JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Primary Amoebic Meningoencephalitis (PAM) Clinical Pathway

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All Children's Hospital

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Table of Contents

Updated: April 10, 2019
Owners: Juan Dumois, MD

Johns Hopkins All Children's Hospital

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Rationale

This protocol was agreed upon by a consensus group of JHACH physicians (representing the Infectious Diseases, Emergency Medicine, Critical Care and Hospitalist services), as well as physicians, nurses, and laboratory personnel from the CDC, the Florida Department of Health, and Florida Hospital Orlando, to optimize the early diagnosis and treatment of patients with PAM, which is crucial to the survival of these patients. It addresses the following clinical problems:

1. A history of nasal exposure to fresh water is elicited too late in some patients with PAM.
2. When a history of nasal exposure to fresh water is elicited for a patient with meningitis, correct testing for PAM often is not performed expediently.
3. Most clinicians are not aware of the CDC-recommended therapeutic protocol for managing patients with PAM.

Background

Introduction: Primary Amoebic Meningoencephalitis (PAM) is caused by infection of the central nervous system with *Naegleria fowleri*, which is found primarily in different warm, fresh water sources (including ponds, lakes, streams, hot springs, and tap water). Despite a high mortality rate of 97%, recent cases of survivors with good neurologic outcome have suggested that early diagnosis and treatment are likely of vital importance. A primary challenge in making a diagnosis of PAM is the need to elicit a history of recent nasal exposure to fresh water.(1, Cope) This guideline intends to recommend interventions to facilitate early diagnosis and treatment.

Definitions

Primary Amoebic Meningoencephalitis (PAM): brain infection due to *Naegleria fowleri*

Epidemiology

N. fowleri has worldwide distribution. In the United States, most cases have been diagnosed in the southern states, especially Florida and Texas, but cases have been diagnosed as far north as Minnesota. It cannot survive in salt water, in dry environments, or at chlorine levels >2 ppm. At fresh water temperatures of <80˚F, it exists in a non-infectious cyst form. At preferred temperatures of 80-115˚F, it converts to a flagellated form or to a trophozoite, depending upon

other environmental conditions. These motile forms are potentially infectious if they enter the nasal cavity. (2, Capewell)

Pathogenesis

Infection with *N. fowleri* requires introduction of the amoeba into the nasal cavity. Warm, fresh water containing the amoeba trophozoites must enter the nasal cavity; the trophozoites must attach to the nasal epithelium, migrate to the olfactory nerve, then migrate up the olfactory nerve to the olfactory bulb of the cerebrum. There, a necrotizing meningoencephalitis begins, followed by cerebral edema and death. (1, Cope)

Clinical Presentation:

Symptoms begin a median of 5 days (range 1-9 days) after nasal exposure to fresh water. Symptoms resemble those of bacterial meningitis, with initial fever, headache, nausea and vomiting, followed by stiff neck, seizures, and altered mental status. Death occurs a median of 5 days (range 1-18 days) after the onset of symptoms. (1, Cope)

Recommendation 1: A history of nasal exposure to fresh water in the 14 days before symptom onset should be asked of any patient who presents with symptoms of acute meningitis. [Evidence level 5, Strongly recommended]

Diagnostic testing:

Routine cerebrospinal fluid (CSF) studies (cell count, glucose, protein, Gram stain, culture) cannot detect *N. fowleri*. The CSF Meningitis/Encephalitis multiplex PCR panel used in the JHACH lab since 2018 does not include *N. fowleri*. Lumbar puncture typically reveals a high opening pressure, a neutrophilic pleocytosis, elevated protein level, and low glucose level. The amoeba can be detected by performing a wet mount of fresh CSF, a CSF Giemsa-Wright stain, or CSF polymerase chain reaction (PCR) for *N. fowleri* (see Appendix A). (3, CDC)

Recommendation 2: When a CSF culture is ordered, the electronic medical record (EMR) should provide a reminder alert to ask about nasal exposure to fresh water. [Evidence level 5, Strongly recommended]

