Amebic infections (encephalitis)

PROTOCOL CHECKLIST

- ☐ Enter available information into Merlin upon receipt of initial report.
- ☐ Review background on disease (see page 2), case definition (see page 4), and laboratory testing (see page 6).
- ☐ Contact provider (see page 8).
- ☐ Interview patient(s) or proxy (see page 8).
  - ☐ Review disease facts.
    - ☐ Confirm diagnosis.
    - ☐ Modes of transmission.
    - ☐ Incubation period.
    - ☐ Symptoms/types of infection.
  - ☐ Determine if patient is immunocompromised.
  - ☐ Ask about exposure to agent specific risk factors (see page 8).
  - ☐ Determine if patient was hospitalized for illness/symptoms consistent with meningitis/encephalitis.
  - ☐ Document pertinent clinical symptoms and confirm laboratory findings.
  - ☐ Arrange to send any laboratory isolates to CDC for definitive testing confirmation.
  - ☐ Identify other possibly exposed contacts/family members who may be at risk.
  - ☐ Provide education on agent specific prevention.
  - ☐ Address case-patient family's questions or concerns.
- ☐ Follow-up on special situations, including environmental assessments of suspect bodies of water or other agent-specific exposures elicited during interviews.
- ☐ Enter additional data obtained from interview into Merlin.

Amebic infections

1. DISEASE REPORTING

A. Purpose of reporting and surveillance

1. To characterize the epidemiology and clinical aspects of this emerging disease.
2. To monitor detection of cases and disease trends.
3. To target prevention and control messages.

B. Legal reporting requirements

Laboratories and physicians are required to report cases to the local county health department (CHD) within one working business day of identification/diagnosis.

C. County health department investigation responsibilities

1. Begin the investigation as soon as possible after receiving report.
2. Facilitate the transport of specimens to Florida Department of Health (FDOH) Bureau of Public Health Laboratories (BPHL) for confirmatory testing. When available, molecular characterization should be reported. Definitive laboratory confirmation and diagnosis by the Centers for Disease Control and Prevention (CDC) is required.
3. Report all probable or confirmed cases to your Regional Environmental Epidemiologist: http://www.doh.state.fl.us/Environment/community/foodsurveillance/contact_docs/Epidemiologist_regions.pdf.
4. Report all probable and confirmed cases in Merlin.
5. Complete the Primary Amebic Meningoencephalitis Case Report Form for PAM case: http://www.doh.state.fl.us/Disease_ctrl/epi/topics/crforms.htm.

2. THE DISEASE AND ITS EPIDEMIOLOGY

A. Etiologic agent

Etiologic agents may include *Naegleria fowleri, a free living ameba,* causing Primary Amebic Meningoencephalitis (PAM); *Balamuthia mandrillaris, a free living ameba,* causing granulomatous amebic *encephalitis (GAE) or Acanthamoeba (several species including: A. castellanii, A. culbertsoni, A. hatchetti, A. healyi, A. polyphaga, A. rhysodes, A. astonyxis, A. lenticulata and A. divionensis) causing GAE and A.* keratitis*, which causes a local infection of the cornea.

B. Description of illness

PAM illness is often clinically compatible to bacterial meningitis, particularly in the early stages. Initial signs and symptoms begin 1-14 days after infection and include sudden onset of headache, fever, nausea, vomiting and stiff neck with + Kernig's and Brudzinski's signs. There may also be alternations in taste or smell, nasal obstruction and nasal discharge. Other symptoms may include photophobia, mental state alterations, lethargy, dizziness, loss of balance, visual disturbances, hallucinations, delirium, seizures, and coma. Most infections are fatal.

***B. mandrillaris* GAE** illness often has a slow and insidious onset, developing as a subacute or chronic disease, frequently in those persons who are immunocompromised, although it has also occurred in young children and older adults without immunosuppression. In some instances, affected individuals have had a relatively rapid clinical course. Initial symptoms may include headache, photophobia, and stiff neck with + Kernig's and Brudzinski's signs. Other symptoms may include nausea & vomiting, low-grade fever, muscle aches, weight loss, mental state alterations, lethargy, dizziness, loss of balance, cranial nerve palsies, hemiparesis, seizures, and coma. It is generally fatal within weeks to months, although a few patients have survived. Most cases of *Balamuthia* are diagnosed right before death or after the patient has died.

