd

Infection	Antibiotic	Problems	Resolution
Clostridium difficile	Metronidazole	Relapse rate up to 20%	Repeat course of treatment, or treatment with vancomycin
	Vancomycin	May be more effective, but much more expensive, than metronidazole Risk of promoting emergence and spread of vancomycin-resistant enterococci	Generally reserved as a second-line agent, for example, where no response to metronidazole, or for patients with severe infection
		Relapse may occur	Repeat course of treatment; various treatment options for patients with repeated relapse
Cryptosporidiosis	Azithromycin	Not always effective	Long-term therapy may be required to control symptoms
		Recommended only for patients who are immunocompromised or have unusually severe or protracted symptoms	Possible alternative agents are not licensed in UK

[a]Ciprofloxacin is not licensed for general paediatric use; it is widely used to treat gastro-intestinal infections in children.

Case studies

Case 37.1

A 12-year-old boy is admitted to hospital with a history of fever, weight loss and malaise 1 week after returning from visiting relatives in Pakistan. Whilst there he was diagnosed as having typhoid fever, and although details are sketchy, it seems that he received treatment with ciprofloxacin. The only other medical history of note is that he experienced an anaphylactic reaction after taking penicillin 4 years ago. Twenty-four hours after admission, *S. enterica* serovar Typhi is isolated from a blood culture.

Questions

1. Why might the patient not have responded fully to the treatment given in Pakistan?
2. Which antibiotic would now be most appropriate as empiric therapy?

Answers

1. Strains of *S. enterica* serovar Typhi that have reduced susceptibility to fluoroquinolones are common in the Indian subcontinent. Although these strains are not usually fully fluoroquinolone resistant, treatment failures have been reported, even when an appropriate dose regimen has been used: in this case, there is not even any assurance that the treatment regimen in Pakistan was adequate.
2. Given the lack of assurance of the adequacy of the ciprofloxacin treatment in Pakistan, one option would be to re-treat with ciprofloxacin. However, given the high likelihood that the strain will have reduced susceptibility to ciprofloxacin, it would be more logical to use an alternative agent. Of those, carbapenems and cephalosporins are beta-lactam antibiotics that would be best avoided, given the history of anaphylaxis following penicillin exposure. Azithromycin would appear, therefore, to be the empiric treatment of choice in this case.

Case 37.2

A mother brings her 6-year-old daughter to her primary care doctor because she has a 2-day history of bloody diarrhoea and abdominal pain. The family had been on a farm visit the previous weekend and had eaten food when there. The mother is anxious for her child to be treated with antibiotics because they will be going on their summer holiday in one week.

Questions

1. Give three possible infective causes of the girl's symptoms.
2. How should the clinician respond to the mother's request for antibiotics?

Answers

1. The two commonest bacterial gastro-intestinal infections, campylobacteriosis and salmonellosis, can both present in this way. Many other bacterial and protozoan causes of gastroenteritis can also cause similar symptoms. One bacterium that is especially important to consider in this case, where there is a history of a farm visit, is *E. coli* O157. Every effort should be made to obtain a stool sample from the patient for microbiological examination.
2. It would not be appropriate to treat this girl's symptoms empirically with antibiotics for a number of reasons. First, antibiotic therapy may make no difference to the speed of clinical resolution; second, where antibiotics are justified, the choice of drug will depend on the aetiological agent; and third, antibiotics are contraindicated in infection with *E. coli* O157, which must feature in the differential diagnosis in this case.

Case 37.3

A businessman is planning a short trip to Egypt. During previous visits to the area, he has experienced troublesome diarrhoea despite being careful about hygiene. Although the diarrhoea has not made him seriously unwell, it has caused him considerable inconvenience during business discussions.

Question

Are there any antimicrobials that he could take to prevent this problem?

Answer

Although traveller's diarrhoea is not usually serious, it can cause considerable inconvenience whether the sufferer is travelling for leisure or business reasons. Simple measures that can help prevent traveller's diarrhoea include taking care with food and drinks (only bottled water from reputable sources should be used). There are two approaches to antibiotic use in traveller's diarrhoea. Either the drug can be taken prophylactically to try to prevent diarrhoea developing, or treatment can be commenced with the onset of diarrhoea. The latter approach is generally preferred because it limits unnecessary exposure to antibiotics and the response to treatment is usually rapid. However, there are instances such as in this case where the inconvenience of even short-lived diarrhoea may be great enough to justify use of prophylaxis.

The choice of antibiotics for traveller's diarrhoea has been made more complicated by the increasing prevalence of antibiotic resistance in many developing countries. Drugs such as amoxicillin or trimethoprim no longer have a role. A fluoroquinolone, such as ciprofloxacin, still represents a reasonable first choice, with azithromycin as a possible alternative in areas where fluoroquinolone resistance is known to be common. For travellers from countries where it can be prescribed, rifaximin may be the agent of choice. For travellers to areas where infections such as amoebic dysentery or giardiasis are common, it may be appropriate to take a supply of metronidazole that can be started if there is no response to the first-line antibacterial prophylaxis.

Case 37.4

An 80-year-old woman on an elderly care ward develops watery diarrhoea and abdominal pain 4 days after commencing therapy with ciprofloxacin for a urinary tract infection. *C. difficile* toxin is detected in a stool sample. Five patients on that ward have also had *C. difficile*-associated diarrhoea during the past 2 months.

Questions

1. How should this patient be managed?
2. What measures might be taken to try to reduce the number of cases of *C. difficile*-associated diarrhoea on the ward?

Answers

1. Treatment with ciprofloxacin should be discontinued. Four-day antibiotic therapy for a urinary tract infection will often suffice, but if further treatment is required, an antibiotic that is less likely to disturb the bowel flora should be prescribed. Metronidazole is the preferred first-line treatment for mild to moderate CDI. The patient should be closely monitored for the frequency and severity of the diarrhoea. Oral vancomycin might be indicated later if her illness became more severe. The patient should be isolated to reduce the risk of spread of the infection.
2. There are two elements to control of *C. difficile* in hospitals. First, it is necessary to ensure that antibiotic prescribing is rational. There should be an antibiotic-prescribing policy that minimises use of antibiotics in general, and in particular, restricts use of antibiotics that are associated with a high risk of *C. difficile* (2nd- and 3rd-generation cephalosporins, clindamycin and fluoroquinolones). Compliance with the policy must be assured through measures such as checking of prescriptions, multidisciplinary antibiotic ward rounds, education of prescribers, and audits of antibiotic prescribing. Second, strict infection control precautions must be enforced, along with improved standards of environmental cleanliness, to reduce the risk of patients being exposed to the bacterium.

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38 Infective meningitis

J. W. Gray

Key points

- The causative agents of meningitis are related to the age of the patient and the presence of underlying disease.
- The most common cause of early-onset neonatal meningitis is the group B streptococcus. Other important causes of neonatal meningitis include *Escherichia coli* and *Listeria monocytogenes*.
- Outside the neonatal period, *Neisseria meningitidis* and *Streptococcus pneumoniae* are the major causes of infective meningitis, accounting for around 75% of confirmed cases.
- Antibiotic treatment of meningitis requires attainment of adequate concentrations of bactericidal antibiotics in the cerebrospinal fluid (CSF).
- Suitable therapies for neonatal meningitis are ampicillin or amoxicillin, combined with either an aminoglycoside or a cephalosporin such as cefotaxime or ceftazidime.
- Increasing resistance to penicillins and concerns about the toxicity of chloramphenicol have led to the widespread use of cefotaxime or ceftriaxone as empiric therapy for meningitis outside the neonatal period.
- Because of the potentially rapid progression of the disease, patients with suspected meningococcal infection should receive emergency therapy with penicillin before admission to hospital.
- Close contacts of patients with meningococcal, and in some circumstances *Haemophilus influenzae* type b, disease should receive chemoprophylaxis.
- There is increasing evidence of the benefit of steroids as adjunctive therapy in the management of bacterial meningitis.
- Introduction into the routine immunisation schedule of vaccines against *H. influenzae* type b, *N. meningitidis* group C and common *S. pneumoniae* serotypes has markedly reduced the incidence of meningitis due to these bacteria.

