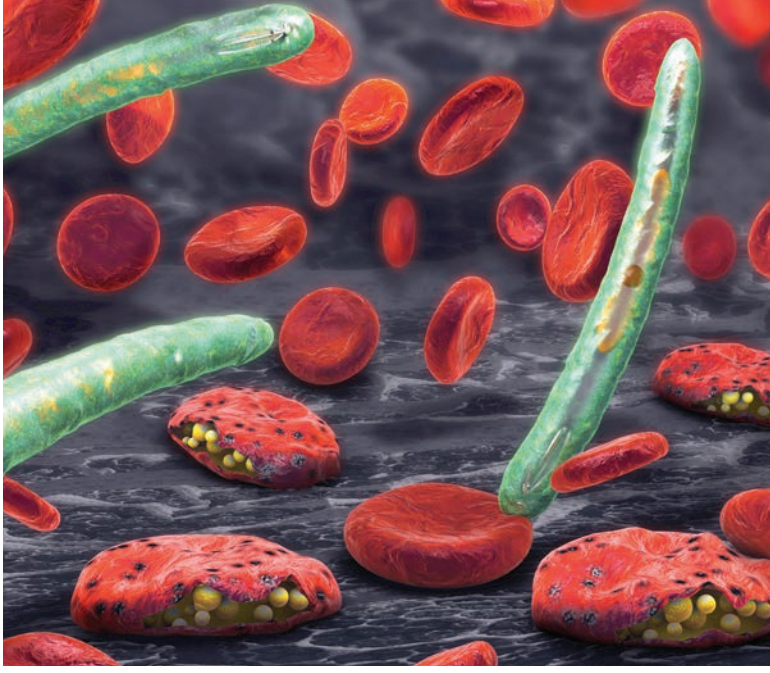
Invasive protozoal infections in Australia



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Protozoal infections remain a significant global health concern, and although uncommon in Australia, they are increasingly seen in returned travellers, migrants and immunosuppressed individuals. Invasive amoebiasis, toxoplasmosis, malaria and leishmaniasis may be encountered in primary care. Subtle or delayed presentations make diagnosis challenging, requiring careful assessment of travel history, exposures and immune status. Improved clinician awareness supports earlier detection, timely management and reduced morbidity.

KEY POINTS

- Returned travellers, migrants and immunosuppressed patients are groups in Australia at higher risk of protozoal infections.
- People with protozoal infections can present with vague or delayed symptoms, creating diagnostic uncertainty in primary care.
- Accurate diagnosis relies on targeted history taking, appropriate investigations and infection-specific clinical features.
- Conditions such as malaria, toxoplasmosis, amoebiasis and leishmaniasis require prompt recognition to prevent complications.
- Prevention strategies, including travel advice and risk mitigation, remain essential in reducing imported infections.

Protozoa are unicellular organisms that may live freely or within a human or other animal host, often causing infection in humans through mechanisms such as antigenic variation or intracellular concealment. Clinically, infections may be broadly classified into intestinal protozoal, free-living amoeba or blood and tissue protozoal infections. These infections pose a significant global health burden, particularly in low- and middle-income countries. Invasive protozoal infections are not often encountered in primary care in Australia, but they are being increasingly observed in returned travellers, migrants and immunosuppressed patients.

Primary health care providers face diagnostic challenges because of subtle or nonspecific clinical presentations that may arise well after exposure to protozoa, compounded by limited familiarity with ordering and interpreting specialised investigations. Although malaria and leishmaniasis are not acquired in Australia, their incidence is rising in the context of global travel and immunosuppression. *Entamoeba histolytica* is more common in travellers but may be locally acquired. Toxoplasmosis is endemic and has important implications in pregnancy and for immunocompromised individuals.

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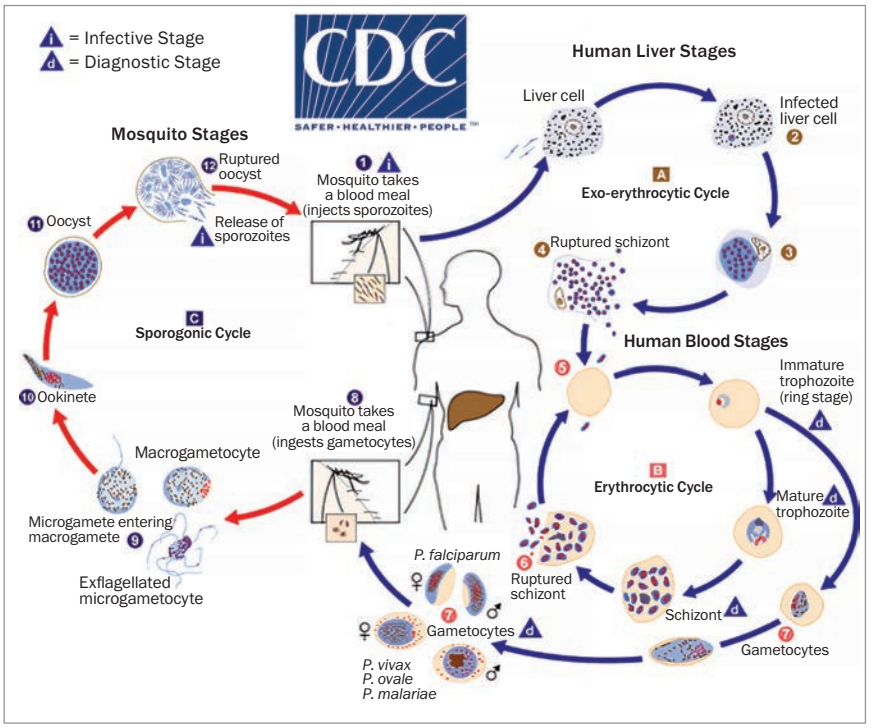

Figure 1. Life cycle of the malaria parasite.[14]
Reproduced from DPDx, US Centers for Disease Control and Prevention (https://www.cdc.gov/dpdx/malaria/index.html).

