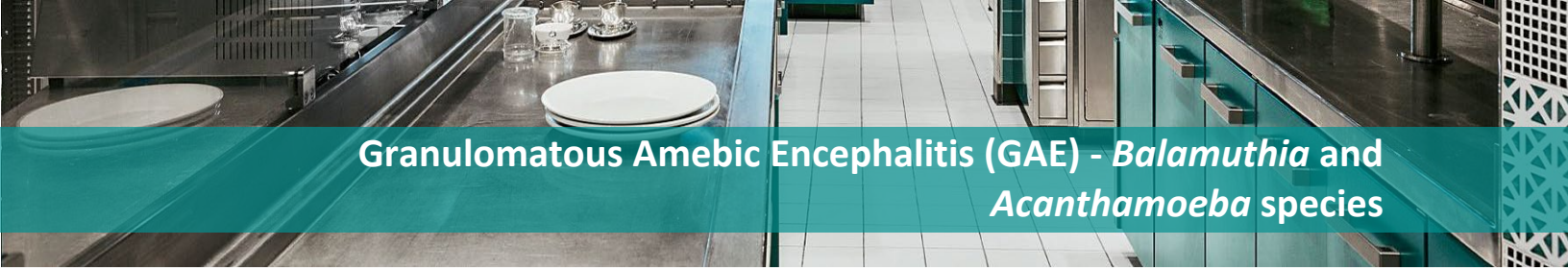

# Granulomatous Amebic Encephalitis (GAE) - *Balamuthia* and *Acanthamoeba* species

**A. Agent:**

*Acanthamoeba* species and *Balamuthia mandrillaris* are free-living amebae that exist as motile, infectious trophozoites and environmentally hardy cysts[1]. Both are naturally present in our environment, and they enter the body through the skin (via a cut or wound) or are breathed into the respiratory tract[1-4]. Once inside the body disseminated infection may occur, often resulting in central nervous system (CNS) involvement[1-4]. Most cases are among those with compromised immune systems including those with HIV/AIDS, organ/tissue transplantation, certain medications (i.e., steroids, excessive antibiotic use), cancer, diabetes, blood disorders, liver conditions, and lupus; however, healthy individuals may rarely be affected[1-4]. Onset is gradual and subtle, and most infections are fatal[1-4].

**B. Clinical Description[13]:**

Symptoms of GAE include:

- Mental status changes
- Loss of coordination
- Fever
- Muscular weakness or partial paralysis affecting one side of the body
- Double vision
- Sensitivity to light
- Other neurologic problems

**GAE caused by *Acanthamoeba* species** may present with headache; nuchal rigidity; nausea; vomiting; fatigue; confusion and personality changes; focal deficits including loss of balance and body control; seizures; and hallucinations[1,2,4]. Some *Acanthamoeba* species may cause granulomatous skin lesions that may not involve the CNS (most common in those with AIDS)[1]. The incubation period for *Acanthamoeba* GAE is not well known, but ranges from weeks to months after exposure[1,2].

Like *Acanthamoeba,* **GAE caused by *Balamuthia mandrillaris*** may present with headache; nuchal rigidity; nausea; vomiting; fatigue; confusion and personality changes; focal deficits including loss of balance and body control; seizures; and hallucinations[1-3]. Additional symptoms can be photophobia, intermittent low-grade fevers, weight loss, partial paralysis, and ataxia[1-3]. The incubation period for *Balamuthia* is not well known, but ranges from weeks to months after exposure[1-3]. Individuals exposed through solid organ transplantation tend to develop symptoms more quickly, usually within a few weeks[1].

- Differential Diagnosis: Bacterial meningitis and brain abscess or tumor.

***Acanthamoeba* keratitis** is an infection of the cornea that occurs mostly among healthy contact lens wearers (85% of cases) and does not cause a disseminated infection[1,2,14]. Risk factors for *Acanthamoeba* keratitis include improper handling or storage of contacts, using non-sterile liquids to sanitize contacts (such as tap water or homemade solutions), swimming or bathing while wearing contacts, and having had trauma to the cornea[14]. This infection may cause eye pain and redness, blurry vision, photophobia, tearing, and the feeling that there is something in the eye[1,14]. It is typically treated with prescription medications, but can be challenging to eliminate[1,14]. Early diagnosis is essential[1,14].