The brain and spinal cord are surrounded by three membranes, which from the outside inwards are the dura mater, the arachnoid mater and the pia mater. Between the arachnoid mater and the pia mater, in the subarachnoid space, is found the cerebrospinal fluid (CSF) (Fig. 38.1). This fluid, of which there is ~150 mL^{-1} in a normal individual, is secreted by the choroid plexuses and vascular structures which are in the third, fourth and lateral ventricles. CSF passes from the ventricles via communicating apertures to the subarachnoid space, after which it flows over the surface of the brain and the spinal cord (see Fig. 38.1). The amount of CSF is controlled by resorption into the bloodstream by vascular structures in the subarachnoid space, called the arachnoid villi. Infective meningitis is an inflammation of the arachnoid and pia mater

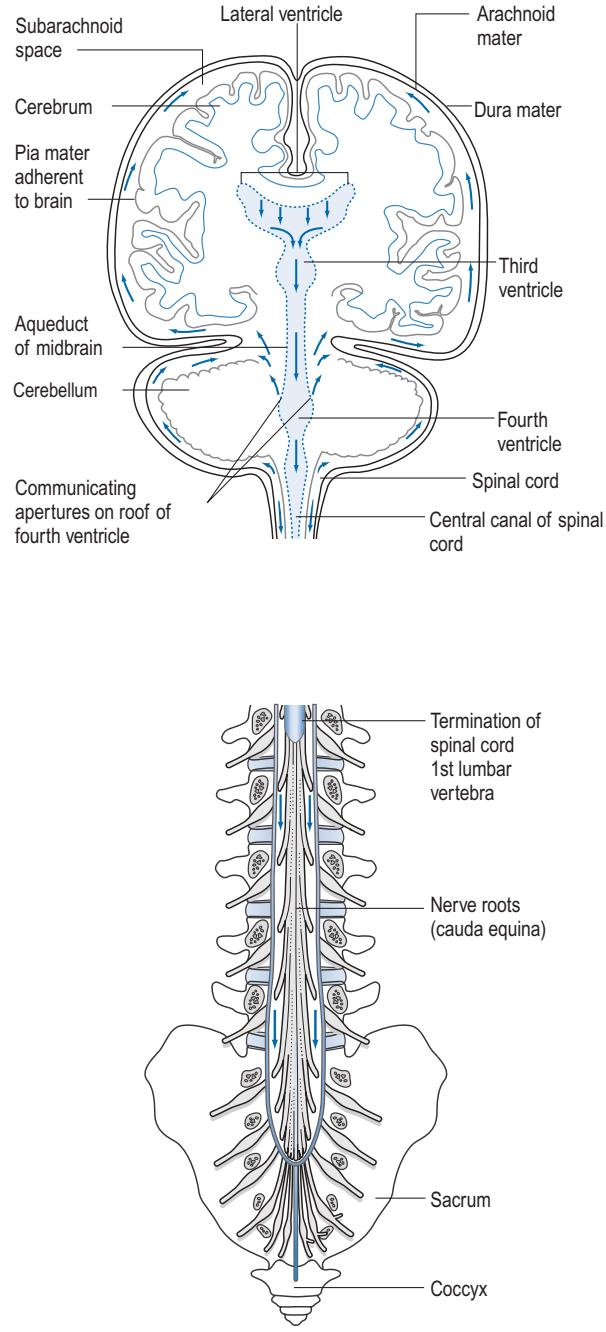

Fig. 38.1 The meninges covering the brain and spinal cord and the flow of cerebrospinal fluid (arrowed) (modified from Ross and Wilson (1981), by permission of Churchill Livingstone).

associated with the presence of bacteria, viruses, fungi or protozoa in the CSF. Meningitis is one of the most emotive of infectious diseases, and for good reason: even today, infective meningitis is associated with significant mortality and risk of serious sequelae in survivors.

Aetiology and epidemiology

In the UK, around 1500 cases of meningitis are notified annually. However, this almost certainly under represents the true incidence of meningitis. Viruses are the most common cause of meningitis, and are often less serious than bacterial or fungal forms of the disease.

Bacterial meningitis

Although bacterial meningitis occurs in all age groups, it is predominantly a disease of young children, with 40–50% of all cases occurring in the first 4 years of life. Two bacteria, *N. meningitidis* and *S. pneumoniae*, account for about 75% of cases. However, the pattern of micro-organisms causing meningitis is related to the age of the patient and the presence of underlying disease.

N. meningitidis is the most common cause of bacterial meningitis from infancy through to middle age, with peaks of incidence in the under-5-year age group and in adolescents. There are several serogroups of *N. meningitidis*, including A, B, C, W135 and Y. In the late twentieth century, serogroups B and C accounted for 60–65% and 35–40% of infections in the UK, respectively. However, with the introduction of vaccination against *N. meningitidis* serogroup C (MenC) into the routine immunisation programme in 1999, serogroup B now accounts for well over 80% of all meningococcal disease. There is currently no vaccine available for *N. meningitidis* serogroup B. Serogroups A and W135 predominate in Africa and the Middle East. A quadrivalent vaccine against serogroups A, C, W135 and Y is available to protect travellers to countries of risk. *S. pneumoniae* is the most common cause of meningitis in adults aged over 45 years, but almost half of all cases of pneumococcal meningitis occur in children aged under 5 years. It has a poorer outcome than meningococcal meningitis. Vaccination against the most common serotypes of *S. pneumoniae* using a conjugate vaccine was added to the routine childhood immunisation programme in the UK in 2006: the original 7-valent vaccine was then replaced by a 13-valent vaccine in Spring 2010. A different 23-valent polysaccharide vaccine is available for certain patient groups at risk of pneumococcal infection.

Haemophilus influenzae type b (Hib) was once the major cause of bacterial meningitis in children aged 3 months to 5 years, but introduction of routine immunisation in 1992 has almost eliminated Hib disease in the UK and other developed countries.

Although patients with meningococcal or Hib meningitis are potentially infectious, most cases of meningitis due to these bacteria are acquired from individuals who are asymptomatic nasopharyngeal carriers. People living in the same household as a patient with meningococcal disease have a 500–1200-fold increased risk of developing infection if they do not receive chemoprophylaxis (see later). Susceptible young children who are household contacts of a case of Hib disease have a similarly increased risk of becoming infected. Epidemics of meningococcal disease sometimes occur. In developed countries, these take the form of clusters of cases among people living in close proximity (e.g. in schools or army camps) or in a particular geographical area. In Africa, large epidemics with many thousands of cases occur, usually during the dry season.

In the neonatal period, group B streptococci are the most common cause of bacterial meningitis. Other causes of neonatal meningitis include *Escherichia coli* and other *Enterobacteriaceae, Listeria monocytogenes*, *Staphylococcus aureus* and enterococci. In most cases, infection is acquired from the maternal genital tract around the time of delivery, but transmission between patients can also occur in hospitals.