Accurate diagnosis requires a careful clinical approach, incorporating a detailed history of travel, exposures, prophylactic measures, immunological status and a focused physical examination. This article reviews key protozoal infections relevant to primary care and aims to support GPs in their clinical assessment and investigation of these conditions.

Malaria

Malaria should be regarded as a medical emergency, and timely diagnosis is crucial to avoid serious complications. Malaria is a protozoal infection caused by *Plasmodium* species. Delays in treatment can result in death, particularly from *Plasmodium falciparum* malaria. It is a vector-borne disease, spread via the bite of an infected female Anopheles mosquito.[1] Five major Plasmodium parasite species cause disease in humans: *P. vivax, P. falciparum, P. malariae, P. ovale* and *P. knowlesi*.[1,2] Global elimination efforts primarily focus on *P. falciparum* and *P. vivax* because of their high prevalence and potential to cause severe disease.[3] Malaria is not endemic in Australia; however, 700 to 800 malaria cases are diagnosed annually in returned travellers.[4]

Epidemiology

In 2023, there were an estimated 263 million new malaria cases in 83 countries worldwide. Although 94% of all global cases occurred in Africa, in Australia most cases were acquired in Oceania and Asia, including Papua New Guinea, Indonesia, the Solomon Islands, the Philippines, Cambodia and Vanuatu. This reflects Australia's geographic proximity, common travel patterns and its composite migrant population.[5-7]

The WHO declared Australia malaria-free in 1981.[8] However, the tropical north of the country remains malaria-receptive because of the presence of *Anopheles* mosquito vectors.[9] Cases reported in Australia are usually travel-related; *P. falciparum* is most frequently acquired from sub-Saharan Africa, whereas *P. vivax* is more often associated with travel to Oceania and Asia and *P. knowlesi* with Malaysia.[8] Of note, although malaria is endemic in many parts of Indonesia, the risk of transmission in Bali is considered low to negligible.[10,11]

Life cycle

Plasmodium sporozoites are injected into the skin when the female *Anopheles* mosquito takes a blood meal. Sporozoites migrate through the blood to the liver, where they multiply asexually within hepatocytes, maturing into schizonts. The schizonts rupture and release merozoites. Fevers coincide with schizont rupture. Merozoites invade and multiply in erythrocytes, which then burst, releasing more merozoites. *P. vivax* and *P. ovale* have a dormant hepatic stage (hypnozoites), which can be responsible for relapses weeks or even years later.

Some parasites differentiate into sexual erythrocytic stages (gametocytes). These gametocytes circulate in the bloodstream and are taken up by *Anopheles* mosquitoes during a blood meal before undergoing sexual reproduction in the mosquito.[12-14] The life cycle of malaria parasites is summarised in Figure 1.[14] Key *Plasmodium* life cycle stages and terms used in this article are summarised in Box 1.

Clinical manifestations

The incubation period of malaria is usually 10 to 14 days. However, it can be up to 18 months if the patient has acquired infection with *P. vivax* or *P. ovale*.[15] The most common presentation of malaria is fever in a returned traveller from an endemic region. Other associated symptoms include chills, headache, myalgia, nausea and vomiting. Some patients may develop the classic malaria paroxysm of fevers, chills and sweats as the disease progresses. These periodic fever responses are caused by rupture of the mature schizonts. Fevers classically occur every 48 hours in cases of *P. vivax, P. falciparum* or *P. ovale*, and every 72 hours in cases of *P. malariae*.[16,17] Fevers in *P. knowlesi* can occur daily. Other associated signs include splenomegaly and jaundice.

Severe malaria is caused by *P. falciparum, P. vivax* and *P. knowlesi*. Major complications include pulmonary oedema, acute renal failure, severe anaemia, haemorrhage and cerebral malaria, the last of which may manifest as delirium, confusion, seizures and coma.[18] Risk factors for severe malaria and death include being older than 65 years of age, female sex, pregnancy, immunocompromised status (including splenectomy), coexisting medical conditions, delay in treatment, no antimalarial prophylaxis and severity of illness at presentation.[19]

Diagnosis

The gold standard for laboratory diagnosis of malaria is microscopic examination of thick and thin blood films performed on whole blood. Thick smears are used to quantify parasitaemia, whereas thin smears aid in species identification. If suspicion of malaria is high, three thick and thin films are recommended at different times to increase sensitivity.[16]

Microscopy assesses the number of parasites relative to the number of red or white blood cells. The term percentage parasitaemia, or percentage of red cells parasitised, is often used to report results and can assist in determining clinical severity. In low-transmission areas, mortality from acute *P. falciparum* malaria begins to increase with parasite levels over 100,000 per microlitre (about 2.5% parasitaemia).[19,20]

A full blood count may reveal lymphopenia, thrombocytopenia and occasional atypical lymphocytes. Renal function, liver function, blood glucose levels and venous blood gas should also be assessed to determine the severity of malaria.

Additionally, laboratories may use rapid diagnostic tests. These include rapid antigen detection tests that detect antigens produced by *P. falciparum, P. vivax, P. ovale* and *P. malariae*. Tests detecting histidine-rich protein 2 have a high sensitivity for *P. falciparum*. Some assays combine histidine-rich protein 2 detection with reagents that detect a 'pan-malaria' group of antigens produced by all four species, which enhances malaria diagnosis, particularly in mixed infections. Rapid immunochromatography assays detect parasite-specific lactate dehydrogenase and perform better for *P. vivax* than tests using the 'pan-malaria' antigen.[21] Nucleic acid amplification testing methods, including polymerase chain reaction (PCR) and loop-mediated isothermal amplification on whole blood, may be used to detect low levels of parasitaemia, especially if clinical suspicion is high despite negative thick and thin blood smears.[21,22] However, these methods are not widely available and still require blood films for species identification and parasitaemia levels.

