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Amebic encephalitis and meningoencephalitis: an update on epidemiology, diagnostic methods, and treatment

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Abstract

Purpose of review—Free-living amebae (FLA) including *Naegleria fowleri, Balamuthia mandrillaris*, and *Acanthamoeba* species can cause rare, yet severe infections that are nearly always fatal. This review describes recent developments in epidemiology, diagnosis, and treatment of amebic meningoencephalitis.

Recent findings—Despite similarities among the three pathogenic FLA, there are notable variations in disease presentations, routes of transmission, populations at risk, and outcomes for each. Recently, molecular diagnostic tools have been used to diagnose a greater number of FLA infections. Treatment regimens for FLA have historically relied on survivor reports; more data is needed about novel treatments, including nitroxoline.

Summary—Research to identify new drugs and guide treatment regimens for amebic meningoencephalitis is lacking. However, improved diagnostic capabilities may lead to earlier diagnoses, allowing earlier treatment initiation and improved outcomes. Public health practitioners should continue to prioritize increasing awareness and providing education to clinicians, laboratorians, and the public about amebic infections.

Keywords

amebic meningoencephalitis; encephalitis; free-living ameba

INTRODUCTION

Naegleria fowleri, *Balamuthia mandrillaris*, and *Acanthamoeba* spp. are pathogenic free-living amebae (FLA) that can cause severe infections, including amebic meningoencephalitis. FLA live primarily in soil and water in multiple forms: trophozoites, cysts, and in the case of *N. fowleri*, flagellate forms. The cyst form allows amebae to survive harsh conditions, and trophozoites are infective forms which can cause severe,

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Conflicts of interest
There are no conflicts of interest.

life-threatening infections in humans if they enter the body through the nose, lungs, or skin [1]. Granulomatous amebic encephalitis (GAE) and primary amebic meningoencephalitis (PAM) are severe infections of the central nervous system (CNS) caused by free-living amebae. *N. fowleri*, known as the 'brain-eating ameba', causes PAM, while *B. mandrillaris* and *Acanthamoeba* cause GAE as well as non-CNS infections.

Amebic meningoencephalitis is rare, affecting less than 30 people annually in the United States [2,3,4■■]. PAM is a rapidly progressive disease acquired when water containing the ameba enters the nose allowing the amebae to travel to the brain, causing diffuse inflammation, cerebral edema, and ultimately, herniation. Initial signs and symptoms can include fever, headache, vomiting, and meningismus, and progresses to death in a median of 5 days. It most commonly occurs in healthy adolescent male individuals in warm, summer months. GAE, in contrast, is more common among adults, has a more insidious onset and course, and likely results from hematogenous spread of amebae to the brain after exposure through inhalation or skin exposure. GAE can present with fever, headache, altered mental status, or seizures, and progresses over weeks to months. The recommended treatment regimens for PAM and GAE each include five or six drugs that are typically used as antibiotics and antifungals, have inconsistent data supporting effectiveness, and are often poorly tolerated. Both PAM and GAE are highly fatal and likely underdiagnosed. Recent developments in epidemiology, diagnostic modalities, and treatment options may provide additional opportunities for prevention, earlier detection, and improved outcomes.

DISEASE PRESENTATION AND OUTCOMES

Although rare, PAM and GAE both are highly fatal. PAM is fatal in more than 97% of cases, with only four known survivors of 157 cases occurring in the United States between 1962 and 2022 [5]. GAE is fatal in 90% of US cases caused by *B. mandrillaris* and 94% of cases caused by *Acanthamoeba* [3,4■■]. Although PAM and *B. mandrillaris* GAE nearly always present with neurologic signs and symptoms in US patients, *Acanthamoeba* GAE may be preceded by cutaneous lesions, sinus disease, or other organ system involvement. A recent review of US cases reported that *Acanthamoeba* was found to affect only the CNS in 55% of cases but presented with other organ system involvement in 45% [4■■]. *Acanthamoeba* GAE is also more commonly seen in immunocompromised hosts compared with PAM and *Balamuthia* GAE. It is crucial that providers caring for immunocompromised patients be aware of the cutaneous and sinus manifestations of *Acanthamoeba*, as early detection and treatment may prevent dissemination to the CNS.

GEOGRAPHIC DISTRIBUTION OF PRIMARY AMEBIC MENINGOENCEPHALITIS IN THE UNITED STATES

Concern has arisen in recent years regarding a northward expansion of reported PAM cases in the United States. Most reported PAM cases have historically had freshwater exposure in Florida, Texas, and southern California. However, a review of US PAM cases published in 2021 described a rise in cases in more northern latitudes since 2010 compared with the decades prior [6■■]. In recent years, cases have been diagnosed after freshwater exposure in Minnesota, Maryland, Indiana, and northern California; these include the northernmost cases reported [7]. Furthermore, two of the three US cases reported in 2022 occurred in Iowa and Nebraska, states in which PAM had not been diagnosed previously [2]. Reported cases in the Midwest have occurred following periods of increased temperatures, suggesting that a changing climate could be partially responsible [6■■]. Because of its thermophilic nature and ability to encyst, *N. fowleri* is quite adaptive and able to tolerate changes in environmental conditions, including rising temperatures [8]. *N. fowleri* has been detected in 6.6% of private well samples after major flooding events related to hurricanes, suggesting that extreme weather events may also impact the risk of disease [9].

