

Amebic Meningitis/Encephalitis rev Jan 2016

BASIC EPIDEMIOLOGY

Infectious Agent

Naegleria fowleri, *Acanthamoeba* spp. and *Balamuthia* are microscopic, free-living amoebae (single-celled living organisms). *Naegleria fowleri* is the causal agent of Primary Amebic Meningoencephalitis (PAM), while *Acanthamoeba* spp. and *Balamuthia* are the causal agents of Granulomatous Amebic Encephalitis (GAE).

- *Naegleria fowleri* is a heat-loving (thermophilic), free-living amoeba (single-celled microbe) commonly found around the world in warm fresh water (e.g., lakes, rivers, hot springs) and soil. *N. fowleri* is the only species of *Naegleria* known to infect people. Most of the time, the amoeba lives in freshwater habitats by feeding on bacteria. However, in rare instances, the amoeba can infect humans by entering the nose during water-related activities.
- *Acanthamoeba* is found worldwide. Most commonly the amoeba is found in soil, dust, fresh water, brackish water (e.g., a marsh) and sea water. *Acanthamoeba* can also be found in swimming pools, hot tubs and drinking water systems (e.g., slime layers in pipes and taps), as well as in heating, ventilating and air conditioning (HVAC) systems and humidifiers. Several species of *Acanthamoeba*, including *A. culbertsoni*, *A. polyphaga*, *A. castellanii*, *A. astronyxis*, *A. hatchetti*, *A. rhysodes*, *A. divionensis*, *A. lugdunensis* and *A. lenticulata* are implicated in human disease.
- *Balamuthia mandrillaris* is found in soil and believed to enter the body through skin wounds and cuts, or when dust containing *Balamuthia* is breathed in or gets in the mouth. Exposure to *Balamuthia* is likely to be common because of how widespread the amoeba is in the environment. However, very few cases of disease in humans have been found worldwide since *Balamuthia* was discovered.

Transmission

Naegleria fowleri

Transmission of *N. fowleri* to humans occurs when water containing amoebae enters the nose. Trophozoites infect humans or animals by penetrating the nasal tissue and migrating to the brain via the olfactory nerves causing primary amebic meningoencephalitis. Exposure occurs when people go swimming or diving in warm freshwater places, like lakes and rivers. People do not become infected by drinking contaminated water. In very rare instances, *Naegleria* infections may also occur when contaminated water from other sources (e.g., inadequately chlorinated swimming pool water or contaminated tap water) enters the nose. Some examples are when people submerge their heads or cleanse during religious practices, and when people irrigate their sinuses (nose) using contaminated tap water. It is also possible that *Naegleria* infection could be acquired through transplantation of organs from an infected donor.

Acanthamoeba

Acanthamoeba can enter the body through the eye, the nasal passages, cuts or skin wounds or by being inhaled into the lungs. The trophozoites are the infective forms, although both cysts and trophozoites gain entry into the body through various means. When *Acanthamoeba* spp. enter the eye they can cause severe keratitis in otherwise healthy individuals, particularly contact lens users. When the amoeba enters the respiratory system or through the skin, it can invade the central

nervous system by hematogenous dissemination causing granulomatous amebic encephalitis (GAE) or disseminated disease, or skin lesions in individuals with compromised immune systems.

Balamuthia

Balamuthia GAE occurs when the amebae infect the body, possibly through skin wounds and cuts, or when dust containing *Balamuthia* is breathed in through the nose or mouth. The trophozoites are the infective forms, although both cysts and trophozoites gain entry into the body through various means. Entry can occur through the nasal passages to the lower respiratory tract, or through ulcerated or broken skin. When *B. mandrillaris* enters the respiratory system or through the skin, it can invade the central nervous system by hematogenous dissemination causing granulomatous amebic encephalitis (GAE) or disseminated disease. The ameba can also cause skin lesions in individuals who are immune competent as well as those with compromised immune systems. *Balamuthia* infection also may be acquired through transplantation of infected donor organs.

