

Section 9: Amebic Meningitis/Encephalitis

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 (like lakes, rivers, and hot springs) and soil. *Naegleria fowleri* is the only species of *Naegleria* known to infect people. Most of the time, it 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 sources (such as lakes, rivers, and hot springs), in brackish water (such as a marsh), and sea water. *Acanthamoeba* can also be found in swimming pools, hot tubs, and drinking water systems (for example, slime layers in pipes and taps), as well as in heating, ventilating, and air conditioning (HVAC) systems and humidifiers. While only one species of *Naegleria*, *N. fowleri*, is known to infect humans, several species of *Acanthamoeba*, including *A. culbertsoni*, *A. polyphaga*, *A. castellanii*, *A. astronyxis*, *A. hatchetti*, *A. rhyodes*, *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 it is in the environment. However, very few cases of disease in humans have been found worldwide since *Balamuthia* was discovered.

Transmission

Transmission of *Naegleria 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. Infection can occur in young immune-competent individuals. Exposure occurs when people go swimming or diving in warm freshwater places, like lakes and rivers. People do not become infected from drinking contaminated water. In very rare instances, *Naegleria* infections may also occur when contaminated water from other sources (such as inadequately chlorinated swimming pool water or heated and contaminated tap water) enters the nose, for example when people submerge their heads or cleanse during religious practices, and when people irrigate their sinuses (nose) using contaminated tap water.

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. enters the eye it can cause severe keratitis in otherwise healthy individuals, particularly contact lens users. When it 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.

Granulomatous Amebic Encephalitis (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 GAE occurs when the amoebae 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 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, or skin lesions in individuals who are immune competent as well as those with compromised immune systems. *Balamuthia* GAE is a very rare but usually fatal disease. The *Balamuthia* amoeba is able to infect anyone, including healthy people. Those at increased risk for infection include immunocompromised individuals: 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.

Incubation Period

Naegleria fowleri:

- Incubation period: Symptoms start 1-7 days (median 5 days) after exposure.
- Duration of illness: Death occurs 1-12 days (median 5.3 days) after symptoms begin.

Balamuthia and *Acanthamoeba*:

- Incubation period: Weeks to months.
- Duration of illness: Weeks to months.

Communicability

Amebic meningitis/encephalitis is not spread person to person.

Clinical Illness

Infections with *Naegleria fowleri* cause the rare disease PAM, a brain infection that leads to the destruction of brain tissue. In its early stages, *Naegleria fowleri* infection may be similar to bacterial meningitis. Initial symptoms of PAM start 1 to 7 days after infection. Symptoms may include headache, fever, nausea, vomiting, and/or stiff neck. Later symptoms may include

confusion, lack of attention to people and surroundings, a loss of balance, seizures, and/or hallucinations. These symptoms are followed by coma and death. After the start of symptoms, the disease progresses rapidly and death occurs within 10 days, usually on the fifth or sixth day.

Granulomatous Amebic Encephalitis (GAE) often has a slow, insidious onset and then develops into a subacute or chronic disease lasting several weeks to months. GAE is caused by *Balamuthia* and *Acanthamoeba* species.

GAE caused by *Acanthamoeba* can cause a serious, usually fatal, infection of the brain and spinal cord. Once infected, a person may suffer with 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.

Balamuthia amebae can infect the skin, sinuses, brain and other organs of the body. Therefore, *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 (tiredness), 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. Often the disease is fatal, with a death rate of more than 95%. Overall, the outlook for people with this disease is poor, although early diagnosis and treatment may increase the chances for survival.

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 ameba). See case definitions for both conditions below.

Clinical Case Definition of PAM

- Is caused by *Naegleria fowleri*, a free-living ameboflagellate. *Naegleria fowleri* 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.
- PAM typically presents 1 to 14 days after infection with signs and symptoms of fever, nausea, vomiting, and meningeal irritation (the triad of 1. nuchal rigidity (neck stiffness), 2. photophobia (intolerance of bright light) and 3. Severe headache). Physical

examination might reveal positive meningeal signs (Kernig's sign, Brudzinski's sign, and nuchal rigidity).

- Other symptoms such as lethargy, dizziness, loss of balance, mental status abnormalities, visual disturbances, hallucinations, delirium, seizures, and coma have been reported as the disease progresses.
- In some cases, abnormalities in taste or smell, nasal obstruction, and nasal discharge have been observed.
- After the onset of symptoms, the disease progresses rapidly and usually results in death within 3 to 7 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

In CSF, biopsy, or tissue specimens detection of *Naegleria fowleri* by

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

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

Amebic meningitis / encephalitis can present with signs and symptoms commonly associated with other causes of meningitis including fever, headache, photophobia or stiff neck. Other signs and symptoms may also be present. One specific type of amebic meningitis is granulomatous amebic meningoencephalitis (GAE). This form of amebic meningitis has a slow, insidious onset and develops into a subacute or chronic disease lasting several weeks to months. GAE is generally fatal though a few patients have survived.

