Pathogenic Free-living Amoeba

There are many varieties of free-living amoeba, but only four genera have been causally associated with disease in humans.[1]

These are *Acanthamoeba* spp., *Balamuthia mandrillaris* (the only known species of *Balamuthia*), *Naegleria fowleri* (sometimes considered not to be an amoeba at all, but more closely related to *Leishmania* and *Trypanosoma*) and *Sappinia pedata*. They are distinct from the more famous *Entamoeba histolytica* (an obligate anaerobic parasite which can cause amoebiasis, amoebic dysentery and amoebic liver abscesses).

- *Acanthamoeba* spp. and *B. mandrillaris* are opportunistic pathogens causing infections of the CNS, lungs, sinuses and skin, mostly in immunocompromised humans.
- *B. mandrillaris* is also associated with disease in immunocompetent children, and *Acanthamoeba* spp. cause a sight-threatening keratitis, mostly in contact lens wearers.
- *N. fowleri* causes an acute and fulminating meningoencephalitis in immunocompetent children and young adults.
- A few human cases of encephalitis caused by *Sappinia diploidea* have been described.[2, 3, 4]

Free-living amoebae cause rare but devastating disease. They are aerobic (other species of amoeba are anaerobic). They have also been called amphizoic amoebae, as they are able to exist as free-living organisms in nature and only occasionally invade a host and live as parasites within host tissue. Most published literature consists of case reports. The lack of established success in treatment means that there is no single, proven, evidence-based treatment that carries a high probability of cure, although in recent times miltefosine shows promise.

Distribution

These organisms are ubiquitous and found worldwide.

*Acanthamoeba* spp. are found in soil, dust, air and water (eg, swimming pool, domestic and sewage), ventilation and air conditioning systems. They have been isolated in hospitals, medicinal pools, dental treatment units, dialysis machines and contact lenses. They have also been found in mammalian cell cultures, human nostrils and throats and human and animal brain, skin, and lung tissues. In cell cultures they are commonly contaminants. This is how they were discovered in the 1950s - they grew on cell cultures grown for the polio vaccine. *Acanthamoeba* spp. can also be found in fish and have been isolated from the nasal and throat mucosa of healthy humans.

*B. mandrillaris* has not been isolated from the environment but has been isolated from autopsy specimens of infected humans and animals.

*N. fowleri* is also ubiquitous and found in soil and warm fresh water.

*Sappinia* spp. are found in soil and tree bark.

Both *Acanthamoeba* spp. and *B. mandrillaris* can act as hosts for other bacterial infections - eg, legionellosis. Further research into this area is ongoing.[2, 5]
Life cycle

There are two stages in the life cycle of Acanthamoeba, Balamuthia and Sappinia species.\cite{2,6}

**Active feeding stage**
- During this stage the trophozoites are actively dividing by feeding on bacteria, yeast and algae or axenically (ie not associated with any other organisms).

**Dormant cyst stage**
- Cysts form once there is a change in the environment of the trophozoites - eg, nutrient deprivation or changes in temperature. The cysts are resistant to chlorination and antibiotics.

There are four stages in the lifecycle of N. fowleri:
- The trophozoites are 10-15 μm in diameter.
- They produce broadly rounded lobopodia.
- Cysts are single-walled, spherical and 8-12 μm in diameter.
- The trophozoites can also transform to a flagellated form.

Clinical features

- Acanthamoeba and Balamuthia species most often cause subacute or chronic granulomatous amoebic encephalitis (GAE), usually in immunocompromised patients.
- In addition, Acanthamoeba spp. can cause:
  - Granulomatous skin lesions.
  - Amoebic keratitis and corneal ulcers following corneal trauma or in association with contact lenses.
- Other Acanthamoeba species can cause illness in immunocompromised hosts - eg, skin lesions or sinusitis.
- N. fowleri lives in freshwater habitats, feeding on bacteria. It can (rarely) infect humans by entering the nose during water-related activities. Once in the nose, the amoeba travels to the brain and causes a severe brain infection called primary meningoencephalitis (PAM), which is usually fatal.
- S. pedata has been identified as a rare cause of amoebic encephalitis.\cite{4}

Granulomatous amoebic encephalitis\cite{6}

GAE is caused both by Acanthamoeba and Balamuthia species.

