Tropical diseases and anaesthesia

Victoria Howell
Tom Bashford

Abstract

The range of infectious diseases encountered while working overseas in resource limited settings varies enormously depending on where in the world one is working, although the majority of low and middle income countries lie within the tropics. Human immunodeficiency virus (HIV), tuberculosis (TB) and malaria are commonly encountered when working in tropical countries and may have an impact upon anaesthesia, either as a direct result of the condition or due to interaction with the drugs used in its management. Other infections such as dengue are less likely to be encountered in a patient undergoing anaesthesia, but may be seen in patients in a high dependency or intensive care unit. Furthermore, the chronic effects of some of these diseases may impact upon anaesthesia or have complications that require surgery. It is essential therefore that the anaesthetist working within these populations has an appreciation of the tropical diseases that are endemic, set against the wider backdrop of a resource-limited population where malnutrition, poorly managed non-communicable disease and trauma may all complicate the clinical picture.

Keywords Anesthesia; coinfection; communicable diseases; global health; HIV; malaria; perioperative care; tuberculosis

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Endemic infectious disease can complicate perioperative care through acute, chronic and therapeutic effects on host physiology, with overlap within these and between different coincident infections. Coinfection is often present on a background of compromised physiology through malnutrition and non-communicable disease. As a result, any approach to perioperative care needs to be grounded in experience of working with a local population and its particular constellation of clinical problems, with a 'textbook' approach likely to be insufficient in providing high-quality care. However, a theoretical overview of the common infectious diseases which complicate perioperative care in many resource poor settings is a useful starting point for clinicians working in these areas.

Victoria Howell *MBChB MPH FRCA DMCC DTM&H The Queen Elizabeth Hospital, King's Lynn NHS Foundation Trust, King's Lynn, UK. Conflicts of interest: none declared.*

Tom Bashford *MBiochem MBBS MRCP FRCA NIHR Global Health Research Group on Neurotrauma, University of Cambridge, Cambridge University Hospitals NHS Foundation Trust, UK. Conflicts of interest: none declared.*

Learning objectives

After reading this article, you should:

- be able to list the diseases occurring in low and middle income countries that may influence the delivery of anaesthesia and peri-operative care
- understand common issues in peri-operative management of patients with concurrent morbidity including infectious diseases such as HIV, TB and malaria
- appreciate the effects of acute and chronic infectious disease processes on surgical presentation and perioperative care
- appreciate the role of polypharmacy on the management of endemic infectious disease and its effect on perioperative pharmacotherapy

Malaria

Endemic in 106 countries, malaria is one of the most common infectious diseases worldwide. Throughout the world in 2017, there were an estimated 219 million cases with approximately 435,000 deaths, the majority occurring in children under 5.[1]

Transmitted by the bite of the female *Anopheles* mosquito, there are five species of the parasite plasmodium that are known to cause malaria in humans. *Plasmodium falciparum* is found throughout the tropics, whereas *Plasmodium ovale* is confined to West Africa. *Plasmodium vivax* has a broader distribution, being found in the Indian subcontinent, China, Central America and Mexico. *Plasmodium knowlesi* occurs in South-East Asia, and *Plasmodium malariae* is distributed throughout the tropics and temperate climates. The malarial parasite is transmitted in the saliva of an infected mosquito, travelling to the liver of the human host where it matures and is subsequently released to infect red blood cells, as seen in Figure 1. It may also be transmitted through blood transfusions and organ donations, as well as via maternal–fetal placental transfer.[2]

The clinical features of malaria may be initially very non-specific, and include fever, malaise, myalgia, headaches and minor gastrointestinal symptoms. These symptoms may occur intermittently due to the cyclical nature of the parasitaemia. Severe malaria may occur in 1–2% of cases and is usually caused by *P. falciparum*. It may be defined by one or more of the following features: impaired consciousness; prostration; multiple convulsions; shock; pulmonary oedema; significant bleeding; hypoglycaemia; acidosis; renal impairment; severe malarial anaemia; jaundice; or hyperparasitaemia.[3] Patients with any of these features may require high dependency or intensive care for increased monitoring and supportive treatment of the complications. Severe malaria should be treated with intravenous (IV) or intramuscular (IM) artesunate for at least 24 hours, or IM artemether if artesunate is not available. Quinine was traditionally used to treat severe malaria; however, multiple trials and a Cochrane review have shown that artestunate is associated with reduced mortality in both adults and children.[3]

