

intercourse is adequate but, in more severe cases, courses may be taken for 3–6 months or on occasions longer. Adult doses given:

- trimethoprim 150 mg (o) nocte

or

- cephalixin 250 mg (o) nocte

Non-antibiotic strategies

Drinking more water is recommended. Women are generally encouraged to gently wash or wipe their bottom from front to back after opening their bowels. Continuous prophylaxis with the bacteriostatic agent methenamine hippurate 1g (o) bd may also be helpful, although evidence is inconsistent. In postmenopausal women with atrophic vaginitis, topical oestrogen therapy may reduce the risk of recurrent UTIs. Cranberry products are no longer recommended.

Urinary tract infection in children

By the age of 10 years, about 3% of boys¹⁵ and 10% of girls will have had at least one episode of a urinary tract infection.

UTI in infants and very young children is often kidney in nature and may be associated with generalised symptoms such as fever, vomiting, diarrhoea and failure to thrive. Offensive urine may be noted. Causes of ‘smelly’ urine in children are urinary infection and/or dehydration, especially with gastroenteritis. Symptoms of dysuria and frequency appear only after the age of 2 years when the child is able to indicate the source of the discomfort. In a girl or boy (rare presentation) with symptoms of dysuria and frequency, an underlying abnormality may be present with a reported incidence of vesicoureteric reflux (VUR) as high as 40% and scarred kidneys (reflux nephropathy) in 27%.³

Thus the early detection of children with VUR and control of recurrent kidney infection could prevent the development of scars, hypertension and chronic kidney failure. Radiological investigation of children with UTIs shows normal kidneys in approximately 66% and reflux in approximately 33%.

Children require further investigation with an ultrasound if they are seriously unwell with a UTI, have complicated or recurrent UTIs. Children with recurrent UTIs may require additional imaging and specialist input is recommended. A low threshold for further investigation is appropriate in children <6 months. A urine specimen is essential before antibiotics are given.

Guidelines for investigation^{15,16}

- <1 year—ultrasound; consider micturating cystourethrogram (MCUG) if US abnormal

if both negative, no further investigation

if abnormal, follow-up referral/investigation

- >1 year—ultrasound

Nuclear scans including dimercaptosuccinic acid scintigraphy (DMSA) and mercaptoacetyltriglycine (MAG3) are occasionally indicated.

Treatment (mild infection in children)^{15,17}

Treat empirically in children one month or more while awaiting culture results. If less than one month, treatment with IV antibiotics is advisable.

Treatment should be taken orally for 3–7 days:

- trimethoprim 4 mg/kg (max. 150 mg) bd (suspension is 50 mg/5 mL)

or

- cephalixin 12.5 mg/kg (max. 500 mg) bd

or

- trimethoprim/sulfamethoxazole 4/20 mg/kg (max. 160/800 mg) bd

Amoxicillin, amoxicillin/clavulanate, norfloxacin or ciprofloxacin may be required based on pathogen susceptibility.

Repeat MCU is not required if children remain asymptomatic after treatment.

Severe infections in children

For empirical treatment in those ≥12 months who appear septic or are vomiting, and infants <12 months, give gentamicin IV + amoxi/ampicillin IV. Subsequent treatment should be guided by culture results and clinical results with early change to oral therapy.

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Duration of therapy: usually 10–14 days.

Vulvovaginitis in children

Although vulvovaginitis can affect women of any age, it is more prevalent in girls between 2 and 8 years. It can be confused with a UTI where there is dysuria, which is a common symptom in this type of dermatitis (see CHAPTER 99).

Urinary infections in the elderly

The typical settings in which UTIs occur in the elderly are in the frail, those who are immobilised, and those with faecal incontinence and inadequate bladder emptying. It is a particular problem in aged care facility residents. The presenting symptoms may be atypical, especially with upper UTI where fever of undetermined origin and behaviour disturbances may be a feature. In men, consider excluding obstructive uropathy from prostatism by ultrasound.

Uncomplicated infections should be treated the same way as for other age groups but no antimicrobial treatment is recommended for asymptomatic bacteriuria.

Genitourinary tuberculosis

The genitourinary tract is involved in 3–5% of cases of tuberculosis.¹⁸ The genital and urinary tracts are often involved together as a result of miliary spread.

The commonest presenting complaints are dysuria and frequency, which can be severe. Other symptoms include strangury when the bladder is severely affected, loin pain and haematuria. Routine urine culture shows sterile pyuria.

Diagnosis is made on specific urine culture for mycobacterium, ESR/CRP (high) or biopsy of bladder lesions or the typical X-ray appearance of distorted calyces and medullary calcification. Treatment is with antituberculous drugs.

Candiduria

The presence of *Candida albicans* in the urine is common. Antifungal therapy is not recommended if associated with indwelling catheters but is recommended if associated with upper UTIs and/or systemic candidiasis. Consider removal of catheter and stents.

Use fluconazole 200 mg (o) daily for 14 days.

Prostatitis

Consider bacterial prostatitis in men with few urinary symptoms (frequency, urgency and dysuria), flu-like illness, fever, low backache and perineal pain. The prostate is exquisitely tender on rectal examination. For mild to moderate infection, give trimethoprim 300 mg (o) daily or cephalexin 500 mg (o) 6 hourly for 2 weeks. If severe, use amoxi/ampicillin 2 g IV 6 hourly plus gentamicin (see [CHAPTER 106](#)).

When to refer

- It is wise to refer all patients with urinary tract abnormalities to a nephrologist or urologist for advice on specific management.
- Refer also if the simple methods outlined above do not control recurrent UTI.

- Refer children with recurrent UTI.
- Refer males with urinary infections that are not clearly localised to the prostate.
- Refer patients with impaired kidney function.

Practice tips

- Most symptomatic UTIs are acute cystitis occurring in sexually active women with anatomically normal urinary tracts.
- A clinical diagnosis based on experience, plus a positive nitrite dipstick test and the finding of pyuria by office microscopy, will generally enable immediate curative treatment.
- A 3-day course of trimethoprim 300 mg daily is a suitable first choice for acute uncomplicated cystitis in women.
- Avoid overinvestigation of patients in whom there is a low likelihood of demonstrating structural abnormalities.
- The ultrasound examination may not detect calculi, small tumours, clubbed calyces and papillary necrosis.
- In males the prostate is the most common source of recurrent UTI.
- UTI is commonly associated with microscopic haematuria (occasionally macroscopic haematuria).
- Persisting haematuria should be investigated, e.g. US, CT-IVP.

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Cystitis in women
- Urine infection in children
- Prostate: prostatitis

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17 Malignant disease

Cancers of the tongue and mouth begin with a small hard lump, and sometimes with a little sore; both of which are attended with pricking pains, and they spread in the same manner with cancerous sores in other parts. It is so great an evil, that the slightest suspicion of it occasions very great uneasiness.

WILLIAM HEBERDEN (1710–1801)

The terms *malignancy*, *cancer* and *neoplasia* are usually used interchangeably. The differences between a malignant tumour and a benign tumour are summarised in TABLE 17.1 .

Table 17.1 Different characteristics of benign and malignant tumours

Benign	Malignant
Well-differentiated	Undifferentiated
Non-invasive	Invasive
Slow growth	Rapid growth
Not anaplastic	Anaplastic
Not metastatic	Metastatic

Malignant disease accounts for 1 in 8 deaths of people under 35 years in Australia and 3 in every 10 (29%) of deaths in those over 45 years.¹ The six most common causes of death from cancer in Australia are cancer of the lung, colorectal, lymphoma, prostate, breast and pancreas.²

Neoplasia, especially malignancy of the silent areas, can present as undifferentiated illness and be a real masquerade. The so-called ‘silent’ malignancies that pose a special problem include cancer of the ovary, pancreas, kidney, caecum and ascending colon, liver (hepatoma), melanoma and haematological tissue.

This chapter focuses on the general features of several of these malignancies in order to promote early diagnosis and urgent referral at the primary care level. Specific common cancers are discussed in other chapters.

Acute emergency problems that can develop with various malignancies include spinal cord compression, malignant effusions, disseminated intravascular coagulation and hypercalcaemia.

Cancer in children^{3,4}

Although uncommon in children under 15 years, cancer is the second most common cause of death in this age group. The most common cancers (in order) are leukaemias, especially acute lymphocytic leukaemia (34%); brain tumours, especially astrocytoma (20%), ependymomas and medulloblastoma; lymphomas, especially non-Hodgkin (13%); neuroblastoma; Wilms tumour; soft tissue tumours, especially rhabdomyosarcoma; and bone tumours.

Survival has improved dramatically in recent decades, indicating the value of early diagnosis and referral for expert treatment. A recent study has revealed that the incidence rates of several childhood cancer types steadily increased during 1983–2015.⁵

Studies have highlighted the importance of GPs responding to concerns of parents even if they could find no abnormality after examination. Parents of children eventually diagnosed with cancer and who were in dispute with their GP were alerted by signs and symptoms which were often vague, non-specific and common, or unusual or ‘scary’. They felt that their child ‘wasn’t right’.³

Red flags for childhood cancer

- Lump or mass, especially neck or stomach
- Unusual bleeding, bruising or rash
- White eye
- Persistent nausea and vomiting
- Constant illness
- Constant tiredness and/or pallor
- Headache, especially early morning
- Continuing unexplained weight loss
- Recurrent or persistent fever
- Changes which occur suddenly and persist

- Increased swelling or persistent pain in bone

Clinical manifestations

The clinical manifestations of malignancy are usually due to:

- pressure effects of the growth
- infiltration or metastases in various organs (e.g. liver, brain, lungs, bone, blood vessels)
- systemic symptoms, including paraneoplastic effects

Systemic symptoms

These can be divided into general non-specific effects and paraneoplastic syndromes,

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Undifferentiated general symptoms

- Tiredness/fatigue/weakness
- Anorexia and nausea
- Weight loss
- Fever
- Thirst (hypercalcaemia)
- Drowsiness (hyponatraemia)

Paraneoplastic effects

The paraneoplastic effects or syndromes are very important clinically because they may provide an early clue to the presence of a specific type of cancer, in addition to the possible lethal effect of the metabolic or toxic effect (e.g. hyponatraemia). These effects include:

- ectopic hormone production
- skin abnormalities
- metabolic effects: fever/sweats, weight loss/cachexia
- haematological disorders: anaemia, erythrocytosis/polycythaemia, coagulation disorder, others

- neuropathies and CNS abnormalities
- collagen vascular disorders
- nephrotic syndrome

A summary of various paraneoplastic syndromes is presented in TABLE 17.2 .

Table 17.2 Paraneoplastic syndromes and associated tumours: more common examples

Hormone excess syndrome	Tumour
Cushing	Lung, kidney, adrenal, thymoma, pancreas
ACTH	Lung, kidney, thymoma, thyroid
Gonadotrophins	Lung, hepatoma, choriocarcinoma
Other syndromes	
Hypercalcaemia	Lung, breast, kidney, multiple myeloma, prostate, pancreas, adrenal, hepatoma
Fever	Kidney, hepatoma, lymphoma, pancreas, thymoma
Neurologic	Lung, breast, thymoma, Hodgkin, prostate
Coagulopathy	Lung, breast, hepatoma, prostate, pancreas
Thrombophlebitis	Kidney, pancreas, prostate
Polycythaemia	Kidney, hepatoma
Dermatomyositis	Lung, breast, pancreas

Clinical approach

A history of constitutional symptoms that are often quite undifferentiated (often bizarre) may provide the clue to the possibility of an underlying malignancy. An occupational history may be relevant to the clinical problem (see TABLE 17.3).

Table 17.3 Occupational causes of cancer

Agent	Occupation	Cancer
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Arsenic	Chemical industry	Lung, skin, liver
Asbestos	Insulation worker	Mesothelioma
Benzene	Glue worker, varnisher	Leukaemia
Radiation	Mining	Various
Soot, coal tar	Chimney sweep	Skin
Ultraviolet light	Farmer, sailor, outdoor worker	Skin
Vinyl chloride	PVC manufacturing	Liver (angiosarcoma)

Familial cancer

Although the great majority of cancer is not inherited, some individuals carry inherited genetic mutations from conception that predispose them to developing certain cancers, particularly colorectal, breast and ovarian cancers. Refer to [CHAPTER 23](#).

Tumour markers⁶

A tumour marker is an abnormal characteristic that is specific for a particular type of malignancy (e.g. the Philadelphia chromosome for chronic myeloid leukaemia). Other examples include human chorionic gonadotrophin (HCG) (elevated in trophoblastic tumours and germ cell neoplasms of the testes and ovaries) and the oncofetal antigens—carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP).

CEA and AFP are not specific markers but are elevated in certain tumours and are very useful in monitoring tumour activity.

Tumour markers have a limited role in diagnosis of malignant disease because several have low sensitivity and specificity. The most valuable are those associated with testis cancer—AFP and β -HCG. Markers may be an adjunct to diagnosis of certain malignancies, including the rather inaccurate CEA for bowel cancer and CA-125 for ovarian cancer. These markers are summarised in [TABLE 17.4](#).

Table 17.4 Common tumour markers

Tumour marker	Condition
AFP	Testicular cancer (non-seminomatous)
	Hepatocellular carcinoma
	GIT cancers with and without liver metastases
CA-125	Ovarian cancer (non-mucinous), breast

CA-15-3	Breast
CA-19-9	Pancreas, colon, ovary
CEA	Colorectal cancer
	Pancreatic, breast, lung, small intestine, stomach, ovaries
PSA*	Prostate cancer
hCG	Choriocarcinoma
	Hydatidiform mole
	Trophoblastic diseases
b ₂ -microglobulin	Multiple myeloma, some lymphomas, CLL

*PSA = prostate-specific antigen

Lung cancer

Apart from non-melanoma skin cancer, lung cancer is one of the most common cancers in Australia in terms of both incidence and death, accounting for at least 20% of cancer deaths.¹ In the US it accounts for 28% of cancer deaths in men and 24% of deaths in women. Only 10–25% are asymptomatic at the time of diagnosis but lung cancer can cause an extraordinary variety of clinical symptoms and signs with a reputation for several paraneoplastic syndromes. Refer to CHAPTERS 32 and 38.

The paraneoplastic syndromes include hypercalcaemia, Cushing syndrome, carcinoid syndrome, dermatomyositis, visual loss progressing to blindness from retinal degeneration, cerebellar degeneration and encephalitis.

The presentation of cough and chest pain renders it less of an ‘occult’ malignancy than several other types.



DxT malaise + weight loss + cough → lung cancer

Kidney tumours

The most important tumours of the kidney are adenocarcinoma (80% of all kidney tumours)⁴ and nephroblastoma (Wilms tumour).

Kidney cell cancer

Kidney cell cancer (adenocarcinoma, hypernephroma) has a great diversity of presenting

symptoms, including:

- general symptoms of neoplasia, e.g. malaise, FUO
- haematuria (60%)
- loin pain (40%)
- loin mass (palpable kidney)
- signs of anaemia
- left supraclavicular lymphadenopathy (Virchow node)
- varicocele (left side)
- hypertension
- symptoms of metastases (to liver, lungs, brain, bones): respiratory symptoms, neurological symptoms and signs, bone pain, pathological fracture (vertebral collapse)
- urinalysis—67% positive for blood

Diagnosis is confirmed by imaging, e.g. CT/MRI.

Refer for radical nephrectomy.

The classic triad of symptoms, although in a small percentage of patients, is as follows.



DxT haematuria + loin pain + palpable kidney mass → kidney cell cancer

Wilms tumour (nephroblastoma)

Wilms tumour is responsible for 10% of all childhood malignancies. Clinical features include:⁴

- peak incidence 2–3 years
- general symptoms of neoplasia
- palpable mass 80%
- abdominal pain 30%
- haematuria 25%

Diagnosis is confirmed by urine cytology, ultrasound or CT/MRI scan.

Early diagnosis with nephrectomy and chemotherapy leads to a very favourable prognosis (90% 5-year survival).



DxT haematuria + abdominal mass + malaise → Wilms tumour

Neuroblastoma⁷

Probably the most common cancer in infancy (usually <2–3 years). 90% present under [Page 162](#) 5 years. It is a tumour of the adrenal medulla (50%) and sympathetic nervous system, especially retroperitoneal neural tissue in abdomen (30%) but also in chest and neck.

First symptoms often vague:

- fatigue, anorexia, nausea, fever
- abdominal pain, abdominal swelling
- anaemia and weight loss

May present with metastases, e.g. bone pain.

Diagnosis: CT scan, skeletal survey; biopsy required.

Treatment is based on surgical resection then chemotherapy ± localised radiotherapy. Good response to therapy especially if <18 months.

Ovarian cancer⁸

Ovarian cancer has the highest mortality rate of all the gynaecological cancers because the majority of patients present in the late stage of the disease. It is responsible for 5% of deaths in females. It is usually asymptomatic prior to the development of metastases. Epithelial tumours are the most common of malignant ovarian tumours. They are uncommon under 40 years of age and the average age of diagnosis is 50 years.

The most common presentation is abdominal swelling (mass and/or ascites), abdominal bloating or discomfort. Non-specific symptoms, which may be present for a long time before diagnosis, include abnormal uterine bleeding, urinary frequency, weight loss, abdominal discomfort, reduced capacity for food, diarrhoea, anorexia, nausea and vomiting (refer to [CHAPTER 95](#)).

Diagnosis is supported by pelvic ultrasound and serum CA-125 tumour marker. A new test is the OvPlex serum test, which measures five serum markers.



DxT abdominal discomfort + anorexia + abdominal bloating/distension → ovarian cancer

Carcinoma of caecum and ascending colon⁵

Malignancy in this area is more likely to present with symptoms of anaemia without the patient noting obvious blood in the faeces or alteration of bowel habit. Refer to [CHAPTER 31](#) .



DxT blood in stools + abdominal discomfort + change in bowel habit → colon cancer

Pancreatic cancer

This is another cancer with vague symptoms, metastasising early and late presentation. It is mainly ductal adenocarcinoma, which, if in the head of the pancreas, presents with painless jaundice and if in the body and/or tail presents with epigastric pain radiating to the back, relieved by sitting forward (refer to [CHAPTER 47](#)).



DxT jaundice + anorexia + abdominal discomfort/pain → pancreatic cancer

The leukaemias⁹

The leukaemias are caused by an acquired malignant transformation in the stem cell in the haemopoietic system. Acute leukaemia has a rapidly fatal course if untreated, while chronic leukaemia has a variable chronic course with an inevitable fatal outcome. See [FIGURE 17.1](#) . The main features of each type are as follows.