L. monocytogenes is also an occasional cause of meningitis in immunocompromised patients. Meningitis can also occur as a complication of neurosurgery, especially in patients who have ventriculoatrial or ventriculoperitoneal shunts. Coagulase-negative staphylococci are the major causes of shunt-associated meningitis, but other bacteria are important, including *Enterobacteriaceae* and *S. aureus*. Meningitis due to *S. aureus* may also be secondary to trauma, or local or haematogenous spread from another infective focus. Meningitis may also be a feature of multisystem bacterial diseases such as syphilis, leptospirosis and Lyme disease.

The decline in the incidence of tuberculous meningitis in developed countries has mirrored the fall in the incidence of tuberculosis in these countries. Tuberculous meningitis may occur as part of the primary infection or as a result of recrudescence of a previous infection.

Viral meningitis

Human enteroviruses such as echoviruses and Coxsackie viruses account for about 70% of cases of viral meningitis in the UK. Herpes simplex and varicella zoster viruses account for most other cases. Occasional causes of viral meningitis include mumps virus and human immunodeficiency viruses.

Fungal meningitis

In Europe, fungal meningitis is rare in individuals without underlying disease. *Candida* species are an occasional cause of shunt-associated meningitis. *Cryptococcus neoformans* has emerged as an important cause of meningitis in patients with late-stage HIV infection and other severe defects of T-cell function. With greater use of fluconazole for oral candidiasis, and especially the advent of highly active antiretroviral therapy, cryptococcosis has become much less common in developed countries. However, in sub-Saharan African countries with the highest HIV prevalence, cryptococcus is the leading cause of infective meningitis. In certain other areas of the world, infections with fungi such as *Coccidioides immitis* and *Histoplasma capsulatum* are endemic.

Pathophysiology

Most cases of bacterial meningitis are preceded by nasopharyngeal colonisation by the causative organism. In most colonised individuals, infection will progress no further, but in susceptible individuals the organism invades the submucosa by circumventing host defences (e.g. physical barriers, local immunity, phagocytes) and gains access to the CNS by invasion of the bloodstream and subsequent haematogenous seeding of the CNS. Other less common routes by which micro-organisms can reach the meninges include:

- direct spread from the nasopharynx
- blood-borne spread from other foci of colonisation or infection
- abnormal communications with the skin or mucous membranes, for example skull fractures, anatomical defects or a meningocoele
- spread from an infected adjacent focus, for example brain abscess, tuberculoma, infected paranasal air sinus or infection of the middle ear.

Once in the subarachnoid space, the infection spreads widely and incites a cascade of meningeal inflammation. The cerebral tissue is not usually directly involved although cerebral abscess may complicate some types of meningitis.

The micro-organisms that most frequently cause meningitis are capable of doing so because they have a variety of virulence factors, including mechanisms for:

- attachment to host mucosal surfaces
- evasion of phagocytosis and other host defences
- meningeal invasion
- disruption of the blood–brain barrier
- induction of pathophysiological changes in the CSF space
- secondary brain damage.

Overall, the net result of infection is vascular endothelial injury and increased blood–brain barrier permeability leading to the entry of many blood components into the subarachnoid space. This contributes to cerebral oedema and elevated CSF protein levels. In response to the cytokine response, neutrophils migrate from the bloodstream into the CSF. Cerebral oedema contributes to intracranial hypertension and a consequent decrease in cerebral blood flow. Anaerobic metabolism ensues, which contributes to increased lactate and decreases glucose concentrations. If this uncontrolled process is not modulated by effective treatment, transient neuronal dysfunction or permanent neuronal injury results.

Clinical manifestations

Acute bacterial meningitis usually presents with sudden-onset headache, neck stiffness, photophobia, fever and vomiting. On examination, Kernig's sign may be positive. This is resistance to extension of the leg when the hip is flexed, due to meningeal irritation in the lumbar area. Where meningitis is complicated by septicaemia, there may be septic shock. The presence of a haemorrhagic skin rash is highly suggestive, but not pathognomic, of meningococcal infection. Untreated patients with bacterial meningitis deteriorate rapidly, with development of seizures, focal cerebral signs and cranial nerve palsies. Finally, obtundation and loss of consciousness herald death.

In infants with meningitis, the early physical signs are usually non-specific and include fever, diarrhoea, lethargy, feeding difficulties and respiratory distress. Focal signs such as seizures or a bulging fontanelle usually only occur at a late stage.

Viral meningitis usually presents with acute onset of low-grade fever, headache, photophobia and neck stiffness. Unless they develop encephalitis, patients usually remain alert and oriented.

Although tuberculous and fungal meningitis sometimes present acutely, these infections typically have a more indolent course. The early stages of the diseases are dominated by general symptoms such as malaise, apathy and anorexia. As they progress, symptoms and signs more typical of meningitis usually appear.

Diagnosis

The definitive diagnosis of meningitis is established by detection of the causative organism and/or demonstration of biochemical changes and a cellular response in CSF. CSF is obtained by lumbar puncture, where a needle is inserted between the posterior space of the third and fourth lumbar vertebrae into the subarachnoid space. Before performing lumbar puncture, the possibility of precipitating or aggravating existing brain herniation in patients with intracranial hypertension must be considered. A CT scan should be performed before undertaking lumbar puncture if any neurological abnormalities are present.

In health, the CSF is a clear colourless fluid which, in the lumbar region of the spinal cord, is at a pressure of 50–150 mmH_2O. There may be up to 5 cells/μL, the protein concentration is up to 0.4 g/L and the glucose concentration is at least 60% of the blood glucose (usually 2.2–4.4 mmol/L). Table 38.1 shows how the cell count and biochemical measurements can be helpful in determining the type of organism causing meningitis.

In bacterial and fungal meningitis, organisms may be visible in Gram-stained smears of the CSF. The common causes of bacterial meningitis are easily distinguished from each other by their Gram stain appearance. Special stains, such as the Ziehl–Neelsen method, are necessary to visualise mycobacteria. However, only small numbers of mycobacteria are present in the CSF in tuberculous meningitis and direct microscopy is often unrevealing. Although cryptococci can be visualised by Gram staining, they are often more easily seen with India ink staining, which highlights their prominent capsules.

Regardless of the microscopic findings, CSF should be cultured to try to confirm the identity of the causative organism and to facilitate further investigations such as antibiotic sensitivity testing and typing. Special cultural techniques are required for mycobacteria, fungi and viruses. Cultures of other

Table 38.1 Cellular and biochemical responses in different forms of infective meningitis

Type of meningitis	Cell count	Protein (g/L)	Glucose
Bacterial	Predominantly polymorphs, 500–2000 μL^{-1} (lymphocytes may predominate in early or partially treated cases)	1–3	<50% blood glucose
Tuberculous	Predominantly lymphocytes, 100–600 μL^{-1}	1–6	<50% blood glucose
Viral	Predominantly lymphocytes, 50–500 μL^{-1}	0.5–1	Usually normal
Cryptococcal	Predominantly lymphocytes, 50–1000 μL^{-1}	1–3	<50% blood glucose

sites are sometimes helpful. In suspected bacterial meningitis, blood for culture should always be obtained. Bacteraemia occurs in only 10% of patients with meningococcal meningitis but is more common in most other forms of meningitis. In suspected meningococcal disease, culture of a nasopharyngeal swab may be helpful because antibiotic penetration at this site is less. It increases the chances of isolating meningococci when antibiotics were administered to the patient before presentation to hospital.

