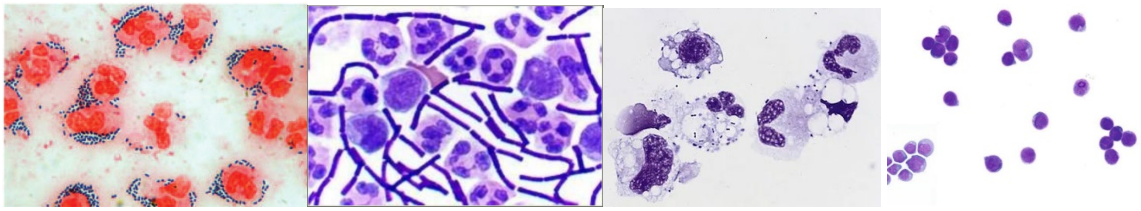
STANDARD DEVIATIONS: March Madness – The Brain Eaters

Greetings,

Ahhh, bacteria in a CSF Gram stain. Those gorgeous clusters, the winding chains, those lonely, but tell-tale, diplococci always get our attention. And when there are no organisms but, instead, swarms of soldiering lymphocytes in our cytoprep cell count, the "virus" lightbulb lights up. To the bench technologist, those sights are spectacular. The thrill (for lab rats like me, and you) is in the chase, teasing out the answer that helps the diagnosis and, hopefully, the patient's recovery.

Okay. Then why am I fascinated by the other encephalopathies?



{Bacteria, bacteria, bacteria, virus. Cool, but common?}

Sure, finding bacterial, and viral, meningitis is what we do. Fungal cases are interesting, but they target specific populations like HIV, diabetic, and cancer patients. And parasites "worm" their way into the brains of people in endemic areas all across the globe. But, come on, let's face it, it's the oddball stuff we rarely (if ever) see that we watch like a **train wreck**.

All aboard! Now boarding the train to Amoebic Encephalitis!

Now, gut amoeba (*Entamoeba histolytica* and *E dispar)* are ubiquitous to millions, routinely treated with numerous drugs, and fairly easy to find with a little fecal fishing. On the other hand, **brain-eating amoebic** diseases are extremely rare, extremely deadly, and extremely difficult to detect in time to do any good.

There are three stops on this train-wreck trek:

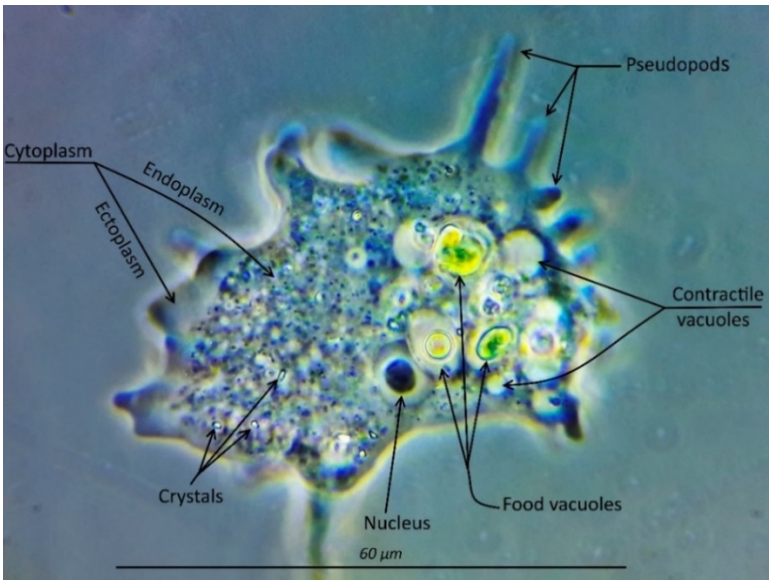
Balamuthia mandrillaris. A soil dwelling amoeba known to cause the rare but deadly neurological condition known as *Balamuthia* amoebic encephalitis (BAE).

***Acanthamoeba*.** Found in soil and water, the *spp*. usually attack the eyes of people who wear contacts. Brain and spinal cord infiltrates are more rare but lethal; AKA granulomatous amoebic encephalitis, or GAE.

Naegleria fowleri. This thermophilic, freshwater bug is notorious for its rapid and lethal attack through the noses of swimmers in warm waters. Naegleriasis kills, fast.

Let's leave our brain-train station with just a basic overview of the lonely amoeba. These are unicellular eukaryotic bugs (Protozoa) without cell walls. They range in size from a few microns to visible to the human eye. They phagocytize other protoists for nutrition, mostly bacteria, but some eat dead organic matter. Our little passengers are like zombies**, they eat human brains**. Spoiler alert. **Amoebas don't eat brain cells by phagocytosis.**

Amoebas are those first things you ever see under a microscope, in fourth grade. Normally they exist as trophozites; sacs of cytoplasm with organelles for digestion, a nucleus, and a neat vacuole that acts like a water pump to regulate osmolality. The classic pseudopods are membrane extrusions that provide phagocytosis and movement.