Anaesthetic implications

In the context of elective surgery and non-severe malarial infection, surgery should generally be postponed until the

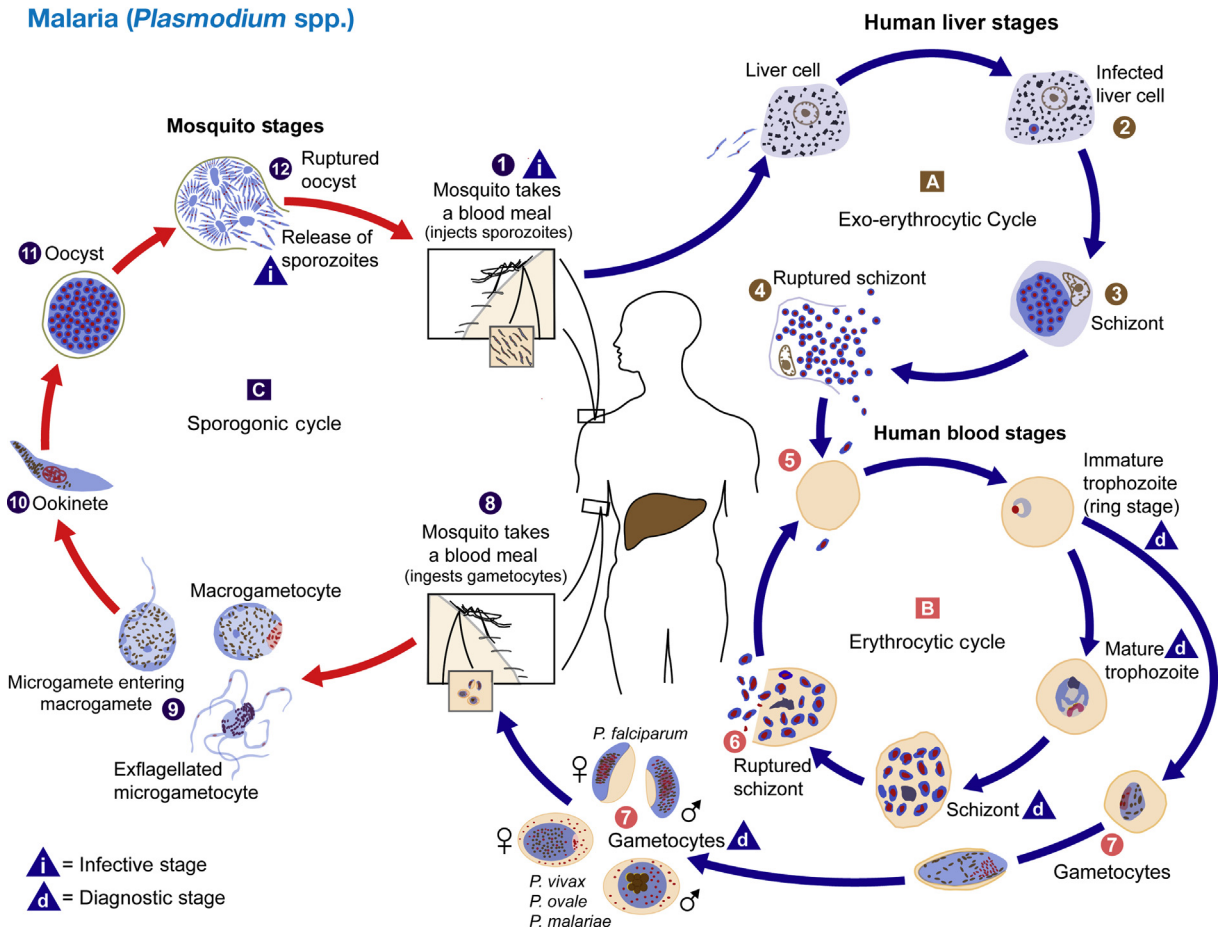

Figure 1 An illustration of the life cycle of the parasites *Plasmodium* that cause malaria. (Content provided by CDC - DPDx/Alexander J. da Silva, PhD; Melanie Moser.)