- **Description:** chronic, slowly progressive infection of the CNS. May also involve the lungs.
- **Causative organism:** several Acanthamoeba spp. and B. mandrillaris may cause GAE.
- **Incubation period:** unknown but estimated at weeks to months.
- **Route of infection:** aerosol or inoculation with haematogenous spread to the CNS.
- **Epidemiology:** GAE is a very rare cause of disease and most publications are case reports.\cite{6}
  - Most cases are not identified until post-mortem, due to the lack of good and reliable diagnostic tests and secondary infections being more common.
  - Most commonly seen in immunocompromised patients, including those with neoplasia, systemic lupus erythematosus, HIV and tuberculosis.
  - However, cases have been seen in the immunocompetent - for example, B. mandrillaris infections in children.\cite{7}
- **Risk factors:** alcoholism, drug abuse, chemotherapy, corticosteroids and organ transplantation.
- **Presentation:**
  - Symptoms include headaches, altered mental status, fever, lethargy, nausea and vomiting and occasionally psychosis, which progresses over several weeks to death.
  - Signs - neck stiffness and focal neurological deficits - eg, hemiparesis, cranial nerve deficits, diplopia, ataxia, positive Babinski's sign and positive Kernig's sign. Patients may also develop raised intracranial pressure.
  - AIDS patients may have disseminated infection, and may also have chronic sinusitis, otitis and skin lesions. Cases of vasculitis and osteomyelitis have also been reported.
  - Diagnosis:
    - Cerebrospinal fluid (CSF) smear (usually lymphocyte predominance and low glucose), culture, immunofluorescence or polymerase chain reaction (PCR).\cite{8}
    - In AIDS patients the CSF may be lacking in cells, making diagnosis difficult.
    - Brain biopsy may be required. CNS imaging (eg, CT and MRI scanning) may reveal enhancing or non-enhancing lesions and is thus non-diagnostic. B. mandrillaris does not grow on agar plates, unlike Acanthamoeba spp. However, similar to Acanthamoeba spp., it is difficult to isolate B. mandrillaris from CSF specimens.\cite{2}
- **Differential diagnosis:**
  - Bacterial or viral meningitis.
  - Other causes of meningoencephalitis.
  - Space-occupying lesion.
- Cerebral haemorrhage.
- Toxoplasmosis.
- CNS vasculitis (last two in AIDS patients).

- **Prognosis:**
  - Mortality of GAE is high, reaching almost 100% when skin lesions and CNS disease both occur together.

- **Treatment:**
  - GAE has been treated with pentamidine, usually in combination with one or more of the following: ketoconazole, hydroxystilbamidine, paromomycin, 5-fluorocytosine polymyxin, sulfadiazine, trimethoprim-sulfamethoxazole and azithromycin.
  - Centers for Disease Control and Prevention (CDC) are now investigating the use of miltefosine (also used to treat leishmaniasis). This drug has shown amoebicidal activity against several free-living species of amoeba in the laboratory and has been used successfully to treat patients infected with *B. mandrillaris* and disseminated *Acanthamoeba* spp.\[^9\]
  - Similar medications are used in the treatment of *B. mandrillaris*.\[^2\]

**Cutaneous acanthamoebiasis**\[^6\]

Cutaneous acanthamoebiasis is caused both by *Acanthamoeba* and *Balamuthia* species.

- **Skin lesions:** hard nodules or non-healing, indurated skin ulcers can occur.
- **Treatment:**
  - Skin lesions are difficult to treat.
  - This is even harder when the CNS is also involved.
  - Regimens including itraconazole, pentamidine, and 5-flucytosine have been used.
  - Miltefosine is currently being used to treat systemic infections, as this drug shows promise.
  - Topical chlorhexidine and ketoconazole are also used in addition to systemic therapies.

- **Prognosis:**
  - 76% mortality is associated with skin disease alone.
  - This approaches 100% when GAE is also present.
Amoebic keratitis

- **Description:** amoebic keratitis is a progressive sight-threatening disease of the cornea.
- **Causative organism:** several *Acanthamoeba* spp. may cause amoebic keratitis.
- **Risk factors:** poor contact lens hygiene, corneal abrasion or exposure of the eye to contaminated water.
- **Epidemiology:**
  - The incidence of amoebic keratitis is 3 per 100,000.
  - Around 85% of cases occur in people who wear contact lenses.
  - An epidemic of amoebic keratitis occurred in the USA in the 1980s which was related to contaminated contact lenses and solutions.

- **Presentation:**
  - Secondary bacterial infection is commonly associated, making it difficult to diagnose.
  - Symptoms: watering eyes, eye pain with photophobia, blurred vision and irritation.
  - Signs: include ptosis, conjunctival hyperaemia, episcleritis, scleritis and loosening of the corneal epithelium. Stromal infiltrates can be seen with a bright light. Trophozoites can (rarely) infiltrate the corneal nerve and retina, leading to chorioretinitis.