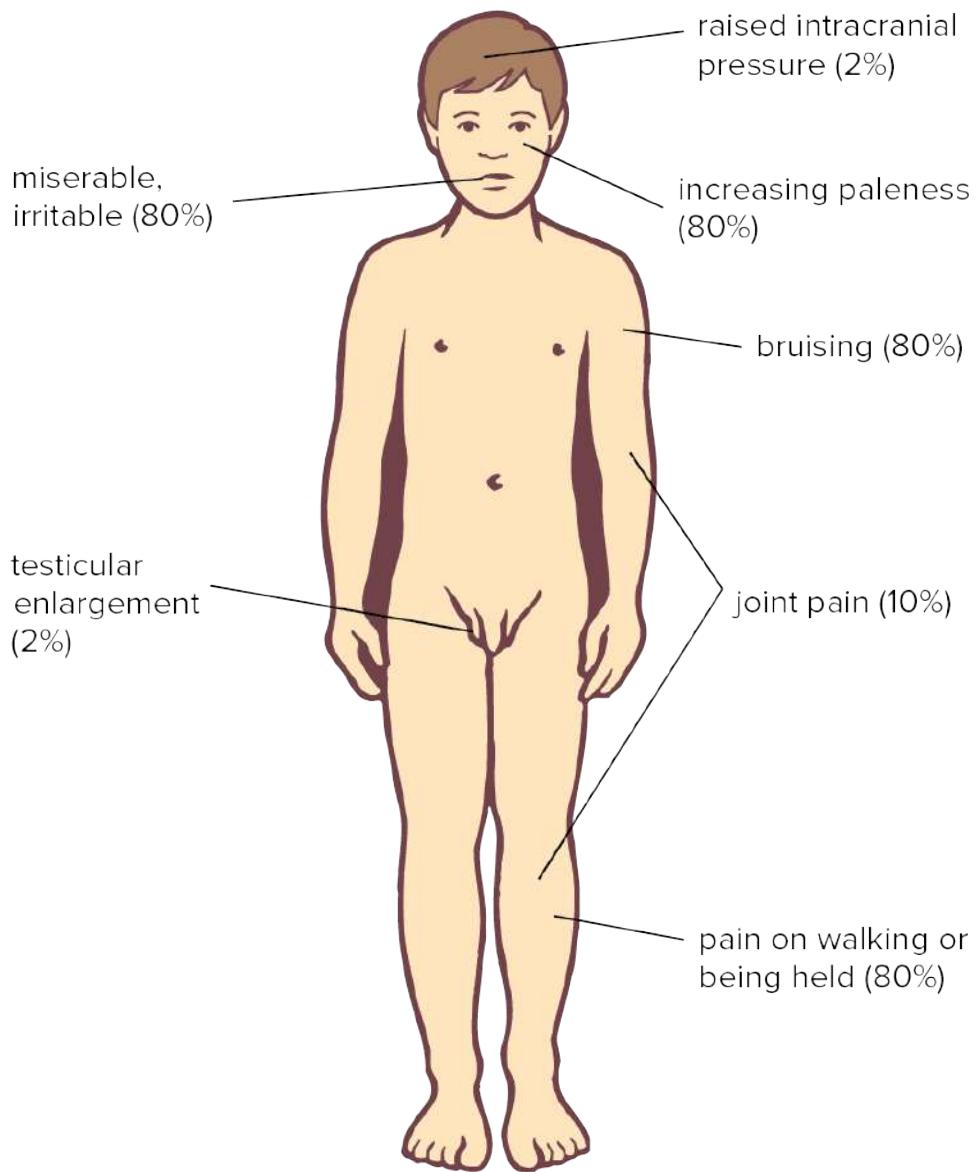


FIGURE 17.1 Clinical features of a child with leukaemia⁸

The usual age range for acute lymphatic leukaemia (ALL) is 2–10 years with a second peak at about 40 years. The median age of presentation of acute myeloid leukaemia (AML) is 55–60 years.

Acute leukaemia

Symptoms

- General constitutional (e.g. malaise)

- Symptoms of anaemia
- Susceptibility to infection (e.g. sore throat, mouth ulceration, chest infection)
- Easy bruising and bleeding (e.g. epistaxis, gingival bleeding)
- Bone pain (notably in children with ALL) and joint pain
- Symptoms due to infiltration of tissues with blast cells (e.g. gingival hypertrophy in AML)

 **DxT** malaise + pallor + bone pain → ALL

DxT malaise + pallor + oral problems → AML

Signs

- Pallor of anaemia
- Petechiae, bruising
- Gum hypertrophy/gingivitis/stomatitis
- Signs of infection
- Variable enlargement of liver, spleen and lymph nodes
- Bone tenderness, especially sternum

Diagnosis

- FBE and film: normochromic/normocytic anaemia; pancytopenia with circulatory blast cells; platelets: usually reduced
- Bone marrow examination
- PCR studies
- Cytogenetics

Treatment: chemotherapy, immunotherapy, stem cell therapy.

Note: As a rule, relapse of acute leukaemia means imminent death unless bone marrow transplantation is successful. The mean 5-year survival rate for childhood ALL is about 75–80%; for adult ALL 30%; for AML it varies with age with poorer survival, about 20%, over 55 years of age.

⌚ Chronic myeloid leukaemia (CML)

Clinical features

- A disorder of middle age, typically 40–60 years
- Insidious onset
- Constitutional symptoms: malaise, weight loss, fever, night sweats
- Symptoms of anaemia
- Splenomegaly (very large); abdominal discomfort
- Priapism
- Gout
- Markedly elevated white cell count (granulocytes)
- Marked left shift in myeloid series
- Presence of Philadelphia chromosome



DxT fatigue + fever/night sweats + abdominal fullness (splenomegaly) → CML

⌚ Chronic lymphocytic leukaemia (CLL)

Clinical features

- A disorder of late middle age and elderly
- Insidious onset
- Constitutional symptoms: malaise, weight loss, fever, night sweats
- Lymphadenopathy (large rubbery nodes)—neck, axilla, groin (80%)
- Moderately enlarged spleen and liver (about 50%)
- Mild anaemia
- Lymphocytosis $>15 \times 10^9/L$
- ‘Mature’ appearance of lymphocytes

- Consider cytogenetics

Note: Most cases, especially early indolent CLL, require no specific therapy but observation.



DxT fatigue + weight loss + fever/night sweats + lymphadenopathy → CLL

The lymphomas⁶

Lymphomas, which are malignant tumours of lymphoid tissue, are classified as Hodgkin lymphoma and non-Hodgkin lymphoma on the basis of histological appearance of the involved lymph tissue.

Hodgkin lymphoma

Clinical features

- Painless (rubbery) lymphadenopathy, especially cervical nodes
- Constitutional symptoms (e.g. malaise, weakness, weight loss)
- Fever and drenching night sweats—undulant (Pel–Ebstein) fever
- Pruritus
- Alcohol-induced pain in any enlarged lymph nodes
- Possible enlarged spleen and liver

Diagnosis is by lymph node biopsy with histological confirmation. Other tests: FBE, CXR, CT/MRI (to stage), bone marrow biopsy, functional isotopic scanning. Staging is by using Ann Arbor nomenclature (IA to IVB). Treatment includes chemotherapy, immunotherapy and radiotherapy.

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DxT malaise + fever/night sweats + pruritus → Hodgkin lymphoma

Non-Hodgkin lymphomas

Non-Hodgkin lymphomas are a heterogeneous group of cancers of lymphocytes derived from the malignant clones of B or T cells.

Clinical features

- Painless lymphadenopathy—localised or widespread
- Constitutional symptoms possible, especially sweating
- Pruritus is uncommon
- Extra nodal sites of disease (e.g. CNS, bone, skin, GIT)
- Possible enlarged liver and spleen
- Possible nodular infiltration of skin (e.g. mycosis fungoides)

Diagnosis is by lymph node biopsy.

CXR and CT abdomen to stage.



DxT malaise + fever/night sweats + lymphadenopathy → non-Hodgkin lymphoma

⌚ Multiple myeloma

Multiple myeloma is a clonal malignancy of the differentiated β lymphocyte—the plasma cell. It is regarded as a disease of the elderly, the mean age of presentation being 65 years.¹⁰ It is asymptomatic in 20% of patients. The classic presenting triad in an older person is anaemia, back pain and elevated ESR, which helps to differentiate it from monoclonal gammopathy of uncertain significance (MGUS).

Other investigations include serum protein electrophoresis and immunofixation, Sestamibi scan.

Clinical features

- Bone pain (e.g. backache)—in more than 80% of patients (possible pathological fracture)
- Bone tenderness, e.g. femur, ribs, spine
- Weakness, tiredness, increased thirst
- Anorexia and weight loss
- Recurrent infections, e.g. chest infection
- Symptoms of anaemia
- Bleeding tendency
- Replacement of bone marrow by malignant plasma cells

- Impaired renal failure → kidney failure
- Associated with amyloidosis and hypercalcaemia



DxT weakness + unexplained back pain + susceptibility to infection → multiple myeloma

Diagnosis

Diagnostic criteria comprise the presence of:⁷

- paraprotein in serum (on electrophoresis)
- Bence–Jones protein in urine
- bony lytic lesions on skeletal survey

Treatment is with chemotherapy including thalidomide or lenalidomide: 5-year survival rate is 50% or longer if diagnosed earlier. The younger patient may be given a stem cell transplant.¹¹

⌚ MGUS

Monoclonal gammopathy of undetermined significance (MGUS) involves the production of paraprotein (M protein) by non-cancerous cells in the absence of other clinical manifestations of multiple myeloma. It is associated with various disorders. MGUS is usually asymptomatic but peripheral neuropathy can occur. No chemotherapy treatment is recommended.

⌚ Waldenstrom macroglobulinaemia

This is a type of primary macroglobulinaemia due to a type of malignant plasma cell abnormality.¹² The bone marrow is infiltrated by plasmacytic lymphocytes. Patients usually present with fatigue related to anaemia. Diagnosis is by FBE, serum protein electrophoresis and bone marrow examination. Specialist treatment includes plasmapheresis, monoclonal antibodies and other cytotoxic agents. An indolent disease with a median survival rate of 5 years.¹²

⌚ Amyloidosis

This uncommon but difficult-to-diagnose disorder caused by the deposition of amyloid protein is classified as primary, familial or secondary (from chronic infection, e.g. TB, inflammation, RA, some cancers, others). It may be localised or generalised. Clinical features depend on the organ targeted such as the heart (CCF), kidney (nephrotic syndrome), GIT (malabsorption), brain (dementia) and peripheral nerves (e.g. CTS). Diagnosis is by tissue biopsy. Treatment, which varies with the type, is basically symptomatic and specialised. In primary amyloid it resembles the treatment for myeloma.

⌚ Carcinoid tumours and syndrome

Hormone secretion by carcinoid cells causes the characteristic carcinoid syndrome long before local growth or metastatic spread of the tumour is apparent (80% metastasise). Most carcinoid tumours are asymptomatic.

Clinical features

- Classic triad: skin flushing (especially face), diarrhoea (with abdominal cramps), valvular heart disease
- Other possible features: wheezing, telangiectasia, hypotension, cyanosis
- Sites of tumours: appendix/ileum, stomach, bronchi

Diagnosis

- 24-hour urine 5-hydroxyindoleacetic acid
- Plasma chromogranin A/hepatic ultrasound

Specialist treatment

- Surgery or other ablation: octreotide/others

⌚ Polycythaemia vera

This is a malignant proliferation of RBCs and also WBCs and platelets.

Clinical features

- Older person
- Fatigue
- Headache, dizziness, tinnitus
- Pruritus after hot bath, shower
- Epistaxis
- Facial plethora
- Splenomegaly
- Thrombosis

Investigations

- FBE and haematocrit
- Bone marrow biopsy
- Genetic mutations—JAK2 mutation

Potentially curable malignant tumours

Several tumours are curable by chemotherapy even in the advanced stage. Such tumours are as follows.

Haematological tumours

- Some lymphomas
- Hodgkin lymphoma
- Acute lymphatic leukaemia
- Acute myeloid leukaemia

Solid tumours

- Choriocarcinoma
- Testicular teratoma
- Neuroblastoma
- Wilms tumour (nephroblastoma)
- Burkitt tumour
- Embryonal rhabdomyosarcoma

Tumours curable by adjuvant chemotherapy

- Breast cancer (especially up to stage 2)
- Osteogenic cancer
- Soft tissue cancer
- Colorectal cancer

Survival rates

Common cancers and their 5-year survival rates have been published by the Cancer Council Victoria (see TABLE 17.5). These show improving trends for many cancers. The lowest survival rate was for mesothelioma at 4%. Updated statistics reveal that the overall 5-year survival has changed from 68% in 2009–2013 to 69% for males and 71% for females in 2017–2018.¹³

Table 17.5 Common cancers and their 5-year survival rates (a collation of surveys)¹⁴

Cancer	%
Testicular	98
Prostate	95
Thyroid	92
Melanoma	91
Breast (female)	91
Hodgkin lymphoma	87
Uterus	84
Bladder	77
Non-Hodgkin lymphoma	72
Colon	72
Ovary	41
Stomach	33
Liver	20
Lung	19
Pancreas	1

Metastatic tumours

It is very helpful for the practitioner to have a working knowledge of possible primary sources of tumour when metastatic lesions are detected in various organs. Page 166

Common sites of metastatic presentation are the lymph nodes, liver, lung, mediastinum and

bone. Other sites include the brain, bone marrow, peritoneum, retroperitoneum, skin and the spinal cord.

These important sites (listed below) are followed by likely primary sources, with the most likely listed first.

- *Bone*. Breast, prostate, lung, Hodgkin lymphoma, kidney, thyroid, melanoma
- *Brain*. Breast, lung, colorectal, lymphoma, kidney, melanoma, prostate
- *Liver*. Colon, pancreas, liver, stomach, breast, lung, melanoma
- *Lung and mediastinum*. Breast, lung, colorectal, kidney, testes, cervix/uterus, Hodgkin lymphoma, melanoma
- *Lymph nodes*:

High cervical. Hodgkin lymphoma, lymphoma, squamous cell carcinoma, oropharynx, nasopharynx

Low cervical. Lung, stomach, lymphoma, Hodgkin lymphoma, oropharynx, larynx, skin, tongue

Axillary. Breast, lung, lymphoma

Inguinal. Lymphoma, ovary, uterus, vulva, prostate, skin

- *Retroperitoneum*. Lymphoma, Hodgkin lymphoma, ovary, uterus, testes, prostate
- *Skin*. Lung, colorectal, melanoma, Kaposi sarcoma

It is important to keep in mind those malignancies that are potentially curable and to refer as soon as possible.

Cancer with an unknown primary

Cancer without a clear primary source is present in about 5% of all cases. Some patients may have no symptoms except undifferentiated general ones, such as fatigue and weight loss, and anorexia may be present. Other symptoms include bone pain, dyspnoea and lymphadenopathy. If the diagnosis cannot be made on the history, physical examination and baseline tests, then the key to excluding treatable primaries is adequate immunohistological staining on a tissue biopsy. It is worth referring for investigation as these could be treatable primaries. Adenocarcinoma is common in 40% resulting from lung, colorectal and pancreatic cancer. Poorly differentiated neoplasms include lymphoma, melanoma and sarcoma. The mean survival time in patients with an unknown primary is 6 months.¹⁵

Prevention

Preventive measures for malignant disease are addressed in more detail in [CHAPTER 6](#). The significant decrease in deaths from cancer of the stomach in this country in recent years is probably reflected in our improved diet with more fresh fruit and vegetables. Important preventive measures include an appropriate healthy diet, no smoking, sun protection, HPV vaccination and perhaps safe sex measures. Of concern is the rapid increase in the incidence of prostate cancer, chronic myeloid leukaemia, myeloma and non-Hodgkin lymphoma, and adenocarcinoma of the oesophagus.

Triads to consider

DxT anorexia + weight loss + jaundice (\pm epigastric pain) → pancreatic cancer

DxT fatigue + dysphagia + weight loss → oesophageal cancer

DxT anorexia + dyspepsia + weight loss → stomach cancer



DxT headache + a/n/v + ataxia → medulloblastoma (children)

DxT fever + malaise (extreme) + a/n/v (\pm anaemia) → neuroblastoma

DxT mental dysfunction + vomiting + (waking) headache → cerebral tumour (late)

DxT indrawn eye + small pupil + ptosis (\pm anhydrosis) → Horner syndrome (?lung cancer)

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Bladder cancer
- Bowel cancer
- Breast cancer/lumps
- Cancer
- Leukaemia
- Lung cancer
- Lymphoma

- Melanoma
- Prostate (various)
- Testicle (various)
- Skin (various)

Resources

Optimal cancer care pathways (prevention, early detection, screening recommendations):
jon.emery@unimelb.edu.au

Royal Australian College of General Practitioners. Early detection of cancers. In: *Guidelines for Preventive Activities in General Practice* (9th edn). Melbourne: RACGP, 2016.

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18 Baffling viral and protozoal infections

It is certainly a one-sided opinion—even though generally adopted at the moment—that all infectious agents which are still unknown must be bacteria. Why should not other microorganisms just as well be able to exist as parasites in the body of animals?

ROBERT KOCH (1843–1910), *ZUR UNTERSUCHUNG VON PATHOGENEN ORGANISMEN* (1881)

Almost any infection, especially if subacute or insidious in its onset, can be baffling and can belong to the ‘fever of undetermined origin’ group of infections. Syphilis and tuberculosis were the great mimics of the past. Now malaria and Epstein–Barr mononucleosis (EBM) can be regarded as important mimics. EBM (Epstein–Barr mononucleosis, infectious mononucleosis, glandular fever) can be a perennial baffle and can be confused with HIV infection in its primary clinical phase. In the past decade we have encountered the emergence of coronaviruses that cause deadly acute respiratory distress syndromes ranging from endemics to pandemics. Any of the febrile diseases can be confusing before declaring themselves with classic symptoms such as the jaundice of hepatitis or the rash of dengue fever, or before serological tests become positive.

