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Tropical medicine and anaesthesia 1

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Key points

- Tropical diseases represent an important subset of anaesthetic comorbidity.
- With increasing travel, tropical disease is no longer geographically constrained.
- Tropical illness may be both a cause for surgery and complicate incidental surgery.
- Acute and chronic infections, parasites, and malnutrition are key factors.
- Many of these can be optimized pre-surgery by treating the underlying causes.

Anaesthesia is complicated by comorbidity, with a variety of diseases endemic to tropical regions that pose specific problems for the anaesthetist. With increasing global travel, these diseases are no longer geographically limited to the tropics, so it is useful to have an appreciation of the impact that these illnesses, and their treatments, may have on the approach to anaesthesia. Tropical illnesses include not only those communicable diseases endemic to given geographical regions, but overlap with conditions of the extreme poverty, which is often prevalent in these areas.

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Tropical infections impacting on anaesthesia

Malaria

Malaria is one of the commonest infectious diseases, with almost 200 million cases worldwide in 2013.[1] In 2016 the UK saw more than 1 500 imported cases of malaria, and in the past 20 yr there have been over 36 000 cases with 167 deaths.[2] Most malaria is contracted through the bite of a female *Anopheles* mosquito; however transmission is also possible through maternal-fetal placental transfer, blood transfusions, and organ donations.[3]

There are five *Plasmodium* subtypes that can cause human malaria, with *Plasmodium falciparum* the most severe. The majority of the multi-system manifestations seen are because of the changes in the parasitized erythrocyte; these show a reduced membrane deformability and increased fragility, with accelerated haemolysis leading to an anaemia that may be complicated by direct bone marrow suppression.[4] Increased adherence to the vascular endothelium causes sequestration of red blood cells and microvascular capillary obstruction of the cardiac, renal, hepatic, splenic, and cerebral circulations. Pro-inflammatory cytokines, such as interleukin-1 and tumour necrosis factor, may generate a systemic inflammatory response.

Malaria typically presents with non-specific intermittent symptoms reflecting the cyclical nature of the parasitaemia: fever, malaise, headache, and myalgia. Severe malaria is

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diagnosed if one or more of the following symptoms are present: impaired consciousness; prostration; multiple convulsions; acidosis; hypoglycaemia; severe malarial anaemia; renal impairment; jaundice; pulmonary oedema; significant bleeding; shock; or hyperparasitaemia.[5]

Treatment of uncomplicated malaria should be with oral artemisinin-based combination therapy (ACT) for 3 days.[5] Severe malaria should be treated with i.v. or i.m. artesunate for at least 24 h, followed by an oral ACT for 3 days. If artesunate is not available, then i.m. artemether is used in preference to i.v. quinine.[5]

Elective surgery should be postponed until after the acute episode of malaria has resolved. Testing of patients before surgery is undertaken routinely in some endemic areas although it is unknown whether asymptomatic malarial parasitaemia has an impact on surgery and anaesthesia. It has been suggested that surgical stress may cause reactivation of dormant *Plamodium vivax* or *Plamodium ovale*.[4]

Preoperative evaluation of patients with malaria should include an assessment of the severity of infection and degree of organ impairment (Table 1).

Considerations for anaesthesia

Beyond several case reports, very little has been published regarding malaria and anaesthesia, with recommendations based largely on clinical experience and an understanding of the underlying pathology.[4] Severe malaria manifests as a multisystem disorder analogous to severe sepsis. The approach to these patients presenting for surgery should consider similar aspects; pre-optimization, appropriate anaesthetic technique, and postoperative care. Unlike in sepsis, little work has been done to quantify the perioperative risk caused by malaria and there is a paucity of published outcome data to guide this.

Central nervous system. Cerebral malaria may cause impaired consciousness, seizures, and raised intracranial pressure (ICP) as a result of obstruction of the cerebral microcirculation and impairment of cerebral autoregulation.[3] A neuroanaesthetic that maintains cerebral perfusion pressure and minimizes increases in ICP is ideal. There is little evidence that volatile agents contribute to a worse outcome despite their role in increased cerebral blood flow. Ketamine should be avoided if possible because of its potential to increase ICP.

Haematological. Anaemia, thrombocytopenia and coagulopathy may all complicate malaria. Transfusion is recommended in malaria when the haematocrit falls below 15% or the haemoglobin <50 g litre^{-1} although this threshold may be higher where there is anticipated significant blood loss.[5]

Cardiovascular. Cardiac function is usually only compromised in severe malaria. Congestive cardiac failure may be caused by severe anaemia, and an ischaemic cardiomyopathy may result from coronary microvascular obstruction. Haemodynamic instability may be exacerbated by either aortocaval compression from massive splenomegaly, or quinine-associated arrhythmias.