- **Diagnosis:** corneal scrape or biopsy.
- **Differential diagnosis:** herpes keratitis or fungal keratitis.
- **Treatment:**
  - Wide epithelial debridement if infection is detected early - but try to achieve medical resolution first.
  - Therapy should include the cationic antiseptic agents, of which chlorhexidine or polyhexamethylene biguanide (PHMB) is the most effective.
  - This is used in combination with propamidine isethionate and neomycin as part of triple therapy.
  - These may have to be used for prolonged periods - eg, more than a year.
  - Imidazoles have also been used but success rates are not great.
  - In severe cases, enucleation may be necessary.

- **Prevention:** killing *Acanthamoeba* spp. from the contact lens. Tap water should not be used to rinse contact lenses. The British Contact Lens Association gives advice to those who wear contact lenses.

Primary amoebic meningoencephalitis

*PAM is caused by N. fowleri.*

- **Description:** acute, rapidly progressive CNS infection, which is usually fatal.
- **Causative organism:** although there are over thirty *Naegleria* spp. the condition is only caused by the *N. fowleri* variety.
- **Incubation period:** unknown.
- **Risk factors:** swimming in contaminated warm water:
  - The amoebae pass through the olfactory mucosa to the CNS by migrating up the olfactory nerve then spreading via the subarachnoid space. No human-to-human spread has been described.

- **Epidemiology:**
  - Most reports are from the USA and India.
  - Very rare - estimated at 1 in 2.6 million exposed individuals.
  - Infection is most common during the summer months, usually when it is hot for prolonged periods, causing higher water temperatures and increased recreational contact with water.
  - Most cases in the USA have occurred in southern states.
  - Two Florida case reports were linked with sinus douching using tap water.
  - In 1978, a girl swimming in the restored Roman baths in the English city of Bath swallowed some of the source water, and died five days later from PAM. *N. fowleri* was cultured from the water.

- **Presentation:** similar to bacterial/viral meningitis:
  - Symptoms: headache, photophobia, nausea and vomiting.
  - Signs: pyrexia, neck stiffness and localising signs - eg, cranial nerve palsies when encephalitis develops. Patients can present in a comatose state.
  - As the amoeba causes extensive destruction of brain tissue, dramatic neurological presentations occur - eg, fits, loss of body control, seizures, and hallucinations.
  - The disease progresses rapidly with death in 3-7 days.

- **Diagnosis/investigations:** these should include tests for any suspected meningoencephalitis, ie FBC, and CT scan of the brain. Definitive diagnosis rests on identifying the trophozoites in the CSF or biopsy specimens. PCR is being used in research centres with good results. Serology testing is unlikely to be helpful, as the short duration means there is virtually no time for an antibody response to be initiated.
- **Differential diagnosis:** bacterial or viral meningoencephalitis.
- **Treatment:** amphotericin has been the drug of choice. Most evidence is based on case reports and amphotericin is usually combined with rifampicin and other broad-spectrum antibiotics. Drugs are usually administered intravenously but intrathecal use has also been described.
CDC is now investigating the use of miltefosine (also used to treat leishmaniasis). This drug has shown amoebicidal activity against several free-living species of amoeba (including *N. fowleri*) in the laboratory and has been used successfully to treat patients infected with *B. mandrillaris* and disseminated Acanthamoeba spp.

Up to 2011 there were only two documented survivors of PAM in the USA. There were two 2013 survivors - both US children treated with miltefosine. One survived neurologically intact - she was treated with miltefosine within 3 hours of symptom onset and also received cooling treatment. The other survived but had permanent neurological impairment. He was not cooled and his treatment began several days after symptom onset. 

**Prognosis:** mortality is nearly 100% and usually within a week of presentation. In the USA only four persons of 132 known cases since 1962 have survived.

**Prevention:** chlorination of swimming pools.

Sappinia amoebic encephalitis

Caused by *S. pedata*. (*S. diploidea* is another species but infections in humans have not been reported.)

**Description:** meningoencephalitis associated with cerebral tumour-like lesion, described in one case only.

**Incubation period, mode of spread and risk factors:** all remain unknown. It is likely to reach the CNS either through the nasal mucosa or the bloodstream.

**Epidemiology:** there is only one case described in the literature.

**Presentation:** sinus infection was followed by headache, vomiting and photophobia.

**Diagnosis:** CT brain scan in the single reported case revealed a tumour-like mass. PCR is likely to be a very important tool in diagnosing this particular infection; the infection was eventually confirmed as *S. pedata*.

**Treatment:** in the reported case, the cerebral lesion was surgically removed and azithromycin, pentamidine,itraconazole and flucytosine were also administered. The patient survived.

**Further reading & references**


9. Naegleria fowleri - Primary Amebic Meningoencephalitis (PAM); Centers for Disease Control and Prevention, 2014


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