Management

Treatment choice for patients with malaria is guided by clinical risk factors and infection severity. Expert advice is recommended for children, pregnant women, immunocompromised people and those returning from the Greater Mekong Subregion due to antimalarial resistance in this area. Those with signs of severe disease should be referred to hospital. Severe disease is defined as the presence of at least one of the following:

- impaired consciousness (Glasgow Coma Scale <11)
- convulsions
- severe anaemia (haemoglobin <70 g/L in adults or <50 g/L in children younger than 12 years of age)
- acute kidney injury
- hypoglycaemia
- acute respiratory distress syndrome
- shock
- disseminated intravascular coagulation
- acidosis
- coma
- liver dysfunction
- parasite density greater than 2% of erythrocytes (in areas of low endemicity).[19,23]

Treatment of uncomplicated malaria is summarised in Table 1.[23-25] It usually involves artemisinin-based combination therapy (artemether/lumefantrine). Additionally, oral primaquine is added to avoid relapse in *P. vivax* or *P. ovale* infection, after glucose-6-phosphate dehydrogenase testing. Tafenoquine can be used for the radical cure of *P. vivax* malaria, but specialised quantitative glucose-6- phosphate dehydrogenase testing is required before starting; specialist advice should be sought.[26]

1. GLOSSARY OF PROTOZOAL LIFE CYCLE TERMS

Malaria (*Plasmodium* species)

- Sporozoite: the form injected by mosquitoes into the human bloodstream; travels to the liver
- Merozoite: the form released from the liver into red blood cells; invades erythrocytes
- Schizont: a stage in liver or blood cells where the parasite multiplies asexually
- Hypnozoite: dormant liver stage seen in *P. vivax* and *P. ovale*; can reactivate weeks to years later
- Gametocyte: sexual stage circulating in blood; taken up by mosquitoes to continue the cycle

Toxoplasmosis (*Toxoplasma gondii*)

- Tachyzoite: rapidly multiplying stage during acute infection
- Bradyzoite: slowly replicating, dormant stage inside tissue cysts; may reactivate in immunosuppression
- Oocyst: environmentally resistant form shed in cat faeces; infective to other hosts

Amoebiasis (*Entamoeba* species)

- Trophozoite: active feeding and multiplying stage in the intestine; can invade tissues
- Cyst: dormant stage excreted in faeces; survives outside the body and is infective

Leishmaniasis (*Leishmania* species)

- Promastigote: flagellated form transmitted by sandflies; infects human host
- Amastigote: intracellular stage multiplying inside macrophages; causes disease in humans

Monitoring treatment effect

The malaria parasite count should be monitored daily during treatment until it is negative. A full blood count and malaria

TABLE 1. TREATMENT OF UNCOMPLICATED MALARIA IN ADULTS[23-25]*

Clinical syndrome	Treatment	Comments
Treatment of choice for nonpregnant patients and pregnant women in all trimesters of pregnancy	• Artemisinin-based combination therapy: artemether 20 mg/lumefantrine 120 mg tablets, for a total of six doses (at 0, 8, 24, 36, 48 and 60 hours)	• To be taken with high-fat food or full-fat milk to help absorption
Infection acquired from the Greater Mekong Subregion or parts of Africa (Eritrea, Rwanda, Uganda, Tanzania) and responds slowly to combination artemether and lumefantrine therapy (persisting parasitaemia 72 hours after initiating treatment)	• Extend artemether 20 mg/lumefantrine 120 mg tablets with additional four doses at 72, 84, 96 and 108 hours, or • Switch to atovaquone 250 mg/proguanil 100 mg tablets daily, for three days, or • Switch to oral quinine sulfate 600 mg every 8 hours, plus either oral doxycycline 100 mg every 12 hours or oral clindamycin 450 mg every 8 hours, for seven days	–
Treatment additions based on species		
Plasmodium falciparum	• A single dose of primaquine 15 mg is recommended in those being treated in malaria-receptive regions in northern Australia† to eliminate the transmissible stages of *P. falciparum*	• Need to exclude glucose-6-phosphate dehydrogenase deficiency before the use of primaquine, as it can cause severe haemolysis in such patients • Do not use primaquine in pregnant women, infants younger than 6 months and breastfeeding women with infants under 6 months
Plasmodium vivax Elimination of hypnozoites, to prevent relapse	• Add oral primaquine 30 mg daily for 14 days, or • In an adult above 70 kg, until a total cumulative dose of 6 mg/kg is reached	
Plasmodium ovale Elimination of hypnozoites, to prevent relapse	• Add oral primaquine 15 mg daily for 14 days	

* Doses for children can be found on the Therapeutic Guidelines website or the Royal Children's Hospital Melbourne Clinical Practice Guidelines.[24,25]
† Malaria-receptive regions of northern Australia include regions north of 19°S latitude. This represents a line from just below Broome on the west coast, through Tennant Creek in the Northern Territory, to just above Townsville on the east coast.

microscopy at seven and 28 days after completion of therapy are recommended to assess for recrudescence.[1]

It is important to be aware of mixed infections; for example, *P. falciparum* may occur within the usual incubation period and *P. vivax* may occur later if primaquine has not been prescribed to eradicate hypnozoites. Patients should be counselled to monitor for recurrence of symptoms.

Prophylaxis

Malaria prophylaxis should include mosquito avoidance in addition to chemoprophylaxis. Chemoprophylaxis is complicated because of multidrug-resistant strains of *P. falciparum* worldwide, particularly in Southeast Asia. Clinicians should ask about planned travel to specific geographical locations. Information on malaria risk, drug resistance and prophylaxis is available from the *US Centers for Disease Control and Prevention (CDC) Yellow Book 2026 Health Information for International Travel*.[10] Referral to a travel medicine clinic is strongly recommended.