Recommendation 3: For patients with meningitis who have a history of recent nasal exposure to fresh water, the CSF specimen should undergo rapid testing for *N. fowleri* using wet mount and Giemsa-Wright stain (Appendix A). [Evidence level 5a, Strongly recommended]

Management

The two main components of clinical management address the control of cerebral edema and the use of drug therapy against the amoebae. (4, CDC) These interventions are recommended by the CDC because they were used in all the recent survivors who had normal neurologic

outcome: dexamethasone, CSF drainage by ventricular drain, hyperosmolar therapy with mannitol and 3% saline, moderate hyperventilation, induced hypothermia, and several antibiotics listed in Appendix B. (5, Linam) One recent survivor with severe neurologic sequelae was treated with the same protocol except for induced hyperthermia, but was not treated until 5 days after symptoms began. (1, Cope)

Recommendation 4: As soon as a clinician receives laboratory notification of the presence of amoebae in a patient's CSF specimen, they immediately should contact the Infectious Diseases service and the Critical Care unit to implement the recommendations in the attached algorithm and Appendix B. The Infectious Diseases consultant will contact the CDC Emergency Operations Center at 770-488-7100 (available 24/7). [Evidence level 5, Strongly recommended]

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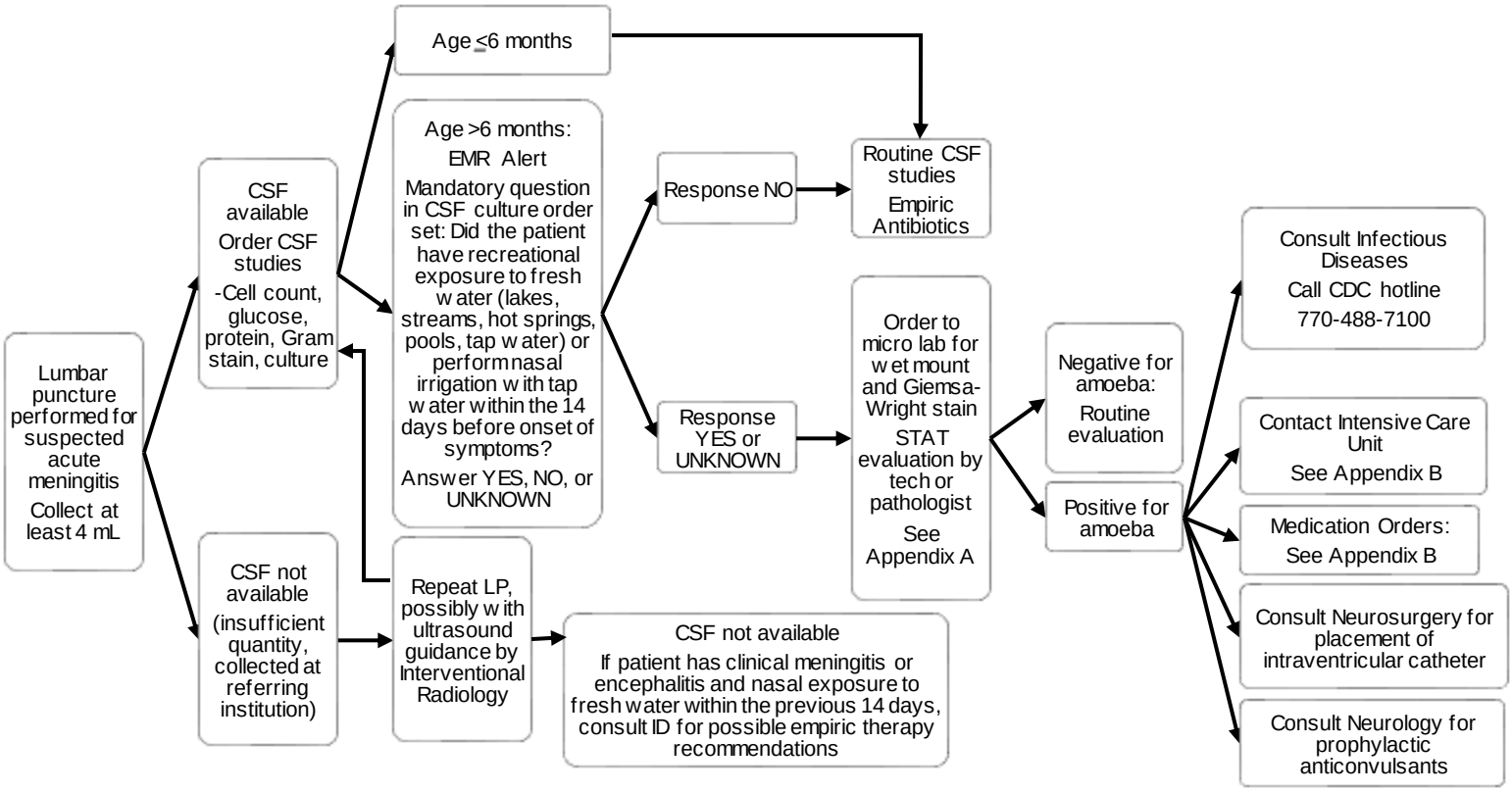