Incubation Period and Illness Duration

Naegleria fowleri:

- Incubation period: Symptoms start 1-14 days (median 5 days) after exposure
- Duration of illness: Death occurs 1-18 days (median 5 days) after symptoms begin

Balamuthia and *Acanthamoeba*:

- Incubation period: Weeks to months (or longer)
- Duration of illness: Weeks to months

Communicability

Amebic meningitis/encephalitis is not spread person-to-person (except in the case of transmission through transplantation of organs from an infected donor).

Clinical Illness

Primary amebic meningoencephalitis (PAM)

Infections with *Naegleria fowleri* cause the rare disease PAM, a brain infection that leads to the destruction of brain tissue. Infection can occur in young immune-competent individuals. In its early stages, the infection may be similar to bacterial meningitis. Initial symptoms of PAM start 1 to 14 days after infection. Symptoms may include headache, fever, nausea, vomiting and stiff neck. Later symptoms may include confusion, lack of attention to people and surroundings, a loss of balance, seizures and hallucinations. These symptoms are followed by coma and death. After the start of symptoms, the disease progresses rapidly and death occurs within 18 days, usually on the fifth or sixth day.

Granulomatous amebic encephalitis (GAE)

GAE—caused by *Balamuthia* and *Acanthamoeba* species—often has a slow, insidious onset and then 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.

GAE caused by *Acanthamoeba* can cause a serious infection of the brain and spinal cord. Symptoms may include headaches, stiff neck, nausea and vomiting, tiredness, confusion, lack of attention to people and surroundings, loss of balance and bodily control, seizures and

hallucinations. Symptoms progress over several weeks and death usually occurs. Skin infections do not necessarily lead to disseminated disease.

GAE and disseminated infection are very rare forms of *Acanthamoeba* infection and primarily affect people with compromised immune systems. While unusual, disseminated infection can also affect healthy children and adults. Conditions that may increase a patient's risk for GAE and disseminated infection include AIDS, organ/tissue transplant, steroids or excessive use of antibiotics, diabetes mellitus, cancer, disorders in which white blood cells in the lymphatic tissue are over-produced or abnormal, disorders in which blood cells or blood clotting mechanisms do not function properly or are abnormal, liver cirrhosis and lupus.

Balamuthia infection can cause a wide range of symptoms. Disease can begin with a skin wound on the face, trunk or limbs and can then progress to the brain where it causes GAE. Diagnosis of *Balamuthia* GAE can be difficult, but some early symptoms may include headaches, stiff neck or head and neck pain with neck movement, sensitivity to light, nausea, vomiting, lethargy and low-grade fever. Other signs of *Balamuthia* GAE may include behavioral changes, seizures, weight loss, partial paralysis, speech difficulties and difficulty walking. *Balamuthia* can also cause a widespread infection involving multiple body parts. The disease might appear mild at first but can become more severe over weeks to several months. *Balamuthia* GAE is a very rare but usually fatal disease. Overall, the outlook for people with this disease is poor, although early diagnosis and treatment may increase the chances for survival.

The *Balamuthia* amoeba is able to infect anyone, including healthy people. Those at increased risk for infection include people with HIV/AIDS, cancer, liver disease or diabetes mellitus; people taking immune system inhibiting drugs; alcoholics; young children or the elderly and pregnant women.

Severity

More than 95% of PAM and GAE cases are fatal. Only 1 person with PAM has survived out of 123 known infected individuals in the United States from 1962 to 2011.

DEFINITIONS

Amebic meningitis/encephalitis is classified as either Primary Amebic Meningoencephalitis (if it is caused by *Naegleria fowleri*) or as Other Amebic Meningitis (if it is caused by another amoeba). See the case definitions for both conditions below.