Toxoplasmosis

Toxoplasmosis, caused by the intracellular protozoal *Toxoplasma gondii*, is a common infection that is often asymptomatic but may present with flu-like symptoms and lymphadenopathy. Cats and other felines serve as definitive hosts, with other mammals and birds acting as intermediate hosts.[27,28] Although generally benign in immunocompetent individuals, toxoplasmosis has important clinical implications in pregnancy and immunosuppression.[27,29]

Epidemiology

T. gondii is found worldwide. The estimated seroprevalence in women of childbearing age in Australia is 20 to 40%.[15,16] Disease incidence is likely underestimated due to asymptomatic presentation and because toxoplasmosis is not a notifiable condition.[30]

Life cycle

Felines ingest *T. gondii* oocysts from contaminated environmental material or animal remains containing *T. gondii* bradyzoite cysts, which are released in their intestine and undergo sexual reproduction. This produces oocysts that are shed in faeces, which become infective after one to five days.

Oocysts can survive for extended periods in the environment. When a person or nonfeline animal ingests oocysts, usually from contaminated food, water or cat litter, the oocysts undergo excystation in the intestines, releasing tachyzoites that spread through the body, potentially causing disseminated disease with a trophism for the brain or eyes. The host immune system eliminates most of the protozoa, but residual tachyzoites return to bradyzoites after

seven to 10 days, remaining latent as tissue cysts. Immunosuppression may reactivate these cysts, causing widespread infection. Infection can also occur through organ transplantation or vertical transmission during acute maternal infection.[27-29] The life cycle of *T. gondii* is summarised in Figure 2.[28] Key *T. gondii* life cycle stages and terms used are summarised in Box 1.

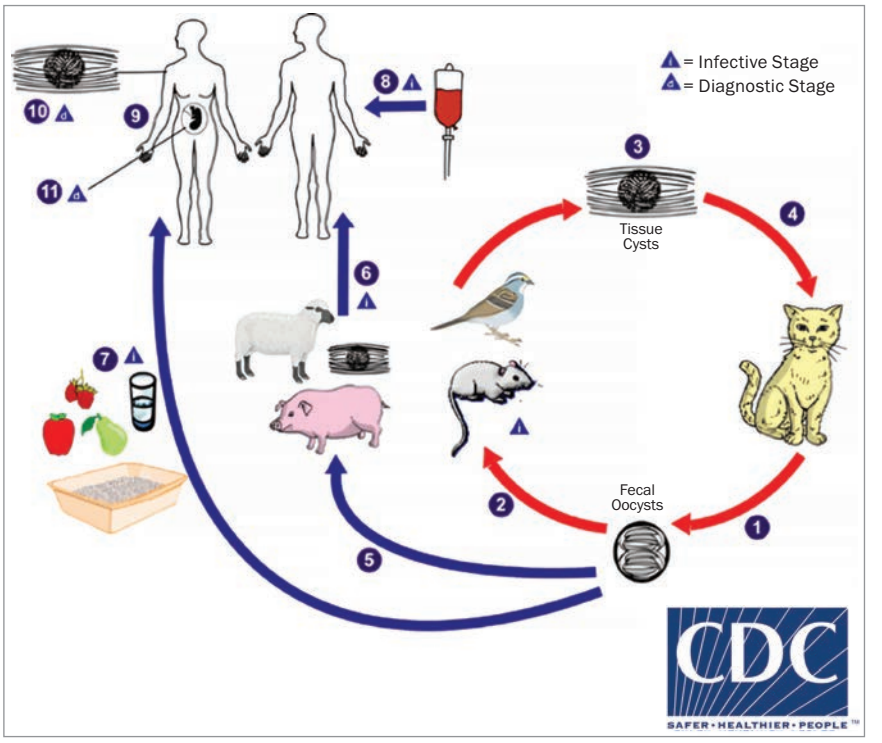

Figure 2. Life cycle of *Toxoplasma gondii*.[28]
Reproduced from DPDx, US Centers for Disease Control and Prevention (https://www.cdc.gov/toxoplasmosis/about/index.html).

Clinical manifestations

Infection with *T. gondii* is usually asymptomatic, although acute infection may be mononucleosis-like, with flu-like symptoms, lymphadenopathy, pharyngitis and hepatosplenomegaly with maculopapular rash. Rare manifestations include myocarditis, pericarditis, hepatitis or chorioretinitis. Severe disease can occur, and this depends on host factors and parasite genotype, which appears to influence virulence.[27,28]

Immunocompromised individuals and the developing fetus are most vulnerable to *T. gondii* infection, and can present with central nervous system involvement ranging from encephalopathy to mass lesions with a typical ring-enhancing appearance. Congenital infection may cause hydrocephalus, chorioretinitis, intracranial calcifications and even fetal death. Infection in the first trimester poses a small risk of transmission to the placenta, with transmission rates rising with gestational age and ranging between 60 and 81% in the third trimester. Although first-trimester infection rates are lower, they carry the highest risk of severe neonatal infection.[30] Nonpregnant women with acute toxoplasmosis should use contraception for six months post-infection to prevent this occurrence.[27-29]

Diagnosis

Unlike in some countries, routine serological screening for *T. gondii* during pregnancy and of newborns is not performed in Australia, because of low neonatal infection incidence, difficulties interpreting positive results and variable evidence of treatment efficacy. Instead, the focus is on prevention such as avoiding eating raw meat and unpasteurised milk products, as well as cleaning cat litter trays daily to remove oocysts before they become infective.[29,31]

Acute infection is primarily diagnosed using serology. *Toxoplasma*-specific immunoglobulin G (IgG) antibodies are produced several weeks after initial exposure and usually remain lifelong. *Toxoplasma*-specific immunoglobulin M (IgM) antibodies produced within a week or two in response to *T. gondii* may indicate recent infection but can persist for months, so require interpretation alongside IgG avidity testing. Low IgG avidity suggests infection within the past three months, whereas high avidity indicates infection later than this.[32] Results are best clarified with a repeat serological sample after two to three weeks to show rising *Toxoplasma*-specific IgG titres (seroconversion). False-positive IgM test results can occur, and this may be due to interfering antibodies. If IgM is positive but IgG remains negative on follow-up serology, and determining acute infection is important (e.g. in pregnancy), discussion with the microbiology laboratory regarding confirmatory IgM testing should be considered.[32] The Australasian Society for Infectious Diseases *Management of Perinatal Infections* guideline provides further information on toxoplasmosis in pregnancy.[33]