parasitaemia has been treated for 3 days with oral artemisinin-based combination therapy (ACT). Many endemic areas will advocate routinely testing patients preoperatively, and this can be done either by examination of a peripheral blood slide to look for parasites, or more commonly with a rapid diagnostic test which tests for the presence of parasitic antigens in a drop of blood. It is possible that surgical stress may reactivate *P. vivax* or *P. ovale* which are able to lie dormant in the liver.[2]

Postponement of surgery may not always be possible for emergency, trauma or obstetric patients, and active malarial infection may have implications on the conduct of anaesthesia.

- Respiratory – a dry cough is common, and acute lung injury may occur in severe malaria from pulmonary oedema.
- Cardiac – usually only affected in severe malaria, congestive cardiac failure may result from ischaemic cardiomyopathy, coronary microvascular occlusion or severe anaemia.
- Renal – acute kidney injury may complicate severe malaria and may result from hypovolaemia, sepsis, haemolysis, rhabdomyolysis or hyperparasitaemia.[2]
- CNS – cerebral malaria may reduce conscious levels, increase intracranial pressure (ICP) and cause seizures. An anaesthetic technique that ideally minimizes any increase in ICP and maintains perfusion pressure should be employed.
- Haematological – malaria may cause anaemia, thrombocytopaenia or coagulopathy, which may impact upon the choice of neuraxial anaesthesia. Transfusion is recommended for malarial anaemia if the haemoglobin is <50 g/litre or haematocrit <15%, however this threshold may be higher if significant blood loss during surgery is anticipated.[3]

Tuberculosis

Tuberculosis (TB) is also endemic in most countries, with approximately one-third of the world's population harbouring the bacilli of *Mycobacterium tuberculosis*.[4] However only 5–10% of those infected will develop active TB, which occurs more commonly in the first year of infection, in children under five, and immunocompromised individuals.

TB is spread by inhalation of infected droplets, and typically initially infects the upper lobe of the lung as a Gohn focus that develops into a granuloma. Active TB infection may then present with a persistent productive cough, haemoptysis, fever, night sweats and weight loss. Extrapulmonary TB can present in any other organ, but typically occurs in lymph nodes, bones, the abdomen, pericardium, pleura and meninges.[4]

TB may be diagnosed either through microscopy of sputum or culture of *M. tuberculosis* however increasingly near patient testing with automated nucleic amplification tests are being used, with good sensitivity and specificity, as well as rifampicin resistance detection which is used as a marker of multi-drug resistance.

Anaesthetic implications

Combination pharmacotherapy for 6 months is required for TB treatment and drug regimens can be complex, depending on the presence of HIV and drug resistance. Rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin are all commonly used, and may have interactions with anaesthetic agents. Rifampicin is a potent inducer of the cytochrome P450 enzyme CYP3A4, which is responsible for the metabolism of midazolam, fentanyl, alfentanil and lidocaine.[4] Therapeutic use potentially reduces the effects of these drugs and may result in an increased generation of toxic metabolites. Conversely, isoniazid inhibits the same cytochrome enzyme, but also induces CYP2E1 which is responsible for halothane metabolism, increasing the risk of halothane hepatitis. Neuromuscular blocking drugs may be potentiated by streptomycin, however the metabolism of rocuronium or vecuronium may be increased due to enzyme induction, mandating careful monitoring of neuromuscular blockade.[5]

In addition to their pharmacodynamic interactions, the side effects of anti-tuberculous medications may also impact upon anaesthesia. Isoniazid, rifampicin or pyrazinamide may induce hepatitis, which if symptomatic has a mortality of around 5%. Thrombocytopenia may be a feature of rifampicin or isoniazid therapy, which may cause a contraindication to neuraxial anaesthesia.

Ideally, elective surgery in patients with TB should be postponed until the patient is no longer infectious. However, anaesthesia may be required either for diagnostic procedures such as bronchoscopy or lymph node biopsy, or due to the complications of TB, for example splenic abscess, intestinal obstruction or hydrocephalus.[4] Patients with TB may be cachectic or anaemic, or have pancytopenia or deranged LFTs from disseminated TB or anti-tuberculous treatment. Respiratory function may be compromised by consolidation, cavitation or pleural effusions, and mediastinal lymphadenopathy can occasionally cause bronchial constriction.