RISK FACTORS AND PREVENTION

PAM cases have most commonly occurred after exposure to warm fresh water from lakes, ponds, or reservoirs, but there have also been cases associated with inadequately treated water in engineered recreational water venues. A recent development in PAM epidemiology has been the discovery of cases related to an artificial whitewater river, a surf venue, and splash pads. In 2016, an adolescent died after rafting on an artificial whitewater river in North Carolina [10]. An adult died after swimming and surfing at a surf venue in Texas [10]. Most recently, two young children died in 2020 and 2021 after each played in splash pads [11]. Investigators found that the water in each of the four venues was inadequately disinfected and maintained. The public health implications of these cases are of great concern, given the number of people participating in activities at engineered recreational water venues, the types of activities performed at such venues, and the potential occurrence of additional cases in the absence of intervention. The Model Aquatic Health Code (MAHC), developed and maintained by the Centers for Disease Control and Prevention (CDC), provides guidance to help prevent illness and injury associated with pools, hot tubs, splash pads, and other such venues open to the public. Through the MAHC and other resources, CDC provides guidance for design, construction, operation, and management of these venues [11,12].

Nasal rinsing has recently emerged as another behavioral risk factor for FLA infections that may provide public health and clinical providers with an opportunity for patient education and infection prevention. Four cases of PAM in the United States have been associated with nasal rinsing using tap water for either health or religious purposes, and at least 14 cases have been reported in other countries [13–16]. Recently, nasal rinsing has also been identified as a risk factor for *Acanthamoeba* GAE [4■■,17]. Patients who perform nasal rinsing or ritual nasal ablution should be educated about FLA infections and counseled to always use distilled water or water that has been sterilized by boiling prior to use [18].

FREE-LIVING AMEBAE WORLDWIDE

Reports of FLA infections in other countries overall resemble the US experience, though with some notable differences. In a recent analysis of 237 worldwide PAM cases, the greatest number of published or otherwise reported cases were attributed to water exposures in the United States, Pakistan, and Mexico, followed by India and Australia [15]. While most US cases were associated with swimming/diving or participating in other water sports, non-US cases were more frequently associated with nasal irrigation. US cases were most often attributed to exposure in a lake, pond, or reservoir, whereas non-US cases commonly reported swimming pool and tap water exposure, which may reflect differences in regulations for monitoring or maintaining water quality between countries. The age and sex distribution of PAM patients is similar in the United States and other countries; most cases occur in adolescent male individuals [15,19]. However, the youngest patient known to have been infected with PAM was diagnosed recently in Turkey at only 11 days of life [20]. The child was likely infected after being bathed in well water during the first week of life and surprisingly lived for 2 months following initiation of treatment.

Case reports have suggested a possible expansion of the worldwide geographic distribution of reported PAM and GAE cases, as cases have been reported for the first time in several countries including South Africa and Italy [21–24]. However, it remains unclear whether this represents a true change in the locations where these diseases can occur or rather may be attributed to increased awareness and improved diagnostic capabilities. Surveillance efforts should continue globally to better characterize trends in the epidemiology of FLA infections.

ENVIRONMENTAL NICHE

FLA are ubiquitous in the environment. Because of their ability to encyst, they are able to withstand extreme environments and resist unfavorable conditions [8,25■]. *N. fowleri* has been found to grow best in warm water, and salinity impairs its growth [26]. It has been detected worldwide in various freshwater sources such as lakes and rivers, in hot springs, and in sediment at the bottom of lakes [25■,27–29]. Although most confirmed infections have occurred after exposure to fresh water, *N. fowleri* has recently been detected in brackish waters [28,30]. Human interaction with these sources is primarily recreational, and efforts have been made to encourage safe swimming in freshwater sources. However, *N. fowleri* has also been detected in roof-harvested rainwater and private wells [9,25■,31]. Humans interact with these water sources much differently, and further studies are needed to determine the human risk of infection from nonrecreational sources.

Acanthamoeba spp. has been found even more widely in the environment. It also has a worldwide distribution, and it has been detected in a variety of niches, including natural freshwater sources (e.g. hot springs, groundwater, and spring water), air conditioning units, and even public swimming pools in some countries [25■,29,32–35]. Furthermore, *Acanthamoeba* has been detected in drinking water systems in many countries, including 51% of households sampled in one US study [36,37].

While *N. fowleri* and *Acanthamoeba* spp. are known to have predilections for water, *B. mandrillaris* has been identified less frequently in water samples, and more often in soil [3]. Fewer studies have explored the ecological niche of *B. mandrillaris*.

DIAGNOSTIC MODALITIES

For several decades following their discovery, FLA infections were diagnosed by microscopy. With the advent of FLA PCR tests in the early 2000s, microscopy was no longer considered the gold standard, and molecular-based testing was used for confirmation in most suspected cases. However, PCR testing has limitations, including limited availability and a requirement for clinical suspicion. Immunohisto-chemistry (IHC) and indirect immunofluorescence (IIF) are alternative diagnostic options but present the same challenges.