PCR testing for *Toxoplasma* DNA in blood, CSF or amniotic fluid is useful in immunocompromised patients or when congenital infection is suspected. Amniotic fluid PCR testing is usually performed between 18 and 20 weeks with supplementary imaging to assess complications. Less frequently, diagnosis can be made through microscopy of biopsied tissue (e.g. lymph nodes, placenta) and PCR analysis of the same material.[29,32,34]

Management

The management of infection with *T. gondii* is summarised in Table 2.[27,29] Pyrimethamine, plus either sulfadiazine or clindamycin, is the treatment of choice for those with ocular disease. Trimethoprim and

TABLE 2. TREATMENT OF TOXOPLASMOSIS INFECTION[27,29]

Patient features	Treatment	Comments
Nonpregnant, immunocompetent individuals, with or without symptoms	• No treatment unless there is ocular disease	–
Ocular disease (e.g. chorioretinitis)	• Pyrimethamine, plus either sulfadiazine or clindamycin for six weeks*	–
People with HIV†	• For primary prophylaxis: trimethoprim and sulfamethoxazole‡ if CD4+ count is less than 100/mcL and the patient has *Toxoplasma gondii* IgG antibodies • For secondary prophylaxis: trimethoprim and sulfamethoxazole‡	• For primary prophylaxis: continue until CD4+ count less than 200/mcL for three months • For primary prophylaxis: continue for six months with sustained CD4+ counts greater than 200/mcL
Pregnant women	• Seek specialist advice	

* Done with supervision of an ophthalmologist.
† Patients usually managed by specialist centre.
‡ Consult Therapeutic Guidelines for updated dosing regimens.
Abbreviation: IgG = immunoglobulin G.

sulfamethoxazole are used as prophylaxis for patients with HIV, depending on their CD4+ count. Suspected infection with *T. gondii* during pregnancy warrants referral to a high-risk pregnancy clinic with consideration of input from maternal-fetal medicine and infectious diseases specialists. Although treatment during pregnancy is controversial and lacks proven efficacy in preventing congenital infection, it is believed to reduce severity.[34]

Amoebiasis

Entamoeba species are the causative agent of amoebiasis. About 500 million people are infected worldwide, with 40,000 to 74,000 deaths occurring annually because of infection.[35,36] Prompt diagnosis and treatment are crucial to prevent complications and onward transmission.

Epidemiology

In Australia, most cases of amoebiasis are acquired following travel to regions of high endemicity; however, sexual exposure to an infected individual, particularly involving faecal contact, and colonic irrigation are recognised risk factors.[37] Higher risk groups include men who have sex with men and people of Aboriginal or Torres Strait Islander background.[38] Cases have also been reported in northern Australia in individuals without traditional risk factors, suggesting possible endemicity.[39]

Life cycle

More than seven species of Entamoeba have been isolated from humans.[36] Of these, *E. histolytica* is a clear pathogen, the pathogenicity of several other microscopically indistinguishable species (*E. dispar, E. moshkovskii* and *E. bangladeshi*) is the subject of ongoing debate and others (including *E. coli* and *E. hartmanni*) are nonpathogenic.[36,40] *Entamoeba* species exist in two main forms: cysts and trophozoites.[41] Mature cysts are ingested from contaminated food or water, or through sexual contact (e.g. oral-anal sex), and pass to the caecum, where they excyst to trophozoites. Trophozoites may remain within the intestinal lumen, invade the colonic mucosa or disseminate to extraintestinal sites. Some trophozoites undergo binary fission and re-encyst, with both forms being passed in faeces; however, only cysts can survive outside of the body.[41] Key *Entamoeba* life cycle stages and terms used are summarised in Box 1.

Clinical manifestations

Over 90% of patients infected with *Entamoeba* species remain asymptomatic, but these patients can shed infectious cysts. In symptomatic patients, intestinal amoebiasis may present as diarrhoea, dysentery or lower abdominal pain mimicking appendicitis. Severe cases can cause colitis and are part of the differential diagnosis for inflammatory bowel disease. Potential complications include dehydration, colonic perforation, peritonitis and formation of amoebic granulomas (amoebomas).[42,43] Patients with severe dysentery may pass trophozoites rapidly, causing infection of perianal skin and the development of necrotic skin lesions.

Extraintestinal manifestations of amoebiasis have also been described; hepatic abscess is a relatively common late presentation and may or may not be preceded by colitis.[37] Other extraintestinal manifestations are rare, but include cerebral, pericardial and pleuropulmonary abscesses.[43-45]

Diagnosis

Diagnostic modalities for amoebiasis include microscopy, PCR and serological tests; the most appropriate test depends on the clinical syndrome and should be interpreted alongside travel history and sexual exposure. These are detailed in Table 3.