References

1. Cope JR, Ali IK. Primary Amebic Encephalitis: What have we learned in the last 5 years? Curr Infect Dis Rep 2016;18:31.
2. Capewell LG, et al. Diagnosis, clinical course, and treatment of primary amoebic encephalitis in the United States, 1937-2013. J Ped Infec Dis Soc 2014;1-8.
3. CDC website. Parasites – Naegleria fowleri – Primary Amebic Meningoencephalitis (PAM) – Amebic Encephalitis. Last updated 2/28/2017. https://www.cdc.gov/parasites/naegleria/index.html
4. CDC website on Naegleria fowleri treatment http://www.cdc.gov/parasites/naegleria/treatment-hcp.html
5. Linam WM et al. Successful treatment of an adolescent with Naegleria fowleri primary amebic encephalitis. Pediatrics 2015;135(3):e744-8.

Outcome Measures

1. Among patients for whom CSF culture is ordered and the answer to the EMR prompt is YES or UNKNOWN, what proportion had a CSF test for amoeba ordered?
2. If a CSF test for amoeba was ordered, how long did it take to be reported to the ordering physician?

Appendix A: Lab Testing

Wet mount of CSF:

A wet-mount of the CSF should be examined immediately after collection under a microscope (preferably equipped with phase-contrast optics) for the presence of actively moving *Naegleria fowleri* trophozoites.

1. Store CSF at room temperature (~25˚C) until examination. Do not refrigerate or freeze.

2. Gently agitate the CSF container to dislodge amoebae adhered to the container.

3. Centrifuge the CSF at 5000 G for 5 minutes to concentrate amoebae at the bottom.

4. Carefully remove CSF supernatant, leaving about 200-300 µL without dislodging any visible pellet.

5. Apply a drop to a microscope slide and warm the slide in a 35-37˚C incubator to stimulate movement of the amoebae.

6. Observe cells for amoeboid movement.

Wright stain

Apply a sample of the centrifuged CSF pellet (cytospin) to a slide and prepare a Wright stain using standard protocols. Look for the *N. fowleri* trophozoite, which can be differentiated from leukocytes by the nucleus that has a large, centrally-placed nucleolus.