Viral and protozoal infections that can present as masquerades include:

- HIV infection (especially primary)
- EBV
- TORCH organisms: toxoplasmosis, rubella, CMV, HSV
- hepatitis A, B, C, D, E
- mosquito-borne infections: malaria, dengue fever, yellow fever/other haemorrhagic fevers, Japanese encephalitis, Ross River fever, West Nile fever
- coronaviruses

The TORCH organisms (TORCH being an acronym for toxoplasmosis, rubella, CMV and herpes) are well known for their adverse intra-uterine effects on the fetus. Three are viral (toxoplasmosis is a protozoan) and the first three of these fetal pathogens are acquired by passage across the placenta. Most of these organisms are noted for being opportunistic infections in immunocompromised patients, especially in later stage HIV infection.

The mosquito-borne infections causing encephalitis and haemorrhagic fevers are mainly viral, apart from the protozoan causing malaria, and are of particular significance in travellers returning from endemic areas (refer to [CHAPTER 129](#)).

The major protozoal diseases of humans are:

- blood: malaria, trypanosomiasis
- GIT: giardiasis, amoebiasis, cryptosporidium
- tissues: toxoplasmosis, leishmaniasis, babesiosis

Most of the world's serious protozoal infections—malaria, African trypanosomiasis, leishmaniasis, amoebiasis—occur in tropical areas and are listed and explained in [CHAPTER 129](#) .

Four similar clinical presentations

Four infections—EBV, primary HIV, CMV and toxoplasmosis—produce almost identical clinical presentations and tend to be diagnosed as glandular fever or pseudoglandular fever. It is important for the first contact practitioner to consider all four possibilities, especially keeping in mind the possibility of HIV infection.

Epstein–Barr mononucleosis

EBM is a febrile illness caused by the human herpes virus 4 (Epstein–Barr) virus, one of the eight known herpes viruses. It is often called ‘the great imitator’ because of its multisystem involvement. It can mimic diseases such as HIV primary infection, streptococcal tonsillitis, viral hepatitis and acute lymphatic leukaemia. There are three forms: the febrile, the anginose (with sore throat, see [FIG. 18.1](#)) and the glandular (with lymphadenopathy).



FIGURE 18.1 Tonsillitis of Epstein–Barr mononucleosis. This is often confused with bacterial tonsillitis.

It may occur at any age but usually between 10 and 35 years; it is commonest in the 15–25 years age group. In most young children primary EBV infection is asymptomatic.

Occurrence and transmission

EBM has an annual incidence of 4–5 new cases in a population of 2500.¹ It usually affects people in their late teenage years or early 20s. It is endemic in most countries, affecting over 95% of the adult population worldwide. Subclinical infection is common in young children. The incubation period is at least 1 month but data are insufficient to define it accurately.

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EBV is excreted in oropharyngeal secretions during the illness and for some months (sometimes years) after the clinical infection. EBM has a low infectivity and isolation is not necessary. It is apparently transmitted only by close contact, such as kissing and sharing drinking vessels.

Progress of the primary infection is checked partly by specific antibodies (which might prevent cell-to-cell spread of the virus) and partly by a cellular immune response, involving cytotoxic T cells, which eliminates the infected cells. This response accounts for the clinical picture. The virus is never eliminated from the body. The nature of EBV is not yet fully understood.

Second attacks and fatalities do occur and there is a possible association between EBM and lymphoma.²

Clinical features

The typical clinical features are presented in TABLE 18.1 and FIGURE 18.2.

Typical symptoms

- fever
- headache
- malaise
- nausea/vomiting
- nasal blockage
- sore throat
- myalgia

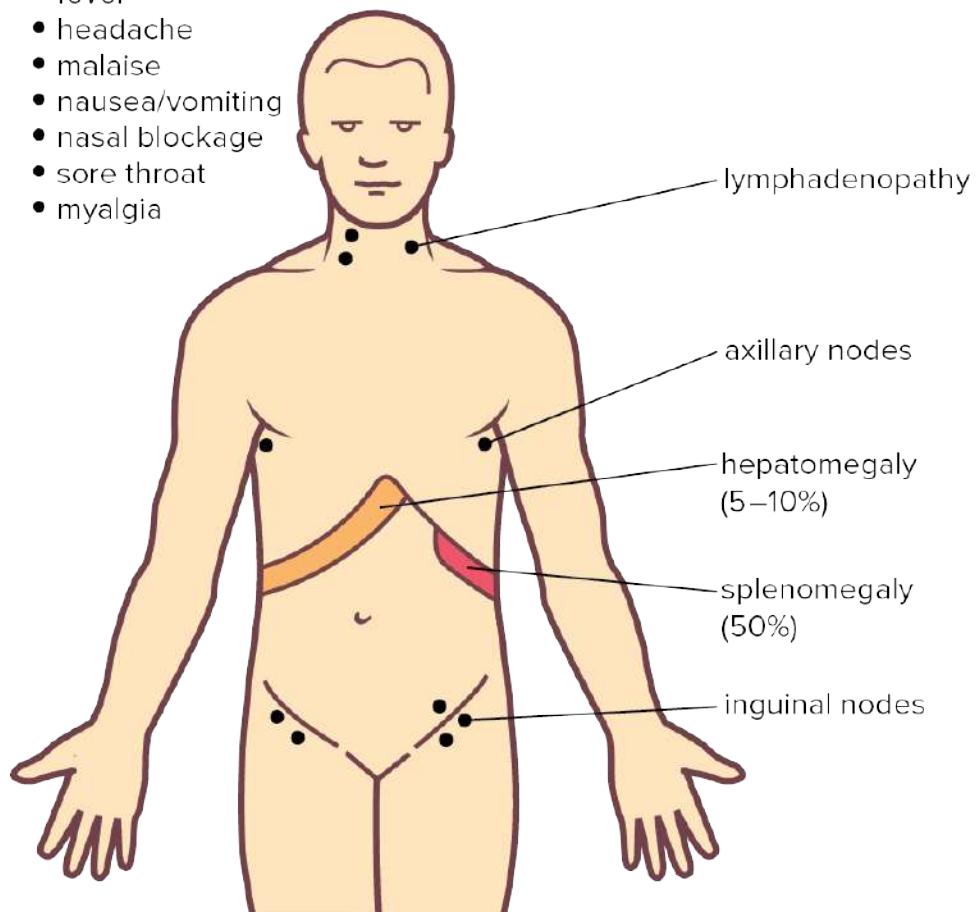


FIGURE 18.2 Clinical features of Epstein–Barr mononucleosis

Table 18.1 Clinical features of EBM^{1,3,4}

Symptoms

Slow-onset malaise 1–6 weeks

Fever

Myalgia

Headaches, anorexia

Blocked nose—mouth breathing

Nasal quality to voice

Sore throat (85%)

Anorexia, nausea ± vomiting

Rash—primary 5%

Dyspepsia

Clinical findings

Exudative pharyngitis (84%)

Petechiae of palate (not pathognomonic) (11%)

Lymphadenopathy, especially posterior cervical

Rash—maculopapular

Splenomegaly (50%)

Jaundice ± hepatomegaly (5–10%)

Clinical or biochemical evidence of hepatitis



DxT malaise + sore throat + fever + lymphadenopathy → EBM

The rash

The rash of EBM is almost always related to antibiotics given for tonsillitis. The primary rash, most often non-specific, pinkish and maculopapular (similar to that of rubella), occurs in about 5% of cases only.

The secondary rash is most often precipitated by one of the penicillins, especially ampicillin or amoxicillin. About 90–100% of patients prescribed ampicillin or amoxicillin will be affected; up to 50% of those given penicillin will develop the rash. It can be extensive and sometimes has a purplish tinge (see FIG. 18.3).

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FIGURE 18.3 Typical purplish maculopapular rash of EBM precipitated by ampicillin prescribed for the acute tonsillitis of EBM

Diagnosis

The following laboratory tests confirm the diagnosis of EBM:

- WCC shows absolute lymphocytosis.
- Blood film shows atypical lymphocytes.
- Paul–Bunnell or Monospot test for heterophile antibody is positive (although positivity can be delayed or absent in 10% of cases; 85% positive in adults and older children).
- Diagnosis confirmed (if necessary) by EBV-specific antibodies, viral capsid antigen (VCA) antibodies—IgM, IgG and EB nuclear antigen (EBN-A).
- Consider throat culture to rule out streptococcal pharyngitis.

Culture for EBV and tests for specific viral antibodies are not performed routinely.

False positives for the Paul–Bunnell test include:

- hepatitis
- Hodgkin lymphoma
- acute leukaemia

Prognosis

EBM usually runs an uncomplicated course over 6–8 weeks. Major symptoms subside within 2–3 weeks. Patients should be advised to take about 4 weeks off work.

Treatment

- Supportive measures (no specific treatment)
- Rest (the best treatment) during the acute stage, preferably at home and indoors
- NSAIDs or paracetamol to relieve discomfort
- Gargle soluble aspirin or 30% glucose or saline to soothe the throat
- Advise against alcohol, fatty foods, continued activity, especially contact sports, for 8 weeks (risk of splenic rupture)
- Ensure adequate hydration
- Corticosteroids reserved for: neurological involvement, thrombocytopenia, threatened airway obstruction (not recommended for uncomplicated cases)

Post-EBM malaise

Some young adults remain debilitated and depressed for some months. Lassitude and malaise

may extend up to a year or so.

⌚ Cytomegalovirus infection

CMV has a worldwide distribution and causes infections that are generally asymptomatic. The virus (human herpes virus 5) may be cultured from various sites of healthy individuals. It has its most severe effects in the immunocompromised, especially those with AIDS, and also in recipients of solid organ transplants and bone marrow grafts; 90% of AIDS patients are infected with CMV and 95% have disseminated CMV at autopsy. CMV infection can be an important development following massive blood transfusion, including those given to infants or from organ transplantation. The incubation period of CMV ranges from 20 to 60 days and the illness generally lasts about 2 to 6 weeks.³

Clinical features

Three important clinical manifestations are described.

1. Perinatal disease

Intra-uterine infection may cause serious abnormalities in the fetus, including CNS involvement (microcephaly, hearing defects, motor disturbances), jaundice, hepatosplenomegaly, haemolytic anaemia and thrombocytopenia. Up to 30% of CMV-affected infants have mental retardation.²

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2. Acquired CMV infection

In healthy adults, CMV produces an illness similar to EBM with fever, malaise, arthralgia and myalgia, generalised lymphadenopathy and hepatomegaly. However, cervical lymphadenopathy and exudative pharyngitis are rare.

The infection may be spread by blood transfusion, and CMV should be suspected on clinical grounds in a patient with a febrile illness resembling EBM following major surgery, such as open heart surgery or kidney transplantation, and where extensive transfusion has been necessary.

The fever often manifests as quotidian intermittent fever spiking to a maximum in the mid-afternoon and falling to normal each day (see CHAPTER 42). There is often a relative lymphocytosis with atypical lymphocytes but the heterophile antibody test is negative. Liver function tests are often abnormal.

Diagnosis: Specific diagnosis can be made by demonstrating rising antibody titres from acute and convalescent (2 weeks) sera. A four-fold increase indicates recent infection. PCR testing can be used. The virus can be isolated from the urine and blood.

3. CMV disease in the immunocompromised host

Disseminated CMV infection occurs in the immune-deficient person, notably HIV infection causing opportunistic severe pneumonia, retinitis (a feature of AIDS), encephalitis and diffuse involvement of the gastrointestinal tract.

Treatment

In the patient with normal immunity no treatment apart from supportive measures is required, as the infection is usually self-limiting. In immunosuppressed patients various antiviral drugs, such as ganciclovir, foscarnet and fomivirsen (intra-ocular) have been used with some benefit.⁵

Toxoplasmosis

Toxoplasmosis, which is caused by *Toxoplasma gondii*, an obligate intracellular protozoan, is a worldwide, albeit rare, infection. The definitive host in its life cycle is the cat (or pig or sheep) and the human is an intermediate host. However, clinical toxoplasmosis is very uncommon. Infection in humans usually occurs through eating foodstuffs contaminated by infected cat faeces. Its main clinical importance is an opportunistic infection.

The five major clinical forms of toxoplasmosis are:⁵

1. asymptomatic lymphadenopathy (the commonest)
2. lymphadenopathy with a febrile illness, similar to EBM
3. acute primary infection: a febrile illness similar to acute leukaemia or EBM; a rash, myocarditis, pneumonitis, chorioretinitis and hepatosplenomegaly can occur
4. neurological abnormalities—includes headache and neck stiffness, sore throat and myalgia
5. congenital toxoplasmosis—this is a rare problem but if it occurs it typically causes CNS involvement and has a poor prognosis

In the immunocompromised, clinical forms 3 and 4 are typical features with meningoencephalitis being a serious development.

Diagnosis

Diagnosis is by serological tests (to show a four-fold rise in antibodies), which are sensitive and reliable.

Treatment

Patients with a mild illness or with asymptomatic infection require no treatment. Children under 5 years may be treated to avoid the possible occurrence of chorioretinitis. Symptomatic patients are treated with pyrimethamine plus sulfadiazine. Clindamycin is usually used in pregnant patients.

HIV/AIDS

HIV: a modern masquerade

Human immunodeficiency virus (HIV), the cause of the well-known AIDS, can rightly be

included as one of the clinical masquerades of modern medicine. Public health measures in the Western world have limited the spread of the infection. By contrast, the incidence in Africa and Asia continues to rise at an alarming rate. According to the World Health Organization, at the end of 2019,⁶ 38 million adults and children were living with HIV worldwide, with 1.7 million newly infected, while 690 000 people died from HIV-related causes.

In 2012, the average age of people newly diagnosed with HIV infection was 37 years Page 172 and about 86% were male; most infections are in men who have sex with men (MSM). The conversion rate of HIV to AIDS has been 33% but it is improving with antiretroviral therapy (ART), which has dramatically changed people's lives. HIV is now a chronic disease management problem. The introduction of combination treatment with the protease inhibitors in November 1995 changed the previously understood natural history of the disease. Interestingly, there has been two reported cases of cure with stem-cell treatment.⁷

The benefit of early diagnosis has become even more impressive since the discovery that HIV is not a latent infection throughout most of its course. Soon after initial infection, an explosive replication of HIV occurs, which is brought under control by the immune system in 6 to 8 weeks as the host-versus-virus interaction reaches an active and dynamic equilibrium. This dynamic situation continues throughout a person's lifetime, with as many as 10 billion new viroids produced and up to 2 billion CD₄ T lymphocytes destroyed and replaced daily. Clinical immunodeficiency develops when the body's ability to replace CD₄ cells is finally exhausted, resulting in further uncontrolled viral replication. Viral load assays based on molecular techniques have revolutionised our understanding of the natural history of HIV disease. These advances make it imperative to make the diagnosis early in the course of the disease in order to start combination treatment to lessen the viral load.

The management of HIV infection is a specialised field but the GP is central in prevention, diagnosis, counselling, monitoring and shared management of HIV disease.

Key facts and checkpoints

- HIV is a retrovirus with two known strains that cause a similar spectrum of syndromes: HIV-1 and HIV-2 (mainly confined to West Africa). It infects T-helper cells bearing the CD₄ receptor.
- Always consider HIV in those at risk: enquire about history of STIs, injection of illicit drugs, past blood transfusions, sexual activities and partners.
- About 50% of patients develop an acute infective illness similar to glandular fever within weeks of acquiring the virus (the HIV seroconversion illness).⁸ The main features are fever, lymphadenopathy, lethargy and possibly sore throat, and a generalised rash.
- If these patients have a negative infectious mononucleosis test, perform an HIV antibody test, which may have to be repeated in 4 weeks or so if negative.

- Patients invariably recover to enter a long period of good health for 5 years or more.⁹
- The so-called ‘set point’ is where the plasma viral load drops to a steady level for many years.
- *Pneumocystis jiroveci* (ex *carinii*) pneumonia (PJP) is the commonest presentation of AIDS.
- Approximately 15–40% of HIV-positive children are infected from HIV-infected mothers.¹⁰
- Infants born to these mothers may develop the disease within a few months, with 30% affected by the age of 18 months.
- The time for the onset of AIDS in HIV-affected adults varies from 2 months to 20 years or longer; the median time is around 10 years.
- In family practice the most common presentation of HIV-related illness is seen in the skin/oral mucosa, for example, candidiasis and herpes.¹¹
- TB is a common, serious but treatable complication of HIV.
- HIV antibody testing is a two-stage process: the antigen–antibody test for screening followed by another method (e.g. Western blot) if positive.
- New rapid HIV tests or point of care HIV tests will overcome barriers, including delays to diagnosis.
- The seroconversion period from acquiring HIV infection to a positive antibody test varies between individuals: this period is known as the ‘window period’.
- All HIV-infected patients require regular monitoring for immune function and viral load. The viral load test monitors viral activity.
- The level of immune depletion is best measured by the CD₄ positive T lymphocyte (T helper cell) count—the CD₄ cell count. The cut-off points for good health (asymptomatic) and severe disease appear to be 500 cells/ μ L and 200 cells/ μ L respectively.⁹
- Most patients with AIDS will need lifelong⁸ daily medication with a combination of antiretroviral drugs.
- Current management focuses on treating HIV as a chronic disease.
- A leading concerning cause of death is cardiovascular disease.

Practice tip

Definition of AIDS: HIV +ve plus one or more of the clinical diseases that are a feature of AIDS, e.g. PJP, KS or CD₄ <200.

Occurrence and transmission

HIV can be isolated from blood, tissues, semen, saliva, breast milk, cervical and vaginal secretions and tears of infected persons. HIV is transmitted in semen, blood and vaginal fluids, transplanted organs and breast milk through:

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- unprotected sexual intercourse (anal or vaginal) and in rare cases oral sex with an infected person
- infected blood entering the body (through blood transfusion or by IV drug users sharing needles/syringes)
- needle-stick injury
- artificial insemination, organ transplantation
- infected mothers (to babies during pregnancy, at birth or in breast milk)

Infection with HIV can occur via the vagina, rectum or open cuts and sores, including any on the lips or in the mouth. Social (non-sexual) contact and insect vectors have not been implicated in transmission.