Non-culture-based methods are increasingly used to investigate the aetiology of meningitis. In particular, molecular amplification techniques such as polymerase chain reaction (PCR) are now widely used to detect meningococci, pneumococci, *Mycobacterium tuberculosis* and various viruses, including herpes simplex viruses and enteroviruses.

Serum antibodies to *N. meningitidis* and various viruses may be detected, but these investigations usually depend on demonstration of seroconversion between two samples collected a week or more apart, and are therefore undertaken more for public health than clinical reasons. Patients with tuberculous meningitis may have a positive Mantoux test or an interferon-gamma release assay.

Drug treatment

Acute bacterial meningitis is a medical emergency that requires urgent administration of antibiotics. Other considerations in some forms of meningitis include the use of adjunctive therapy such as steroids, and the administration of antibiotics to prevent secondary cases.

Antimicrobial therapy

Pharmacokinetic considerations

The antimicrobial therapy of meningitis requires attainment of adequate levels of bactericidal agents within the CSF. The principal route of entry of antibiotics into CSF is by the choroid plexus; an alternative route is via the capillaries of the central nervous system into the extracellular fluid and hence into the ventricles and subarachnoid space (see Fig. 38.1). The passage of antibiotics into CSF is dependent on the degree of meningeal inflammation and integrity of the blood–brain barrier created by capillary endothelial cells, as well as the following properties of the antibiotic:

- lipid solubility (the choroidal epithelium is highly impermeable to lipid-insoluble molecules)
- ionic dissociation at blood pH
- protein binding
- molecular size
- concentration of the drug in the serum.

Antimicrobials fall into three categories according to their ability to penetrate the CSF:

- those that penetrate even when the meninges are not inflamed, for example chloramphenicol, metronidazole, isoniazid and pyrazinamide
- those that generally penetrate only when the meninges are inflamed, and used in high doses, for example most β-lactam antibiotics, the quinolones and rifampicin
- those that penetrate poorly under all circumstances, including the aminoglycosides, vancomycin and erythromycin.

Recommended regimens

Clinical urgency determines that empirical antimicrobial therapy will usually have to be prescribed before the identity of the causative organism or its antibiotic sensitivities are known. Consideration of the epidemiological features of the case, together with microscopic examination of the CSF, is often helpful in identifying the likely pathogen. However, empiric therapy is usually with broad-spectrum antimicrobial therapy to cover all likely pathogens, at least until definitive microbiological information is available. For the purpose of selecting empiric antimicrobial therapy, patients with acute bacterial meningitis can be categorised into four broad groups: neonates and infants aged below 3 months; immunocompetent older infants, children and adults; immunocompromised patients; and those with ventricular shunts.

Antibiotics for meningitis in neonates and infants aged below 3 months. The most important pathogens in neonates include group B streptococci, *E. coli* and other *Enterobacteriaceae*, *L. monocytogenes*. In many centres, a third-generation cephalosporin such as cefotaxime or ceftazidime, along with amoxicillin or ampicillin, is the empiric therapy of choice for neonatal meningitis (Galiza and Heath, 2009). Cephalosporins

penetrate into CSF better than aminoglycosides, and their use in Gram-negative bacillary meningitis has contributed to a reduction in mortality to less than 10%. Other centres continue to use an aminoglycoside, such as gentamicin, together with benzylpenicillin, ampicillin or amoxicillin as empiric therapy. This approach remains appropriate, especially in countries such as the UK where group B streptococci are by far the predominant cause of early-onset neonatal meningitis. Whichever empiric regimen is used, therapy can be altered as appropriate once the pathogen has been identified. Suitable dosages are shown in Table 38.2.

In infants outside the immediate neonatal period, the classic neonatal pathogens account for a decreasing number of cases of meningitis and the common bacteria of meningitis in childhood (see later) become increasingly important. Amoxicillin or ampicillin plus cefotaxime or ceftriaxone is the recommended treatment. Therapy with amoxicillin or ampicillin and gentamicin is unsuitable for this age group because it provides inadequate cover against *H. influenzae*.

Antibiotics for meningitis in older infants, children and adults. Antimicrobial therapy has to cover *S. pneumoniae*, *N. meningitidis* and, in children aged below 5 years, *H. influenzae* (Yogev and Guzman-Cottrill, 2005). Achievable antibiotic CSF concentrations are compared with the susceptibilities of the common agents of meningitis in Table 38.3. Third-generation cephalosporins, such as cefotaxime, are now widely used in place of the traditional agents of choice, chloramphenicol, ampicillin, amoxicillin and penicillin (see Table 38.2). This change has stemmed from concern over the rare but potentially serious adverse effects of chloramphenicol and the emergence of resistance to penicillin, ampicillin and chloramphenicol among *S. pneumoniae* and *H. influenzae* in particular. Chloramphenicol resistance and reduced susceptibility to penicillin have also been reported in *N. meningitidis*. The third-generation cephalosporins have a broad spectrum of activity that encompasses not only the three classic causes of bacterial meningitis but also many other bacteria that are infrequent causes of meningitis. However, cephalosporins are inactive against *L. monocytogenes*, and amoxicillin or ampicillin should be added where it is possible that the patient may have listeriosis, for example in elderly patients, or where Gram-positive bacilli are seen on Gram stain. Although earlier-generation cephalosporins such as cefuroxime achieve reasonable CSF penetration and are active against the agents of meningitis *in vitro*, they do not effectively sterilise the CSF and should not be used to treat meningitis.

Ceftriaxone is a third-generation cephalosporin with a spectrum of activity comparable to that of cefotaxime. However, because of the potential for calcium chelation *in vivo*, ceftriaxone must not be administered within 48 h of the completion

Table 38.2 Suitable antibiotic regimens for treatment of acute bacterial meningitis in different age groups

Age group	First-choice antibiotic therapy	Alternative therapies
Neonates, aged <8 days	Ampicillin, 50 mg/kg twice daily or amoxicillin 25 mg/kg twice daily and cefotaxime 50 mg/kg twice daily or ceftazidime 50 mg/kg twice daily	Benzylpenicillin 50 mg twice daily and ampicillin 50 mg/kg twice daily or amoxicillin 25 mg/kg twice daily and gentamicin 2.5 mg/kg twice daily
Neonates, aged 8–28 days	Ampicillin 50 mg/kg four times daily or amoxicillin 25 mg/kg three times daily and cefotaxime 50 mg/kg three times daily or ceftazidime 50 mg/kg three times daily	Benzylpencillin 50 mg three or four times daily or ampicillin 50 mg/kg three or four times daily or amoxicillin 25 mg/kg three times daily and gentamicin 2.5 mg/kg three times daily
Infants, aged 1–3 months	Ampicillin 50 mg/kg four times daily or amoxicillin 25 mg/kg three times daily and cefotaxime 50 mg/kg three times daily or ceftriaxone 75–100 mg/kg once daily	
Infants and children aged >3 months[a]	Cefotaxime 50 mg/kg three times daily or ceftriaxone[b] 75–100 mg/kg once daily	Ampicillin 50 mg/kg four times daily or amoxicillin 25 mg/kg three times daily or benzylpenicillin[c] 30 mg/kg 4-hourly and chloramphenicol[d] 12.5–25 mg/kg four times daily
Adults	Cefotaxime[e] 2 g three times daily or ceftriaxone[b,e] 2–4 g once daily	Benzylpenicillin 2.4 g 4-hourly or ampicillin 2–3 g four times daily or amoxicillin 2 g three or four times daily and chloramphenicol[d] 12.5–25 mg/kg four times daily

[a]Calculated doses for children should not exceed maximum recommended doses for adults.
[b]Ceftriaxone should not be administered to neonates within 48 h of completion of infusions of calcium-containing solutions; caution should be exercised in older age groups.
[c]Benzylpenicillin is inactive against *H. influenzae* and should therefore not be used in children aged <5 years.
[d]Monitoring of serum chloramphenicol levels is recommended, especially in children aged ≤4 years.
[e]Add ampicillin or amoxicillin to cover *L. monocytogenes* in elderly patients or where Gram-positive bacilli seen in CSF.