Protocol for sending CSF to CDC for *N. fowleri* PCR:

1. Send 1 mL (minimum 0.5 mL) fluid at ambient temperature.

2, Complete CDC specimen submission form 50.34, which can be found at this link: http://www.cdc.gov/laboratory/specimen-submission/form.html

3. Use overnight priority mail for specimen shipment. Send the shipment tracking number as early as possible (by sending an e-mail to lAli@cdc.gov and JCope@cdc.gov) to ensure that the specimen is received and processed in a timely manner. The specimen should be shipped to the following address:

CDC
SMB/STAT Lab
Attn: Unit 53 (Ibne Ali)
1600 Clifton Road
Atlanta, GA 30329
USA

Phone: 404-718-4157

Appendix B: Management

Monitor and manage cerebral edema: hyperventilation (goal PaCO2 30-35 mm Hg), hyperosmolar therapy (3% saline, mannitol), induced moderate hypothermia (32-34˚C), and a prophylactic anticonvulsant. Consider use of induced pentobarbital coma. The intracranial pressure goal is <20 mm Hg.

Place nasogastric tube for miltefosine administration.

Drug	Dose	Route	Maximum Dose	Duration
Amphotericin B *	1.5 mg/kg/day in 2 divided doses for 3 days, then 1 mg/kg/day once daily for 11 days	IV	1.5 mg/kg/day	14 day course
Amphotericin B *	1.5 mg once daily for 2 days, then 1 mg/day every other day for 8 days	Intraventricular	1.5 mg/day	10 day course
Azithromycin	10 mg/kg/day once daily	IV/PO	500 mg/day	28 days
Fluconazole **	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days
Rifampin	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days
Miltefosine ***	Weight<45 kg 50 mg BID Weight≥45kg 50 mg TID	PO	2.5 mg/kg/day	28 days
Dexamethasone	0.6 mg/kg/day in 4 divided doses	IV	0.6 mg/kg/day	4 days

* Conventional amphotericin deoxycholate (AMB) is preferred. When AMB was compared with liposomal AMB against Naegleria fowleri, the minimum inhibitory concentration (MIC) for AMB was 0.1 µg/mL, while that of liposomal AMB was 10x higher at 1 µg/ml. Liposomal AMB was found to be less effective in the mouse model and in in vitro testing than the more toxic form of AMB.

** Voriconazole may be considered as an alternative to fluconazole for the treatment of PAM, based on in vitro data suggesting good inhibitory activity superior to that of fluconazole [Schuster FL et al. J Eukaryot Microbiol 2006;53(2):121-6]. However, voriconazole has not yet been used to treat a case of PAM. Recommended doses are: <12 years old – 9 mg/kg/dose IV every 12 hours (maximum dose 350 mg); ≥12 years old – 6 mg/kg/dose IV every 12 hours for 2 doses, then 4 mg/kg/dose every 12 hours.

*** The investigational drug, miltefosine, a breast cancer and anti-leishmania drug, has shown some promise against the free-living amebae in combination with some of these other drugs. These standard doses are the maximal tolerated with respect to gastrointestinal symptoms. A higher dose would lead to increased nausea, vomiting, or diarrhea. Miltefosine is mildly nephrotoxic and the dosing might need to be adjusted for patients with impaired kidney function. However, because few data are available about the effective dose for amoebic infection, the risk for nephrotoxicity should be balanced with the risk for mortality from PAM. Miltefosine is available from the JHACH inpatient pharmacy. Capsules may be opened and the powder placed into an enteral tube, followed by a sterile water flush.

Table of Evidence Levels (see note above)

Quality level	*Definition*
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5a or 5b	Other: General review, expert opinion, case report, consensus report, or guideline
5	Local Consensus

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

Strength	*Definition*
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
"Recommended"	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient *(direct benefit)*
4. Burden to patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to healthcare system *(balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis)*
6. Directness *(the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome])*
7. Impact on morbidity/mortality or quality of life

Primary Amoebic Meningoencephalitis (PAM) Clinical Practice Guideline

Johns Hopkins All Children's Hospital

Owner(s): Juan Dumois, MD, Infectious Disease

Clinical Practice Guideline Management Team: Joseph Perno, MD; Courtney Titus, PA-C

Approved by JHACH Clinical Practice Council: February 19, 2019

Last Revised: March 13, 2019

Available on Connect: April 1, 2019

Disclaimer

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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