Stages

The clinical stages of HIV disease are summarised in TABLE 18.2 .¹²

Table 18.2 Clinical stages of HIV disease^{12,13}

Clinical stage	Common clinical features	CD ₄ count
Seroconversion illness (self-limited 1–3 weeks)	Fever, headache (may have aseptic meningitis), sore throat, maculopapular rash, lymphadenopathy, splenomegaly Atypical lymphocytes on FBE cells	Transient decrease, commonly followed by a return to near-normal levels

Asymptomatic	Headaches Persistent generalised lymphadenopathy	Usually >500 cells/ µL Gradual decrease of 50–80 cells/µL
Symptomatic—early	Oral and vaginal candidiasis, oral hairy leukoplakia, seborrhoeic dermatitis, psoriasis, recurrent varicella zoster infection, cervical dysplasia, unexplained fever, sweats, weight loss, diarrhoea, tuberculosis	Usually 150–500 cells/µL
Symptomatic—late	PJP, Kaposi sarcoma (KS), oesophageal candidiasis, cerebral toxoplasmosis, lymphoma, HIV-1 associated dementia complex, cryptococcal meningitis	Usually <150 cells/ µL
Advanced	CMV retinitis, cerebral lymphoma, <i>Mycobacterium avium</i> complex (MAC) infection	Usually <50 cells/µL

Source: Reproduced with permission from McCoy R., Alarm bells. When to worry about your patient with HIV. Aust Fam Physician, 1997; 26: 803–9

Acute (seroconversion) illness

At least 50% of patients have an acute illness associated with seroconversion. The illness usually occurs within 6 weeks of infection and is characterised by fever, night sweats, malaise, severe lethargy, anorexia, nausea, myalgia, arthralgia, headache, photophobia, sore throat, diarrhoea, lymphadenopathy, generalised maculoerythematous rash and thrombocytopenia. The main symptoms are headache, photophobia and malaise/fatigue. Neurological manifestations, including meningoencephalitis and peripheral neuritis, can occur. Acute HIV infection should be considered in the differential diagnosis of illnesses resembling glandular fever. This illness, which resembles infectious mononucleosis, is self-limiting and usually resolves within 1 to 3 weeks. However, chronic lethargy, depression and irritability may persist after the acute illness. Non-specific viraemic sequelae such as mucosal ulceration, desquamation, exacerbation of seborrhoea and recurrences of herpes simplex may occur (see FIG. 18.4).

Acute illness may be accompanied by neutropenia, lymphopenia, thrombocytopenia, and mildly elevated ESR and serum transaminases. During recovery lymphocytosis may occur with appearance of atypical mononuclear cells and an inversion of the $CD_4^+ : CD_8^+$ ratio due to elevation of CD_8^+ cells. It is seronegative for EBV.

Differential diagnoses are given in TABLE 18.3 .

Table 18.3 Differential diagnoses of primary HIV infection

Epstein–Barr mononucleosis

Syphilis: secondary

TORCH organisms:

- toxoplasmosis
- rubella
- CMV (especially)
- herpes simplex

Disseminated gonococcal infection

Hepatitis A, B, C, D or E

Influenza

Other virus infections



DxT fever + severe malaise + lymphadenopathy → acute HIV

Subsequent stage

After the acute illness, HIV disease passes into an asymptomatic stage of variable length, up to several years, but 30% have persistent generalised lymphadenopathy.

Later constitutional symptoms develop along with minor opportunistic infections such as oral candidiasis, herpes simplex and herpes zoster. This early symptomatic stage is referred to as AIDS-related complex and is regarded as a prodromal to AIDS.

AIDS-defining conditions

The original US Centers for Disease Control (CDC) classification has been modified with time to provide a more simplified scheme for defining AIDS. The HIV/AIDS case surveillance system simply specifies a list of clinical conditions associated with the late stages of HIV infection as being ‘AIDS-defining’.¹³

The AIDS-defining conditions are:

- candidiasis of bronchi, trachea or lungs

- candidiasis, oesophageal
- cervical cancer, invasive
- coccidioidomycosis, disseminated or extrapulmonary
- cryptococcosis, extrapulmonary
- cryptosporidiosis, chronic intestinal (>1 month's duration)
- cytomegalovirus (CMV) disease (other than liver, spleen or nodes)
- CMV retinitis (with loss of vision)
- encephalopathy, HIV-related
- herpes simplex virus (HSV): chronic ulcer(s) (>1 month's duration); or bronchitis, pneumonitis or oesophagitis
- histoplasmosis, disseminated or extrapulmonary
- isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- lymphoma, Burkitt (or equivalent term)
- lymphoma, immunoblastic (or equivalent term)
- lymphoma, primary, of brain
- *Mycobacterium avium* complex of *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* pneumonia (PJP)
- *Salmonella* septicaemia, recurrent
- toxoplasmosis of brain
- wasting syndrome due to HIV

The Australian AIDS surveillance case definition does not refer to the CD₄ cell count, although in the US AIDS is also defined by a CD₄ cell count of <200/ μ L, regardless of clinical condition. At levels below this, people will become increasingly vulnerable to AIDS-defining conditions.

Clinical features

There is a multiplicity of clinical findings in HIV infection (see FIG. 18.4).

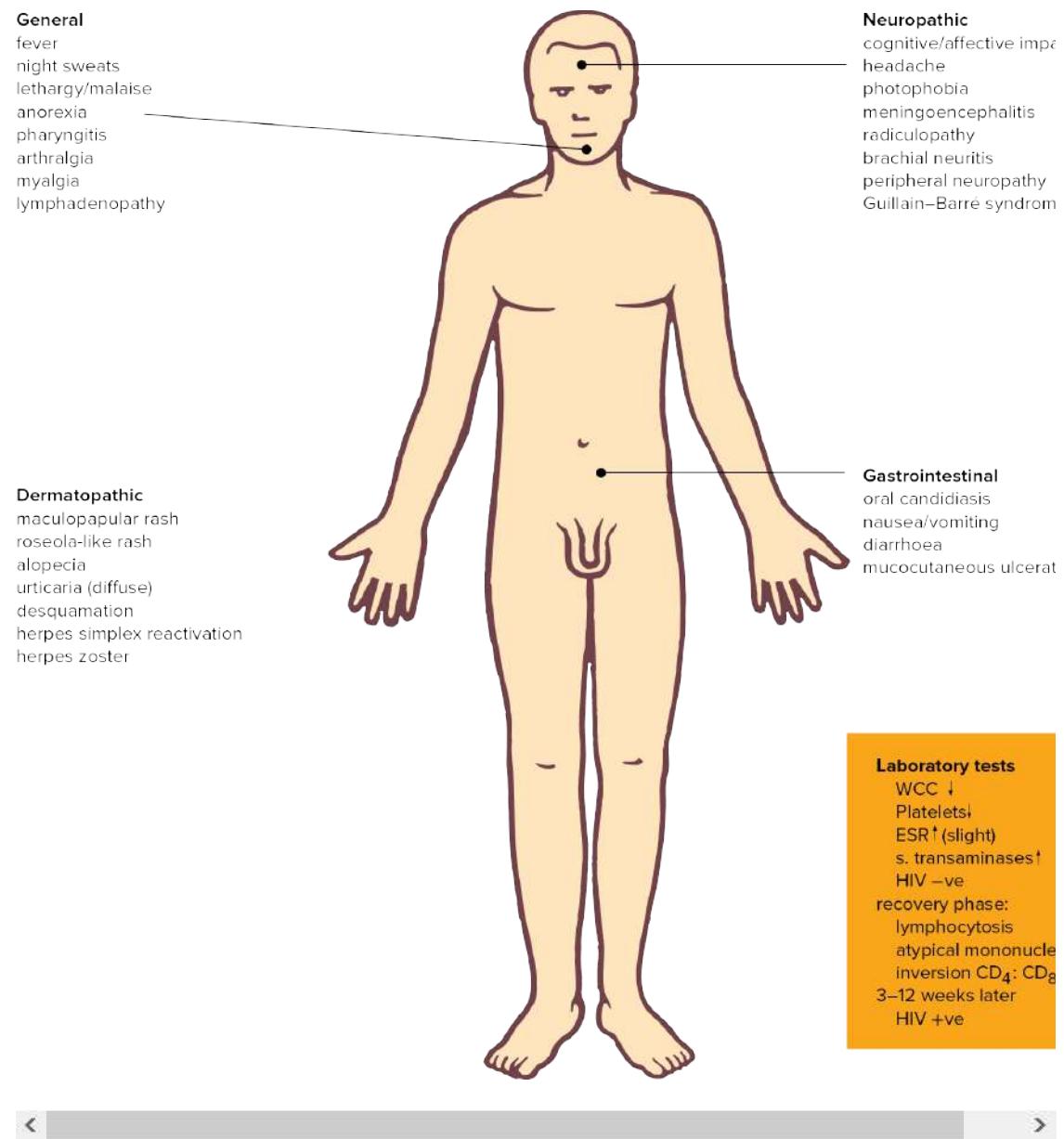


FIGURE 18.4 Possible clinical features of primary HIV infection

Clinical features of progression—chronic fever, cough <1 month, chronic diarrhoea, oral thrush, weight loss.

Fever

- Usually this is of unknown origin

Weight loss

- Usually severe and muscle wasting

Respiratory

- Sinusitis
- Non-productive cough, increasing dyspnoea and fever: due to opportunistic pneumonias

More than 50% of patients present with PJP which may have an abrupt or insidious onset.⁶ With the insidious type of onset, examination and chest X-ray are often normal early. Many other agents (e.g. CMV, cryptococcosis and TB) can be responsible. Exclusion of PJP is important as this condition carries a high mortality if untreated.¹²

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Practice tip

Severe PJP can have little or no chest signs, and, unless treated, patients can rapidly deteriorate and die.

Gastrointestinal

- Chronic diarrhoea (many causes) with weight loss or dehydration

Neurological

- Headache
- Progressive dementia (HIV encephalopathy)
- Ataxia due to myelopathy
- Seizures
- Mononeuritis
- Guillain–Barré type mononeuropathy
- Toxoplasma encephalitis
- Cryptococcal meningitis
- Peripheral neuropathy
- Progressive visual loss (CMV retinitis)
- CNS lymphoma

Oral cavity

- Aphthous ulcers
- Angular cheilitis
- Periodontal/gingival disease
- Tonsillitis
- Oral candidiasis
- Oral hairy cell leukoplakia (frequently mistaken for candidiasis but affects lateral border of tongue)

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Genitourinary

- Cervical dysplasia
- Vaginal candidiasis
- Various STIs (e.g. HSV, HPV)

Skin

- Impetigo
- Warts
- HSV
- Shingles, especially multidermatomal
- Seborrhoeic dermatitis
- Cutaneous mycoses
- Kaposi sarcoma (painless red-purple lesions on any part of the body including palms, soles, oral cavity and other parts of the GIT) (see FIG. 18.5).



FIGURE 18.5 Kaposi sarcoma of the skin on the face of a man with AIDS

Photo courtesy Hugh Newton-John

Psychological

FIGURE 18.6 presents the chronology of HIV-induced disease correlated with time since infection and CD₄ cell levels.

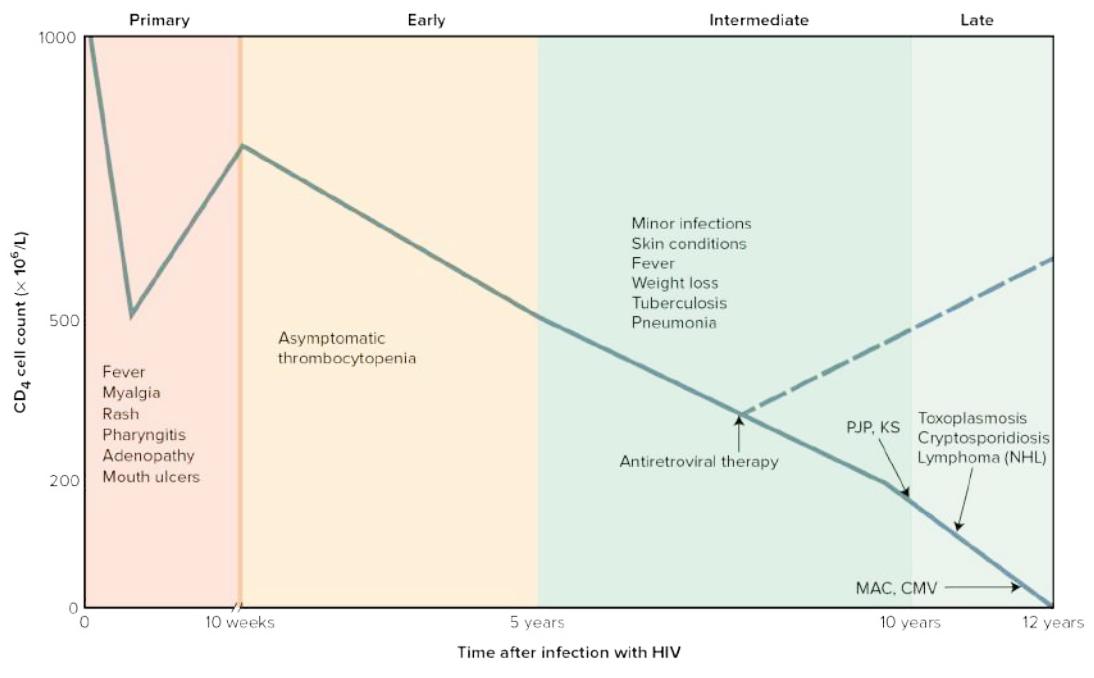


FIGURE 18.6 Chronology of HIV-induced disease correlated with time since infection

Abbreviations: CMV = cytomegalovirus; HIV = human immunodeficiency virus; KS = Kaposi sarcoma; MAC = *Mycobacterium avium*

complex; NHL = non-Hodgkin lymphoma; PJP = *Pneumocystis jiroveci* pneumonia.

Source: David Baker et. al. HIV infection as a chronic disease. MedicineToday, 2014; 15 (2): 18. Courtesy of ASHM. Reproduced with permission from the Australasian Society for HIV Medicine (ASHM).

Investigations and diagnosis¹²

The laboratory investigation of AIDS covers three broad areas:

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1. Tests for HIV infection:

- antigen–antibody test (ELISA screen) or HIV rapid test (at point of care). If positive—Western blot technique (used for confirmation)

2. Tests of immune function:

- CD₄ lymphocyte counts—the strongest predictor of possible clinical manifestations of HIV infection
- low CD₄ cells (counts <500 cells/µL) = defective cell immunity^{9,11}
- counts <200 cells/µL = severe immunodeficiency

3. Plasma HIV RNA (viral load): a measure of the serum level of RNA of the HIV virus—correlates with response to treatment and progression to AIDS and death

4. Genotype resistance (HLA B5701 if treatment with abacavir planned)

5. Tests for opportunistic infections and other problems, e.g. other STIs, EBV, CMV, hepatitis, Mantoux test

6. Routine general health tests, e.g. FBE, U&E, blood glucose, lipids, eGFR, LFTs

Management

Patients with HIV infection who invariably have to cope with profound psychological stress require considerable psychosocial support, counselling and regular assessment from a non-judgmental, caring practitioner. Best practice is referral to a specialist clinic for shared care.

The holistic approach

Most people with HIV infection will take ‘natural therapies’. This should be viewed as being complementary to the management suggested by the GP, and the patient should be encouraged to tell his or her doctors of the alternative medicines being taken. Anecdotal reports suggest that 75% of people with HIV regularly use ‘natural therapies’,¹⁴ and in the setting of the long-term nature of the condition it is important for doctors to be supportive and create a climate of acceptance around these health practices.

Positive lifestyle factors include:

- a very healthy balanced diet: high fruit and vegetable intake, pure fruit juices, high fibre, low fat, high complex carbohydrates
- toxic avoidance: processed foods, caffeine, illicit drugs, alcohol, cigarettes
- relaxation and meditation (reduction and self-monitoring of stress levels)
- appropriate sleep and exercise
- consider supplementary antioxidants
- support groups and continuing counselling

Treatment (medication)^{15,16}

Optimal antiretroviral therapy (ART), which has dramatically changed the outlook, now depends on the use of combinations of drugs. Monotherapy is no longer accepted practice. The recommendations for the use of antiretroviral therapy are constantly changing. Updated guidelines can be found on the internet at: www.bhiva.org, www.ashm.org.au or www.aidsinfo.nih.gov/guidelines. Viral resistance is the limiting factor, no matter how potent an individual drug may be at reducing viral load initially. The trials of combined zidovudine and lamivudine demonstrated both a more sustained decrease in plasma viral load than either drug did alone, and a more delayed development of viral resistance. There are now many antiretroviral drugs available for use in Australia (see TABLE 18.4) and clinicians have a much wider scope of treatments available. However, many questions remain about combination therapy and further trials using viral load as a clinical endpoint should provide pointers for treatment. Currently the use of three drugs, referred to as highly active antiretroviral therapy (HAART), is favoured. There are many possible combinations. Side effects, which are often severe—including cardiovascular disease—and affect the quality of life, remain a problem. Resistance to HAART is now a problem. Effective (90%) results have been achieved with triple therapy.¹⁷ Investigators are evaluating the benefits of dual therapy through studies which show promising outcomes.¹⁸ Long-term treatment with fewer agents would be popular if of proven efficacy. Subcutaneous injections of interleukin-2 have been shown to boost immunity.

Currently available antiretroviral drugs¹⁵

T [*] TIs)	Non-nucleoside RT inhibitors (NNRTIs)	Protease inhibitors (HIV PIs)	Fusion (entry) inhibitors	Integrase inhibitors
e	<ul style="list-style-type: none"> • nevirapine (NEV) • delavirdine (DLV) 	<ul style="list-style-type: none"> • saquinavir (SQV) • indinavir (IDV) • ritonavir (RTV) 	<ul style="list-style-type: none"> • enfuvirtide (T20) • maraviroc (MVC)[#] 	<ul style="list-style-type: none"> • raltegravir (RAL) • dolutegravir • elvitegavir

e	<ul style="list-style-type: none"> • efavirenz (EFV) 	<ul style="list-style-type: none"> • fosamprenavir (FAPV) 	Combination of classes
ine	<ul style="list-style-type: none"> • etravirine (ETR) 	<ul style="list-style-type: none"> • lopinavir/ritonavir (LPV) 	e.g.
	<ul style="list-style-type: none"> • rilpivirine (RPV) 	<ul style="list-style-type: none"> • atazanavir (ATZ) 	<ul style="list-style-type: none"> • Atripla (TFV, EFV, FTC)
e		<ul style="list-style-type: none"> • tipranavir (TPV) 	<ul style="list-style-type: none"> • Eviplera (TFV, FTC, RPV)
C		<ul style="list-style-type: none"> • darunavir (DRV) 	
)			
C			
r			



*RT = reverse transcriptase

**a nucleotide analogue RTI

#a CCR5 antagonist

When to start^{19,20}

Treatment should be initiated and monitored by a specialist in HIV medicine.