{Amoeba morphology. In 3D it's like a porcupine.}

When the environment is hostile, amoebas encyst to adopt a dormant form, the amoebic cyst. The cyst has a dense calcified shell that enables it to survive long periods of harsh conditions. When the cyst realizes a change for the better (temperature, pH, salinity, etc.), it will excyst, and revert back to its trophozite (feeding) state, through a small pore or ostiole.

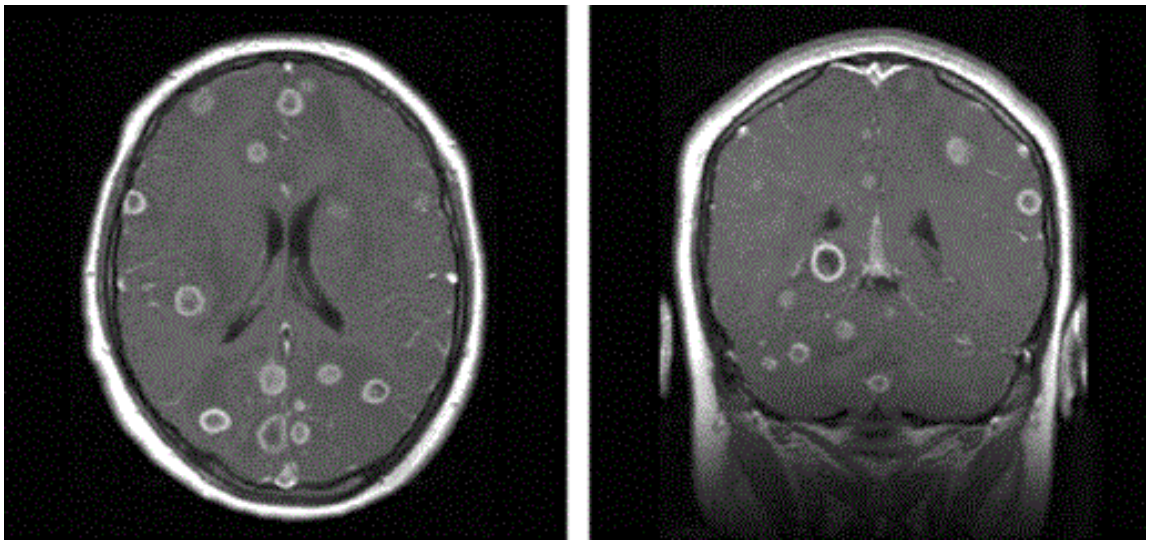
{The cyst is a survival strategy. Note the ostiole.}

When these guys are happy and well-fed, they reproduce by binary fission, a simple mitosis.

There it is. We've known about amoeba since the late eighteenth century. Grade school kids can recognize them. Yet, we still don't understand how they cross the blood-brain barrier (BBB) nor do we have effective treatments for brain eating amoeba. The train's about to jump the rails.

First stop ***Balamuthia mandrillaris*** **encephalitis (BAE)**.

This amoeba is found in dust and soil in many places around the world. Its main route of entry (ROE) is through broken skin and it is carried through the bloodstream where it disseminates throughout the body and somehow (?) crosses the BBB. It has an affinity for the blood vessel endothelium. Over several days to weeks, it feeds and replicates, forming ring lesions and the neurological symptoms of severe headache, lethargy, seizure, palsy, and emesis. The chronic infection becomes more acute, and death soon follows.



{BAE ring lesions.}

BAE presents like meningitis but is usually only detected in post-mortem biopsy. There is serology but most every case has been too late to matter. BAE cases have been diagnosed as neurocysticercosis, tumor, tuberculosis, or viral encephalitis or have been undiagnosed. The bug doesn't show up in CSF. It doesn't grow in routine culture. The drugs that get thrown at it in the chronic phase don't cross the BBB. By the time the routine therapies are exhausted the disease has progressed to the fatal acute stage.

Currently, there are no known ways to prevent infection with *Balamuthia* since it is unclear how and why some people become infected while others don't.

There have been no reports of a *Balamuthia* infection spreading from one person to another **except through organ donation/transplantation**.

A lot of drugs have been used but only one has any real efficacy, Miltefosine (Impavido = trade name). That's the good news. The bad? **Impavido costs $58,000 per regimen** and it typically gets used too late.

Our next whistle-stop is ***Acanthamoeba* infection**.