Clinical Case Definition of PAM

Naegleria fowleri is a free-living ameboflagellate that invades the brain and meninges via the nasal mucosa and olfactory nerve to cause acute, fulminant hemorrhagic meningoencephalitis (primary amebic meningoencephalitis – PAM), primarily in healthy children and young adults with a recent history of exposure to warm fresh water. Initial signs and symptoms of PAM begin one to 14 days after infection and include sudden onset of headache, fever, nausea, vomiting, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. In some cases, abnormalities in taste or smell, nasal obstruction and nasal discharge might be seen. Other symptoms might include photophobia, mental-state abnormalities, lethargy, dizziness, loss of balance, other visual disturbances, hallucinations, delirium, seizures, and coma. After the onset of symptoms, the disease progresses rapidly and usually results in death within three to seven days. Although a

variety of treatments have been shown to be active against amebae in vitro and have been used to treat infected persons, most infections have still been fatal.

Laboratory Confirmation of PAM

Confirmed presence of *Naegleria fowleri* in CSF, biopsy or tissue specimens via:

- Microscopic examination, or
- Detection of nucleic acid (e.g., PCR), or
- Detection of antigen (e.g., DFA)

Note: When available, molecular characterization (e.g., genotype) should be reported.

Case Classifications for PAM

- **Confirmed:** A clinically compatible case that is laboratory confirmed
- **Probable:** No probable case definition

Clinical Case Definition of Other Amebic Meningitis

There are three amebae other than *Naegleria fowleri* that are known to cause human amebic central nervous system (CNS) infections: *Balamuthia mandrillaris*, *Acanthamoeba* species, and *Sappinia* species. *Acanthamoeba* species, *Balamuthia mandrillaris*, and *Sappinia* species are 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. Amebic CNS infection may also occur through organ transplantation. Once in the brain, *Acanthamoeba* species cause granulomatous amebic encephalitis (GAE), *Balamuthia* causes meningoencephalitis and/or GAE, and *Sappinia* species cause amebic encephalitis. The incubation period for *Balamuthia* is not well-characterized but has been observed to range from two weeks to months or possibly years. GAE caused by *Acanthamoeba* and *Balamuthia* often has a slow and 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. Although immunosuppressed persons (e.g., HIV/AIDS, organ transplantation) are likely at greater risk of amebic CNS infection, these infections can also occur in immunocompetent persons.

Initial symptoms of amebic CNS infection 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. For *Balamuthia* infections, 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 one month to approximately two years. Once *Acanthamoeba* or *Balamuthia* disease progresses to neurologic infection, it is generally fatal within weeks or months; however, a few patients have survived this infection. Only one case of amebic encephalitis from *Sappinia* infection has been reported worldwide, and the patient survived.

Laboratory Confirmation of Other Amebic Meningitis

In CSF, biopsy or tissue specimens, detection of free-living amebic organisms (**other than *Naegleria fowleri***) by:

- Microscopic examination, or
- Detection of nucleic acid (e.g., PCR), or
- Detection of antigen (e.g., DFA)

Comments: *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. A negative test on CSF does not rule out *Acanthamoeba* or *Balamuthia* infection because these organisms are not commonly present in the CSF.

Case Classifications for Other Amebic Meningitis

- **Confirmed:** A clinically compatible case that is laboratory confirmed
- **Probable:** No probable case definition

Cluster and Outbreak Definitions for PAM and Other Amebic Meningitis

- Cluster:
 - Two or more cases linked by place of residence or places visited within 1 year
- Outbreak:
 - Two or more cases associated with the same body of water or other common water exposure event/practice (e.g., Neti pot usage for nasal irrigation) within 1 year

SURVEILLANCE AND CASE INVESTIGATION

Case Investigation

Local and regional health departments should investigate all reports of suspected amebic meningitis or encephalitis. Primary amebic meningoencephalitis cases tend to receive substantial amounts of attention from the community and the media.

Case Investigation Checklist

- Confirm that laboratory results meet the case definition.
- Arrange for specimens to be sent to the Centers for Disease Control and Prevention (CDC) (if specimens have not already been sent).
- Review medical records or speak to an infection preventionist or physician to verify that the case meets case definition, and to obtain information on underlying health conditions and course of illness.
- Interview the case (or surrogate) to identify risk factors.
 - If multiple attempts were made to contact the case or surrogate and attempts were unsuccessful, please fill out the case investigation form with as much information as possible and indicate the reason for missing information (e.g., lost to follow-up - patient did not return call; multiple messages left).
- Ensure that appropriate control measures are implemented (see Control Measures section, below).
- Complete the Free Living Ameba Case Report form (available at <http://www.dshs.state.tx.us/idcu/investigation>) and fax it to DSHS.
- Enter and submit for notification in the NEDSS Base System (NBS) all confirmed case investigations.