This is a controversial issue. CD₄ cell count guidelines:

- <350/ μ L—treat with ART
- 350–500/ μ L—strongly consider, offer or closely monitor (data support evidence at this level)¹⁵

Current thinking favours early treatment. Refer to current international guidelines (see [Page 178](#) Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine: www.ashm.org.au). The most widely used and preferred regimen consists of 2 NRTIs plus either an NNRTI or a protease inhibitor or an integrase inhibitor.¹⁵

Be aware of:

- drug interactions (www.hiv-druginteractions.org)
- contraindicated drug combinations¹⁵
- adverse effects¹⁵
- opportunistic infections

HAART (highly active antiretroviral therapy)

This is a combination of three (or more) agents with one or more penetrating the blood–brain barrier.

***Pneumocystis jiroveci*¹⁵**

This is an important cause of pneumonia and not usually seen until the CD₄⁺ cell count is <200/µL. Treatment, which is determined by the severity of the disease, is usually treated with trimethoprim + sulfamethoxazole (cotrimoxazole) oral or IV for 21 days depending on severity, which is also given orally as prophylaxis when the cell count reaches <200. Supplementary or alternative agents are IV pentamidine or oral dapsone, clindamycin, primaquine and atovaquone.¹⁵

Acute HIV infection

Treatment of seroconversion illness is not of proven clinical benefit (to date) but is optional and some clinics offer it.

Pre-exposure prophylaxis (PrEP)

This can be considered for those at risk. Selected tablets such as tenofovir or Truvada are taken around time of sex.^{21,22} Refer to your local sexual health clinic (SHC).

Post-exposure prophylaxis (PEP)

Undertake a risk assessment—PEP is not recommended for low-risk cases but those with significant high risk should be considered for PEP. It should be commenced within 72 hours of exposure and usually involves 2–3 antiretroviral agents taken daily for 28 days.²² Refer to ‘Needle-stick and sharps injuries’ for protocol (see CHAPTER 123) and your consultant or SHC.

The HIV test: the role of the family doctor²⁰

The astute GP will use the opportunity of a request for an HIV test to explore preventive and sexual health issues. A full sexual history and drug history must incorporate the ‘three Cs’ of counselling, confidentiality and consent in the pre-test interview.

Many HIV-positive patients have described how the results left them bewildered and devastated, especially with an unexpected positive result. Part of the reason given was the lack of any form of pre-test counselling. Ideally, management involves shared care with an expert consultant, with whom close liaison is essential.

Contact tracing

Contacts of HIV-positive patients should be traced and offered testing with counselling.¹⁶ Patients with HIV infection must be advised of the risk they pose to seronegative sexual partners. A person who has HIV or is at risk of HIV infection must not make any blood, semen or tissue donation. Because of the probable association between genital ulcerative disease and HIV transmission, the effective management of STIs is part of the general strategy for HIV control.

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Table 18.5 Red flags for HIV infection¹⁶

Persistent

Fever
Headache
Weight loss
Diarrhoea
Dry cough
Dyspnoea on exertion
Visual disturbance

Neurological

- seizures
- peripheral neuropathy
- others

Psychiatric

- depression/mania
- sleep disturbance
- signs of dementia

Laboratory

Viral count >10 000 copies/mm
Cell count 200–250/ μL or less

Prevention of HIV infection

Counselling the person at risk regarding ‘safer practices’

No effective vaccine has been developed. Modification of behaviour is the only valid strategy for prevention of HIV infection. Education programs to encourage sexual practices that reduce the exchange of genital secretions (safe sex) may achieve risk reduction for sexually active individuals. Condoms provide a barrier if used properly and consistently but may be too easily

damaged to offer reliable protection during anal intercourse. A water-based lubricant such as K-Y gel or Lubafax should be used: oil-based lubricants such as Vaseline weaken condoms.

Discuss alternative sex practices, including touching, cuddling, body-to-body rubbing and mutual masturbation.

Emphasise the importance of being in control with drug taking, IV usage, safe sex practices and the needle-exchange program.

Of special importance is the finding that the most important biological risk factor for HIV transmission is the presence of other active STIs in either partner. This includes chlamydia, gonorrhoea, syphilis and genital herpes. Herpes is also likely to increase the risk of HIV transmission during both homosexual and heterosexual intercourse, even in the presence of condoms.^{20,21,22}

Health professionals

Care should be exercised whenever blood samples are taken or sharps have been used. Advise safe disposal of sharps and other disposables and appropriate sterilisation of material. Gloves should be worn for all invasive procedures. Management of needle-stick injuries and other at-risk exposures is described in [CHAPTER 123](#). Blood donors need to be carefully screened.

Community education

Educating the community in a non-emotional, responsible way about AIDS should be a priority. While the personal, community and global benefits of effective AIDS education are generally acknowledged, the fear of addressing such a sensitive issue sometimes results in failure to act.^{23,24} AIDS education in schools in particular can be an important strategy. People with HIV infection would be appropriate resource educators and the use of videos would be a most appropriate medium for education.

When to refer²⁵

Most patients with HIV disease need referral to a specialist or clinic that can manage the patient expertly and sympathetically.

Referral should take place at the time of:

- onset of a life-threatening opportunistic infection
- the need to initiate antiretroviral drug therapy
- administration of prophylactic pentamidine therapy
- serious psychological problems related to HIV-positive status

Viruses and respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) with its concomitant possible severe viral pneumonia can be caused by novel (new) coronaviruses, which are responsible for severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS). Influenza virus (e.g. avian and swine) can also cause the syndrome.

Coronaviruses (CoV) are a large family of viruses. Human CoV generally cause mild illness such as the common cold. The novel CoV, which are one of several to infect humans, have four subgroups designated α , β , δ and γ . It is the less common novel types that cause disease in humans, usually spread from person to person by miasma from uncovered coughing and sneezing.

Severe ARS (SARS-CoV) was identified in China in 2002, but has since been diagnosed in many countries. The potential for severe pandemic was controlled through identification and isolation of infected patients. MERS-CoV, which was first identified in Saudi Arabia in 2012, ranged from asymptomatic infection to ARDS. The clinical features of these conditions is presented in [CHAPTER 38](#). A 3–7 day prodrome of fever, malaise, headache and myalgia can progress to non-productive cough, dyspnoea and respiratory failure. The usual test is nucleic acid PCR tests on oropharyngeal and nasopharyngeal swabs \pm sputum (if available). In 2020, the world experienced the pandemic caused by a new coronavirus identified as SARS-CoV-2, which causes the disease COVID-19.

Pandemics

A pandemic is an infectious outbreak, usually involving large numbers, which occurs across a number of international borders. The declaration of a pandemic is made by the World Health Organization. Pandemic viruses are novel viruses, sufficiently immunologically distinct from circulating viruses that few if any people have any level of immunity.

In comparison, an epidemic is an outbreak of disease with a higher number of cases than expected within a population, while endemic disease occurs at a relatively stable level.²⁶

At the time of writing, May 2020, the world was experiencing the first coronavirus pandemic from SARS-CoV-2. Globally, by mid July 2021, over 191 million people were infected and over 4.1 million had died, and numbers were still climbing.²⁷

The zoonotic bridge

Novel viruses that create pandemics usually originate from animals and have crossed the zoonotic bridge to humans, particularly in regions where high densities of people and animals cohabit. Bats often host these zoonotic viruses, which can infect humans through an intermediary host. In the 2019 SARS-CoV-2 pandemic, the intermediate host was thought to be pangolins.²⁸

The stages of pandemic development evolve progressively:

- disease only in animals
- disease in humans infected by animals with no human-to-human spread
- small clusters of human-to-human spread
- wide-spread sustained community transmission around the world²⁹

Transmissibility and clinical severity

The two crucial features of a pandemic virus are its transmissibility and the clinical severity of the disease. These determine the rate of spread and the impact.

Transmissibility is described by the R nought (R_0), the basic reproduction number, which determines the average number of people each new case is likely to infect in a non-immune population. For measles, R_0 is usually 12–18 or higher.³⁰ Clinical severity is reflected by the case fatality rate (CFR), the percentage of reported cases that are fatal. Both these numbers change as our understanding of the virus and its impact increases. FIGURE 18.7 shows these characteristics for past pandemic viruses. It highlights important differences between H1N1 ‘Spanish flu’ and H1N1 ‘Swine flu’ where the former was more infectious, more severe and resulted in higher levels of mortality than the latter. These different characteristics inform different management strategies for ‘mild’ and more ‘severe’ pandemics. The R_0 for SARS-CoV has ranged between 2–4.

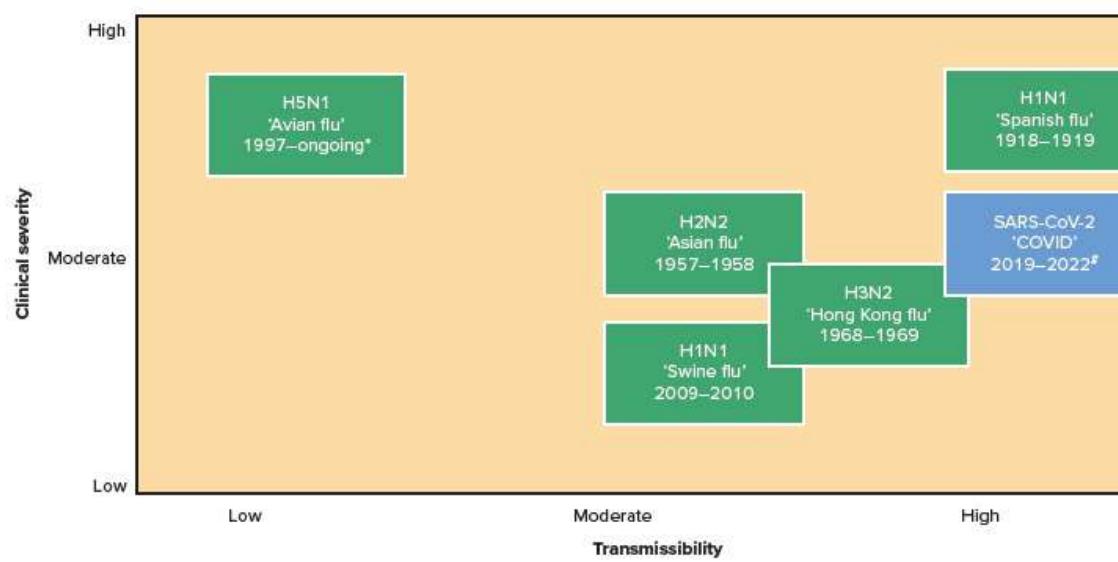


FIGURE 18.7 Contribution of transmissibility and severity on population impact of previous pandemics, with suggested position for the ongoing SARS-CoV-2 pandemic³¹

Source: Adapted from Australian Government. Australian Health Management Plan for Pandemic Influenza. Department of Health: Commonwealth of Australia, 2019. Available from:

Waves within pandemics

Waves, or large increases in cases, occur as new pockets of non-immune people are infected. An example of this was the 1918 Spanish influenza due to an H1N1 influenza virus of avian origin. An estimated 500 million, or one-third, of the world's population was infected. Mortality was estimated at 50 million. This pandemic had three waves over a year, from March 1918 to June 1919. The second wave was the most deadly.

A systematic national approach

Pandemic management requires a national top-down approach, i.e. national to state to local. State and territories, however, make local decisions to accommodate local geographical differences in phases of the pandemic.³¹ These reflect the PPRR (Prevention Preparedness Response Recovery) of disaster management systems (see [CHAPTER 120](#)).

Aims of the Australian Government response to pandemics are to:³¹

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- minimise the number of people who become infected or unwell
- minimise the degree of morbidity and decrease mortality
- reduce the health system burden, so provision of usual health care can continue
- help Australian families and communities reduce their own risk

Table 18.6 Stages of pandemic response planning for Australian general practices^{26,31,32}

National pandemic preparedness planning stages in Australia	
Stage	Activities
Preparedness	Review pandemic plan and resources available. Ongoing surveillance.
Response—Standby	Alert of a potential pandemic has been made. Monitor communications on the emerging disease, ensure practice and staff readiness to respond immediately and heighten surveillance for clinical cases.
Response—Action—Initial	Declaration of a pandemic is made, usually by the WHO. Little is known about the virus or the clinical disease and information is still being gathered.
Response—Action—Targeted	Enough is known about the disease to respond more specifically to refine the response, including clinical management and identifying those more vulnerable.
Response—	Move back to business as usual, review and manage

Stand down	effects of disruption to usual quality patient care and revise plans for future pandemics.
------------	--

Source: Adapted from the pandemic stages in Australian Health Management Plan for Pandemic Influenza. August 2019. Department of Health, Commonwealth of Australia: 10.

The impact of pandemics

This varies depending on the following.

Characteristics of the virus

- Transmissibility (R_0)
- Clinical severity (CFR)

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Characteristics of the population

- Any pre-existing immunity
- Factors increasing vulnerability, e.g. chronic disease

Effectiveness of infection control and public health measures

- Contact, droplet and aerosol infection control as appropriate
- Social distancing, isolation and quarantine
- Surveillance for new cases with rapid contact tracing to contain spread

Effectiveness of clinical management and prevention

- Potential clinical treatments
- Development of a vaccine

GP roles in pandemics

GP roles through the stages of the pandemic are articulated in the RACGP *Pandemic Flu Kit* documents.^{29,32} During pandemics, general practices will be required to flexibly adapt their usual practice processes to contribute to the response while maintaining business continuity and well-being of staff and self.

Key activities for GPs in pandemics include:²⁹

- revision of roles and responsibilities of staff as the pandemic evolves
- keeping up-to-date on reliable advice
- infection prevention and control (IPC) depending on the virus, e.g. contact, droplet and airborne precautions
- business continuity, including reorganisation of practice processes and patient flow; social

- distancing; telehealth delivery; mass vaccination delivery; business viability
- clinical management and comorbidities updates
 - psychological support for practice staff and patients, including physical and mental health, psychosocial health and well-being, and potential financial effects
 - review of processes for home and residential care visits
 - workforce GP-led respiratory clinics

Key facts and checkpoints

- The next pandemic may be evolving now.
- General practice is a crucial part of the front-line response.
- Each pandemic is unique and requires a flexible response.
- GP self-care is crucial.

The next pandemic

The world's population, urbanisation and international travel is increasing. There is increasing contact between humans and animals. This creates an environment of increased risk of more frequent pandemics in the future. General practice is a vital part of the health care response and needs to be prepared.

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Glandular fever
- Hepatitis B
- Hepatitis C
- Influenza
- Malaria
- Pertussis
- HIV infection and AIDS
- HIV post-exposure prophylaxis

Resources

Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Patient fact sheets. Available from: www.ashm.org.au.

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19 Baffling bacterial infections

In its beginning the malady is easier to cure but difficult to detect, but later it becomes easy to detect but difficult to cure.

NICCOLÒ MACHIAVELLI (1469–1527), ON TUBERCULOSIS

Bacterial infections can present diagnostic brain-teasers, and a high index of suspicion is needed to pinpoint the diagnosis. Many are rarely encountered, thus making diagnosis more difficult yet demanding vigilance and clinical flexibility.

The list includes:

- tuberculosis
- infective endocarditis
- syphilis
- septicaemia
- the zoonoses (e.g. brucellosis, Lyme disease)
- clostridial infections: tetanus, gas gangrene, puerperal infection, botulism, pseudomembranous colitis (*C. difficile*)
- hidden suppuration: abscess, osteomyelitis
- mycoplasma infections: atypical pneumonia
- *Chlamydia* infections: psittacosis, non-specific arthritis, pelvic inflammatory disease, trachoma, atypical pneumonia
- legionnaire disease
- Hansen disease (see CHAPTER 129)

Chlamydia and rickettsial organisms have been confirmed as being small bacterial organisms.

Tuberculosis

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, still has a worldwide distribution with a very high prevalence in Asian countries where 60–80% of children below the age of 14 years are affected.¹ This has special implication in Australia, where large numbers of Asian migrants are settling. The WHO estimates that one-third of the world's population is infected by the tubercle bacillus, with 10 million new cases in 2019. It remains a deadly disease, with about 1.5 million people worldwide dying of TB every year and 10 million new cases a year.

Clinical features

TB can be a mimic of other diseases and a high level of suspicion is necessary to consider the diagnosis, especially if there are only extrapulmonary manifestations. There may be no symptoms or signs, even in advanced disease, and may be detected by mass screening. Ideally patients should be referred early for specialist management.

Respiratory symptoms

- Cough
- Sputum: initially mucoid, later purulent
- Haemoptysis
- Dyspnoea (esp. with complications)
- Pleuritic pain

General clinical features (usually insidious)

- Anorexia
- Fatigue
- Weight loss
- Fever (low grade)
- Night sweats

Physical examination

- May be no respiratory signs or may be signs of fibrosis, consolidation or cavitation (amphoric breathing)
- Finger clubbing

High-risk people/situations

- Newborn and infants
- Adults over 60 years
- Patients with HIV/AIDS
- Chronic disease, e.g. diabetes
- Crowded or unsanitary living conditions
- People affected by alcohol and drugs
- Immigrants and refugees from endemic countries (especially Indian subcontinent, Papua New Guinea, South-East Asia, Sub Sahara and South Africa)



DxT malaise + cough + weight loss ± fever/night sweats + haemoptysis → pulmonary TB

Primary infection

The primary infection usually involves the lungs. Transmission is by droplet infection. Page 185
The focus is usually subpleural in the upper to mid zones and is almost always accompanied by lymph node involvement.

Erythema nodosum may accompany the primary infection (see FIG. 19.1). Primary TB is symptomless in most cases, although there may be a vague, ‘not feeling well’ illness associated with a cough. In most people this pulmonary focus heals but leaves some surviving tubercle bacilli, even if it becomes calcified (the Ghon focus).



FIGURE 19.1 Classic erythema nodosum involving the legs of a patient with pulmonary tuberculosis

Progressive primary tuberculosis

If the immune response is inadequate, progressive primary TB develops, with constitutional and pulmonary symptoms. Rarely, haematogenous spread can occur to the lungs ('miliary tuberculosis'), to the pleural space (tuberculosis pleural effusion) or to extrapulmonary sites such as the meninges and bone.