Table 38.3 Achievable CSF concentrations of antibiotics in meningitis and MIC values for common central nervous system pathogens

			MIC_{90} (mg/L) values for		
Antibiotic	CSF:serum ratio	Peak CSF level (mg/L)	*N. meningitidis*	*H. influenzae*	*S. pneumoniae*
Ampicillin	1:10	10	0.02	0.25	0.05
Benzylpenicillin	1:20	1.5	0.02	1.0	0.02
Cefotaxime	1:20	10	0.01	0.06	0.25
Ceftriaxone	1:15	15	0.01	0.06	0.12
Chloramphenicol	1:2	15	1.0	1.0	2.5
Ciprofloxacin	1:5	0.6	0.004	0.015	1.0
Daptomycin	1:20	3.0	>4.0	>4.0	0.25
Gentamicin	1:40	<0.5	2.0	0.5	16
Imipenem	1:15	2.0	0.1	1.0	0.05
Linezolid	1:1.25	5.0	>8.0	>8.0	2.0
Meropenem	1:15	4.0	0.03	0.1	0.1
Rifampicin	1:20	1.0	0.5	1.0	2.0
Vancomycin	1:40	1.0	>4.0	>4.0	0.2

MIC_{90}, minimum concentration of antibiotic that is inhibitory for 90% of isolates; CSF, cerebrospinal fluid.

of infusions of calcium-containing solutions in neonates. The risk of precipitation is much lower in patients >28 days of age. Nevertheless, caution should still be exercised when treating older age groups, especially in the early treatment of meningococcal infections (where calcium-containing products are commonly used for resuscitation).

In meningitis due to *N. meningitidis* and *H. influenzae*, prompt administration of chemoprophylaxis to eliminate nasopharyngeal carriage can reduce the risk of secondary cases in close contacts of the case.

N. meningitidis. In view of the potentially rapid clinical progression of meningococcal disease, it is recommended that treatment should begin with the emergency administration of benzylpenicillin. Primary care clinicians should give penicillin while arranging transfer of the patient to hospital. The dose is 1200 mg for adults and children aged 10 years and above, 600 mg for children aged 1–9 years and 300 mg for children aged below 1 year. Ideally, this should be given intravenously. The intramuscular route is less likely to be effective in shocked patients but can be used if venous access cannot be obtained. The only contraindication is allergy to penicillin, where cefotaxime (1 g for adults, 50 mg/kg for children aged <12 years) or chloramphenicol (1.2 g for adults, 25 mg/kg for children aged <12 years) may be given, if available. However, it is not recommended that primary care clinicians routinely carry these alternative antibiotics.

Strains of *N. meningitidis* with reduced sensitivity to penicillin are well known and presently account for 5–10% of isolates in Europe and the USA. In general, these cases respond to treatment with adequate doses of benzylpenicillin, and failure of penicillin treatment has rarely been reported. Nevertheless, cefotaxime and ceftriaxone are now widely used in preference to benzylpenicillin or chloramphenicol.

S. pneumoniae. Benzylpenicillin was once widely regarded as the treatment of choice for pneumococcal meningitis. However, pneumococci resistant to penicillin have emerged across the world, presenting a major therapeutic challenge in view of the severity of pneumococcal meningitis.

Although currently only about 5% of pneumococci in the UK are penicillin resistant, the frequency of resistance is increasing, and resistance rates of more than 50% have been reported in other countries, including Spain, Hungary and South Africa. Penicillin resistance in pneumococci is defined in terms of the minimum inhibitory concentration (MIC) of penicillin. Most strains have a MIC value of 0.1–2.0 mg/L and are defined as having moderate resistance; strains with an MIC value of more than 2 mg/L are considered highly resistant. This distinction is relevant for less serious infections with moderately resistant strains, which may still respond to adequate doses of some β-lactam antibiotics, such as cefotaxime, ceftriaxone or a carbapenem. However, the clinical outcome of meningitis with penicillin-resistant pneumococci treated

with a β-lactam antibiotic as monotherapy is less good. For this reason, many guidelines, including those produced by the Infectious Diseases Society of America, now recommend therapy with a combination of a third-generation cephalosporin and vancomycin (McIntosh, 2005). This approach has not been adopted universally in the UK but should certainly be considered for patients who might have acquired their infection in a location where the incidence of penicillin resistance is high. Where vancomycin is given intravenously to treat meningitis, it is important to aim for trough serum levels of 15–20 mg/L because of the limited CSF penetration of vancomycin. Another problem is the emergence of pneumococci that are tolerant to vancomycin, that is, they are able to survive, but not proliferate, in the presence of vancomycin. Although such strains are uncommon, the outcome of meningitis treated with vancomycin is poor (Cottagnoud and Tauber, 2004).

Other antibiotics may be useful in treating pneumococcal meningitis. Use of rifampicin in combination with a cephalosporin and/or vancomycin is sometimes recommended, but there are few data confirming this can improve the response rate in either penicillin-sensitive or -resistant pneumococcal meningitis. The dose of rifampicin is 600 mg twice daily in adults or 10 mg/kg (maximum 600 mg) twice daily in children. Chloramphenicol is a suitable alternative to penicillin for treatment of meningitis due to penicillin-sensitive strains, for example in patients who are penicillin allergic. However, chloramphenicol is not recommended for treating penicillin-resistant pneumococcal meningitis: although isolates may appear sensitive to chloramphenicol on routine laboratory testing, bactericidal activity is often absent and the clinical response is usually poor.

Consideration of alternative antibiotics for treatment of penicillin-resistant pneumococcal meningitis is largely based on case reports rather than clinical trials. Success has been reported with meropenem as monotherapy, and in conjunction with rifampicin. Moxifloxacin is a new-generation quinolone antibiotic with enhanced activity against Gram-positive bacteria, including *S. pneumoniae*, which has shown promise in experimental pneumococcal meningitis. Linezolid has excellent CSF penetration but does not have bactericidal activity, and clinical experience in treating meningitis has been variable (Rupprecht and Pfister, 2005).

Daptomycin is an interesting option that has potent bactericidal activity against penicillin-sensitive and -resistant pneumococci, but without being bacteriolytic. This may be an advantage in that bacterial intracellular components that contribute to the inflammatory response are not liberated by bacterial killing. Indeed, in treating experimental pneumococcal meningitis, daptomycin gives a better clinical outcome than conventional treatment.

The unpredictable nature of the response to therapy of penicillin-resistant pneumococcal meningitis means that patients require close observation during treatment, for example monitoring of C-reactive protein (CRP). Repeat examination of CSF during therapy should also be considered.

H. influenzae. A third-generation cephalosporin such as cefotaxime or ceftriaxone is generally the treatment of choice for *H. influenzae* meningitis. These agents have superseded the traditional therapies of chloramphenicol and/or ampicillin or amoxicillin.

Other bacteria. Meningitis in immunocompetent individuals is rarely due to other bacteria. The definitive treatment for these individuals should be determined on an individual basis in the light of careful clinical and microbiological assessment.