***Acanthamoeba* GAE** has a slow and insidious onset and develops as a subacute or chronic disease lasting several weeks to months. It generally affects immunosuppressed persons, although it has been found in individuals without obvious signs of immunosuppression. Initial symptoms are similar to GAE illness above. Painless skin plaques may also develop prior to the onset of neurological symptoms. Once the disease progresses to the acute stage, it is generally fatal within weeks to months, although a few patients have survived.

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.

C. Reservoirs

Naegleria fowleri can be found in bodies of warm freshwater, such as lakes and rivers, geothermal (naturally hot) water, such as hot springs, warm water discharge from industrial plants, geothermal (naturally hot) drinking water sources, soil, swimming pools that are poorly maintained, minimally-chlorinated, and/or un-chlorinated water heaters with temperatures less than 47°C.

Balamuthia amebae live freely in soil around the world. Gardening, playing with dirt, or breathing in soil carried by the wind might increase the risk for infection.

Acanthamoeba is found worldwide in the environment, most commonly, 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, drinking

water systems (for example, slime layers in pipes and taps), as well as in heating, ventilating, and air conditioning (HVAC) systems and humidifiers.

D. Modes of transmission

Naegleria fowleri is thought to infect humans by entering the body through the nose. This typically occurs when people go swimming or diving in warm freshwater places, like lakes and rivers. The *Naegleria fowleri* ameba travels up the nose to the brain where it destroys the brain tissue. You **cannot** be infected with *Naegleria fowleri* by **drinking** contaminated water. Exposure typically occurs through swimming, diving, jumping into infected water sources. The organism can also enter the nose through any introduction of improperly treated or prepared fresh water through religious rituals, sinus cleansing, or other such activities. The organism may enter the blood stream through the sinuses and middle ear, or through a primary infection in the skin such as an ulcer or dermatitis.

Balamuthia is thought to enter the body when soil containing *Balamuthia* comes in contact with skin wounds and cuts, or when dust containing *Balamuthia* is breathed in or gets in the mouth. Once inside the body, the ameba can travel through the blood stream to the brain, where they cause GAE. There are also a few reports of dogs that might have become infected after swimming in ponds. Transplant-transmitted infections have been reported to public health officials.

Disseminated infection caused by *Acanthamoeba* occurs more frequently in people with compromised immune systems or those who are chronically ill. *Acanthamoeba* can also cause disseminated infection by entering the skin through a cut, wound, or through the nostrils. Once inside the body, the ameba travel through the bloodstream to other parts of the body, especially the lungs, brain, and spinal cord.

*A. keratitis** is typically spread to the eye through contact lens use.

E. Incubation period

PAM incubation ranges from 1-14 days.

GAE (for both *Balamuthia* and *Acanthamoeba*) latency period is slow and insidious, and symptoms may not occur until weeks to months, up to two years, after exposure.

A. keratitis* has an incubation period of several days to weeks.

F. Period of communicability

There is no person-to-person communicability of any of these amebic infections, except possibly through organ transplantation.

G. Treatment

Although a variety of treatments have been shown to be active against ameba in vitro, and have been utilized by the investigation drug-use protocols to treat infected persons, however most PAM infections are fatal. GAE is often fatal within weeks to months of developing acute disease, although some persons have survived.

H. Prophylaxis

None indicated

I. Amebic Encephalitis (*Naegleria fowleri, Balamuthia mandrillaris, Acanthamoeba spp.*) in Florida

During 2000 – 2011, there were ten cases of fatal primary amebic meningoencephalitis reported in Florida, nine males and one female with an age range of eight to 22 years and a mean of 13 years. Nine reported exposure to freshwater lakes or rivers and one had unknown exposures. Counties of exposures include Orange (5), Brevard (1), Putnam (1), Madison (1), Polk (1), Volusia (1), and Seminole (1). Note: possible exposures for one case were reported in two counties.