The anaesthetist is at risk of contracting TB from those with active infection during laryngoscopy, tracheal intubation or suctioning. Personal protective equipment including gloves, eye protection and a filtering face piece (FFP3) mask should be worn if available. It is important to prevent contamination of the anaesthetic machine and circuit, and filters should be used where available. If healthcare workers have a significant exposure to TB, a tuberculin skin test may be required and, if positive, 6–9 months of isoniazid as chemoprophylaxis to prevent progression to active disease.

Human immunodeficiency virus

HIV is of particular importance in low- and middle-income countries, where more than 95% of those with HIV live. In 2017, 36.9 million people globally were living with the condition, with around 940,000 people dying from AIDS-related illnesses.

The HIV virus is transmitted in body fluids and spread through sexual intercourse, shared intravenous needles, blood transfusion and through mother-to-child transmission. Once inside the body, it enters cells with CD4 surface antigens such as helper T-cells and macrophages. Figure 2 shows how the viral RNA is transcribed to DNA and incorporated within host DNA, allowing billions of new HIV particles to be produced daily. The immune system responds by destroying these infected cells, however, is eventually overwhelmed as T-cells cannot be replaced quickly enough. This results in reduced cell-mediated and humoral immunity, with associated increase in opportunistic infections, the nature of which depends on geographically endemic diseases and the degree of immunosuppression.

Around 50% of patients have an acute seroconversion illness, with non-specific features of myalgia, arthralgia, headache, sore throat, fever, generalized lymphadenopathy and a maculopapular rash. Following this, patients remain asymptomatic until their immune system is significantly compromised. Generalized features including weight loss, weakness, diarrhoea and peripheral neuropathy may occur as well as being increasingly symptomatic of opportunistic infections as the CD4 count declines.[6]

Diagnosis is most commonly made by rapid diagnostic tests which detect anti-HIV IgG and IgM antigens in samples of oral fluid, serum, plasma or whole blood. Repeated testing is required to make a positive diagnosis, and the tests may be inaccurate during seroconversion. When laboratory facilities are available, fourth-generation immunoassays have greater sensitivity and specificity.

WHO recommendations are that retroviral therapy should be started for everyone with HIV, regardless of CD4 count.[7] The three main classes of anti-retrovirals are:

- nucleoside reverse transcriptase inhibitors (NRTIs)
- non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- protease inhibitors (PIs).

Combined therapy is advocated and many different drug regimens exist, with a combination of tenofovir, lamivudine and dolutegravir being first line therapy.[7] For those patients without any clinical evidence of active TB, 6 months prophylaxis with isoniazid is also recommended. Patients with severe or advanced HIV disease or CD4 counts <350 cells/mm^3 are given co-trimoxazole to prevent opportunist bacterial infections such as *Pneumocystis jirovecii* and *Toxoplasma gondii*.

Anaesthetic implications

Asymptomatic or managed HIV infection is not associated with increased perioperative mortality. However, with advanced disease, the comorbidities and infections may impact upon anaesthesia.

- Respiratory – infections are common in advanced disease, usually caused by bacterial pneumonia, but TB should always be excluded. Pulmonary Kaposi's sarcoma or lymphoma may impact respiratory function, as may empyema which may require draining.
- Cardiac – infection may also cause a myocarditis, which may progress to a dilated cardiomyopathy. Bacterial infection may cause endocarditis and congestive cardiac failure.
- Gastrointestinal – chronic diarrhoea is relatively common, and if severe may lead to electrolyte disturbances and fluid imbalance.