Chemoprophylaxis against meningococccal and Hib infection. In meningococcal meningitis, spread between family members and other close contacts is well recognised; these individuals should receive chemoprophylaxis as soon as possible, preferably within 24 h. Sometimes, chemoprophylaxis may be indicated for other contacts, but the decision to offer prophylaxis beyond household contacts should only be made after obtaining expert advice (Box 38.1). Of the antibiotics conventionally used to treat meningococcal infections, only ceftriaxone reliably eliminates nasopharyngeal carriage; where another antibiotic has been used for treatment, the index case also requires chemoprophylaxis. A number of antibiotics are suitable as prophylaxis (Box 38.2).

Box 38.1 Indications for chemoprophylaxis in contacts of cases of infection with *N. meningitidis* or *H. influenzae* type b

Neisseria meningitidis

Household and other close contacts: prophylaxis usually initiated as soon as possible by clinicians caring for the patient

- Persons who have slept in the same house as the patient at any time during the 7 days before the onset of symptoms
- Boy/girl friends of the patient
- Unless treated with ceftriaxone (which reliably eliminates nasopharyngeal carriage), the index patient should also receive antibiotic prophylaxis as soon as he or she is able to take oral medication

Healthcare workers: prophylaxis should only be initiated after consultation with hospital infection control team or public health doctor

- Individuals who have administered mouth-to-mouth resuscitation or had some other form of prolonged close face-to-face contact with the patient
- Other contacts: prophylaxis should be initiated by a public health doctor
- Schools, nurseries, universities and other closed communities where two or more linked cases have occurred

Invasive *Haemophilus influenzae* type b infection

Household and other close contacts: prophylaxis usually initiated as soon as possible by clinicians caring for the patient

- Indicated only where there is another child aged less than 4 years who has not been immunised in the same household as the index patient. In such circumstances, prophylaxis should be given to all household contacts aged 1 month or older, unless there are contraindications. The index patient should also receive antibiotic prophylaxis as soon as he or she is able to take oral medication

Other contacts: prophylaxis very rarely necessary and should only be initiated by a public health physician

Box 38.2 Recommended prophylactic regimens for contacts of cases of infection with *N. meningitidis* or *H. influenzae* type b

Meningococcal infection	
Ciprofloxacin[a] *(oral)*	
Children aged 1 month – 4 years	125 mg as a single dose
Children aged 5–12 years	250 mg as a single dose
Adults	500 mg as a single dose
Rifampicin (oral)	
Children aged <1 year	5 mg/kg twice daily on 2 consecutive days
Children aged 1–12 years	10 mg/kg (max 600 mg) twice daily on 2 consecutive days
Adults	600 mg twice daily on 2 consecutive days
Azithromycin[a] *(oral)*	
Pregnant women	500 mg as a single dose
Ceftriaxone[a] *(intramuscular)*	
Children aged <12 years	125 mg as a single dose
Adults	250 mg as a single dose
Invasive *Haemophilus influenzae* type b infection	
Rifampicin (oral)	
Children aged 1–3 months	10 mg/kg once daily for 4 days
Children aged >3 months	20 mg/kg once daily (max 600 mg) for 4 days
Adults[b]	600 mg once daily for 4 days

[a]Not licensed for this indication.
[b]For pregnant women, obtain expert advice.

Ciprofloxacin is now widely recommended for contacts of all ages (including pregnant and breast-feeding women) because of the convenience of single-dose administration and, unlike rifampicin, it does not interact with oral contraceptives and is readily available in community pharmacies. Although anaphylactoid reactions have been reported to occur in individuals receiving ciprofloxacin as chemoprophylaxis, none of these reactions has been fatal. If the strain is confirmed as group C (or A, W135 or Y), vaccination is normally offered to contacts who were given prophylaxis. There is no need to vaccinate the patient. There is currently no vaccine that protects against group B disease, which accounts for about 70% of cases of meningococcal disease in Europe.

Chemoprophylaxis against Hib infection is usually only indicated where there is an unimmunised child in the vulnerable age group in the household (see Box 38.1). Only rifampicin has been proved to be effective in eliminating nasopharyngeal carriage (see Box 38.2). Unimmunised household contacts aged below 4 years should also receive Hib vaccine. The index case should also receive rifampicin in order to eliminate nasopharyngeal carriage, and should be immunised, irrespective of age.

Antibiotics for meningitis in special groups

Immunocompromised host. In the immunocompromised neutropenic patient, the meninges can become infected. Possible causes of meningitis include *Enterobacteriaceae* and *Pseudomonas aeruginosa*, as well as the classic bacterial causes of meningitis. The choice of therapy is governed by the need to attain broad-spectrum coverage, using agents with good CSF penetration. Meropenem may now be the drug of choice for meningitis in this setting, although many other regimens are also appropriate.

Patients with cellular immune dysfunction are vulnerable to meningitis due to *L. monocytogenes* and *C. neoformans.* Ampicillin or amoxicillin, along with cefotaxime or ceftriaxone, is recommended as empirical antibacterial therapy for meningitis in these patients. Definitive treatment of listeria meningitis is normally with high-dose ampicillin (3 g four times daily) or amoxicillin (2 g four times daily), with the addition of gentamicin in order to obtain a synergistic effect. The most appropriate treatment for patients who are penicillin allergic, or in the rare circumstance of infection with a strain that is ampicillin resistant, is uncertain and specialist microbiological advice should be sought. Specific therapies for cryptococcal meningitis are described in detail as follows.

Splenectomised patients are susceptible to invasive infections with encapsulated bacteria, including *S. pneumoniae* and Hib. Standard therapy with either cefotaxime or ceftriaxone is appropriate.

Shunt-associated meningitis. Patients who have a ventricular shunt are at increased risk of meningitis. Shunt-associated infections are classified according to the site of initial infection. Internal infections, where the lumen of the shunt is colonised, constitute the majority of cases. External shunt infections involve the tissues surrounding the shunt. Most internal shunt infections are caused by coagulase-negative staphylococci. *S. aureus* and *Enterobacteriaceae* account for most external infections. It is generally held that management of shunt infections should include shunt removal, as well as antibiotic therapy (Infection in Neurosurgery Working Party, 2000), although the need for this has been questioned (Arnell et al., 2007). Appropriate antimicrobial regimens are shown in Table 38.4.

Tuberculous meningitis. The outcome in tuberculous meningitis relates directly to the severity of the patient's clinical condition on commencement of therapy. A satisfactory response demands a high degree of clinical suspicion such that appropriate chemotherapy is initiated early, even if tubercle bacilli are not demonstrated on initial microscopy. Most currently used antituberculous agents achieve effective concentrations in the CSF in tuberculous meningitis. Detailed discussion of antituberculous therapy is given in Chapter 40. Adjunctive steroid therapy is of value in patients with more severe disease, particularly those who suddenly develop cerebral oedema soon after starting treatment or who appear to be developing a spinal block. However, routine use of steroids is not recommended. They may suppress informative changes in the CSF and interfere with antibiotic penetration by restoring the blood–brain barrier. Early neurosurgical management of hydrocephalus by means of a ventriculoperitoneal or ventriculoatrial shunt is also important in improving the prospects for neurological recovery.