Control Measures

- Provide education on amebic meningitis as needed with emphasis on the rarity of disease.
 - Although infections are severe, the risk of *Naegleria fowleri* infection is very low. There have been 30 reported infections in the U.S. during the 10 years from 2000–2009, despite millions of recreational water exposures each year. By

comparison, during the 10 years from 1996–2005, there were over 36,000 drowning deaths in the U.S.

- It is likely that a low risk of *Naegleria fowleri* infection will always exist with recreational use of warm freshwater lakes, rivers and hot springs. The low number of infections makes it difficult to know why some people have been infected compared to the millions of other people using the same or similar waters across the U.S.
- The only way to prevent *Naegleria fowleri* infections is to refrain from water-related activities. For individuals who plan to take part in water-related activities, provide education on risk reduction (see below).
- Provide education on prevention of exposure.
 - <http://www.cdc.gov/parasites/naegleria/prevention.html>
 - Avoid water-related activities in bodies of warm freshwater during periods of high water temperature and low water levels.
 - Hold the nose shut or use nose clips when taking part in water-related activities in bodies of warm freshwater such as lakes, rivers or hot springs.
 - Avoid digging in or stirring up the sediment while taking part in water-related activities in shallow, warm, freshwater areas.
 - *Naegleria fowleri* infections have been reported when people put their heads underwater, rinse their sinuses through the nose, and cleanse their noses during religious practices (e.g., ritual nasal rinsing and ablution) using contaminated tap or faucet water. If you perform nasal irrigation or sinus flushes (e.g., using a Neti pot) for any reason, be sure to use only sterile, distilled or lukewarm previously boiled water.
- Recommend that anyone experiencing symptoms be evaluated by a physician.
- Posting of signs mentioning the presence of *Naegleria fowleri* in bodies of water is not generally recommended since the *N. fowleri* amoeba is ubiquitous in nature. There are no guidelines or supporting evidence for the posting or removal of such signs. Posting of safe swimming practices might be a preferred alternative.
- Several drugs are effective against *Naegleria fowleri* in the laboratory. However, their effectiveness in humans is unclear since almost all infections have been fatal even when people were treated. See the CDC's Primary Amebic Meningoencephalitis (PAM) treatment website for more information on available treatments for patients with free-living amoeba infections at <http://www.cdc.gov/parasites/naegleria/treatment-hcp.html>.

School/Daycare Exclusion Criteria

No exclusion is required for disease control purposes.

MANAGING SPECIAL SITUATIONS

Multiple Cases Associated with a Single Water Source

If one or more cases occur that are associated with a single water source within a one-year period, notify the DSHS EAIDB at **(800) 252-8239** or **(512) 776-7676**.

REPORTING AND DATA ENTRY REQUIREMENTS

Provider, School, Child-Care Facility, and General Public Reporting Requirements

Confirmed and clinically suspected cases are required to be reported **within 1 week** to the local or regional health department or to DSHS EAIDB at **(800) 252-8239** or **(512) 776-7676**.

Local and Regional Reporting and Follow-up Responsibilities

Local and regional health departments should:

- Enter the case into NBS and submit an NBS notification on all **confirmed** cases to DSHS within 30 days of receiving a report of a confirmed case.
 - Please refer to the *NBS Data Entry Guidelines* for disease-specific entry rules.
 - A notification can be sent as soon as the case criteria have been met. Additional information from the investigation may be entered upon completion of the investigation.
- Fax (or mail) a completed investigation form when the NBS notification is submitted.
 - Investigation forms may be faxed to **512-776-7616** or mailed to:
Infectious Disease Control Unit
Texas Department of State Health Services
Mail Code: 1960
PO Box 149347
Austin, TX 78714-9347