- Differential Diagnosis: keratitis caused by herpes simplex virus or other bacterial keratitis.

**C. Reservoirs:**

*Acanthamoeba* species are distributed worldwide and are found in soil; dust; cooling towers of electric and nuclear power plants; heating, ventilating, and air conditioning units; fresh and brackish water; whirlpool baths; and physiotherapy pools[1].

*Balamuthia mandrillaris* is also found worldwide in soil and may exist in bodies of fresh water[1-3].

**D. Mode of Transmission:**

GAE infections occur when the ameba is inhaled into the respiratory tract, or enters the body through the skin via a wound or cut[1-4]. Upon entering the body, the amebas can travel through the bloodstream to the CNS and lungs[1,3].

A small number of cases of *Balamuthia* GAE following organ transplantation have been recorded[1,2].

**E. Incubation Period:**

The incubation periods for *Acanthamoeba* and *Balamuthia* GAE are unknown. It is believed to take several weeks or months to develop the first symptoms of CNS disease following exposure to the amebae. Chronic progression (1–2 years) to CNS symptoms has been reported in children. Patients exposed to *Balamuthia* through solid organ transplantation can develop symptoms of *Balamuthia* GAE more quickly—within a few weeks[1].

**F. Period of Communicability:**

Neither GAE nor *Acanthameoba* keratitis are communicable person to person[1,3].

**G. Susceptibility and Resistance:**

Most GAE infections occur among those with compromised immune systems, though cases among healthy individuals have occurred[1-4].

Most cases of *Acanthameoba* keratitis are among healthy contact lens wearers, though those who do not wear contacts may also be affected[14].

**H. Treatment:**

GAE that has spread to the CNS is almost always fatal[1-4]. However, infections with *Acanthamoeba* species that is isolated to the skin and has not spread to the CNS are treatable. Early diagnosis is key[1,4].

CDC no longer provides miltefosine for treatment of free-living ameba infections. Miltefosine is now commercially available[7]. Clinicians should visit impavido.com for more information on obtaining miltefosine in the United States. If you have a patient with suspected free-living ameba infection, please contact the CDC Emergency Operations Center at 770-488-7100 to consult with a CDC expert regarding the use of this drug[7] and report the suspect case immediately to local public health.

GAE treatment recommendations based upon surviving cases are available through the CDC[7]. See also: case reports of successful GAE treatment.

Prescription medications are available to treat *Ancathamoeba* keratitis[1,2,14]. Early diagnosis with an eye doctor is critical[1,14].

## I. Clinical Case Definition:

**GAE - *Acanthamoeba* Disease excluding keratitis**[8]

The genus *Acanthamoeba* includes several species of opportunistic free-living amebae that might invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis) or sinuses. Once in the brain, the amebae cause granulomatous amebic encephalitis (GAE). *Acanthamoeba* GAE has a slow and insidious onset and develops into a subacute or chronic disease lasting several weeks to months. *Acanthamoeba* GAE affects both immunocompetent persons and persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, organ transplantation). Initial symptoms of *Acanthamoeba* GAE might include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms might include nausea, vomiting, low-grade fever, muscle aches, weight loss, mental-state abnormalities, lethargy, dizziness, loss of balance, cranial nerve palsies, other visual disturbances, hemiparesis, seizures, and coma. Once the disease progresses to neurologic infection, it is generally fatal within weeks or months. However, a few patients have survived this infection.