Fresh stool or stool collected in fixative is suitable for detecting *Entamoeba* cysts and occasionally trophozoites, with sensitivity increasing if three stool samples are

TABLE 3. TESTS AVAILABLE IN PRIMARY CARE FOR SUSPECTED AMOEBIASIS

Testing modality*	Suitable specimens	Comments
Microscopy (ova, cysts, parasites; 'Faeces OCP')	• Faeces (fresh or in fixative) • Colonic and liver aspirates	• Sensitivity increases if three stool samples collected • Cannot reliably distinguish between pathogenic and nonpathogenic species • Trophozoite detection is low as trophozoites are subject to rapid degradation
Microscopy ('Histopathology')	• Colonic biopsies	• Incidental finding during workup of other suspected conditions (e.g. inflammatory bowel disease) • May show ulcerations and trophozoites
Antigen detection	• Faeces (fresh)	• Useful adjunct to microscopy and distinguishes *Entamoeba histolytica* from *E. dispar, E. bangladeshi* and *E. moshkovskii* • Largely replaced by commercial multiplex assays
PCR ('Entamoeba PCR')	• Faeces (fresh) • Colonic and liver aspirates	• High sensitivity and fast turnaround time • Can detect other viral, bacterial or parasitic causes of diarrhoea
Serology ('Entamoeba serology' or 'Amoebic serology')	• Blood (serum)	• Highly sensitive for hepatic abscess (>95%) and useful when invasive disease is suspected • Hepatic abscess with negative serology virtually rules out amoebiasis • Positive serology may persist for several years

* Inverted commas are used to highlight recommended terms for pathology request forms.
Abbreviation: OCP = ova, cysts and the parasites; PCR = polymerase chain reaction.

collected. However, microscopy cannot reliably differentiate between Entamoeba species. By contrast, PCR can distinguish *E. histolytica* from the nonpathogenic *Entamoeba* species, and several commercial multiplexed PCR assays are available for testing stool samples from patients presenting with diarrhoeal symptoms.[46] PCR has increased sensitivity and can potentially detect co-pathogens causing diarrhoea, including viral (e.g. norovirus, rotavirus), bacterial (*Salmonella* spp., *Campylobacter* spp.) and parasitic causes (e.g. Giardia).

Serological assays are useful to confirm invasive disease; *Entamoeba* antibodies are usually positive in more than 95% of patients with extraintestinal disease, 70% of those with amoebic colitis and 10% of asymptomatic cyst carriers.[43] Specificity is high (95%), although positive results may be present in patients from endemic areas with infection within the past 10 years. Direct antigen detection kits exist but are not routinely available in Australia and are mostly supplanted by PCR. Both microscopy and PCR can be performed on colonic and liver aspirates.[43,47] Histopathological examination of colonic tissue may show ulcerations or trophozoites; this may occur if patients undergo workup for another condition, such as inflammatory bowel disease.[43]

Management and prevention

Treatment is recommended for all patients infected with *E. histolytica*, regardless of symptoms. Asymptomatic patients should be treated with a luminal-active agent, such as paromomycin 500 mg every eight hours for seven days (or 10 mg/kg up to 500 mg for children, per dose), available through the Special Access Scheme in Australia. Paromomycin is active against the cyst form of *E. histolytica*, reducing the risk of persistence and secondary transmission. Patients with acute amoebic colitis or extraintestinal disease are recommended to receive a tissue-active agent (e.g. metronidazole 600 to 800 mg every eight hours for seven days) first, followed by paromomycin to eradicate intestinal carriage.[48,49] Hand hygiene is recommended during travel. No vaccines are available, although research is ongoing; prophylaxis with antimicrobials is not routinely recommended.[50]

Leishmaniasis

Leishmaniasis is a vector-borne disease caused by protozoa of the genus *Leishmania* transmitted by the bite of an infected female phlebotomine sandfly. *Leishmania* species cause a diverse range of disease, with three main clinical forms: visceral, cutaneous and mucocutaneous. Each form's clinical presentation is influenced by the infecting species and the host's immune response.[51]

Cutaneous leishmaniasis is the most common form, typically presenting with one or more chronic skin lesions at the site of inoculation. While often self-limiting, lesions can be slow to heal and may result in disfiguring scars. Visceral leishmaniasis, also known as kala-azar, is a more severe systemic illness affecting the liver, spleen and bone marrow, presenting with prolonged fever, weight loss, hepatosplenomegaly and pancytopenia. Visceral leishmaniasis is usually fatal without treatment and requires urgent inpatient assessment and management, often in specialist settings. Mucocutaneous leishmaniasis is less common, usually arising from cutaneous infection, and involves destructive lesions of the nose, mouth or throat. It is most often caused by species from Central and South America.[51]