When an outbreak is investigated, local and regional health departments should:

- Report outbreaks within 24 hours of identification to the regional DSHS office or to EAIDB at **512-776-7676**.
- For waterborne outbreaks, submit a completed **National Outbreak Reporting System (NORS)** outbreak form at the conclusion of the outbreak investigation.
 - Enter into NORS online reporting system at <https://wwwn.cdc.gov/nors/login.aspx>
 - Forms, training materials, and other resources are available at <http://www.cdc.gov/nors/>
- To request a NORS account, please email FoodborneTexas@dshs.state.tx.us
 - Please put in Subject Line: NORS User Account Request
 - Information needed from requestor: name, email address, and agency name
 - After an account has been created a reply email will be sent with a username, password, and instructions for logging in.

LABORATORY PROCEDURES

It is recommended that CSF, serum and tissue specimens (including biopsy, surgical or necropsy specimens) be collected for the detection of free-living amebae (*Naegleria*, *Balamuthia* and *Acanthamoeba*) and sent directly to the CDC along with the CDC Form for Free-living Amebae (FLA) Testing (request by emailing dpx@cdc.gov) and the CDC 50.34 Submission Form (available at <http://www.cdc.gov/laboratory/specimen-submission/index.html>).

Clinicians who suspect amebic meningitis/encephalitis (including PAM) should contact their state health department and/or CDC (24/7 Emergency Operation Center—770-488-1700). CDC can assist with diagnosis and provide treatment recommendations. Telediagnosis can be arranged at

CDC by emailing photos through DPDx, CDC's Division of Parasitic Diseases and Malaria telediagnosis tool. Instructions for submitting photos through DPDx are available at the [DPDx Contact Us page](#).

Important note: For CSF samples - Do NOT refrigerate or freeze; Do NOT centrifuge (Refrigeration or freezing will rapidly lyse and kill the amebae, preventing visual detection and identification.)

- The DSHS Parasitology Laboratory may be contacted for assistance and coordination in submitting specimen samples and electronic images to the CDC. The team lead, Cathy Snider, will work with the hospital to coordinate all CSF specimen shipments to the CDC.

Cathy Snider – Team leader – Parasitology
DSHS Parasitology Lab
1100 West 49th Street
Austin, TX 78756
Phone: 512-458-7560
Email: cathy.snider@dshs.state.tx.us

Specimen Collection

The following CDC guidelines are available at <http://www.cdc.gov/parasites/naegleria/diagnosis-hcp.html>. Tissue specimens—including biopsy, surgical or necropsy specimens—may be collected for the detection of free-living amebae (*Naegleria*, *Balamuthia* and *Acanthamoeba*).

A. Specimens Needed for Pre-Mortem Diagnosis

Clinical Pre-Mortem Specimens for Diagnosis at CDC:

If possible, CDC requests that the following specimens be sent for diagnostic testing at CDC:

- Fresh CSF (Please DO NOT FREEZE and DO NOT REFRIGERATE as this kills the amebae)
- If the patient has had a biopsy, the following are also requested:
 - Fresh brain tissue (Please DO NOT FREEZE and DO NOT REFRIGERATE)
 - Formalin-fixed and paraffin embedded tissues
 - Three stained hematoxylin and eosin (H&E) slides
 - Six unstained slides

B. Specimens Needed for Post-Mortem and Autopsy Diagnosis

To better understand the pathogenesis of PAM and the potential for transmission via organ transplantation, CDC would like to encourage autopsies for PAM case patients whose families consent.