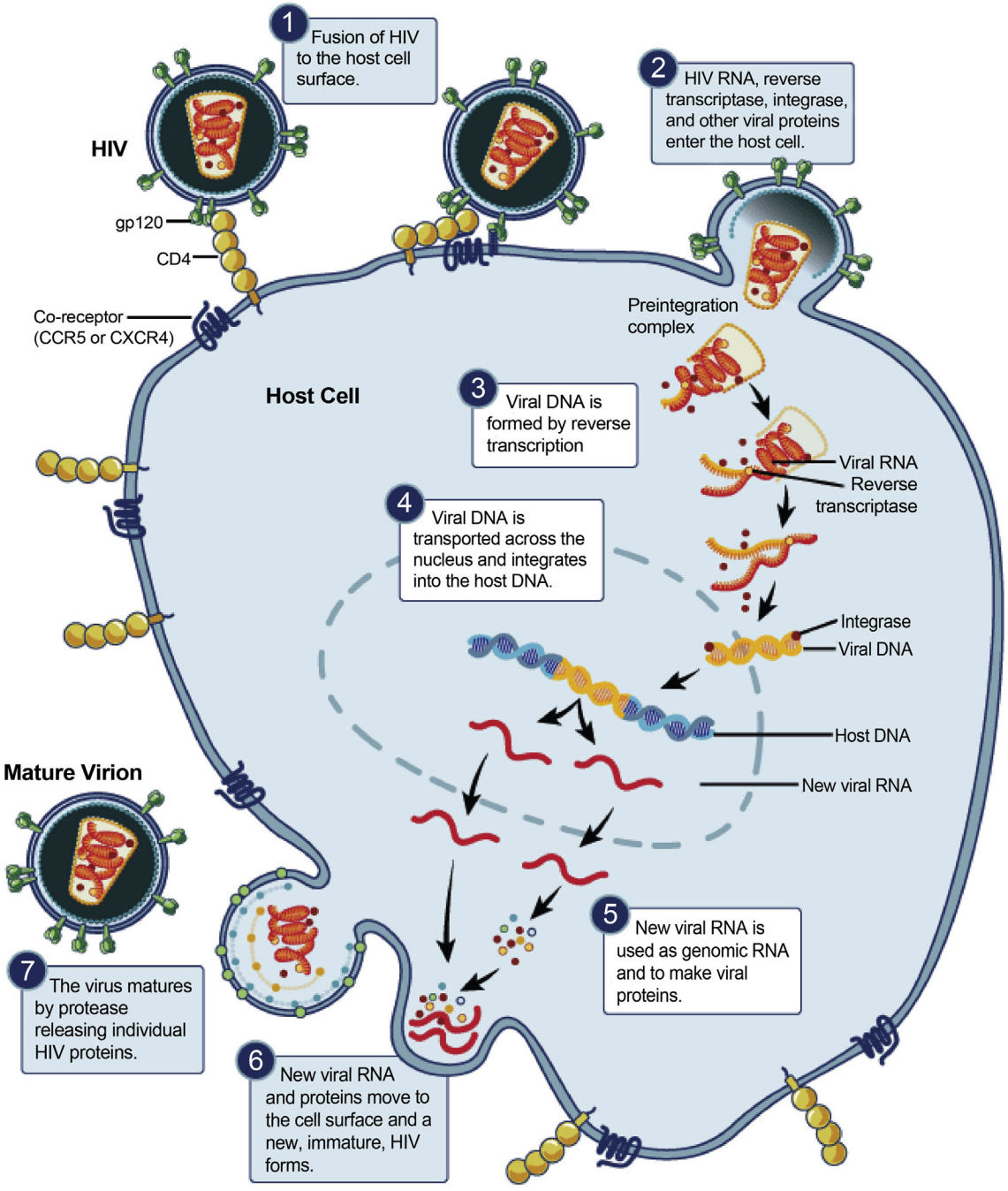

Figure 2 Produced by the National Institute of Allergy and Infectious Diseases (NIAID), this illustration depicts the human immunodeficiency virus replication cycle involving a host cell within the human body.

- Central nervous system – neurological complications may range from peripheral neuropathy to meningitis and encephalitis.
- Haematological – anaemia, thrombocytopaenia and leucopenia are common.

Anti-retroviral drugs may also have an impact on anaesthesia. Several of the drugs interact with the cytochrome P450 enzyme system that metabolize many anaesthetic drugs. For example ritonavir, a protease inhibitor, inhibits the CYP3A4 isoenzyme and reduces the metabolism of fentanyl, pethidine and midazolam, which may have a clinically significant effect. Dexamethasone and thiopentone may themselves reduce protease inhibitor concentration, thus making the drugs less effective. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, induces cytochrome P450 enzymes. These drugs are frequently used in combination, which may have an unpredictable effect on co-administered anaesthetic agents.