**GAE - *Balamuthia mandrillaris***[8]

*B. mandrillaris* is an opportunistic free-living ameba that can invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis), sinuses, or via organ transplantation. The incubation period is not well-characterized but has been observed to range from 2 weeks to months or possibly years. Once in the brain, the amebae can cause meningoencephalitis and/or granulomatous amebic encephalitis (GAE). *B. mandrillaris* GAE often has a slow, insidious onset and develops into a subacute or chronic disease lasting several weeks to months; however, *B. mandrillaris* infections associated with organ transplantation have an especially rapid clinical course. *B. mandrillaris* GAE affects both immunocompetent persons and persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, organ transplantation). Initial symptoms of *B. mandrillaris* GAE might include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms might include nausea, vomiting, low-grade fever, muscle aches, weight loss, mental-state abnormalities, lethargy, dizziness, loss of balance, cranial nerve palsies, other visual disturbances, hemiparesis, seizures, and coma. Painless skin lesions appearing as plaques a few millimeters thick and one to several centimeters wide have been observed in some patients, especially patients outside the U.S., preceding the onset of neurologic symptoms by 1 month to approximately 2 years. Once the disease progresses to neurologic infection, it is generally fatal within weeks or months; however, a few patients have survived this infection.

***Acanthamoeba* keratitis**[8]

*Acanthamoeba* keratitis is a local infection of the cornea (outer layer of the visual pathway of the eye) caused by a microscopic, free-living ameba belonging to the genus *Acanthamoeba*. Symptoms include foreign body sensation, photophobia, decreased visual acuity, tearing, pain, and redness of the eye. It occurs most typically among healthy, contact lens users, but can occur in anyone. Although treatable with topical medications, affected individuals are at risk for permanent visual impairment or blindness. *Acanthamoeba* organisms are ubiquitous in nature and can be found in bodies of water (e.g., lakes and oceans), soil, and air.

## J. Laboratory Criteria for Diagnosis:

**GAE - *Acanthamoeba* Disease excluding keratitis**[8]

Confirmatory Testing

Detection of *Acanthamoeba* antigen or nucleic acid (e.g., immunohistochemistry or PCR) from a clinical specimen (e.g., tissue) or culture.

| Case Classification[8] | |
|---|---|
| **Confirmed** | A case that meets the clinical criteria and confirmatory laboratory criteria for diagnosis |

Comment:
*Acanthamoeba* and *B. mandrillaris* can cause clinically similar illnesses and might be difficult to differentiate using commonly available laboratory procedures. Definitive diagnosis by a reference laboratory might be required. Several species of *Acanthamoeba* are associated with infection (i.e., *A. castellanii, A. culbertsoni, A. hatchetti, A. healyi, A. polyphaga, A. rhysodes, A. astonyxis, A. lenticulata and A. divionensis*). A negative test on CSF does not rule out *Acanthamoeba* infection because the organism is not commonly present in the CSF. Although it is unknown if *Acanthamoeba* spp. can be transmitted via organ transplantation, patients presenting with the above clinical criteria who have received a solid organ transplant should be further investigated to determine if the infection was transmitted through the transplanted organ. An investigation of the donor should be initiated through notification of the organ procurement organization (OPO) and transplant center.

**GAE - *Balamuthia mandrillaris*[8]**
Confirmatory Testing
Detection of *B. mandrillaris* antigen or nucleic acid (e.g., immunohistochemistry or PCR) from a clinical specimen (e.g., tissue) or culture.

| Case Classification[8] | |
|---|---|
| **Confirmed** | A case that meets the clinical criteria and confirmatory laboratory criteria for diagnosis |

Comment:
*B. mandrillaris* and *Acanthamoeba* spp. can cause clinically similar illnesses and might be difficult to differentiate using commonly available laboratory procedures. Definitive diagnosis by a reference laboratory might be required. A negative test on CSF does not rule out *B. mandrillaris* infection because the organism is not commonly present in the CSF. Once the disease progresses to neurologic infection, it is generally fatal within weeks or months; however, a few patients have survived this infection. Patients presenting with the above clinical criteria who have received a solid organ transplant should be further investigated to determine if the infection was transmitted through the transplanted organ. An investigation of the donor should be initiated through notification of the organ procurement organization (OPO) and transplant center.

***Acanthamoeba* keratitis[8]**
Laboratory-confirmed *Acanthamoeba* spp. keratitis infections are defined as the detection of *Acanthamoeba* spp.

