Naegleria fowleri infection—Primary amebic meningoencephalitis (11-14-2007)

Epidemiology: *Naegleria fowleri* is a free-living ameba that is ubiquitous worldwide in warm freshwater bodies, including lakes, ponds, rivers, minimally chlorinated swimming pools, hot springs, thermally polluted water (i.e., around power plants), and soil or air. Two hundred to 300 cases have been reported worldwide with a total of 25 (mostly young children) recreational water-associated cases reported in the United States during 1995-2004 (Two additional cases were drinking water system associated). Infections are usually during summer, particularly during heat waves, in the southern tier of the US when water temperatures rise.

Exposure: Usually a result of swimming in freshwater habitats where the ameba enters the nose and travels to the brain via the olfactory nerve. Other exposures include hot springs and thermally polluted areas near power plants, etc. Occasional incidents of drinking water transmission (showers, bathtubs) and poorly chlorinated swimming pools have been documented.

Incubation period: 1-14 days,

Course of disease: Usually fatal (only one case of ~100 infections has survived in the U.S.) with death following 3-7 days after onset of symptoms.

Symptoms: Sore throat, stiff neck, severe frontal headache, olfactory hallucinations, nausea, vomiting, drowsiness, high fever, combativeness. An initial diagnosis of bacterial meningitis is common. Autopsy findings show acute hemorrhagic necrosis of olfactory bulbs and cerebral cortex.

Diagnosis:
A) Visualization of motile amebae in a wet-mount preparation of a fresh-centrifuged specimen of CSF (cannot be frozen or the amebas will be killed). Fixation and staining with Giemsa-Wright and modified trichrome stain is recommended,
B) Indirect fluorescent antibody visualization of amebas in H&E-stained, unfixed/frozen brain or fixed necropsy slide sections,
C) PCR: DNA has been successfully amplified from CSF and unfixed tissue samples. Typing of the isolates can be done but little is known about the natural populations found to put these data in a biological context.

Sampling:
<u>Clinical Samples:</u>
1) CSF shipped at ambient temperature to CDC where the lab will attempt culturing. The lab will also utilize PCR technology to assay and genotype the ameba if present.
2) Autopsy tissue collected from the nasal-olfactory lobes has the best chance of detecting amebas by PCR and *Naegleria fowleri*-specific IFA. To do this the lab will need:

a. H&E stained slides or
b. Formalin-fixed necropsy slides or
c. Unfixed frozen brain tissue (for culture attempts) or unfixed tissue slides (PCR) or

d. A paraffin embedded block of tissue would also be helpful in the molecular or other analysis

Environmental Samples (For potential culturing of *Naegleria fowleri*)
This requires heavy resource investment. As a result, this will be done only under special circumstances and requires prior consultation with CDC before collection and shipping.

Collect samples in 100 or 200 ml bottles that are filled half full to keep enough oxygen in the sample for shipping. Collect samples near vegetation down by the sediment layer or run the mouth of the bottle over the sediment layer to catch material from the water/sediment interface.

Both clinical and environmental samples should be shipped un-refrigerated (i.e., ambient temperature) overnight to:

Serology: Tests do exist but are felt to be inadequate. A commercial ELISA kit exists (Indicia Biotechnology, France) but it not felt to be adequate

Treatment: Vish is the resident expert who has spoken with physicians treating most cases that have occurred in the US. Only one documented domestic case has survived. One case survived following treatment with intravenous and intrathecal amphotericin B/miconazole and oral rifampin (2). No subsequent persons with *Naegleria* infection have survived following use of this treatment protocol although it is usually attempted. This may indicate that treatment must be early and aggressive to be successful. Current Medical Letter guidelines are:

Amphotericin B[1, 2, 3] (see footnotes below): Adult and Pediatric Dosages: 1.5 mg/kg/d IV in 2 doses x 3d, then 1 mg/kg/d x 6d AND 1.5 mg/d intrathecally x 2d, then 1 mg intrathecally every other day x 8d.

Footnotes
1. *Naegleria fowleri* infection was treated successfully in a 9-year-old child with intravenous and intrathecal use of both amphotericin B and miconazole plus oral rifampin (JS Seidel et al, NEJM 1982; 306:346); it was believed that amphotericin B and miconazole had a synergistic effect but that rifampin was without effect (GS Visvesvara et al, FEMS Immunol Med Microbiol June 2007; 50:1-26). However, parenteral miconazole is no longer available in the United States. Other reportedly successful treatment courses have included amphotericin B, ornidazole and rifampin (R Jain et al, Neurol India 2002; 50:470; Ornidazole 500 mg every 8 hours for adult), and amphotericin B, fluconazole and rifampin (J Vargas-Zepeda et al, Arch Med Research 2005; 36:83; fluconazole 10 mg/kg/day every 24 hours IV). Additional reports of successful therapy have been described (FL Schuster and GS Visvesvara, Int J Parasitiol 2004; 34:1001).
2. An approved drug, but considered investigational for this condition by the FDA.
3. Azithromycin, 500 mg/day in an adult and 14 mg/kg/day in a child, has been used to treat *Balamuthia* infection. In both cases, azithromycin was changed to clarithromycin because of persistent elevation of creatinine levels, concern about interstitial nephritis in

the child, and better penetration of clarithromycin into the cerebrospinal fluid in the adult. Both patients survived (TR Deetz et al, Clin Infect Dis 2003; 37:1304). Clarithromycin is less effective than azithromycin in vitro against *Naegleria* (FL Schuster and GS Visvesvara, Drug Resistance Updates 2004; 7:41). Therefore, azithromycin may be tried as an adjunct to Amphotericin B in patients with *Naegleria* infection.

Prevention: *Naegleria* is found in many freshwater lakes and rivers in the United States, particularly in southern tier states. Therefore, it is likely that a low risk of *Naegleria* infection will always be associated with swimming in warm freshwater lakes, rivers, and hot springs. Some measures that may reduce this risk include:

- Avoid swimming or jumping into bodies of warm freshwater, hot springs, and thermally-polluted water such as water around power plants.
- Avoid swimming or jumping into freshwater during periods of high temperature and low water volume.
- Hold the nose shut or use nose clips when jumping or diving into bodies of warm freshwater such as lakes, rivers, or hot springs.
- Avoid digging in or stirring up the sediment while swimming in shallow, warm freshwater areas.
- Do not swim in areas posted as "no swimming" or in areas warning about an increased risk of *Naegleria* infection.

References:

1) GS Visvesvara, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea* FEMS Immunol Med Microbiol June 2007; 50:1-26.
2) Visvesvara GS, Stehr-Green JK. Epidemiology of free-living ameba infections. J Protozool 1990 37:25S-33S.
3) Seidel et al. Successful treatment of PAM. NEJM 1982 306:346-348.
4) CDC, Primary Amebic Meningoencephalitis -- Georgia, 2002. MMWR 2003 52:962-964.