Pulmonary. Up to half of patients with malaria will have a symptomatic dry cough. Severe malaria can lead to acute lung injury through either cardiogenic pulmonary oedema from fluid overload, or non-cardiogenic pulmonary oedema thought to be because of a combination of sequestered parasitized erythrocytes in the pulmonary capillaries, and the host immune response.[3] Intraoperative ventilation may be difficult in these patients and a period of postoperative ventilation may be required.

Endocrine. Hypoglycaemia is common in severe malaria because of increased utilization of plasma glucose by the parasites, or quinine-stimulated insulin release. Fasting before surgery may significantly contribute to hypoglycaemia, and regular blood sugar monitoring is important.

Renal. Acute kidney injury is a common consequence of severe malaria. This may be caused by a combination of hyperparasitaemia, pyrexia, sepsis, hypovolaemia, haemolysis, and rhabdomyolysis.[3] Malarial nephrotic syndrome may occur in children with *Plasmodium malariae* infection, while Blackwater fever is caused by haemoglobinuria from quinine-induced lysis of erythrocytes. Preoperative assessment of renal function, and maintaining adequate renal blood flow and perfusion pressure, are important. Renal replacement therapy may be required perioperatively.

Tuberculosis

Tuberculosis (TB) is endemic in most tropical countries, with a third of the world's population estimated to harbour the bacilli.[6] *Mycobacterium tuberculosis* is usually spread by the inhalation of infected droplets; most person to person transmission occurs following prolonged exposure, but only a few bacteria are necessary to acquire the infection. However, only about 5–10% of those who are infected go on to develop active TB, and there is often a period of latency before the disease

Table 1 Preoperative investigations for patients with malaria

Preoperative investigation	Explanation
Full blood count	Examine degree of anaemia and thrombocytopenia
Blood film	Diagnose type of malaria and level of parasitaemia
Urea and creatinine	Assessment of renal function
Electrolytes	Hyponatraemia and hyperkalaemia may be present
Liver function tests	Assessment of liver impairment
Coagulation studies	May reveal evidence of dissemination intravascular coagulation and assess hepatic synthetic function
Blood glucose	Hypoglycaemia may be a feature of malaria, and may also be caused by quinine therapy
Arterial blood gas	Acidosis (base deficit >8 mEq litre^{-1}) or hyperlactataemia (≥5 mmol litre^{-1}) are features of severe malaria Hypoxia from acute respiratory distress syndrome (ARDS)
Chest X-ray	May reveal pulmonary oedema or ARDS in severe malaria
ECG	Quinine may prolong QT interval

manifests. Those who have TB and contract human immunodeficiency virus are at increased risk of developing active disease at around 15% per year. In addition, those with HIV infection are at increased risk of acquiring new TB infection, with two thirds of TB patients also having HIV.[7]

The most common presenting features are cough and haemoptysis, but patients also present with constitutional symptoms such as fever, weight loss, night sweats, or failure to thrive. Extra-pulmonary TB can present in almost any other organ with typical sites being the bones, abdomen, meninges, pericardium, lymph nodes, and pleura.[8] Disseminated TB occurs because of widespread haematogenous distribution of TB bacilli, and is more commonly seen in patients with HIV.

Culturing *M. tuberculosis* to provide a definitive diagnosis requires between 2 and 12 weeks. Acid fast bacilli may be seen under the microscope of a Ziehl-Neelsen stained sputum smear, however, point of care tests using automated nucleic acid amplification tests are increasingly used. These can also detect resistance to rifampicin, which is taken as a surrogate for multi-drug resistant TB.[7] Chest X-rays may not always show the typical apical cavitating lesion and those with HIV co-infection may have other abnormal radiographic changes. Tuberculin skin tests may be used as a marker of TB infection, but false-positives can occur in those who have been vaccinated, and false-negatives in those with a poor immune response. In the UK, TB is a notifiable disease, and positive cases may require contact tracing. Specific NICE guidance exists on when this is required, and those who should be offered screening.

Treatment of TB requires a minimum of 6 months of combination therapy and direct observation of therapy is often used to ensure patient compliance with treatment. First line drugs include rifampicin, isoniazid, ethambutol, and pyrazinamide. These drugs not only have significant side effects that may impact on anaesthesia, but also have many important interactions with anaesthetic agents; discussed further in the second article in this series. Multi-drug resistant TB, defined as resistance to isoniazid and rifampicin, and extensively drug resistant TB, which shows additional resistance to a fluoroquinolone and a second-line injectable drug, are increasingly problematic.