- Organisms in corneal scraping, or biopsy specimens, or
- Nucleic acid (e.g., polymerase chain reaction) in corneal scraping, or biopsy specimens, or
- Antigen (e.g., direct fluorescent antibody) in corneal scraping, or biopsy specimens.

| Case Classification[8] | |
|---|---|
| **Confirmed** | A clinically compatible illness that is laboratory confirmed. When available, species designation and molecular characterization (e.g., genotype) should be documented. |
| **Probable** | A clinically compatible illness with positive identification of *Acanthamoeba* trophozoites or cysts using confocal microscopy |

**K. Classification of Import Status:**

Import status reflects where the GAE infection was acquired: in county, in state, international, out of county but in Arizona, out of state but in U.S., or location of infection is unknown.

**L. Laboratory Testing:**

Diagnosis of *Balamuthia* GAE is typically complete post-mortem, and can be detected through blood, CSF, and tissue samples[1,2,9]. In addition, the following tests* can confirm GAE[9]:

- indirect immunofluorescence assay (IFA), which tests for antibodies of amebas,
- immunohistochemistry (IHC) , which uses antibodies to detect the amebas
- polymerase chain reaction (PCR), which detects ameba DNA

Corneal scrapings and confocal microscopy in vivo in the cornea are used to diagnose *Acanthamoeba* keratitis[1,2].

**Testing must be arranged through public health and CDC.** All submissions to CDC for CLIA diagnostic testing require pre-approval by the CDC Infectious Diseases Laboratory point of contact (POC) for the testing being requested. ADHS enteric staff will assist with specimen testing coordination with CDC. Detailed information about specimen type, collection, storage and shipping is available here. A CDC specimen submission form 50-34 is required to submit to CDC.

Telediagnosis can be arranged through the CDC's Division of Parasitic Diseases and Malaria (DPDx). More information on this resource can be found here.

**M. Assessing Laboratory Results:**

A case should not be counted as a new case if laboratory results were reported within 6 months of a previously reported infection in the same individual[8].

**N. Outbreak Definition:**

Investigators may initiate an outbreak investigation for a single case of probable or confirmed PAM with evidence of transmission, as the one case may be representative of other undiagnosed or unidentified cases.

**O. Time Frame:**

Providers must submit a report by telephone or through an electronic reporting system authorized by the Department within 24 hours after a case or suspect case is diagnosed, treated, or detected, or an occurrence is detected[11]. Local health agencies must submit an epidemiologic investigation report within 30 calendar days after receiving a report[11].



**P. Forms:**

Please refer to the Department-provided formats for submitting Epidemiologic Investigation Reports for guidance on the required fields and forms for each morbidity.

CDC's Free Living Ameba Case Report Form should be used when investigating GAE infections. This form can be found on the ADHS Disease Investigation Resources webpage.

**Q. Investigation Steps:**

- **Confirm Diagnosis - GAE**
    - Obtain information from the health provider/medical facility regarding the patient's clinical presentation, as well as the patient's water and soil exposure history in the months prior to onset. Inquire about what information has been shared with the case's family/proxy.

- Obtain laboratory testing results. Facilitate testing by contacting the CDC Emergency Operations Center 24/7 at 770-488-7100. Encourage medical providers to utilize CDC's Division of Parasitic Diseases and Malaria (DPDx) telediagnosis tool[10]. For treatment, clinicians should visit impavido.com for more information on obtaining miltefosine in the United States[10]. Treatment should not wait for confirmatory testing[1].

- **Confirm Diagnosis - *Acanthamoeba* keratitis**
  - Obtain information from the health provider/medical facility regarding clinical presentation, as well as water and soil exposure history in the months prior to onset.
  - Obtain laboratory testing results.
  - Review case definitions to determine case classification.