Universal precautions should be used for all patients, especially in areas of high HIV prevalence. If there is exposure to high-risk body fluids, such as after a needle-stick injury, post-exposure prophylaxis (PEP) should be started as soon as

possible. Current recommendations for PEP are for tenofovir with emtricitabine plus lopinavir with ritonavir for 28 days.[7]

Dengue

Dengue is endemic in more than 120 countries in the tropics. It is a viral infection transmitted by the day-biting female *Aedes aegypti* mosquito, and is clinically separated into dengue fever with or without warning signs, and severe dengue, formally known as dengue haemorrhagic fever. Dengue fever typically presents with non-specific features of a flu-like illness with high fever, headache, retro-orbital pain, nausea and vomiting, lymphadenopathy, rash, arthralgia and myalgia.[8] Features of severe disease usually occur 3–7 days after first symptoms and are associated with a reducing temperature. Warning signs include:

- persistent vomiting
- haematemesis
- abdominal pain or tenderness
- respiratory distress
- mucosal haemorrhage
- fatigue or restlessness
- rapid decrease in platelet count, associated with an increase in haematocrit (>20% above baseline).

Severe dengue is associated with severe plasma leakage, which may lead to cardiovascular collapse or fluid accumulation and associated respiratory distress. Severe haemorrhage may occur, along with severe organ impairment seen as a liver transaminase >1000 iu/L, impaired consciousness or other organ involvement.

The pathophysiology of dengue occurs due to the immune response. There are four serotypes of the dengue virus that affect humans, and infection with one serotype confers immunity. However, cross-immunity to other serotypes is only partial and transient. Previous dengue infection causes antibody-dependant enhancement, increasing entry of a second dengue serotype into macrophages, leading to increased severity of infection. These macrophages release vasoactive mediators, massively increasing vascular permeability leading to plasma leakage, hypovolaemia and shock. Fragile capillaries and thrombocytopenia leads to bleeding, with activation of clotting and fibrinolytic pathways that may lead to disseminated intravascular coagulation (DIC).

While most cases of dengue are mild and self-limiting, severe dengue may require fluid resuscitation, blood transfusions and invasive monitoring.

Lymphatic filariasis

Endemic in more than 80 countries where it is transmitted by mosquitoes, lymphatic filariasis affects around 120 million people. Infection with *Wuchereria bancrofti*, the parasitic roundworm that is the major cause of lymphatic filariasis, usually occurs in childhood but the chronic manifestations of the disease develop months or years later. Figure 3 shows the lifecycle of the parasite within both human and mosquito hosts. Acute infection may be