Considerations for anaesthesia

Patients with TB may present for incidental surgery, for diagnostic procedures such as lymph node biopsy or bronchoscopy, or because of complications from TB such as intestinal obstruction, hydrocephalus, or splenic abscess.[8] Elective surgery should ideally be delayed until the patient is no longer infectious.

Patients may be acutely unwell, cachectic, anaemic, and those with disseminated TB may have pancytopaenia and deranged liver function tests. Mediastinal lymphadenopathy can cause bronchial constriction, manifested as wheeze on auscultation. Areas of cavitation or consolidation, as well as pleural effusions, can all compromise respiratory function, as well as the bronchiectasis or fibrosis that may occur with longstanding TB. Catastrophic haemoptysis may occur if the cavitating lesion erodes into a blood vessel.

The anaesthetist is particularly susceptible to transmission during procedures such as bronchoscopy, laryngoscopy, tracheal intubation, and suctioning.[9] An increased duration of exposure and higher concentration of infectious droplets increases the likelihood. Protective measures include immunization against TB and the use of personal protective equipment, such as gloves, eye protection, and a filtering face piece (FFP3) mask. It is important to prevent the contamination of anaesthetic equipment and in addition to antibacterial breathing filters, The Association of Anaesthetists of Great Britain and Ireland Safety Guideline on Infection Control in Anaesthesia recommends changing breathing circuits after anaesthetizing a patient with active TB infection and the sterilization of any other equipment used. Soda lime change is not recommended, with the advice to change this routinely in line with individual manufacturers' recommendations.[10] If significant exposure to TB does occur, a tuberculin test may be required and, if positive, 6–9 months of chemoprophylaxis with isoniazid indicated to prevent progression to active disease.[9]

Chagas' disease

Chagas' disease (South American trypanosomiasis) is caused by *Trypanosoma cruzi* transmitted by triatomine or 'kissing' bugs, from the Reduviidae family. Transmission may also occur through blood transfusion, transplant, or maternal-fetal infection. Acute infection is most common in children, but only about one third of those infected are symptomatic.[7] Swelling at the entry site (a chagoma), lymphadenopathy, and hepatosplenomegaly may be seen. Death from cardiac damage or meningoencephalitis is rare, and symptoms usually resolve spontaneously within a few months. Diagnosis can be made by microscopy in the acute infection, however, serological tests may be required in the chronic phase. Treatment with the antiparasitic drugs benznidazole or nifurtimox will treat the acute infection.

Considerations for anaesthesia

Chronic Chagas' disease can occur 10–20 yr after the initial infection, with important cardiac and gastrointestinal consequences.

A slowly progressive myocarditis with destruction of the myocardium leads to a dilated cardiomyopathy, with scarring of the conduction system leading to a high incidence of heart block and arrhythmias.[11] Echocardiography, electrocardiography changes, and the presence of cardiomegaly on chest X-ray can help to guide the severity of the cardiac dysfunction. Impaired left ventricular function is an independent predictor of mortality. Sudden cardiac death, usually because of ventricular tachycardia or fibrillation, is the main cause of death, although refractory heart failure and thromboembolism may also occur.

Destruction of the autonomic ganglia within the gut may cause dilatation of any part of the gastrointestinal tract. Megacolon is the most common manifestation, followed by megaoesophagus, although patients may also present with both conditions. Chagasic achalasia may present with dysphagia and malnutrition, and may develop into megaoesophagus. The oesophageal complications of Chagas' disease pose an increased risk of aspiration during the perioperative period, while management of the gastrointestinal complications may require surgery.

Endomyocardial fibrosis

Endomyocardial fibrosis (EMF) is a condition almost exclusively of tropical regions that mainly affects children and young adults from low income backgrounds. The exact aetiology is unknown but has some similarities to

hypereosinophilic syndrome. Other theories involve various infectious agents such as parasites, toxoplasmosis or malaria, malnutrition, or certain toxins.[12]

Prognosis of the condition may be difficult to determine, as there are both acute and chronic forms. If left untreated, it is progressive and patients typically die within 2 yr of diagnosis.[12] Medical management focuses on preventing and treating heart failure, arrhythmias, and thromboembolism. Surgical intervention may improve survival if it is undertaken before irreversible cardiac or hepatic damage, but the availability of cardiac surgery is often limited in countries where the condition typically presents.[13]

Considerations for anaesthesia

EMF causes distortion of the myocardium and a restrictive cardiomyopathy. A subendocardial fibrosis affecting mainly the apex of the right, left, or both ventricles, leads to limitation of ventricular filling and tethering of the papillary muscles, which may cause valvular regurgitation.[12] Diastolic dysfunction is the main clinical feature, presenting with cardiac failure or ascites.