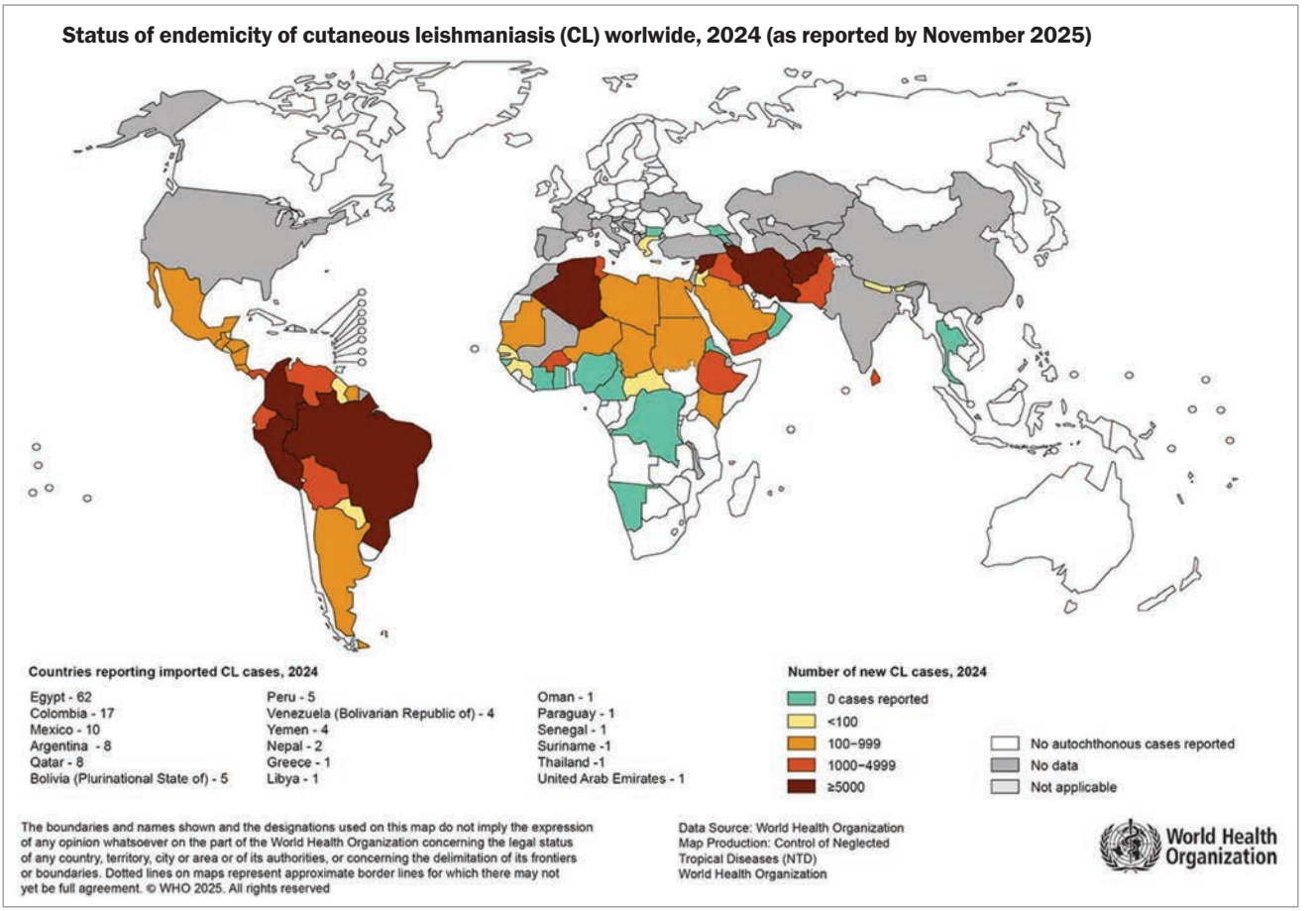

Figure 3. Cutaneous leishmaniasis distribution map. Countries are colour coded according to the number of newly reported locally acquired cases, with annotations for countries reporting imported cases.

Reproduced with permission from the Map Gallery, Global Health Observatory, World Health Organization (https://www.who.int/data/gho/map-gallery-search-results?&maptopics=910b5dfc-ce2e-4440-8b43-8d83f4a85485&term=Leishmaniasis).

This article focuses on cutaneous leishmaniasis, as patients with this form are most likely to present to primary care.

Epidemiology

More than one billion people live in regions endemic for leishmaniasis, putting them at risk of infection, with about 700,000 to 1,000,000 new cases annually.[51,52] Many cases go unreported, so global incidence is likely higher. It is prevalent in more than 90 countries, primarily in tropical and subtropical regions. More than 20 species of *Leishmania* cause disease in humans.[51] Geographical origin, classified as Old World (Europe, Middle East, Asia) or New World (Americas), can help infer the likely species causing infection.[53] Figure 3 shows the global status of endemicity and new cases of cutaneous leishmaniasis in 2023. Climate change is expected to expand the range of sandfly vectors, potentially increasing global spread.

Although not endemic to Australia, cases (especially cutaneous forms) are increasingly reported among migrants, travellers and immunocompromised individuals.[51,54]

Life cycle

Transmission of *Leishmania* occurs when the infective promastigote stage is transmitted to humans via sandfly bites, followed by a second (amastigote) stage, during which the protozoa replicate within monocytes and macrophages, evading host immune defences.[55,56] The disease presents significant diagnostic and treatment challenges because of its varied clinical manifestations and complex intracellular life cycle, as shown in Figure 4.[56] Its intracellular persistence also makes treating the amastigote stage difficult.[51] Key *Leishmania* life cycle stages and terms used are summarised in Box 1.

Clinical syndromes

Leishmaniasis has a variable incubation period of two weeks to several years, necessitating review of travel over this time frame. Cutaneous disease typically begins at the sandfly bite site as a firm, painless papule, which may ulcerate and scar, a characteristic feature of all three forms of leishmaniasis.[51]

Sandfly mouth parts cannot penetrate clothing, so cutaneous leishmaniasis typically presents as nodules, plaques or nonhealing ulcers on exposed body parts. Ulcers often have an indurated border, are painless and may be associated with local lymphadenopathy. Satellite lesions may occur along lymphatics and may be palpable without ulceration.[57] These lesions develop weeks to months after a sandfly bite. Although not life threatening, disfiguring scars can result in social stigma and psychological distress.[58]

Mucocutaneous leishmaniasis often develops as a progression from initial cutaneous leishmaniasis, with mucosal lesions appearing months to years after the primary skin lesion heals. This can contribute to difficulty in diagnosis.[56]

Visceral leishmaniasis should be considered in cases of prolonged fever, cytopenia (due to bone marrow invasion) and relevant epidemiology.[59,60]