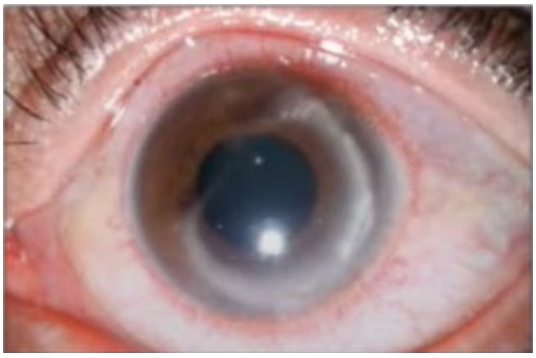
Acanthamoeba spp. are among the most prevalent protozoa found. They are worldwide, and have been isolated from soil, air, sewage, seawater, chlorinated swimming pools, domestic tap water, bottled water, dental treatment units, hospitals, air-conditioning units, and contact lens cases.

It presents a couple ways:

Acanthamoeba keratitis has been linked to contact lens use. It is the more common complaint and affects around 100 Americans/year.

The symptoms can persist several weeks to months and may include:

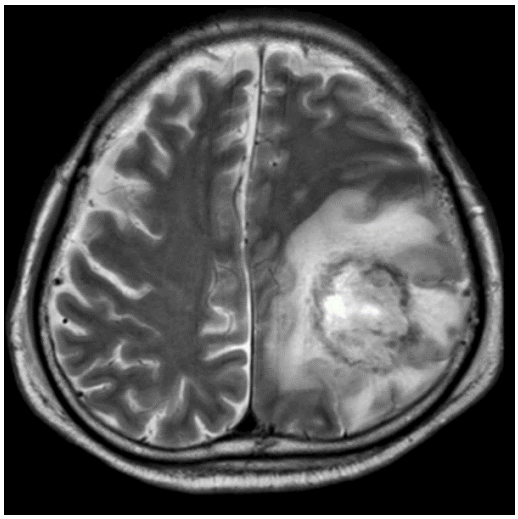
- Eye pain
- Eye redness
- Blurred vision
- Sensitivity to light
- Sensation of something in the eye
- Excessive tearing



{Ring infiltrate with *Acanthamoeba* keratitis.}

Contact lens risk includes handling, storage, improper cleaning, wearing them while swimming or contact with contaminated water. Eye infection with *Acanthamoeba* has never been known to cause infections in other parts of the body. Blindness in the eye is common but not usually deadly. Lengthy drug treatments are used but surgery is often the only recourse.

On the other hand, **Granulomatous Encephalitis (GAE)** affects the brain and spinal cord and presents like a meningitis but acts more like BAE, worsening over weeks to months before leading to death. Immunocompromised people are susceptible to this bug. Its ROE is through skin abrasions or inhalation and disseminates within the body and/or the brain and CNS.



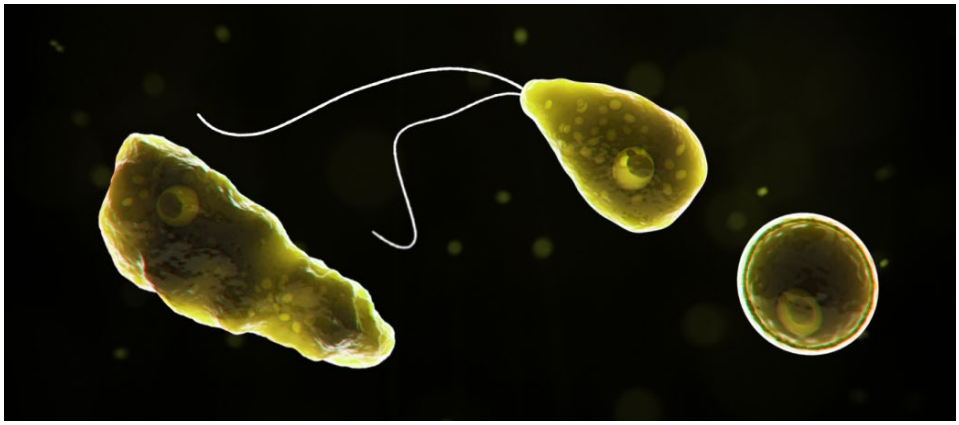
{GAE brain necrosis.}

Good news? Miltefosine. Bad news? That $58K.

And then there's the **train wreck**.

With **Naegleriasis** on board, the route is invariably quick, agonizing, and then fatal**.**

This amoeba differs from the others, above. *Naegleria fowleri* is a thermophilic, warm water dwelling beast. It will encyst at temperatures below 50 ^{o}F but thrives in warm fresh water. It also has a third morphology; it morphs into a flagellated form under hypotonic conditions.