The electrocardiogram is useful as it may show low voltage or atrioventricular block caused by fibrosis of the conducting system. Approximately one third of patients with EMF have atrial fibrillation. The chest X-ray can be normal, or may show cardiomegaly from pericardial effusions.

Echocardiography is a useful diagnostic tool and will typically show the obliteration of the ventricular apices. Tricuspid and mitral regurgitation is common and patients often have a pericardial effusion.[13] In addition, ventriculography shows fibrotic distortion of the left or right chambers together with valvular regurgitation.

General condition of the patient

Malnutrition

Protein-energy malnutrition (PEM) is common and can complicate many tropical diseases. Clinically it can be thought of as a disease spectrum, ranging from underweight, through to the more severe marasmus, marasmic-kwashiorkor, or kwashiorkor.[14] PEM has complex systemic consequences resulting in long-term health effects, which vary depending on the duration of malnutrition, prevalent co-morbidities, and co-existing micronutrient deficiency.

Considerations for anaesthesia

Predisposition to infection is a major complication, occurring as a result of deficiencies in immune mediators.[14] Protein deficiency also contributes to the oedema that is a feature of kwashiorkor, although aflatoxins produced by certain fungi have also been implicated.[15] Reduced carbohydrate intake leads to abnormal lipid metabolism and reduced adipose tissue.

PEM can have a significant effect on drug disposition. Volume of distribution is affected by the increased total body water, the reduction in adipose reservoirs, and the reduced levels of circulating albumin. There may be reduced enzyme activity related to the degree of severity of malnutrition, with reduced levels of plasma cholinesterase resulting in suxamethonium apnoea.[16]

Malnutrition is the underlying cause of Cancrum oris, or Noma, a rapidly progressive destructive polymicrobial infection of the mouth that can lead to an almost unmanageable airway. Malnutrition may affect the respiratory system, by reducing respiratory drive and increasing the incidence of nosocomial infection. Myocardial dysfunction may also occur, compounded by specific vitamin deficiencies such as thiamine deficiency. These cardiovascular effects may last well beyond the period of malnutrition, with long term damage leading to hypertension and impaired cardiac function in adult survivors of childhood malnutrition.[17,18]

Malnutrition is associated with suboptimal perioperative outcomes, including increased risk of infection, poor wound healing, increased hospital length of stay, and increased mortality after some types of major operation. Where practical, surgery should be postponed until the patient is no longer malnourished.

Anaemia

The World Health Organization defines anaemia as Hb < 130 g litre^{-1} for men and Hb < 120 g litre^{-1} for non-pregnant women.[19] Anaemia is one of the commonest conditions worldwide, and the second leading cause of disability.[20] It is particularly problematic in tropical regions where over half of children and pregnant women are anaemic and may be because of a combination of infection, malnutrition, and red cell abnormalities.

Infections

Malaria, HIV infection, and TB are all causes of anaemia. This may complicate parasitic anaemia caused by hookworm infections, schistosomiasis, and trichuriasis in endemic areas. Any infection that causes chronic inflammation may also contribute to anaemia caused by cytokine depression of erythropoiesis.

Hookworms such as *Ancylostoma duodenale* and *Necator americanus* affect approximately 600 million people living in the tropical and subtropical regions of the world.[7] Larvae are typically found in the soil, and invade the body through cracks in the skin or hair follicles. After migrating through the lymphatics and lungs, they attach to the proximal half of the small intestine and feed on blood. Most people with hookworm infection are asymptomatic, and treatment with albendazole or mebendazole is usually effective.

Trichuriasis, or whipworm (*Trichuris trichiura*) infection, occurs when eggs are swallowed from contaminated food or soil. The worms are subsequently found in the mucosa of the large bowel and feed on tissue juices, rather than blood.[7] However, bleeding from the mucosa may occur, leading to an iron-deficiency anaemia, particularly in those on poor diets. Infections may be asymptomatic, however, severe trichuriasis may cause dysentery leading to rectal prolapse. Albendazole and mebendazole are both used for treatment, as well as ivermectin and nitazoxanide.

Malnutrition

Nutritional deficiency of iron, folate, or Vitamin B_{12} is common and may lead to anaemia. Due to the seasonal availability of fresh green vegetables in tropical climates, folate deficiency may be seasonal, as body stores are quickly depleted during poor intake.