Cryptococcal meningitis. The standard treatment of cryptococcal meningitis is amphotericin B, given intravenously at a dose of 0.7–1.0 mg/kg/day, with or without flucytosine 100 mg/kg/day, for 6–10 weeks. Addition of flucytosine results in quicker clearance of yeasts from the CSF, although it is debatable whether this results in improved clinical outcome. Lipid formulations of amphotericin B, such as liposomal

Table 38.4 Antimicrobial regimens for treatment of shunt meningitis

Type of infection	First-choice antibiotic regimen	Other antibiotic regimens	Duration of therapy before reshunting
Internal shunt infection caused by Gram-positive bacteria	Intraventricular vancomycin + intravenous or oral rifampicin	Substitute flucloxacillin or intravenous vancomycin for rifampicin in cases of rifampicin resistance, except in the case of enterococci, where an aminoglycoside (e.g. gentamicin) should be used	7–10 days intravenous
External shunt infection caused by *S. Aureus*	As earlier, with the addition of intravenous flucloxacillin	Substitute intravenous vancomycin for flucloxacillin in the case of methicillin resistance (MRSA)	12–14 days
Enterobacteriaceae	Intravenous cefotaxime ± an aminoglycoside + intraventricular aminoglycoside	Substitute ceftazidime or meropenem for cefotaxime in the case of cefotaxime resistance	14 days
Polymicrobial ventriculoperitoneal shunt infections	Intravenous amoxicillin, metronidazole, cefotaxime ± an aminoglycoside + intraventricular aminoglycoside	Seek specialist advice	14 days
Candida	Intravenous amphotericin B + flucytosine	Intravenous fluconazole	10–14 days (antifungal fungal therapy should continue for 1 week after reshunting)

amphotericin B, at doses of 4–6 mg/kg/day have comparable efficacy to, and fewer side effects than, conventional amphotericin B at a dose of 0.7 mg/kg. As an alternative to prolonged therapy with two potentially toxic drugs, 2 weeks therapy with amphotericin B and flucytosine may be given, followed by consolidation therapy with fluconazole 400 mg/day for at least 10 weeks. Initial treatment with fluconazole 400–800 mg/day plus flucytosine is clinically inferior to amphotericin B-based regimens, and in any case is no better tolerated than amphotericin B-based regimens. Regular haematological and biochemical monitoring is recommended during treatment, along with measurement of serum concentrations of flucytosine (which should not exceed 80 mg/L).

The clinical response to treatment of cryptococcal meningitis is slow, and it often takes 2 or 3 weeks to sterilise the CSF. Monitoring of intracranial pressure is essential, with large-volume CSF drainage indicated if the opening pressure reaches 250 mmHg. Serial CSF cultures are occasionally helpful in following the response to treatment, but monitoring of cryptococcal antigen titres in serum or CSF is of little value.

Patients with HIV infection treated for cryptococcal meningitis should then receive fluconazole indefinitely, or at least until immune reconstitution occurs. The dose of fluconazole may be reduced to 200 mg/day, depending on the patient's clinical condition (Bicanic and Harrison, 2004). Itraconazole offers less good CSF penetration than fluconazole, but is a suitable alternative as maintenance therapy at a dose of 200–400 mg/day for patients unable to tolerate fluconazole. Clinical data with newer triazoles such as voriconazole and posaconazole remain limited, but these agents may be useful, especially in the rare situation of fluconazole-resistant cryptococcal meningitis. The echinocandin class of antifungals does not possess useful activity against *Cryptococcus*.

Viral meningitis. None of the currently available antiviral agents has useful activity against human enteroviruses, the commonest causes of viral meningitis (Big et al., 2009). Fortunately, however, the condition is usually self-limiting. The viruses that commonly cause this condition, herpes simplex and varicella zoster meningoencephalitis, are treated with high-dose aciclovir, 10 mg/kg three times daily for at least 10 days (adults and children aged 12 years and over). For younger children, the recommended doses are 20 mg/kg three times daily for infants up to age 3 months, and 500 mg/m^2 three times daily for those aged 3 months to 12 years.

Steroids as adjunctive therapy in bacterial meningitis. In pharmacological doses, corticosteroids, and in particular dexamethasone, regulate many components of the inflammatory response and also lower CSF hydrostatic pressure. However, by reducing inflammation and restoring the blood–brain barrier, they may reduce CSF penetration of antibiotics. The benefits of steroids in the initial management of meningitis due to *M. tuberculosis* and Hib are well established, although in other forms of bacterial meningitis the evidence has been less compelling. Methodological flaws have been identified in older studies where no benefit was seen from use of adjunctive steroid therapy. Recent work has found that adjunctive dexamethasone therapy reduces the rate of unfavourable outcomes from 25% to 15% in adults with bacterial meningitis. In this series, adjunctive treatment with dexamethasone was given before or with the first dose of antibiotics, without serious adverse effects. Overall, corticosteroids significantly reduce rates of mortality, severe hearing loss and neurological sequelae. The use of adjunctive dexamethasone is now recommended for children and adults with community-acquired bacterial meningitis, regardless of bacterial aetiology (Brouwer et al., 2010). Adjunctive therapy

should be initiated before or with the first dose of antibiotics and continued for 4 days. The recommended dose for adults is 10 mg four times daily for 4 days (children 0.15 mg/kg four times daily for 4 days).

Intrathecal and intraventricular administration of antibiotics. Intrathecal administration, that is, administration into the lumbar subarachnoid space, of antibiotics was once widely used to supplement levels attained by concomitant systemic therapy. However, there is little evidence for the efficacy of this route of delivery, and it is now rarely used. In particular, it produces only low concentrations of antibiotic in the ventricles and therefore does little to prevent ventriculitis, one of the most serious complications of meningitis. Direct intraventricular administration of antibiotics in meningitis is important in certain types of meningitis, especially where it is necessary to use an agent, for example vancomycin or an aminoglycoside, that penetrates CSF poorly (Shah et al., 2004). The most common situation is in shunt-associated meningitis, where multiple antibiotic-resistant coagulase-negative staphylococci are the major pathogens, and where conveniently the patient will often have an external ventricular drain through which antibiotics can be administered.

There are considerable differences in recommended doses of antibiotics for intrathecal or intraventricular administration. A dose of 15–20 mg vancomycin per day is recommended for treatment of shunt-associated meningitis in adults with an extraventricular drain, and 10 mg/day for neonates and children. The paediatric dose may need to be reduced to 5 mg/day if ventricular size is reduced, or increased to 15–20 mg/day if the ventricular size is increased. In all patients, the dose frequency should be decreased to once every 2–3 days if CSF is not draining freely. The CSF vancomycin concentration should be measured after 3–4 days, aiming for a trough concentration of <10 mg/L. Recommended doses of antibiotics are otherwise largely based on anecdotal experience (Table 38.5).

Patient care

Common problems in the treatment of meningitis are set out in Table 38.6.

Table 38.5 Daily[a] doses (mg) of gentamicin and vancomycin for intraventricular administration

Antibiotic	Adult	Child ≥2 years	Child <2 years
Gentamicin	1.0[b]	1.0	1.0
Vancomycin	15–20	10[c]	10[c]

[a]If CSF is not draining freely, reduce dose frequency to once every 2–3 days.
[b]Dose can be increased to up to 5 mg in the most severe cases.
[c]Reduce dose to 5 mg if ventricular size is reduced, or increase to 15–20 mg/day if ventricular size is increased.