There have been no reported cases of GAE in Florida.

3. CASE DEFINITION

A. Naegleria fowleri Causing Primary Amebic Meningoencephalitis (PAM)

1. **Clinical description** *N. 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 may be seen. Other symptoms may 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.

2. **Laboratory criteria for diagnosis** Laboratory-confirmed *N. fowleri* infection is defined as the detection of *N. fowleri*
   - Organisms in CSF, biopsy, or tissue specimens,
     OR
   - Nucleic acid (e.g., polymerase chain reaction) in CSF, biopsy, or tissue specimens,
     OR
   - Antigen (e.g., direct fluorescent antibody) in CSF, biopsy, or tissue specimens.

3. **Case classification** Confirmed: A clinically compatible illness that is laboratory confirmed. When available, molecular characterization should be reported (e.g., genotype).

4. **Comment** *N. fowleri* may cause clinically similar illness to bacterial meningitis, particularly in its early stages. Definitive diagnosis by a reference laboratory may be

required. Unlike *B. mandrillaris* and *Acanthamoeba* spp., *N. fowleri* is commonly found in CSF.

B. Balamuthia mandrillaris Disease

1. **Clinical description** *B. mandrillaris* is an opportunistic free-living ameba that may invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis), the sinuses and middle ear (from rhinitis, sinusitis, or otitis media), or via organ transplantation. The incubation period is not well-characterized but has been observed to range from two weeks to months or possibly years. Once in the brain, the amebae can cause meningoencephalitis or granulomatous amebic encephalitis (GAE). The amebae may also invade the brain via the nasal mucosa and olfactory nerve. *B. mandrillaris* GAE often has a slow and insidious onset and develops as 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 generally affects persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, IV drug use). However, cases have also occurred in young children and older adults with no obvious signs of immunosuppression. In some instances, affected individuals have had a relatively rapid clinical course. Initial symptoms of *B. mandrillaris* GAE may include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms may 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 neurological symptoms by one month to approximately two years. Once the disease progresses to the acute stage, it is generally fatal within weeks or months. However, a few patients have survived this infection.

2. **Laboratory criteria for diagnosis** Laboratory-confirmed *B. mandrillaris* infection is defined as the detection of *B. mandrillaris*
   - Organisms in CSF, biopsy, or tissue specimens,

     OR
   - Nucleic acid (e.g., polymerase chain reaction) in CSF, biopsy, or tissue specimens, OR
   - Antigen (e.g., direct fluorescent antibody) in CSF, biopsy, or tissue specimens.

3. **Case classification** Confirmed: A clinically compatible illness that is laboratory confirmed. When available, molecular characterization should be reported (e.g., genotype).

4. **Comment** *B. mandrillaris* and *Acanthamoeba* spp. may cause clinically similar illnesses and may be difficult to differentiate using commonly available laboratory procedures. Definitive diagnosis by a reference laboratory may be required. A negative test on CSF does not rule out *B. mandrillaris* infection because the organism load in the CSF is often low.

C. Acanthamoeba Disease (Excluding Keratitis)

1. **Clinical description** The genus *Acanthamoeba* includes several species of opportunistic free-living ameba that may invade the brain through the blood, probably from a primary infection in the skin (from ulcers or dermatitis) or the sinuses and middle ear (from rhinitis, sinusitis, or otitis media). Once in the brain, the ameba cause a granulomatous amebic encephalitis (GAE). The ameba may also invade the brain via the nasal mucosa and olfactory nerve. *Acanthamoeba* GAE has a slow and insidious onset and develops as a subacute or chronic disease lasting several weeks to months. *Acanthamoeba* GAE generally affects persons who are immunosuppressed from a variety of causes (e.g., HIV/AIDS, diabetes, organ transplantation). However, a few cases have been described in individuals with no obvious signs of immunosuppression. Initial symptoms of *Acanthamoeba* GAE may include headache, photophobia, and stiff neck accompanied by positive Kernig's and Brudzinski's signs. Other symptoms may 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 the acute stage, it is generally fatal within weeks or months. However, a few patients have survived this infection.