As with many rare infections, metagenomic next-generation sequencing (mNGS) methods, or shotgun sequencing methods, are gaining attention in FLA diagnostics. Several recent FLA cases have been diagnosed or confirmed using mNGS methods that detect FLA DNA in CSF, tissue, and serum samples. In the past 2 years, there have been several international case reports describing both *B. mandrillaris* and *N. fowleri* cases diagnosed by mNGS in Saudi Arabia, Japan, and China, including a GAE survivor [38–44]. For some of these patients, the diagnosis was made in the absence of clinical suspicion for FLA. FLA infections have been diagnosed by performing metagenomic sequencing of CSF samples for patients in the United States as well, including two cases of *B. mandrillaris* GAE [45,46]. An additional *B. mandrillaris* GAE case in the United States was diagnosed by performing microbial cell-free DNA testing of a serum sample using NGS methods by Karius, Inc. [47]. In a 2023 preprint article published by researchers from Karius, Inc., the private company reported detection of *Acanthamoeba*, *B. mandrillaris*, and *N. fowleri* in one patient sample each between 2018 and 2021 [48]. Although this may suggest utility in serum NGS testing in some cases, the proportion of patients with GAE or PAM that have detectable DNA in the serum is currently unknown.

At this time, PCR remains the gold standard for diagnosis of FLA infections; however, mNGS will likely continue to identify additional cases as it grows in popularity and accessibility. Metagenomic sequencing methods have the potential to shorten the time to diagnosis for many patients, as the shotgun approach allows testing for multiple pathogens at once without requiring large amounts of patient specimens. Cases identified by any detection method should be reported to the patient's local health jurisdiction and to CDC to inform surveillance and prevention efforts.

NITROXOLINE FOR TREATMENT OF FREE-LIVING AMEBAE INFECTIONS

There are no approved drugs for the treatment of PAM or GAE in the United States. For many years, FLA infections have been treated with various medication regimens consisting of multiple antimicrobial drugs that have either shown in-vitro antiamebic activity or have been used to treat patients who survived. Miltefosine, a drug licensed for the treatment of leishmaniasis, was the most recent drug added to CDC's recommended PAM and GAE treatment regimens, in 2013. PAM is often treated with a combination of amphotericin B, azithromycin, fluconazole, rifampin, miltefosine, and dexamethasone, while GAE is treated with a combination of sulfadiazine, fluconazole, flucytosine, miltefosine, and sometimes pentamidine and azithromycin. However, many of these recommended drugs cause side effects that often limit their use, and mortality remains high, even among patients who receive these recommended regimens.

Nitroxoline was first suggested as a possible treatment for GAE in 2018 [49]. It is a hydroxyqui-nolone derivative used in many countries for uncomplicated urinary tract infections, and it has a broad antibiotic spectrum and a favorable safety profile [50]. A drug-discovery study performed by researchers from the University of California San Francisco

(UCSF) identified nitroxoline as having strong in-vitro activity against *B. mandrillaris* [49]. In 2021, a 54-year-old patient with *B. mandrillaris* GAE treated at UCSF became the first known GAE patient in the United States to be treated with nitroxoline [51■■]. He was treated for more than 2 months with the recommended six-drug regimen but had persistent brain lesions that grew in size and number, and he developed multiple adverse effects of the medication regimen, including acute kidney injury and myelosuppression. Nitroxoline was initiated, and the patient experienced a rapid and remarkable improvement in imaging findings. He was discharged from the hospital and was still living independently approximately 1 year later.

A subsequent in-vitro study performed by a different laboratory group also demonstrated activity of nitroxoline not only against *B. mandrillaris*, but also *N. fowleri* and *Acanthamoeba* species [52]. There is no clinical data yet to support nitroxoline's effectiveness for other genera of FLA; however, its use could be considered in future FLA infection cases. Of note, nitroxoline is not currently approved for the treatment of any condition in the United States, it is not commercially available in the United States, and its use is considered investigational.

CONCLUSION

FLA are rare causes of encephalitis and meningoencephalitis, but they can cause rapidly progressive and almost always fatal infections. Clinicians should consider amebic meningoencephalitis in patients who present with specific risk factors and should initiate treatment rapidly. Earlier diagnosis and additional treatment options could improve patient outcomes. More work is needed to spread awareness of these infections and develop effective treatment regimens.

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KEY POINTS

- The geographic distribution of PAM is changing, both within the United States and worldwide, possibly due to changing climates, highlighting a need for enhanced surveillance and increased education in areas where these infections were not previously detected.
- Nasal rinsing has been associated with both PAM and GAE, and people who perform nasal rinsing should be educated about the risks of nasal rinsing with unsterile water, either for health or religious purposes.
- Although most CNS FLA infections are diagnosed using PCR testing, mNGS is increasing as a diagnostic modality that may offer important benefits for these rare and often unsuspected pathogens.
- Current treatments used for PAM and GAE are largely ineffective as the diseases remain mostly fatal at this time; research is ongoing to identify new therapeutic options, including nitroxoline.