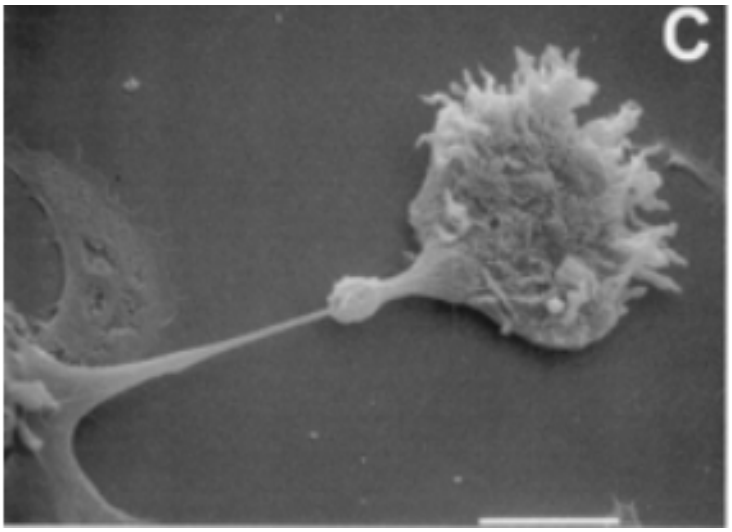


{*N fowleri* in cyst, trophozite and flagellate forms.}

Naegleria fowleri is commonly found in warm, freshwater lakes, ponds, rivers, and hot springs. Exposure to the amoeba usually occurs during swimming or other water sports.

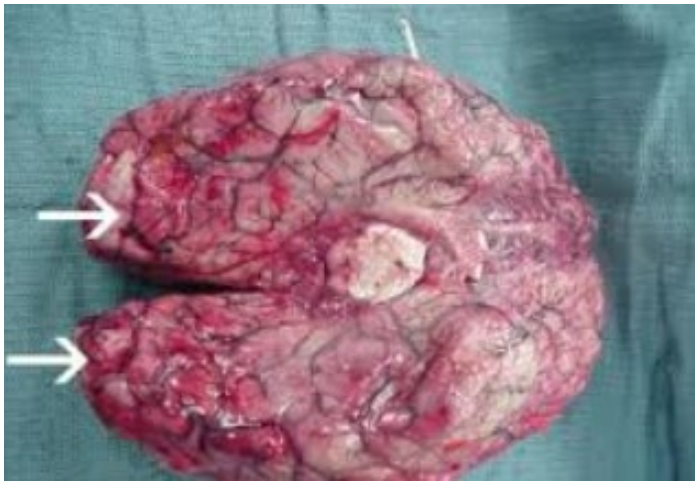
Naegleria infection causes a disease called **primary amebic meningoencephalitis (PAM)**. The amoeba enters through the nose and follows the olfactory nerve fibers through ethmoid bone into the skull. There, it migrates to the olfactory bulbs where it feeds on the nerve tissue.

Remember that spoiler alert? Amoebae consume astrocytes/cells of the brain, piecemeal, by means of an amoebostome, or food cup, a unique actin-rich sucking apparatus extended from its cell surface.



{Scanning EM: trophozite ingesting a cultured nerve cell. **Not phagocytosis**.}

PAM symptoms are, again, meningitis-like, with headache, fever, nausea, vomiting, a stiff neck, confusion, hallucinations, and seizures. The disease progresses rapidly and typically leads to death within about five days. Although infections are rare, it almost inevitably results in death. Of the 450 or so known Naegleriasis cases in the past 60 years, only seven have survived (a case fatality rate of 98.5%).



{Necrosis from Naegleria eating astrocytes of the frontal cortex. cdc.gov}

OUCH. Amebic meningoencephalitis is an extremely rare central nervous system (CNS) disorder caused by free-living amoebae, mostly found in freshwater lakes and rivers. Amoebas are everywhere and we really have no idea why only a handful of cases occur.

These bugs are hard, ridiculously hard, to pick up by our routine testing. The initial symptoms of amebic encephalitis mimic and are practically indistinguishable from bacterial meningitis. A diagnosis is typically made by observing motile amebae in a wet mount of cerebrospinal fluid (CSF) or visualization on CSF Wright or Giemsa stain, when we get lucky. Most diagnoses are made post-mortem.

A common, and sensible, principle in pathology is to **think horses when you hear hoof beats**. Amoebas are zebras. Our medical technology is maddeningly far from a good diagnostic algorithm, and that's a real headache.

{*N. fowleri* is found in Teton and Yellowstone NP.}

Have a great week and be safe,

Bryan