Latent TB infection (LTBI)

LTBI is the presence of infection without evidence of active disease (contained by the immune system) and inability to transmit the infection. However, reactivation may occur if the host's immune defences are impaired (occurs in about 10%). LTBI is very common in children in and from developing countries. Consider HIV in these people. The tuberculin skin test is primarily intended to identify these people with a view to prophylaxis therapy. The standard preferred regimen is isoniazid (10 mg/kg up to 300 mg (o) daily for 6–9 months). This decision should be made by a consultant.

Post-primary or adult-type pulmonary TB

Most cases of TB in adults are due to reactivation of disease some years later and not to re-infection. Symptoms of active TB include persistent cough, sputum production, haemoptysis, fever, sweating, malaise, weight loss and anorexia. The factors causing this include poor social living conditions with malnutrition, diabetes and other factors lowering natural immunity, such as immunosuppressant drugs, corticosteroids, lymphoma and HIV infection (later stage). The chest X-ray is usually abnormal—classic apical disease with infiltration and cavitation with fibrotic changes.

Practice tip

TB! – Think HIV.

Reactivated pulmonary TB

This usually presents with constitutional symptoms of poor health and night sweats, and a cough that is initially dry but may become productive and be bloodstained (see [CHAPTER 32](#)). Sometimes the infection will be asymptomatic. The natural history of TB infection is illustrated in [FIGURE 19.2](#) .

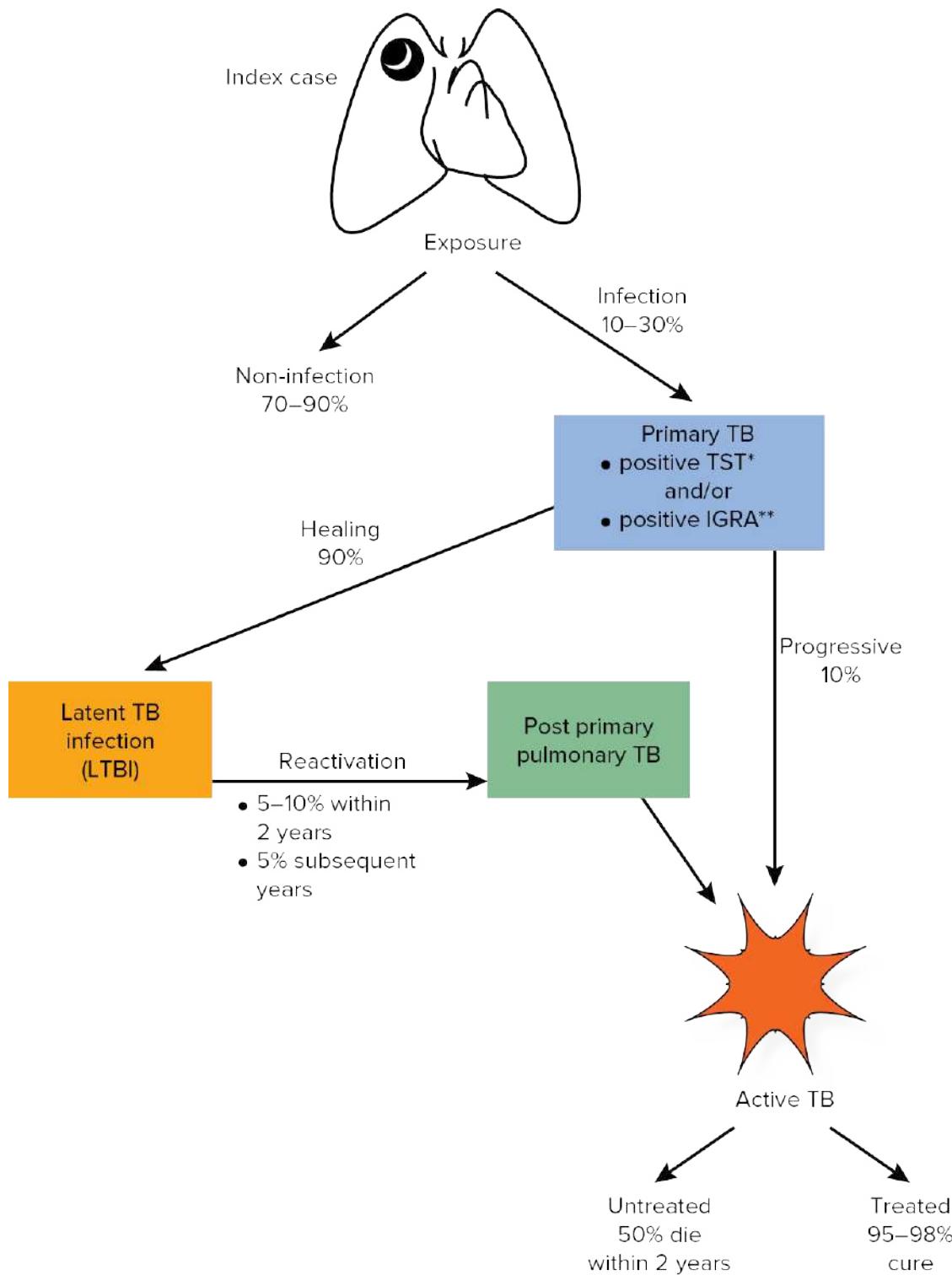


FIGURE 19.2 Natural history of TB infection

*TST = tuberculin skin test

**IGRA = interferon gamma release assay

Source: Based on WHO algorithm and Dr Grant Jenkin (personal communication)

Extrapulmonary TB

The main sites of extrapulmonary disease (in order of frequency in Australia) are the lymph nodes (the commonest, especially in young adults and children), genitourinary tract (kidney, epididymis, Fallopian tubes), pleura and pericardium, the skeletal system (arthritis and osteomyelitis with cold abscess formation), CNS (meningitis and tuberculomas), the eye (choroiditis, iridocyclitis), the skin (lupus vulgaris), the adrenal glands (Addison disease—see CHAPTER 14) and the GIT (ileocaecal area and peritoneum). This is increasing, especially in HIV patients.

These sites are illustrated in FIGURE 19.3 .

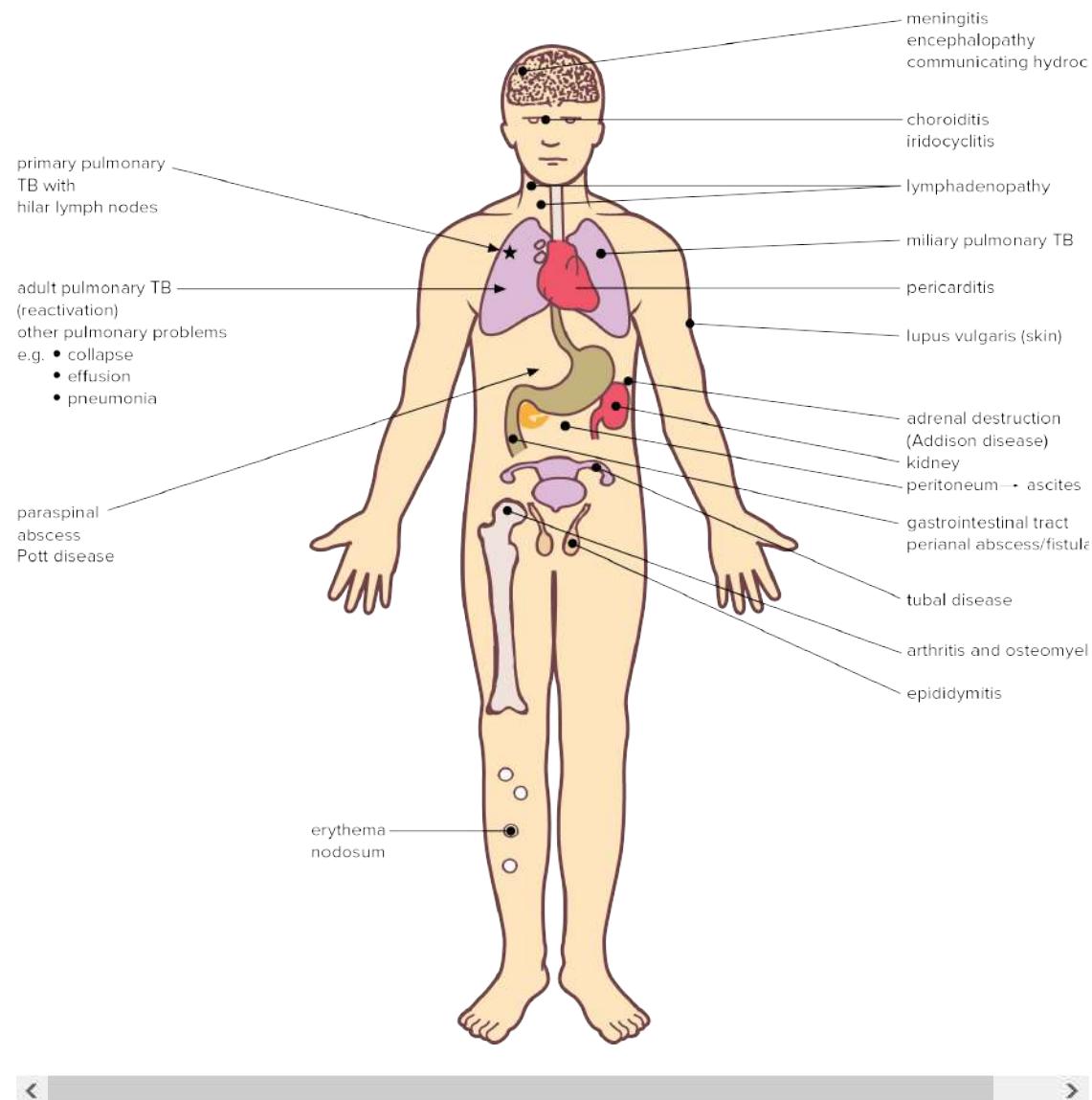


FIGURE 19.3 Pulmonary and extrapulmonary distribution of tuberculosis: the primary infection starts in the lung and then spreads throughout the body,

especially to the lymph nodes

Miliary tuberculosis

This disorder follows diffuse dissemination of tubercle bacilli via the bloodstream, especially in those with chronic disease and immunosuppression. It can occur within 3 years of the primary infection or much later because of reactivation.

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The symptoms, which are insidious, include weight loss, fever and malaise. Choroidal tubercles are pathognomonic. The classic chest X-ray is multiple 1–2 mm nodules in lung fields. It is fatal without treatment.

TB in children²

Children living in close contact with people with smear-positive pulmonary TB are highly vulnerable to acquiring the primary infection. A possible complication is miliary TB. The lifetime risk of TB disease in children with LTBI is in the order of 5–15%.³ Children with LTBI should be considered for prophylaxis with a course of isoniazid.

Primary disease is the more common form in young children. Reactivation is more common in adolescents.

Diagnosis⁴

A high index of suspicion is critical for the diagnosis of TB. Tests include:

- Mantoux tuberculin test (TST) (a guide only)
- chest X-ray; CT scan if doubtful
- sputum or bronchial excretion or gastric aspirates for stain (acid-fast bacilli) and culture (takes about 6–8 weeks but important); ideally requires 3 specimens over 3 days including one early morning
- immunochromatographic finger-prick test (new and promising)
- interferon gamma release assay (IGRA)
- QuantiFERON-TB Gold blood test
- NAAT/PCR test—less sensitive than culture
- biopsies on lesions/lymph nodes may be necessary; the hallmark is caseating granulomata
- fibre-optic bronchoscopy to obtain sputum may be necessary
- consider HIV studies

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Tuberculin (Mantoux) testing and BCG vaccination

A tuberculin (Mantoux) test should be performed prior to BCG vaccination in all individuals over 6 months of age. (It is read at 48–72 hours.) It is not a good test to diagnose TB.

If area of induration:

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- <5 mm—negative (*note:* may be negative in presence of very active pulmonary infection)
- 5–10 mm—typical of past BCG vaccination
- >5 mm—significant in immunocompromised, close contacts and HIV infection
- >10 mm—positive = tuberculosis infection (active or inactive)
- >15 mm—highly significant for ‘normal’ people

The BCG vaccination should be given if the reaction is <5 mm induration. Do not give it for a reaction >5 mm.

BCG vaccination is recommended for:

- Aboriginal and Torres Strait Islander neonates in regions of high incidence
- neonates born to patients with leprosy or family history of leprosy
- children <5 years travelling for long periods to countries of high TB prevalence

BCG vaccination should be considered for:

- neonates in household with immigrants or visitors recently arrived from countries of high prevalence (e.g. South-East Asia) (*note:* tuberculin test not necessary for neonates <14 days)
- children and adolescents <16 years with continued exposure to active TB patient and where isoniazid therapy is contraindicated
- others at increased risk (and where value of BCG vaccine uncertain), such as health care workers, travellers >5 years with significant exposure

BCG vaccination is contraindicated for:

- tuberculin reactions >5 mm
- immunocompromised or malignancies involving bone marrow lymphatics (can disseminate infection)
- high-risk HIV infection
- significant fever or intercurrent illness

- generalised skin diseases, including keloid tendency
- pregnancy
- previous infection

Areas of concern

Drug resistance

This includes the increasing emergence of forms resistant to two or more front-line drugs—multidrug-resistant TB (MDR-TB). TB is much more aggressive in the immunocompromised and if not adequately treated can be fatal in 2 months, especially if they have MDR-TB. Treatment compliance is a huge issue and so the directly observed therapy (DOT) strategy for isoniazid in children is a WHO priority, as is ‘DOTS plus’ to control MDR-TB. TB is a more pressing problem in children requiring early treatment.

Management and treatment^{5,6}

Referral to experienced specialist care is appropriate. The current antimicrobial treatment is the standard short-course therapy with four antituberculous drugs initially (rifampicin + isoniazid + pyrazinamide + ethambutol) daily for 2 months, then rifampicin + isoniazid daily for a further 4 months. The usual precautions with adverse reactions are required. Pyridoxine 25 mg daily is recommended for adults taking isoniazid. A 3-times-weekly regimen is also an option if DOT is employed. Corticosteroids may be prescribed. Notify appropriate jurisdictional public health authorities. Promote healthy lifestyle advice.

Syphilis

Although syphilis is uncommon, it is increasing in the general population and in HIV patients. It is extremely common in certain Indigenous groups and is frequently acquired from sexual contacts overseas.^{5,7}

It presents either as a primary lesion or through the chance finding of positive syphilis serology (reagins tests, treponemal antibody tests, PCR). Family physicians should be alert to the various manifestations of secondary syphilis, which can cause difficulties in diagnosis. Congenital syphilis is rare where there is general serological screening of antenatal patients. Early syphilis—less than 2 years duration and based on positive serology—includes primary, secondary and latent syphilis.

Clinical features^{7,8}

Primary syphilis

The primary lesion or chancre usually develops at the point of inoculation after an incubation period averaging 21 days. The chancre is typically firm, painless, punched out and clean (see

FIG 19.4). The adjacent lymph nodes are discretely enlarged, firm and non-suppurating. Any anorectal ulcer or sore should be considered as syphilis until proved otherwise.



FIGURE 19.4 Chancre of primary syphilis in adolescent. This painless, innocuous-looking lesion was associated with a firm, enlarged inguinal lymph node. Dark field examination revealed many motile treponema.

Untreated, early clinical syphilis usually resolves spontaneously within 4 weeks, leading to latent disease, which may proceed to late destructive lesions.

Secondary syphilis

The interval between the appearance of the primary chancre and the onset of secondary manifestations varies from 6 to 12 weeks after infection. Constitutional symptoms, including fever, headache, malaise and general aches and pains, may precede or accompany the signs of secondary syphilis.

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The most common feature of the secondary stage of infection is a rash, which is present in about 80% of cases. The rash is typically a symmetrical, generalised, coppery-red maculopapular eruption on the face, trunk, palms and soles and is neither itchy nor tender. It can resemble any skin disease except those characterised by vesicles.

Latent syphilis

Positive serology in a patient without symptoms or signs of disease is referred to as latent syphilis and is the commonest presentation of syphilis in Australia today. Possibly because of the widespread use of antibiotics, the infection often proceeds to the latent stage without a

recognised primary or secondary stage.

Late (tertiary) syphilis

Tertiary manifestation of syphilis (follows >2 years latency), which is very rare, may be ‘benign’ with development of gummas (granulomatous lesions) in almost any organ, or more serious with cardiovascular or CNS involvement. Benign gummatous disease is rare but cardiovascular disease and neurosyphilis occasionally occur. Careful management and follow-up of patients with early or latent disease is essential to prevent late sequelae. It can only be detected by blood tests.

Neurosyphilis includes:

- meningovascular (e.g. cranial nerve palsies)
- tabes dorsalis (e.g. sensory ataxia, lightning pains, Charcot joints)
- general paresis of the insane (e.g. dementia, psychosis)

Think of syphilis

Syphilis should not be overlooked as a cause of oral, ocular or anorectal lesions. The diagnosis of syphilis depends on a detailed history, careful clinical examination and specific examinations.

Underlying these approaches is the need to think of the possibility of syphilis with concurrent STIs.

Syphilis and HIV infection⁷

HIV and syphilis are commonly associated. In patients with AIDS and syphilis, standard regimens for syphilis are not always curative. Seronegative syphilis has been reported in patients with HIV infection. Lymphadenopathy in a patient with HIV infection may be due to coexisting secondary syphilis.

Diagnosis

Dark field examination⁸

Spirochaetes can be demonstrated by microscopic examination of smears from early lesions using dark field techniques and provide an immediate diagnosis in symptomatic syphilis. The direct fluorescent antibody techniques (FTAABS) can be used on this smear.

Serology

Serological tests provide indirect evidence of infection, and the diagnosis of asymptomatic syphilis relies heavily on these tests. The main types of tests are:

- reagin tests (VDRL and RPR)—not specific for syphilis but useful for screening
- treponemal tests (TPPA, TPI, EIA, FTAABS)—specific tests, with the latter being sensitive and widely used
- PCR (blood or CSF)—very sensitive

Treatment

It is based on parenteral benzylpenicillin or procaine penicillin. Refer to [CHAPTER 109](#).

Infective endocarditis

Infective endocarditis, although uncommon, has high morbidity and mortality. It can be [Page 190](#) a difficult problem to diagnose but must be considered in the differential diagnosis of fever, especially in patients with a history of cardiac valvular disorders. It is caused by microbial infection of the cardiac valves or endocardium. Previously referred to as bacterial endocarditis, the term *infective endocarditis* is preferred because not all the infecting organisms are bacteria.