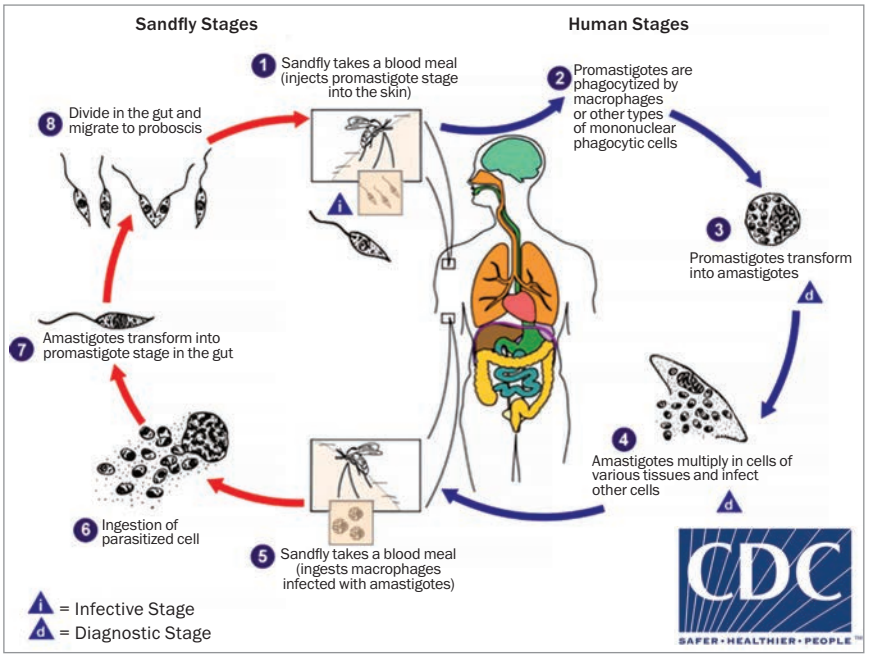

Figure 4. Leishmaniasis life cycle.[56]
Reproduced from DPDx, US Centers for Disease Control and Prevention (https://www.cdc.gov/dpdx/leishmaniasis/index.html).

Diagnosis

Leishmania species differ in drug sensitivity and treatment response. Traditional diagnostics include direct smear, histopathology and culture, although species are morphologically indistinguishable. Molecular methods, such as PCR on cultured promastigotes (the extracellular form), provide accurate species differentiation and

TABLE 4. DIAGNOSTIC TESTS FOR LEISHMANIASIS[56,60]

Testing modality	Suitable specimens	Suggested use	Comments
Microscopy	• Tissue biopsy, slit skin smear, border scraping or aspirate of the lesion • Punch biopsy taken from the border of the lesion at full thickness, with at least two samples (one in saline and one in formalin)	• Diagnosis of CL or ML	• Contact the microbiologist to ensure availability of specialised culture media (Schneider's Drosophila media) • Histology on skin biopsy or other tissue may show intracellular amastigotes within macrophages or monocytes • The laboratory may determine necessary further testing depending on included clinical information on the request form
PCR	• Tissue, lymph node, splenic or bone marrow samples	• Diagnosis of VL or CL	• Identifies to species level for guiding treatment • Sensitivity varies: lymph node aspirate: 50%; splenic smear: greater than 95%; bone marrow smear: 60–85% (these last two are highly specialised and are usually performed for the diagnosis of VL)
Serology	• Blood	• Detects exposure to *Leishmania* species	• Reduced sensitivity in the immunocompromised • Limited value in CL as there is less tissue invasion to incite a humoral immune response • May cross-react with *Trypanosoma cruzi*
Rapid ICT	• Finger prick blood test	• Field testing only for *Leishmania infantum*	• Detects antibodies to recombinant antigen (rK39), present in the leishmania parasite • Used in endemic regions only

Abbreviations: CL = cutaneous leishmaniasis; ICT = rapid immunochromatographic test; ML = mucocutaneous leishmaniasis; PCR = polymerase chain reaction; VL = visceral leishmaniasis.

2. PROTOZOAL INFECTIONS: KEY POINTS FOR GPS

Malaria
- Fever in a returned traveller from an endemic region should be considered malaria until proven otherwise
- Diagnosis: three thick and thin blood films
- Provide laboratory contact numbers for urgent result follow up
- Management: severe cases require hospitalisation and intravenous therapy
- Drug resistance is increasingly common in some regions

Amoebiasis
- Presentation can occur months to years after travel to an endemic area
- Common presentations: diarrhoea, dysentery, hepatic abscess
- Eradication of cysts is essential to prevent relapse

Toxoplasmosis
- Usually asymptomatic; critical in pregnancy and in immunocompromised individuals
- Refer to a high-risk obstetrics service if suspected during pregnancy

Leishmaniasis
- Suspect in patients with nonhealing ulcers and relevant exposure
- Species identification via molecular testing (polymerase chain reaction) on tissue, combined with epidemiology, is important to guide appropriate treatment

Key clinical approach
- Obtain a detailed travel history
- Maintain a high index of suspicion in returned travellers, migrants and immunocompromised patients
- Seek specialist advice for severe malaria, suspected visceral leishmaniasis, toxoplasmosis in pregnancy and systemic or complicated presentations

can be combined with epidemiological information (e.g. geographic exposure risk) to guide appropriate treatment.[51,59] Testing for *Leishmania* species should be considered in patients with atypical ulcers, systemic symptoms and travel to endemic regions. A summary of the various diagnostic tests is shown in Table 4.[56,60] Serology is of limited value in the diagnosis of cutaneous leishmaniasis, as there is less tissue invasion to incite a humoral immune response. Additionally, the rapid immunochromatographic test is only used in endemic regions.

Management

Antimicrobial treatment of leishmaniasis can be challenging because of limited availability and the complexity of therapy, which depends on clinical syndrome, illness stage and the species of Leishmania. Given these complexities, referral to an infectious diseases physician is recommended for systemic or complicated cases.

For uncomplicated cutaneous leishmaniasis, local therapies such as cryotherapy may be appropriate. Other treatments include intralesional antimonials or topical azoles, which are not readily available and may require specialist consultation or liaison with a compounding pharmacy.[58] Systemic therapy is required for diffuse or complex lesions. Although lesions may self-remit, treatment helps prevent scarring.[56] Leishmaniasis prevention for travellers should focus on minimising sandfly exposure using protective clothing, insect repellents and bed nets, as no vaccine is available.[52]

Conclusion

A high degree of clinical suspicion alongside a thorough travel and exposure history is imperative when evaluating suspected invasive or systemic protozoal infections such as malaria, toxoplasmosis, amoebiasis and leishmaniasis. This is particularly important with returned travellers and immunocompromised patients. If uncertain, discussion with infectious diseases or microbiology specialists can help in appropriate test selection and treatment. Box 2 provides a quick reference for GPs on the diagnosis and management of these four protozoal infections. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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Invasive protozoal infections in Australia

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