Red cell abnormalities

Sickle cell disease. A genetic disorder of haemoglobin, with a structural abnormality of the β-globin chain resulting in the

production of abnormal haemoglobin S or C. Sickle cell trait (HbAS) protects from severe malaria, and consequently this carrier state has a prevalence of 25–30% in tropical African countries, but the trait does not cause anaemia.[20]

HbS causes sickling of red cells in hypoxic conditions. With repeated sickling, the cells become irreversibly misshapen resulting in a reduced life-span with associated jaundice and anaemia. Clumping of sickled cells activates coagulation pathways and can lead to infarction.[20] Sickle cell patients are at increased risk of infection because of hyposplenism, and reduced cell-mediated immunity. They are also at increased risk of developing acute anaemia from haemolytic crises or acute splenic sequestration.

β-thalassaemia. Results in reduced production of the β-globin chain. Approximately 1.5% of the global population are carriers for this condition, with half of these from India, Thailand, or Indonesia.[21] In β-thalassaemia major, patients are unable to make HbA so have severe, transfusion-dependent, anaemia and die in early childhood without treatment. Regular blood transfusions should maintain the Hb > 120 g litre^{-1} with regular chelation to remove excess iron.

Glucose 6-phosphate deficiency. The most common metabolic disorder of red blood cells and provides some protection from malaria. Anaemia in patients with the deficiency may be precipitated by certain drugs or infections, where acute intravascular haemolysis occurs 2–3 days following exposure.

Investigations

Without laboratory testing, mild anaemia may be difficult to diagnose. Pallor of the tongue and conjunctiva has poor sensitivity and specificity and is only reliably seen in severe anaemia.

Haemoglobin concentration and a peripheral blood film will give much information about the degree of anaemia and possible causes. Thorough examination of a blood film may indicate iron or folate deficiency, haemoglobinopathies, enzymopathies, and malignant or proliferative haematological disorders.[7]

Features of sickle cell disease (SCD) may be seen on the blood film, but haemoglobin electrophoresis, isoelectric focusing or high-performance liquid chromatography may confirm the diagnosis.[20] Sickledex, a rapid screening test, is useful in emergencies, but cannot distinguish between sickle cell anaemia and trait.

Considerations for anaesthesia

Perioperative anaemia is associated with adverse outcomes: wound infections; sepsis; respiratory, urinary, and thromboembolic complications; and mortality. It increases the risk of requiring a blood transfusion, which carries risks in both high- and low-income environments. Specific issues around blood transfusion in resource-poor settings are explored in the second article in this series.

The implications for anaesthesia of SCD have been extensively reviewed, and the perioperative period is associated with an increased incidence of SCD-related complications.[22] Management of these patients should include a well-delivered anaesthetic that avoids any of the factors that may precipitate a vaso-occlusive crisis. Acute chest syndrome, often precipitated perioperatively, may result in life-threatening hypoxia and respiratory failure. This is defined as the onset of a new lobar infiltration on chest X-ray accompanied by a fever greater than 38°C, respiratory distress, or chest pain. It often presents 2–3 days after surgery, with management based around good pulmonary toilet and treatment common to other vaso-occlusive crises, i.e., avoidance of hypoxia, normothermia, analgesia, and hydration. Pain crises may also require anaesthetic input. Ischaemia or infarction of bone marrow is the typical cause of long-bone pain, but visceral pain as a result of organ infarction is also possible. Patients may be very opioid tolerant because of past use, but care should be taken where renal function is impaired.

A recent clinical trial has supported the use of transfusion in SCD patients to ameliorate some of the perioperative vaso-occlusive complications.[23] In low resource environments, this potential benefit needs to be offset against the risks of blood transfusion, and the lack of available blood, which are issues dealt with in detail in the second article in this series. Repeat blood transfusions increase the risk of haemosiderosis that may lead to diastolic dysfunction, an increased risk of arrhythmias and dilated cardiomyopathy.[24] In patients with glucose 6-phosphate deficiency, drugs that are known to precipitate haemolysis, such as thiopentone and non-steroidal anti-inflammatory drugs, should be avoided.

Thalassaemia also presents a number of potential anaesthetic complications including cardiomyopathy, pulmonary hypertension, cardiac failure, restrictive lung dysfunction, anaemia, and thromboembolic events.[25] These multisystem effects may occur as a result of both the underlying disease or the resultant repeat transfusion, iron overload, and chelating therapy. The possibility for a difficult intubation should be considered in light of the oro-facial malformation that results from bone marrow hypertrophy, osteopenic facial fractures, and poor dentition.

Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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