Table 38.6 Practice points in infective meningitis

Infection	Antibiotic	Common problems	Resolution
Bacterial meningitis	Chloramphenicol	Risk of serious toxicity, especially in neonates	Avoid use if possible Close monitoring of serum levels where use essential
Neonatal meningitis	Aminoglycosides (e.g. gentamicin)	Poor CSF penetration provides unreliable activity against Gram-negative bacteria Unpredictable neonatal pharmacokinetics (especially preterm neonates)	Substitute with, or add, an antibiotic with better CSF penetration (e.g. a cephalosporin) Close monitoring of serum levels
S. pneumoniae meningitis	Penicillin Cefotaxime or ceftriaxone Vancomycin (intravenous)	Resistance is increasing Treatment failure in meningitis due to penicillin Resistant strains Unreliable CSF penetration	Use cefotaxime or ceftriaxone ± vancomycin as empiric therapy Add rifampicin or vancomycin Consider one of the newer antibiotics with good activity against multiresistant Gram-positive bacteria
L. monocytogenes meningitis	Any	Relapse rate up to 10% after short courses of therapy	Give prolonged therapy (usually 3–4 weeks)
Cryptococcal meningitis	Amphotericin B Flucytosine Fluconazole	High incidence of side effects, for example fever, nausea, vomiting, anaemia, hypokalaemia, impaired renal function Risk of side effects, for example deranged liver function, bone marrow depression Low cure rate when used as monotherapy (except as consolidation therapy)	Change to lipid-based preparation of amphotericin B, or replace with fluconazole Close monitoring of serum levels Combine with flucytosine

Prevention of person-to-person transmission

Patients with meningitis may be infectious to others. Neonates with meningitis usually have generalised infections, and the causative organisms can often be isolated from body fluids and faeces. Babies with meningitis should therefore be isolated to prevent infection spreading to other patients. Patients with meningococcal or Hib meningitis should be isolated until after at least 48 h of antibiotic therapy. Contacts of these patients may be asymptomatic carriers and potentially infectious to others and/or at risk of developing invasive infection themselves. Chemoprophylaxis and vaccination can reduce these risks (see earlier). Patients with most other types of meningitis do not represent a significant infectious hazard, and enhanced infection control precautions are not usually necessary.

Case studies

Case 38.1

A 4-week-old premature infant presents on the hospital neonatal unit with poor feeding, fever and increasing drowsiness. Lumbar puncture reveals 1200 WBC/μL (80% of which are polymorphs), and low glucose and elevated protein levels. No organisms are seen on a Gram-stained smear of the CSF. The diagnosis is acute purulent meningitis.

Questions

1. What are the likely aetiological agents?
2. Which other investigations other than CSF culture might help in establishing the aetiological diagnosis?
3. What empiric antibiotic therapy should be commenced?

Answers

1. At 4 weeks of age, the possible causes include neonatal pathogens (group B streptococci, *Escherichia coli* and *Listeria monocytogenes*), nosocomial pathogens such as *Staphylococcus aureus* and Gram-negative bacilli and the usual causes of meningitis in older infants (especially *Neisseria meningitidis* and *Streptococcus pneumoniae*). Most group B streptococcal disease presents in the first few days of life, whilst listeria meningitis is very uncommon, meaning that of the neonatal pathogens there is a greater likelihood of Gram-negative bacillary meningitis.
2. It is important to collect blood cultures because neonatal meningitis is not uncommonly accompanied by bacteraemia. Molecular tests on CSF may be undertaken, but the commonly used tests are not directed against the most likely pathogens in this case. The results of any recent cultures from other anatomic sites may also be useful, especially in ensuring that empiric antibiotic therapy is active against potential pathogens the baby is known to harbour.
3. Given the range of potential pathogens, a combination of ampicillin or amoxicillin plus cefotaxime or ceftazidime would be the treatment of choice, unless the patient is known to be colonised with antibiotic-resistant bacteria such as MRSA or Gram-negative bacteria.

Case 38.2

A 70-year-old man is being treated for meningitis due to *Streptococcus pneumoniae* that is moderately resistant to penicillin (MIC value 0.75 mg/L). Despite 7 days' treatment with intravenous vancomycin and cefotaxime, there has been little improvement in his clinical condition. A CT scan has shown meningeal inflammation consistent with meningitis, but no evidence of intracranial complications that might explain his poor clinical response. The most recent trough (predose) serum vancomycin concentration was 5.3 mg/L.

Questions

1. Why might there have been an inadequate response to treatment with cefotaxime and vancomycin?
2. What options are there to modify his antimicrobial therapy?

Answers

1. CSF penetration of vancomycin is poor and the serum vancomycin concentration in any case low. It is therefore doubtful that the vancomcyin concentration in the CSF would be bactericidal. Even if the vancomycin concentration in CSF were adequate, the infection may be due to a vancomycin-tolerant strain of *S. pneumoniae*. Tolerant strains appear fully sensitive to vancomycin by routine laboratory antimicrobial susceptibility sensitivity testing. Cefotaxime alone may not adequately treat infections with penicillin-resistant pneumococci.
2. It is important to optimise the patient's treatment as quickly as possible. He might respond to increasing the dose of vancomycin with or without addition of rifampicin. However, these strategies give little assurance of success. It would probably be preferable to switch to an alternative agent. Meropenem is probably the agent with which there is most experience, which could continue to be combined with an increased dose vancomycin for extra assurance. Linezolid or daptomycin would be alternative options.

Case 38.3

An 18-year-old man is referred as an emergency with suspected meningitis. He was given intravenous penicillin by the primary care doctor before admission to hospital. On examination he is fully conscious, and neck stiffness is elicited. He is haemodynamically stable and no rash is present.

Questions

1. What investigations would you undertake to establish the diagnosis?
2. What treatment would you give?
3. What further action will be required if a diagnosis of meningococcal meningitis is likely?

Answers

1. Blood cultures and a nasopharyngeal swab for culture should be collected. There are no clinical contraindications to lumbar puncture, and in most centres this would be undertaken without a prior CT scan. The white cell count and glucose and protein concentrations in the CSF should be measured. A Gram stain should be undertaken, which may give immediate information on the likely identity of the pathogen, as well as culture and PCR. Some laboratories might also undertake antigen testing to try to establish an early aetiological diagnosis.

2. Antibiotic treatment should be with a third-generation cephalosporin (cefotaxime or ceftriaxone). The latter should be entirely safe to use in this situation given that it sounds unlikely that the patient will have required resuscitation with calcium-containing fluids. In addition, adjunctive therapy with dexamethasone, for which there appear to be no contraindications, should be considered.
3. Meningitis is a notifiable disease. If a diagnosis of meningococcal meningitis is considered likely, then prophylaxis should be offered to the patient and to close contacts as soon as possible to eliminate nasopharyngeal carriage and prevent secondary cases.

Case 38.4

A 46-year-old renal transplant recipient received 2 weeks treatment with amphotericin and flucytosine, and was then switched to fluconazole which he has received for a further 6 weeks (latterly as a hospital out-patient). However, after complaining of headaches, a repeat lumbar puncture has been undertaken and has shown that cryptococci are still present in the CSF.

Questions

1. Give three reasons why his treatment to date might have failed.
2. How would you now manage the situation?

Answers

1. It may be that the patient has not been adherent with his medication; the initial 2-week course of treatment with amphotericin may have been too short; or the infecting strain of *Cryptococcus* may be fluconazole resistant.
2. The first step should be to readmit the patient and recommence treatment with amphotericin and flucytosine. The microbiology laboratory should be asked to determine the sensitivity of the patient's isolate to fluconazole. Once that result has been ascertained, it will be possible to plan the patient's longer term management. Options would include completing a full course of amphotericin and flucytosine, or switching to one of the new triazoles such as posaconazole at some point. Close monitoring of the patient's response will be required.

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