- CNS Tissue: *Naegleria fowleri* is most likely detected in biopsy or autopsy tissue collected from the area surrounding the nasal-olfactory bulbs in the brain. However, CDC requests that tissues be collected from other CNS sites in addition to the olfactory bulb to look for other possible locations of ameba entry into the brain, such as around the auditory nerve.
- Extra-CNS Tissue: All possible steps should be taken to minimize the possibility of cross-tissue contamination between CNS and extra-CNS tissues. These steps should, at a minimum, include:
 - Completing the gross examination and sample collection from all extra-CNS tissues prior to examination of the CNS tissues
 - Utilizing separate workspaces and dissecting tools for the extra-CNS and CNS tissues

- Placing recovered samples of extra-CNS and CNS tissues in separate formalin containers
- Processing all tissues, particularly extra-CNS and CNS, separately
- Cutting extra-CNS and CNS tissues separately
 - If the same equipment is used to cut the tissue, cut extra-CNS tissues first and include a cleaning step in between different tissues.

Specimens can then be sent to CDC.

Clinical Post-Mortem Specimens for Diagnosis at CDC

If possible, please send the following specimens:

- Fresh CSF (Please DO NOT FREEZE and DO NOT REFRIGERATE as this kills the amebae)
- Fresh, unfixed brain tissue
- Fresh, unfixed tissue (other than brain)
- Formalin-fixed, paraffin-embedded, tissue
 - Three H&E-stained slides
 - Six unstained slides (for indirect immunofluorescence, or IIF)
 - Paraffin-embedded tissue block
- Photos of gross brain morphology
 - Particularly around olfactory and auditory areas
- Serum

Submission Forms

- The FLA specimen submission form for free-living amebae (FLA) testing can be requested by emailing dpx@cdc.gov. In addition, the CDC 50.34 Specimen Submission Form (available at <http://www.cdc.gov/laboratory/specimen-submission/form.html>) is also required for FLA testing.

Specimen Shipping

- Ship samples according to shipping guidelines and requirements available at <http://www.cdc.gov/dpdx/diagnosticProcedures/other/FLA.html> and <http://www.cdc.gov/dpdx/diagnosticProcedures/other/shipment.html>.
- Unfixed specimens for culture should be sent at ambient temperature by overnight priority mail. For PCR, sterile unfixed specimens or specimens in 70-90% ethanol should be sent by overnight priority mail on ice packs. Care should be taken to pack glass slides securely, as they can be damaged in shipment if not packed in a crush-proof container.
- **Please arrange Monday through Friday delivery only.** Packages cannot be accepted on weekends or federal holidays. Please send any fresh tissue, CSF, whole blood or serum specimens by overnight express:

CDC
SMB/STAT Lab
Attn: Unit 53
1600 Clifton Road, NE
Atlanta, GA 30333

Ph: 404-718-4157; 404-718-1433

- For additional information about tissue specimens or shipping, please contact the CDC Division of Parasitic Diseases at dpx@cdc.gov or 404-718-4157 or 404-718-1433.

Digital Laboratory and Pathology Image Submission

- Please send your diagnostic request to dpx@cdc.gov. Attaching several images will assist in making an identification. When submitting a digital image, please include the following information along with your message:
 - Your name
 - Your affiliation
 - Your telephone contact number (optional)
 - Mailing address for final reporting
 - Specimen ID code
 - Type of specimen
 - Date specimen was collected
 - Stain used, and magnification of the microscopic field captured
 - Presumed diagnosis
 - Any other pertinent data (e.g., pre or post treatment, travel history, etc.).
 - If you have other relevant supporting documents or clinical information, please attach them.

UPDATES

- Basic Epidemiology: added organ transplantation to Transmission; changed incubation and duration periods for PAM; updated Communicability and Clinical Illness sections
- Definitions: changed Clinical Case Definition and Laboratory Confirmation for both PAM and Other Amebic to make this document consistent with the Epi Case Criteria Guide (ECCG).
- Surveillance and Case Investigation: added location of FLA form on DSHS website to Case Investigation Checklist; added some clarifications in Control Measures section, and added information on religious practices (ritual nasal rinsing and ablution) as a possible source of infection
- Reporting and Data Entry Requirements: clarified that only waterborne outbreaks of amebic meningitis/encephalitis should be reported in NORS
- Laboratory Procedures: included telediagnosis information, edited CDC DPDx laboratory contact information, edited the specimen submission form requirements, and included various other changes