It may present as a fulminating or acute infection but more commonly runs an insidious course and is referred to as subacute (bacterial) endocarditis. Its incidence is increasing, probably due to the increasing number of elderly people with degenerative valve disease, more invasive procedures, IV drug use and increased cardiac catheterisation.⁹



DxT FUO + cardiac murmur + embolism → endocarditis

Risk factors

- Past history of endocarditis
- Rheumatically abnormal valves, especially Aboriginal and Torres Strait Islander people
- Congenitally abnormal valves
- Mitral valve prolapse
- Calcified aortic valve
- Congenital cardiac defects (e.g. VSD, PDA)
- Prosthetic valves, shunts, conduits
- IV drug use
- Central venous catheters

- Temporary pacemaker electrode catheters

Note: Only about 50% of patients with infective endocarditis have previously known heart disease.⁸ Consider the possibility of IV drug use.

Responsible organisms¹⁰

- *Streptococcus viridans* (50% of cases) most susceptible to penicillin
- *Streptococcus bovis*
- *Enterococcus faecalis*
- *Staphylococcus aureus* (causes 50% of acute form)
- *Candida albicans/Aspergillus* (IV drug users)
- *Staphylococcus epidermidis*
- *Coxiella burnetii* (Q fever)
- HACEK group (Gram –ve bacilli) (5–10% of cases)

Presentations

- Acute endocarditis
- Subacute endocarditis
- Prosthetic endocarditis

Infective endocarditis without cardiac murmur is frequently seen in IV drug users who develop infection on the tricuspid valve.

Warning signs for development of endocarditis

- Change in character of heart murmur
- Development of a new murmur
- Unexplained fever and cardiac murmur = infective endocarditis (until proved otherwise)
- A febrile illness developing after instrumentation (e.g. urethral dilatation) or minor and major surgical procedures (e.g. dental extraction, tonsillectomy, abortion)

The ‘classic tetrad’ of clinical features:⁹ signs of infection, signs of heart disease, signs of embolism, immunological phenomena.

There is a significant high mortality and morbidity from infective endocarditis, which is often related to a delay in diagnosis.

A golden rule

Culture the blood of every patient who has a fever and a heart murmur.

Clinical features

The classic clinical features are summarised in [FIGURE 19.5](#).

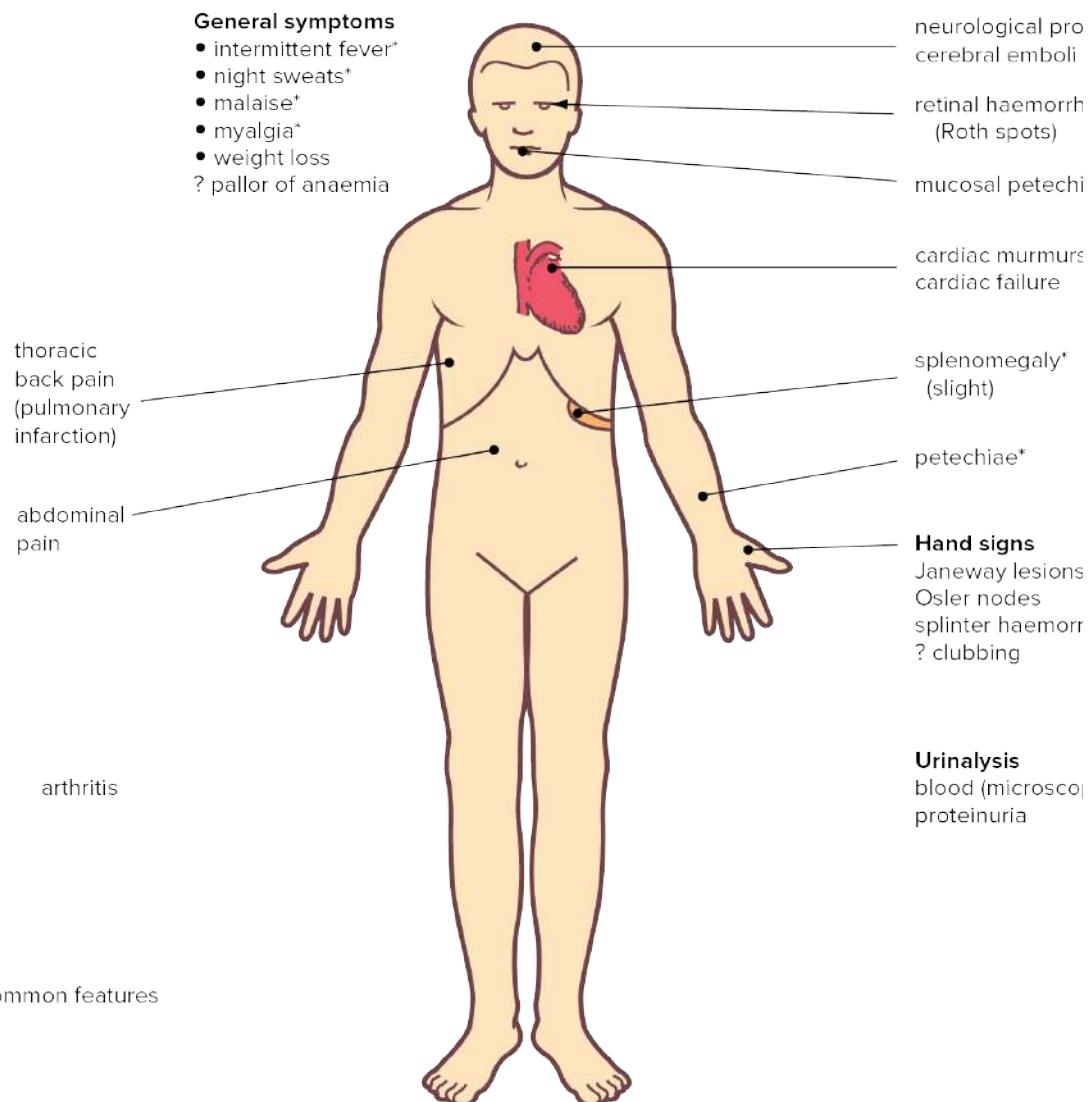




FIGURE 19.5 Infective endocarditis: possible clinical features

The patients are often elderly, appear pale and ill, with intermittent fever, and complain of vague aches and pains. The full clinical presentation takes time to develop. A febrile illness of 1 to 2 weeks duration is a common presentation.

Investigation

This includes:

- FBE and ESR: ESR ↑, anaemia and leukocytosis
- urine: proteinuria and microscopic haematuria
- blood culture: positive in about 75%⁸ (at least 3 sets of samples— aerobic and anaerobic culture)
- echocardiography—to visualise vegetations (TOE more sensitive than TTE)
- chest X-ray
- ECG

Consider kidney function tests and C-reactive protein.

Management

The patient should be referred because optimal management requires close cooperation between physician, microbiologist and cardiac surgeon.

Any underlying infection should be treated (e.g. drainage of dental abscess).

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Bactericidal antibiotics are chosen on the basis of the results of the blood culture and antibiotic sensitivities. Four blood cultures should be sent to the laboratory within the first hour of admission and treatment should seldom be delayed longer than 24 hours.

Antimicrobial treatment^{10,11}

There are two important principles of management:

- treatment must be given IV for at least 2 weeks
- treatment is prolonged—usually 4–6 weeks

Consultation with an infectious diseases physician or clinical microbiologist should be sought. Once cultures have been taken, prompt empirical antimicrobial treatment should be commenced, esp. in fulminating infection suspected to be endocarditis.

- Benzylpenicillin + gentamicin + di(flu)cloxacillin are recommended
- Vancomycin needs to be considered if hospital acquired, MRSA suspected or prosthetic cardiac valve

Prevention

Value of prophylaxis is unclear.

Low-risk patients (no prosthetic valves or previous attack of endocarditis): prophylaxis not recommended.

High-risk patients (prosthetic valves, all acquired valvular disease, past history, most congenital heart disease, mitral valve prolapse with regurgitation) having invasive dental procedures, oral or upper respiratory tract surgery, GIT or genitourinary surgery (consult an infectious disease physician); example:

- amoxicillin 2 g (child: 50 mg/kg up to 2 g) orally, 1 hr beforehand (if not on long-term penicillin)
- or*
- (amoxi)ampicillin 2 g (child: 50 mg/kg up to 2g) IV just before procedure commences or IM 30 minutes before: if having a general anaesthetic; if hypersensitive to penicillin: clindamycin or cephalexin

Zoonoses

Zoonoses are those diseases and infections that are naturally transmitted between vertebrate animals and humans (see TABLE 19.1). Zoonotic diseases (which are not restricted to farming communities) can present as a mild illness but are prolonged in duration and can have debilitating sequelae.¹² There is a long list of diseases, which vary from country to country, and includes plague, rabies, scrub typhus, Lyme disease, tularemia, hydatid disease, orf, anthrax, erysipeloid, listeriosis, campylobacteriosis and ornithosis (psittacosis).

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Table 19.1 Major zoonoses in Australia

Zoonosis	Organism(s)	Animal host	Mode of transmission	Main presenting features
Q fever	<i>Coxiella burnetii</i>	Various wild and domestic animals	Inhaled dust Animal contact Unpasteurised	Fever, rigor, myalgia, headache, dry cough

			milk	
Leptospirosis	<i>Leptospira interrogans</i> or <i>pomona</i>	Various domestic animals	Infected urine contaminating cuts or sores	Fever, myalgia, severe headache, macular rash
Brucellosis	<i>Brucella abortus</i>	Cattle	Contamination of cuts or sores by animal tissues Unpasteurised milk	Fever (undiagnosed), sweats, myalgia, headache, lymphadenopathy
Lyme disease	<i>Borrelia burgdorferi</i>	Marsupials (probable)	Tick bites	Fever, myalgia, arthritis, backache, doughnut-shaped rash
Psittacosis	<i>Chlamydia psittaci</i>	Birds: parrots, pigeons, ducks, etc.	Inhaled dust	Fever, myalgia, headache, dry cough
Bovine tuberculosis	<i>Mycobacterium bovis</i>	Cattle	Unpasteurised milk	Fever, sweating, weight loss (as for human pulmonary TB)
Listeriosis	<i>Listeria monocytogenes</i>	Various wild and domestic animals	Unpasteurised milk or cheese Contaminated vegetables Person to person	Mild febrile illness (in most) Meningoencephalitis in those susceptible (neonates, pregnancy, etc.)



Diagnosis¹³

If a zoonosis is overlooked in the differential diagnosis, many will remain undiagnosed and untreated.

Practice tip

Think of a zoonosis in patients presenting with a flu-like illness and features of atypical pneumonia.

Fever and sweats (flu-like illness)

Any patient with undiagnosed fever should be questioned about exposure to animals, recent travel both in and out of Australia, animal bites, cat scratches, consumption of raw milk, mosquito and tick bites, pets and occupation.

Rash

- Consider rickettsial illness such as leptospirosis, Q fever, Lyme disease

Cough or atypical pneumonia

- Consider Q fever, psittacosis, bovine TB

Arthralgia/arthritis

- Consider Lyme-like disease, Ross River fever

Meat workers

- Consider Q fever, leptospirosis, orf, anthrax

Papular/pustular lesions

- Consider orf, anthrax (black)

Brucellosis

Brucellosis (undulant fever, Malta fever) has diminished in prevalence since the campaign to eradicate it from cattle. Entry is mainly by the mouth, or abraded or cut skin.

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Clinical features (acute brucellosis)

- Incubation period 1–3 weeks
- Insidious onset: malaise, headache, weakness
- A prolonged febrile illness
- The classic fever pattern is undulant (refer to CHAPTER 42)

Possible:

- arthralgia

- lymphadenopathy
- hepatomegaly
- spinal tenderness
- splenomegaly (if severe)

Complications such as epididymo-orchitis, osteomyelitis and endocarditis can occur. Localised infections in sites such as bones, joints, lungs, CSF, testes and cardiac valves are possible but uncommon.

Symptoms of chronic brucellosis are virtually indistinguishable from chronic fatigue syndrome and can present with FUO.



DxT malaise + headache + undulant fever → brucellosis

Diagnosis

- Blood cultures if febrile (positive in 50% during acute phase)^{10,14}
- *Brucella* agglutination test (rising titre)—acute and convalescent (3–4 weeks) samples
- *Brucella* PCR testing—sensitive and rapid

Treatment²

- Adults: doxycycline 100 mg (o) bd for 6 weeks + rifampicin 600 mg (o) daily for 6 weeks
or
gentamicin 4–6 mg/kg/day IV statim then daily for 2 weeks (monitor)
- Children: cotrimoxazole + rifampicin
or
gentamicin
- Relapses do occur (10%)—prolonged therapy

Prevention and control

Involves eradication of brucellosis in cattle, care handling infected animals and pasteurisation of milk. No vaccine is currently available for use in humans.

⌚ Q fever

Q fever is a zoonosis due to *Coxiella burnetii*. It is the most common abattoir-associated

infection in Australia and can also occur in farmers and hunters. It usually resolves spontaneously within 2 weeks. Rash is not a major feature but can occur if the infection persists without treatment. It is transmitted by inhaled dust, animals (wild or domestic) and unpasteurised milk.

Clinical features

- Incubation period 1–3 weeks
- Sudden onset fever, rigors and myalgia
- Dry cough (may be pneumonia in 20%)¹⁴
- Petechial rash (if persisting infection)
- ± Abdominal pain

Persistent infection may cause pneumonia or endocarditis so patients with valvular disease are at risk of endocarditis (culture is negative). It is a rare cause of hepatitis. The acute illness may resolve spontaneously but a chronic relapsing disease may follow. Untreated chronic infection is usually fatal.



DxT fever + headache + prostration → Q fever

Diagnosis

- Serodiagnosis is by antibody levels in acute phase and 2–3 weeks later (fourfold increase)
- *Coxiella burnetii* PCR is effective

Treatment²

- Doxycycline 100 mg (o) bd for 14 days
- For endocarditis or chronic disease: prolonged course of doxycycline plus clindamycin or rifampicin
- Children: >8 same antibiotics according to weight; <8 cotrimoxazole (instead of doxycycline)

Prevention

The disease can be prevented in abattoir workers by using Q fever vaccine.

Leptospirosis

Leptospirosis follows contamination of abraded or cut skin or mucous membranes with Page 194*Leptospira*-infected urine of many animals including pigs, cattle, horses, rats and dogs.

In Australia it is almost exclusively an occupational infection¹² of farmers (especially with flooded farmland in tropics) and workers in the meat industry. There is a risk to dairy farmers splashed with urine during milking, especially if through open cuts or sores. Early diagnosis is important to prevent it passing into the immune phase.

Clinical features

- Incubation period 3–20 days (average 10)
- Fever, chills, myalgia
- Severe headache
- Chest pain (possibly haemoptysis)
- Macular rash
- Light-sensitive conjunctivitis (marked suffusion)

Some may develop the immune phase (after an asymptomatic period of 1–3 days) with aseptic meningitis or jaundice and nephritis (icterohaemorrhagic fever, Weil syndrome) with a significant mortality.



DxT abrupt fever + headache + conjunctivitis → leptospirosis

Diagnosis

- High or rising titre of antibodies: can be cultured
- PCR

Treatment⁵

Mild cases may not require treatment (adult doses shown).

- Doxycycline 100 mg (o) bd for 7 days
or
- benzylpenicillin 1200 mg IV, 6 hourly for 7 days
or
- ceftriaxone 1 g IV daily for 7 days

Lyme and lyme-like disease

Lyme disease (known as Lyme borreliosis) was first described in 1975 and named after the town Lyme in Connecticut (US). It is widespread in the US and is now appearing in other countries but is not known to be endemic in Australia. Sporadic cases are seen in visitors or travellers. The illness encountered here and in other countries is described as debilitating symptom complexes attributed to ticks. Traditional Lyme disease, which is highly infective, is caused by a spirochaete, *Borrelia burgdorferi*, and transmitted by *Ixodes* ticks, so that people living and working in the bush are susceptible. It has been reported in deer farmers. Lyme disease presents in three stages. If suspected, refer to an infectious disease physician for expert advice.

The pathognomonic sign is erythema migrans—a characteristic pathognomonic rash, usually a doughnut-shaped, well-defined rash about 6 cm in diameter at the bite site.

Stage 1: erythema migrans, flu-like illness

Stage 2: neurological problems such as limb weakness and cardiac problems

Stage 3: arthritis

Diagnosis

- Clinical pattern especially rash of erythema migrans + serology and PCR

Treatment

- Remove tick
- A typical regimen for adults is doxycycline 100 mg bd for 21 days or amoxicillin

Psittacosis ('bird fancier's disease')

Most patients are bird fanciers. Psittacosis accounts for 1–5% of hospital admissions for pneumonia. The disease may follow a low-grade course over several months but can have a dramatically acute presentation of flu-like illness. It is indistinguishable from other atypical pneumonias except for history of contact with birds.

Clinical features

- Incubation period 1–2 weeks
- Fever, malaise, myalgia
- Headache
- Cough (usually dry)

- Minimal chest signs
- Splenomegaly (sometimes)

Mortality can be as high as 20% if untreated.

Diagnosis

- Serology—rising antibody and PCR
- Chest X-ray

Treatment²

- Adults: doxycycline 200 mg (o) or clarithromycin 250–500 mg, 12 hourly for 7 days (o)

§ Listeriosis¹³

Listeriosis is caused by *Listeria monocytogenes*, a bacterium widespread in nature that can contaminate food and has been found in many fresh (e.g. fruit and vegetables) and processed foods (e.g. dairy products, especially unpasteurised milk, soft cheese, processed meats and smoked seafood). Its significance lies in the mortality rate in high-risk groups such as pregnant women, the immunocompromised, frail aged and very young, but especially neonates and fetuses. Babies may be stillborn or aborted.

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Clinical features

It may be subclinical but possible presentations include:

- influenza-like illness (usually mild)
- food poisoning, gastroenteritis (atypical)
- meningitis, especially infants, elderly
- septicaemia (in susceptible)
- pneumonia (in susceptible)

Diagnosis

- PCR
- Microscopy, culture or isolation of organism from infected site or blood
- Serological tests available

Treatment

- Amoxicillin 1 g (o) 8 hourly or IV for 10–14 days^{5,14}

Other zoonoses

- Mosquito-transmitted infections: Murray Valley encephalitis, Ross River virus, Barmah Forest virus
- Infections from bites and scratches: cat-scratch disorder, rat bite fever
- Hydatid disease, orf, milker's nodules
- Toxoplasmosis, histoplasmosis, hookworm

Clostridial infections

Clostridia are spore-forming, gram-positive bacilli widely present in dust, soil and vegetation and as normal flora in the GI tracts of mammals.