Laboratory Confirmation of Other Amebic Meningitis

In CSF, biopsy, or tissue specimens detection of a 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)

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) within 1 year

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 the laboratory results meet the case definition.
- Review medical records or speak to an infection preventionist or physician to verify case definition, underlying health conditions and course of illness.
- Interview 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 reason for missing information (e.g. lost to follow up – patient did not return call; multiple messages left).
- Complete the Free Living Ameba Case Report form and fax it to DSHS.
- All confirmed case investigations must be entered and submitted for notification in the NEDSS Base System (NBS). Please refer to the *NBS Data Entry Guidelines* for disease specific entry rules.

Control Measures

- Provide education on amebic meningitis as needed with emphasis on 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 ten years from 1996 to 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. If you do plan to take part in water-related activities, here are some measures that might reduce risk:
- Provide education on prevention of exposure
 - 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.
- If you use a Neti Pot or syringe for nasal irrigation or sinus flushes be sure to use only sterile, distilled, or lukewarm previously boiled water.
- Recommend that anyone experiencing symptoms be evaluated by a physician.
- 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.

Exclusion

No exclusion 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 Infectious Disease Control Unit (IDCU) at **(800) 252-8239** or **(512) 776-7676**.

REPORTING AND DATA ENTRY REQUIREMENTS

Provider, School & Child-Care Facilities, and General Public Reporting Requirements

Confirmed and suspected cases of amebic meningitis should be reported within 1 week of suspicion to the local or regional health department or the Texas Department of State Health Services (DSHS), Infectious Disease Control Unit at **(800) 252-8239** or **(512) 512-7676**.

Local and Regional Reporting and Follow-up Responsibilities

Local and regional health departments should fax (or mail) a completed investigation form and submit an NBS notification on all confirmed cases to DSHS within 30 days of receiving a report of amebic meningitis. Please refer to the *NBS Data Entry Guidelines* for disease specific entry rules. Investigations 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

Local and regional health departments should report suspected outbreaks within 24 hours of identification to the regional DSHS office or to 512-776-7676 and submit a completed NORS outbreak form at the conclusion of the outbreak investigation (enter into NORS and fax a copy to the DSHS regional office and/or IDCU 512-776-7676) .

LABORATORY PROCEDURES

Important note: For CSF samples - Do NOT refrigerate or freeze; Do NOT centrifuge (refrigeration or freezing will rapidly LYSE & KILL the ameba, preventing visual detection and identification.)

- 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 be sent directly to the CDC along with the CDC Form for Free-living Amebae (FLA) Testing which can be requested by emailing dpdx@cdc.gov.
- 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 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

- Fresh CSF (Please DO NOT FREEZE and DO NOT REFRIGERATE as this kills the amebae)
 - If the patient has had a biopsy, we also request:
 - Fresh brain tissue (Please DO NOT FREEZE and DO NOT REFRIGERATE);
 - Formalin-fixed and paraffin embedded tissues
 - Three stained 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

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 hematoxylin and eosin (H&E) - stained slides
- Six unstained slides (for indirect Immunofluorescence, or IIF)
- Paraffin-embedded tissue block
- Unfixed corneal scrapings (for Acanthamoeba).
- Photos of gross brain morphology
- Particularly around olfactory and auditory areas
- Serum

Submission Form

- Specimen submission forms for free-living amebae (FLA) testing can be requested by emailing: dpx@cdc.gov.

Specimen Shipping

- Ship samples according to shipping guidelines and requirements available at http://www.dpd.cdc.gov/dpdx/HTML/Frames/DiagnosticProcedures/body_dp_otherspec_shipment.htm. 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. If specimens have been previously frozen, please send on dry ice or 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–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 to the following address, using the “FLA” form:

Dr. Govinda Visvesvara
Centers for Disease Control and Prevention
Bldg 23, Room 9-621, Mailstop D-66 (note; online says 624)
1600 Clifton Road
Atlanta, GA 30333
Phone: 404-718-4159; 404-718-417

- For additional information about tissue specimens or shipping, please call the Division of Parasitic Diseases at (770) 488-4474.

Digital laboratory and pathology image submission

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