2. **Laboratory criteria for diagnosis**
   Laboratory-confirmed *Acanthamoeba* spp. infections (excluding keratitis) are defined as the detection of *Acanthamoeba* spp.

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

3. **Case classification** Confirmed: A clinically compatible illness that is laboratory confirmed. When available, species designation and molecular characterization (e.g., genotype) should be reported.

4. **Comment** *Acanthamoeba* and *B. mandrillaris* may cause clinically-similar illnesses and may be difficult to differentiate using commonly-available laboratory procedures. Definitive diagnosis by a reference laboratory may 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 CSF.

D. *Acanthamoeba Keratitis- individual cases are not reportable; however, outbreak associated cases are. If case could be outbreak associated, please notify your Laboratory Liaison.

1. ***Clinical description*** *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.

2. Laboratory criteria for diagnosis

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.

3. Case classification Confirmed: A clinically compatible illness that is laboratory confirmed. When available, species designation and molecular characterization (e.g., genotype) should be reported. Probable: A clinically compatible illness with positive identification of *Acanthamoeba* trophozoites or cysts using confocal microscopy.

4. LABORATORY TESTING

A. Criteria for diagnosis

The Centers for Disease Control and Prevention (CDC) offers diagnostic assistance to physicians and scientists through their Division of Parasitic Disease and Malaria through DPx at: http://www.dpd.cdc.gov/dpdx/HTML/Contactus.htm.

In *Naegleria* infections, the diagnosis can be made by microscopic examination of cerebrospinal fluid (CSF). A wet mount may detect motile trophozoites, and a Giemsa-stained smear will show trophozoites with typical morphology. In *Acanthamoeba* infections, the diagnosis can be made from microscopic examination of stained smears of biopsy specimens (brain tissue, skin, and cornea) or of corneal scrapings, which may detect trophozoites and cysts. Confocal microscopy or cultivation of the causal organism, and its identification by direct immunofluorescent antibody, may also prove useful. An increasing number of PCR-based techniques (conventional and real-time PCR) have been described for detection and identification of free-living amebic infections in the clinical samples listed above. Such techniques may be available in selected reference diagnostic laboratories.

There are three types of tests that can help confirm the diagnosis of GAE. The indirect immunofluorescence assay (IFA) is a test used to detect antibodies attached to *Balamuthia* amebae in body tissues. In contrast, immunohistochemistry (IHC) uses specific antibodies against *Balamuthia* to detect the amebae. Finally, a polymerase chain reaction (PCR) molecular assay can detect *Balamuthia* DNA.

B. Services available at the FDOH Bureau of Public Health Laboratories (BPHL)

The BPHL can help facilitate transfer of specimens to CDC laboratories for definitive confirmatory testing that is not available outside of the special reference laboratories.

C. Testing requests

Guidance for specimen collection is available at:
http://dpd.cdc.gov/dpdx/HTML/DiagnosticProcedures.htm

5. CASE INVESTIGATION

A. Contact the physician or hospital

1. Confirm the diagnosis**.** Since the diagnosis may have non-specific symptoms that overlap with other etiologies of meningoencephalitis, a careful review of the history, risk factors and definitive testing at the CDC reference laboratory will be necessary to confirm diagnosis.

2. Obtain all relevant demographic and clinical information to complete the case report form.

3. Ask what information has been shared with the patient and family.

4. Notify the physician that you will be contacting the case as DOH follows up on all cases of PAM and GAE to assess risk factors, to better characterize the occurrence of PAM and GAE in Florida and to identify potential means of preventing further transmission.