    ***NOTE: Acanthamoeba keratitis is not reportable in the state of Arizona.***

- **Conduct Case Investigation - GAE**
  - Confirmed and suspect cases of GAE will immediately be entered into MEDSIS and contacted by the investigator. Investigators should inform the program manager or other management of the case, as needed.
    - Cases should be entered into MEDSIS under the morbidity "encephalitis, parasitic".
    - The investigator will attempt three phone calls, or text messages following unreturned voicemails, before sending a letter to the patient's address (depending upon local health department's protocols and capacity).
    - All interview attempts, even if unsuccessful (i.e., leaving a voicemail or text message), should be entered into the Case Contacted & Interviews table in MEDSIS as close to real time as possible.
    - If phone numbers appear invalid or non-functioning, contact food@azdhs.gov to request a LexisNexis search. This can be conducted for individuals 18 years and older. For those younger than 18, a parent/guardian name must be used to search in LexisNexis; otherwise, a search can be conducted in ASIIS for the individual under 18 years of age.
  - Interview the patient or the patient's proxy (spouse, adult offspring, etc.) about the patient's activities and movements in the few months before onset.
    - Be sure to take a good travel history, including dates of travel and address of lodging.
    - Inquire about the case's outdoor activities that may have exposed them to bodies of water including lakes; rivers; streams; pools; springs; run off water or discharge from industrial or power plants; poorly maintained pools; water heaters; and HVAC units. Assess for exposure to soil through high winds, gardening, or playing with dirt.
    - Complete the ADHS Free Living Ameba Case Report Form found on the ADHS Disease Investigation Resources webpage and submit to ADHS.

- **Conduct Contact Investigation**
  - Contacts are only at risk if they are exposed to the same source[2].

- **Initiate Control and Prevention Measures - GAE**
  - Provide education on reservoirs for *Balamuthia* and *Acanthamoeba* species.
  - There are no clearly defined recommendations to prevent infection with GAE[1,2,3,4].

- **Initiate Control and Prevention Measures- *Acanthamoeba* keratitis**
  - Provide education on reservoirs for *Acanthamoeba* keratitis.

- To prevent *Acanthamoeba* keratitis[1,2,14]:
  - Visit an eye care provider regularly, and use contact lenses as they are prescribed.
  - Do not swim or bathe while wearing contact lenses.
  - Wash and dry hands prior to handling contact lenses.
  - Clean contacts with fresh disinfectant solution, making sure to clean, rub and rinse lenses each time they are removed from the eye.
  - Use sterile contact lens solution to rinse and rub contact lens storage cases. Empty and allow them to dry between uses. Replace cases at least every 3 months.

- **Isolation, Work and Child Care Restrictions**
  Standard Precautions are recommended.

- **Case Management**
  None.

- **Contact Management, Including Susceptible Contacts**
  None; unless required as part of an active investigation with state and/or CDC.

- **Environmental Measures**
  i. Measures should be taken to identify the source and to eliminate the contamination, if possible, such as in the case of an unchlorinated or under-chlorinated body of water.
  ii. It should be noted that routine surveillance of environmental sources is not recommended because the organism is natural in the environment.

- **Notifications**
  i. All cases should be reported within 24 hours[11].
  ii. The local health agency must submit an epidemiologic investigation report within 30 calendar days after receiving a report[11].

**R. Outbreak Guidelines:**
It is unlikely that multiple cases will be linked to the same exposure, however, others exposed to the same source should be educated and instructed to seek immediate medical attention if they develop symptoms of GAE.

**S. Special Situations:**
N/A

# Additional Information & Resources

**CDC**

- *Balamuthia mandrillaris* GAE: http://www.cdc.gov/parasites/balamuthia/general.html
- *Acanthamoeba* GAE: http://www.cdc.gov/parasites/acanthamoeba/

**Laboratory References:**

- CDC guide to GAE testing:
  - *Acanthamoeba*: http://www.cdc.gov/parasites/acanthamoeba/diagnosis.html
  - *B. mandrillaris:* http://www.cdc.gov/parasites/balamuthia/diagnosis.html
- CDC test order instructions: http://www.cdc.gov/parasites/naegleria/
- CDC lab submission form 50-34: https://www.cdc.gov/laboratory/specimen-submission/form.html

**Foodborne and Waterborne Disease Outbreak Investigation Resource Manual:**
http://www.azdhs.gov/phs/oids/pdf/manuals/AZOutbreakManual.pdf

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