Tetanus

This sometimes misdiagnosed bacterial infection (*Clostridium tetani*) can appear from one day to several months after the injury, which may have been forgotten. A total of 10–20% of patients with tetanus have no identifiable wound of entry.¹⁵ Neonatal tetanus can occur from contamination of the umbilical stump. It is a significant cause of postpartum maternal mortality worldwide.

Clinical features

- Prodrome: fever, malaise, headache
- Trismus (patient cannot open mouth)
- Risus sardonicus (a grin-like effect from hypertonic facial muscles)
- Opisthotonus (arched trunk with hyperextended neck)
- Spasms, precipitated by minimal stimuli

Differential diagnosis: phenothiazine toxicity, strychnine poisoning, rabies, dental abscess

Management

- Give tetanus antitoxin and human tetanus immunoglobulin (see CHAPTER 6)

- Refer immediately to expert centre
- Intubate and ventilate if necessary

Gangrene/gas gangrene⁵

Gangrene (necrotising soft tissue infection) can involve skin and subcutaneous fat, fascia and muscle.

Gas gangrene (clostridial myonecrosis) is caused by entry of one of several clostridia organisms, for example, *Clostridium perfringens*, into devitalised tissue, such as exists following severe trauma to a leg.

Clinical features

- Sudden onset of pain and swelling in the contaminated wound
- Brownish serous exudate
- Gas in the tissue on palpation or X-ray
- Prostration and systemic toxicity
- Circulatory failure ('shock')

Management

- Refer immediately to surgical centre for debridement
- Start benzylpenicillin 2.4 g IV, 4 hourly + clindamycin
- Hyperbaric oxygen if available

Botulism⁵

Botulism is food poisoning caused by the neurotoxin of *Clostridium botulinum*. It can be infant botulism, of wound origin or food borne. From 12 to 36 hours after ingesting the toxin from canned, smoked or vacuum-packed food (e.g. home-canned vegetables or meat) visual problems such as diplopia suddenly appear. Suspect botulism if cranial nerve weakness with normal sensation. General muscle paralysis and prostration quickly develop. Refer immediately for antitoxin and intensive care.

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Pneumonia

Surprisingly the initial presentation of pneumonia can be misleading, especially when the patient presents with constitutional symptoms such as fever, malaise and headache rather than

respiratory symptoms. A cough, although usually present, can be relatively insignificant in the total clinical picture. This problem applies particularly to atypical pneumonia but can occur with bacterial pneumonia, especially lobar pneumonia (refer to CHAPTER 32).

The atypical pneumonias^{5,16}

Refer to CHAPTER 32 .

Clinical features

- Fever, malaise
- Headache
- Minimal respiratory symptoms, non-productive cough
- Signs of consolidation absent
- Chest X-ray (diffuse infiltration) incompatible with chest signs



DxT 'flu' + headache + dry cough → atypical pneumonia

Serology tests and treatment

Blood tests and PCR tests are available for all the following causative organisms:

Mycoplasma pneumoniae (the commonest)

- Adolescents and young adults: treat with doxycycline (first line) 200 mg statim then 100 mg daily for 14 days
 - or
 - roxithromycin 300 mg (o) daily for 14 days

Legionella pneumophila (legionnaire disease)

- Related to cooling systems in large buildings
- Incubation 2–10 days
- Diagnostic criteria include: prodromal-like illness; a dry cough, influenza-like illness, confusion or diarrhoea; lymphopenia with marked leukocytosis; hyponatraemia; PCR test and urinary antigen assay
- Treatment for mild disease: azithromycin 500 mg (o) daily for 5 days or doxycycline 100 mg (o) 12 hourly for 10–14 days

- Patients can become very prostrate with complications—treat with azithromycin (o or IV) or erythromycin (IV or o) *plus* (if very severe) add ciprofloxacin or rifampicin for 14–21 days

Chlamydia psittaci (psittacosis)

- Treat with doxycycline 100 mg bd for 14 days

Coxiella burnetii (see Q fever section)

Acknowledgment

Part of this text, on the clinical manifestations of syphilis, is reproduced from the *Handbook on Sexually Transmitted Diseases*⁷ (copyright Commonwealth of Australia, reproduced by permission).

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20 Infections of the central nervous system

Bacterial meningitis is a medical emergency especially meningococcus meningitis which can cause rapid deterioration of the patient. Consider it if a sudden onset of the classical triad [fever, nuchal rigidity, altered conscious state] is accompanied by high fever and the signs of a very sick child. Meningococcal meningitis may be accompanied by a petechial rash and septic shock (Waterhouse–Friderichsen syndrome).

ANISHA BAHRA & KATIA CIKUREL, NEUROLOGY, 1999¹

Infections of the central nervous system cover general conditions such as meningitis and encephalitis, and specific organisms such as syphilis and polio. This section is highlighted because the conditions that are difficult to diagnose can have morbid outcomes, especially if the conditions are misdiagnosed. They are representative of classic ‘not-to-be-missed’ conditions.

Key symptoms suggestive of cerebral infection are headache, seizures and altered conscious level.

⌚ Meningitis

Meningitis is inflammation of the meninges (pia and arachnoid) and the cerebrospinal fluid (CSF).

The classic triad is:

- headache
- photophobia
- neck stiffness

Other symptoms include malaise, vomiting, fever and drowsiness.

Causes (organisms)^{1,2}

Bacteria

- *Streptococcus pneumoniae*, *Haemophilus influenzae* (especially children), *Neisseria meningitidis* (the big three)
- *Listeria monocytogenes*, *Mycobacterium tuberculosis*, Group B *Streptococcus*, *Strep. agalactiae* (common in newborn), *Staphylococcus spp.*, Gram –ve bacilli, such as *Escherichia coli*, *Borrelia burgdorferi*, *Treponema pallidum*

Viruses

- Enteroviruses (Coxsackie, echovirus, poliovirus); mumps; herpes simplex HSV type 1, 2 or 6; varicella zoster virus; EBV; HIV (primary infection)

Fungi

- *Cryptococcus neoformans* or *C. gattii*
- *Histoplasma capsulatum*

Investigations

- Lumbar puncture (see TABLE 20.1)
- CT scan
- Blood culture—all patients with suspected meningitis
- CSF microculture/PCR (PCR useful even if antibiotics given)
- Specific serology, e.g. HIV, EBV

Note: If significant delay with these investigations, do not withhold treatment.

Table 20.1 CSF findings in meningitis

	Bacterial (pyogenic)	Tuberculosis	Viral (aseptic)
CSF appearance	Cloudy/pus	Opalescent	Usually clear
CSF pressure	↑ ↑ ↑	↑ ↑ or N	↑ or N
Predominant cell	Neutrophils	Lymphocytes	Lymphocytes
Cell count/mm³	100–1000 +	50–1000	10–1000
Glucose	↓ ↓ ↓	↓ ↓	Normal

Bacterial meningitis²

Bacterial meningitis is basically a childhood infection. Neonates and children aged 6–12 months are at greatest risk. Meningococcal disease can take the form of either meningitis or septicaemia (meningococcaemia) or both. Most cases begin as septicaemia, usually via the nasopharynx. The onset is usually sudden (see [CHAPTER 89](#)).

Clinical features (typical)

Infancy

- Fever, pallor, vomiting ± altered conscious and mental state
- Lethargy
- Increasing irritability with drowsiness
- Refusal to feed, indifference to mother
- Neck stiffness (not always present)
- Cold extremities (a reliable sign)
- May be bulging fontanelle
- Kernig sign (see [FIG. 20.1](#)): unreliable
- Brudzinski sign (see [FIG. 20.2](#)): more reliable sign of meningeal irritation
- Opisthotonus (see [FIG. 20.3](#)): rare

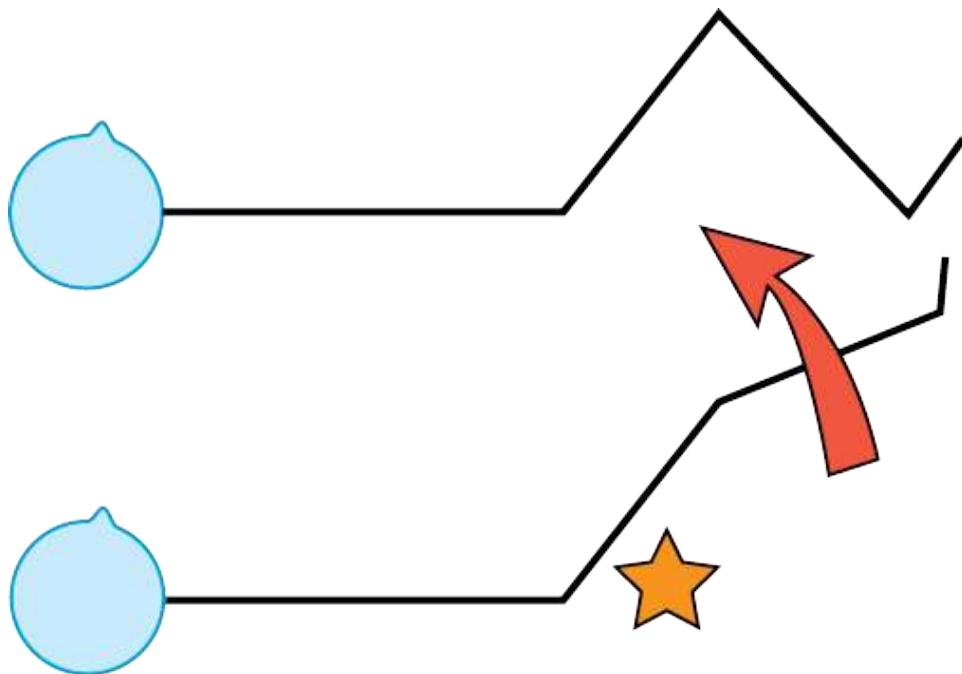


FIGURE 20.1 Kernig sign: pain in hamstrings with inability to straighten leg on passive knee extension with hip flexed at 90°

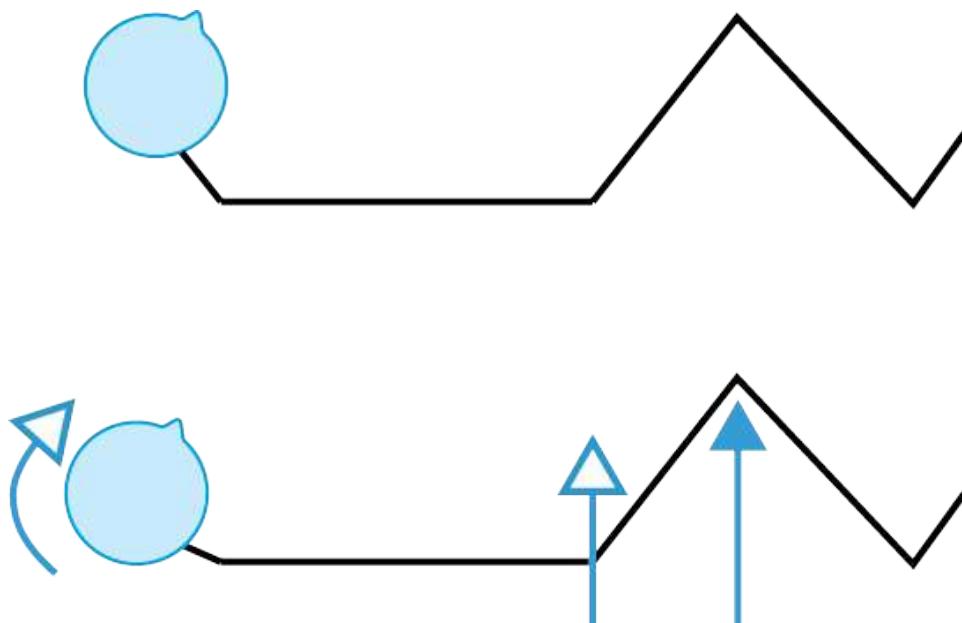


FIGURE 20.2 Brudzinski sign: neck flexion causes involuntary flexion of hip and knee



FIGURE 20.3 Opisthotonus caused by advanced meningitis

Children over 3 years, adolescents, adults

- Meningeal irritation more obvious (e.g. headache, fever, vomiting, neck stiffness)
- Later: delirium, altered conscious state

Note: Antibiotics may mask symptoms. Suspect meningitis if fever >3 days in reasonably well child on antibiotics.³

Fulminating

- Dramatic sudden-onset shock, purpura (does not blanch on pressure) ± coma
- Usually due to meningococcal septicaemia, also *H. influenzae* type B, *Streptococcus pneumoniae*, *Listeria monocytogenes*

Note: Septic shock may ensue without signs of meningitis.

Treatment (suspected meningitis)⁴

First: oxygen + IV access and consult

- Take blood for culture (within 30 minutes of assessment)—ideally prior to hospitalisation
- For child give bolus of 10–20 mL/kg of N saline with added bolus up to total 60 ml/kg if signs of hypoperfusion
- Admit to hospital for lumbar puncture (preliminary CT scan to assess safety of LP in adults)
- Dexamethasone 0.15 mg/kg up to 10 mg IV (start at same time as or 15 minutes before antibiotics—controversial but shown to improve outcome)⁵
- Ceftriaxone 2 g (child >1 month: 50 mg/kg up to 2 g) IV statim then 12 hourly for 4 days
or
cefotaxime 2 g (child: 50 mg/kg up to 2 g) IV
6 hourly for 3–5 days (note that IM injection is painful)

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Note: IV preferable but IM or interosseous better than nothing.

Antibiotics of proven effectiveness are cefotaxime, ceftriaxone, meropenem and penicillin. Risk of resistance with *S. pneumoniae*. The choice of antibiotic is directed by the knowledge of the organism and known susceptibility.

Treatment (meningococcaemia—all ages)

Treatment is extremely urgent once suspected (e.g. petechial or purpuric rash on trunk and limbs) (see FIG. 20.4). It should be given before reaching hospital. Empirical treatment is:

- benzylpenicillin 2.4 g (child: 60 mg/kg IV up to 2.4 g) statim (continue for 5 days)
- if IV access not possible give IM or (*especially if hypersensitive to penicillin*)

- ceftriaxone 2 g (child >1 month 50 mg/kg up to 2 g) IV or IM 12 hourly for 5 days

Note: Penicillin dose guide for suspected meningitis in child: <1 year 300 mg, 1–9 years 600 mg, 10+ years 1.2 g.

Specific organisms—*streptococcus pneumoniae*: benzylpenicillin or cephalosporin; Group B *streptococcus*: benzylpenicillin; *H influenzae*: cephalosporin.



FIGURE 20.4 Meningococcaemia with typical early purpuric rash in a 2-year-old child

Prevention

- Meningococcal vaccines—B and ACWY given separately

⌚ Viral meningitis^{1,6}

This is basically a childhood infection. The most common causes are human herpes virus 6 (the cause of roseola infantum) and enteroviruses (Coxsackie and echovirus).

Most cases are benign and self-limiting, but the clinical presentation can mimic bacterial meningitis, although there are fewer obvious signs of meningeal irritation. Lumbar puncture is important for diagnosis and also PCR for enterovirus. If positive, it can allow early cessation of antibiotics if commenced empirically.² Treatment which is symptomatic includes rehydration and analgesics. Aciclovir is given for herpes meningitis. The immunocompromised require special management.

Practice tip

Very cold hands? Think meningitis.

⌚ Encephalitis^{1,6}

Encephalitis is inflammation of the brain parenchyma. It is mainly caused by viruses, although other organisms including some bacteria, *Mycoplasma*, *Rickettsia* and *Histoplasma* can cause encephalitis. Suspect it when a viral prodrome is followed by irrational behaviour, altered conscious state and possibly cranial nerve lesions.

Practice tip

Consider the possibility of (non-infective) autoimmune encephalitis.

Clinical features

These can vary from mild to severe.

- Constitutional: fever (not inevitable), malaise, myalgia
- Meningeal features: headache, photophobia, neck stiffness
- Cerebral dysfunction: altered consciousness—confusion, drowsiness, personality changes, irrational behaviour, seizures, coma
- Focal neurological deficit

Causes (viral organisms)

- Herpes simplex type 1 or 2, enteroviruses, mumps, CMV, EBV, HIV, measles, influenza, arboviruses (e.g. Japanese B, West Nile, Murray Valley encephalitis, Ross River)
- Consider cerebral malaria in the differential diagnosis

There are three forms of mediated viral encephalitis: direct, delayed (latent) and immune mediated (postinfectious encephalomyelitis).

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Toxoplasma gondii

A protozoal infection seen in immunocompromised patients, especially HIV. Refer for specialist advice.

Investigations

- Lumbar puncture: CSF (usually aseptic meningitis)
- CSF PCR for viral studies, esp. HSV, toxoplasma
- CT scan—often shows cerebral oedema
- Gadolinium-enhanced MRI
- EEG—characteristic waves

Treatment

Organise hospitalisation where treatment will be supportive. Suspected herpes simplex encephalitis should be treated with IV aciclovir immediately.

Note: Meningoencephalitis is meningitis plus some parenchymal involvement of brain substance.

⌚ Autoimmune encephalitis

This is a recently identified group of neuropsychiatric disorders seen typically in young people.⁷ There is a prodrome of fever and headache followed by days or weeks of psychiatric behavioural problems with bizarre symptoms and movements. It may be related to a paraneoplastic manifestation, e.g. ovarian cancer. Diagnosis is confirmed by blood and CSF antibody testing (anti-NMDA receptor). Specialist referral for diagnosis and specific immunotherapy is appropriate.

⌚ Brain abscess and subdural empyema^{4,8}

A brain (cerebral) abscess is a focal area of infection in the cerebrum or cerebellum. It presents as a space-occupying intracerebral lesion. Suspect in any patient with a raised intracranial pressure. The infection can reach the brain by local spread or via the bloodstream; for example, endocarditis or bronchiectasis. There may be no clue to a focus of infection elsewhere but it can follow ear, sinus, dental, periodontal or other infection and also a skull fracture. The organisms are polymicrobial, especially microaerophilic cocci and anaerobic bacteria in the non-immunosuppressed. In the immunosuppressed, *Toxoplasma*, *Nocardia* sp. and fungi.

Clinical features

Raised intracranial pressure

- Headache
- Nausea and vomiting