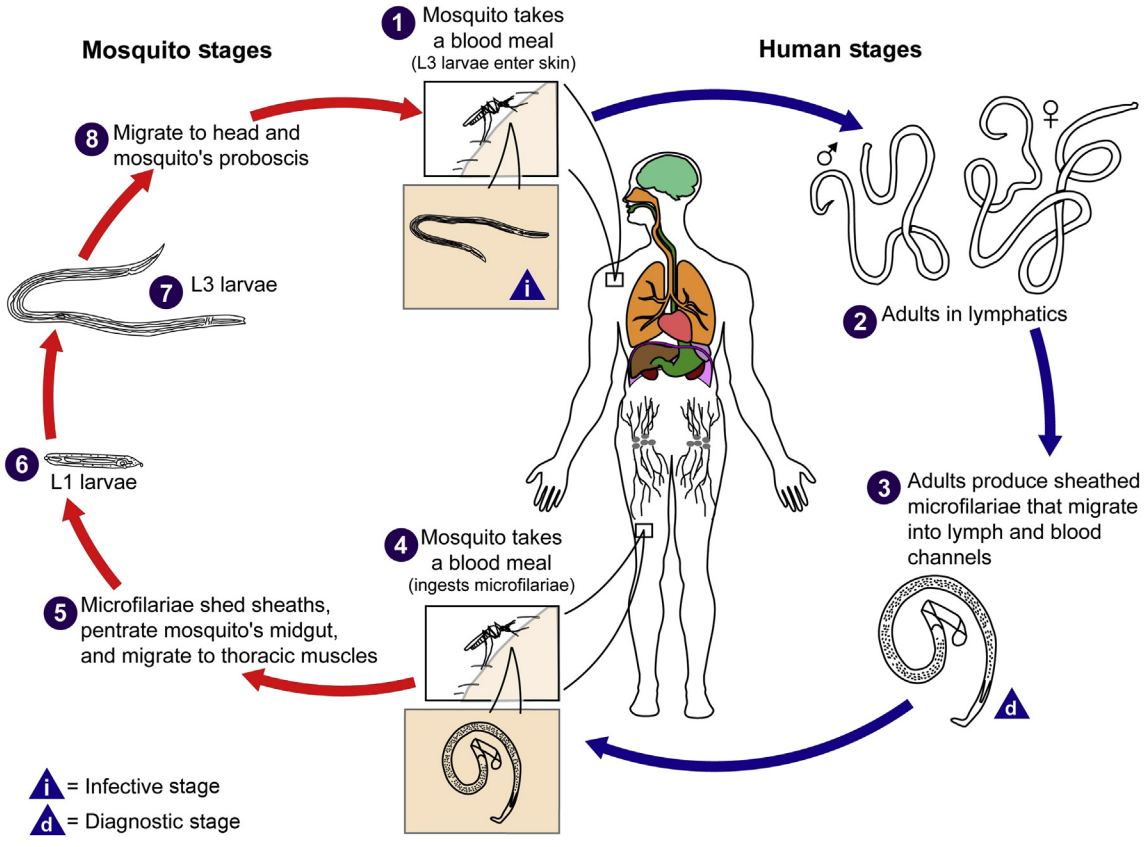

Figure 3 An illustration depicting the life cycle of the nematode *Wuchereria bancrofti*, one of the causal agents of the parasitic disease lymphatic filariasis. (Content provided by CDC/Alexander J. da Silva, PhD; Melanie Moser.)

asymptomatic or may be seen as filarial fever, acute filarial lymphangitis or tropical pulmonary eosinophilia.[8] Chronic filariasis obstructs the lymphatics leading to lymphoedema of the legs and elephantiasis. Chyluria, chylous diarrhoea and chylous ascites may all occur if distended lymphatics rupture. Surgery may be required for hydroceles that develop.

Antihelmintic treatment has traditionally been used; however, these do not kill adult worms and are often associated with significant adverse effects. A symbiotic parasite living within the filarial worm, *Wolbachia* can be targeted with doxycycline. A 6-week course of doxycycline has been shown to eliminate worm nests from the scrotum of men with filarial hydroceles. However, hydrocelectomy may still be required for those unresponsive to drug therapy. In resource limited settings, this has been done successfully under local anaesthesia with spermatic cord block and local infiltration.

South American trypanosomiasis

South American trypanosomiasis or Chagas' disease is caused by *Trypanosoma cruzi* transmitted by triatomine or 'kissing' bugs. Transmission may also occur through blood transfusion, transplanted organs or maternal–fetal transfer. Acute infection is most common in children, but is frequently asymptomatic. A chagoma may occur from swelling around the site of entry, along with lymphadenopathy and hepatosplenomegaly. Meningioencephalitis or cardiac damage are rare complications and symptoms usually resolve spontaneously within a few months.

Chronic Chagas' disease typically presents 10–20 years after initial infection and may have significant cardiac or gastrointestinal effects that can affect anaesthesia. Arrhythmias or heart block may occur due to scarring of the conduction system, and a slowly progressive myocarditis may lead to a dilated cardiomyopathy. Death may be due to refractory heart failure or thromboembolism, although the majority are sudden cardiac deaths from ventricular fibrillation or tachycardia. Pre-operative investigations such as a chest X-ray, an electrocardiogram or an echocardiogram if available, may help guide the severity of cardiac dysfunction.

Chagas' disease destroys the autonomic ganglia within the gut, resulting in dilatation of the gastrointestinal tract. This typically manifests as megacolon, which may require surgery, but patients are also at risk of megaoesophagus. Malnutrition and dysphagia may be caused by chagasic achalasia which can lead to megaoesophagus and increased the risk of aspiration in the perioperative period. ◆

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