B. Interview the case

1. As case may be unavailable, interview patient's next of kin or guardian.

2. Complete the Primary Amebic Meningoencephalitis Case Report Form for PAM cases.

3. There is not a case report form for GAE.

4. Ask all risk factor questions as appropriate for specific agent.

C. Environmental evaluation

In the event of a locally acquired case, it may be appropriate to conduct an assessment of the environment where the case was possibly exposed, and notify the public to prevent additional exposures. The Bureau of Environmental Public Health Medicine can provide further guidance as needed. Contact your Regional Environmental Epidemiologist.

D. Merlin data entry

Create a case in Merlin under disease code **AMEBIC ENCEPHALITIS-13620**. Enter the data collected into Merlin, being sure to include all required fields on the Basic Data screen, complete the Case Symptoms screen, and attach all relevant labs. Please attach **ALL** labs received via electronic laboratory reporting (ELR) to the case.

6. CONTROLLING FURTHER SPREAD

A. Patient/ household education on prevention recommendations

1. According to the Centers for Disease Control and Prevention (CDC), the only known way to prevent *Naegleria fowleri* infections is to refrain from fresh water-related activities. However, some measures that might reduce risk by limiting the chance of contaminated water going up the nose include:

    - Avoid water-related activities in bodies of warm freshwater, hot springs, and thermally-polluted water such as water around power plants.
    - Avoid water-related activities in 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.

2. Unfortunately, at this point in time it is unclear what steps can be taken to prevent **Granulomatous Amebic Encephalitis** (GAE) and **disseminated infection**, both of which are very rare. Since persons with weakened immune systems are more susceptible to *Acanthamoeba* infection, they should follow the advice of their treating physician carefully.

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

B. Isolation of cases

Not indicated

C. Management of contacts

Not indicated

D. Laboratory testing during outbreaks

Not indicated

E. Food or water is implicated as the source of an outbreak

Recreational water users should assume that there is always a low level of risk whenever they enter warm freshwater (for example, when swimming, diving, or waterskiing). Posting signs is unlikely to be an effective way to prevent infections. This is because the location and number of ameba in the water can vary over time. In addition, posted signs might create a misconception that bodies of water without signs are *Naegleria fowleri*-free. Risk communication messaging for PAM is available at: http://www.doh.state.fl.us/Environment/medicine/foodsurveillance/RecWaterDisease.htm or the CDC recreational water websites.

7. MANAGING SENSITIVE SITUATIONS

A. Determining a sensitive situation

It is unusual to have multiple cases with the same exposure. However, other persons potentially exposed to the same source as the case should be educated about symptoms of amebic encephalitis and told to seek immediate medical attention if they develop characteristic symptoms.

The risk for infection from *Naegleria fowleri* might be reduced by measures that minimize opportunities for water to enter the nose when using warm freshwater lakes or rivers. For further information, please visit the CDC website: http://dpd.cdc.gov/dpdx/HTML/FreeLivingAmebic.htm

B. Case or symptomatic contact attends or works at a day care facility

Not applicable

C. Case or symptomatic contact is a food handler

Not applicable

D. Case or symptomatic contact works at a health care facility

Not applicable

E. Managing Suspected Transplant-Transmitted Infection

Contact your Regional Environmental Epidemiologist for consultation as this requires coordination with additional agencies.

8. IMPORTANT LINKS

A. Bureau of Epidemiology, Waterborne Disease Links: http://www.myfloridaeh.com/medicine/foodsurveillance/RecWaterDisease.htm.

B. CDC, Naegleria FAQ Sheet: http://www.cdc.gov/parasites/naegleria/faqs.html.

C. CDC, Balamuthia website: http://www.cdc.gov/parasites/balamuthia/.

***D.* CDC. *Balamuthia mandrillaris* transmitted through organ transplantation--Mississippi, 2009. *MMWR* Morb Mortal Wkly Rep. 2010; 59(36);1165-1170.**

E. CDC. Notes from the field: Transplant-transmitted *Balamuthia mandrillaris*---Arizona, 2010. *MMWR* Morb Mortal Wkly Rep. 2010; 59(36);1182