JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Primary Amoebic Meningoencephalitis (PAM) Clinical Pathway

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This pathway is intended as a guide for physicians, physician assistants, nurse practitioners, and other healthcare providers. It should be tailored to the care of specific patients based on their individual circumstances and the clinician's professional judgment.

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

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Summary:

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) physicians, pharmacists, and laboratory personnel to standardize the management of pediatric patients undergoing diagnosis and treatment for primary amoebic meningoencephalitis (PAM). This clinical pathway addresses the following questions or problems:

1. Determining a history of nasal exposure to fresh water.
2. Accurately and expeditiously test for PAM in a patient with meningitis who has a recent history of nasal exposure to fresh water.
3. Awareness of the Centers for Disease Control (CDC)-recommended therapeutic protocol for managing patients with PAM.

Background:

PAM is caused by infection of the central nervous system with *Naegleria fowleri*, which is found primarily in warm freshwater sources (including ponds, lakes, streams, hot springs, and tap water). In rare instances, people have become infected at recreational water venues, such as splash pads and water parks, that lacked sufficient chlorine levels (Centers for Disease Control and Prevention [CDC], 2025).

Despite a high mortality rate of 97%, cases of survivors with good neurologic outcomes have suggested that early diagnosis and treatment are likely of vital importance. A primary challenge in diagnosing PAM is eliciting a history of recent nasal exposure to fresh water (Cope & Ali, 2016).

N. fowleri has a 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 parts per million (ppm). At freshwater temperatures of < 80° Fahrenheit (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 (Capewell et al, 2014).

Definition:

Primary Amoebic Meningoencephalitis (PAM): A rare but fatal brain infection caused by the amoeba *Naegleria fowleri* (CDC, 2025).

Pathogenesis:

Infection with *N. fowleri* requires the 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 (Cope & Ali, 2016).

Clinical Presentation:

Symptoms begin at a median of 5 days (range 1-9 days) after nasal exposure to freshwater. Symptoms resemble those of bacterial meningitis, with initial fever, headache, nausea, and vomiting, followed by stiff neck, photophobia, seizures, and altered mental status. Death occurs at a median of 5 days (range 1-18 days) after the onset of symptoms (Cope & Ali, 2016).

Diagnosis:

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].

Routine cerebrospinal fluid (CSF) studies (cell count, glucose, protein, Gram stain, culture) cannot detect *N. fowleri*. The CSF Meningitis/Encephalitis multiplex polymerase chain reaction (PCR) panel used in the JHACH lab since 2018 does not include *N. fowleri*. Lumbar puncture typically reveals high opening pressure, neutrophilic pleocytosis, elevated protein levels, and low glucose levels. The amoeba can be detected by performing a wet mount of fresh CSF, a CSF Giemsa-Wright stain, or CSF PCR for *N. fowleri* (see Appendix A) (CDC, 2024).

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] (CDC, 2024).

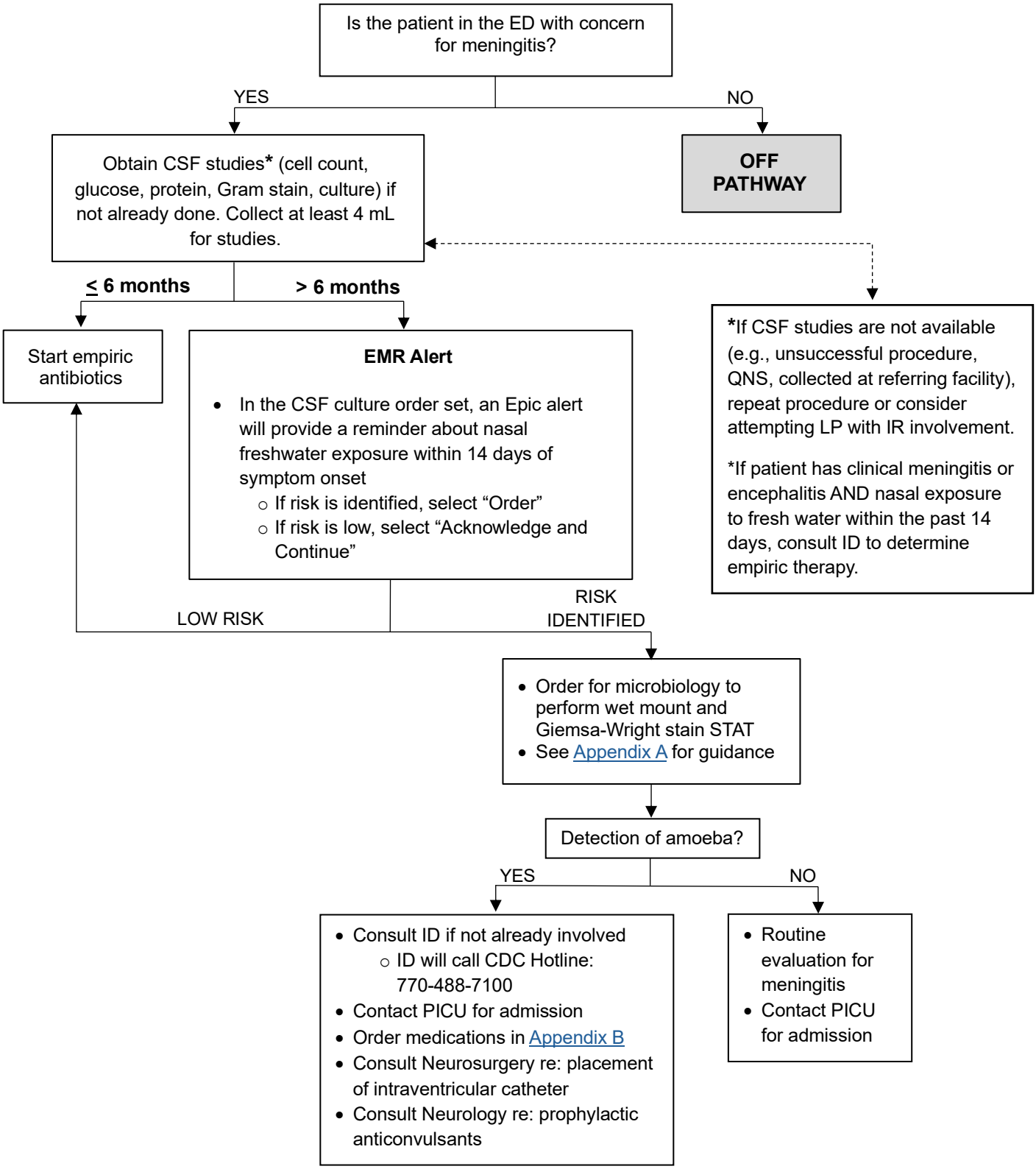
Clinical Management:

The two main components of clinical management address controlling cerebral edema and using drug therapy against the amoebae. All survivors with normal neurologic outcomes received dexamethasone, CSF drainage via a ventricular drain, hyperosmolar therapy with mannitol and 3% saline, moderate hyperventilation, induced hypothermia, and the antibiotics listed in Appendix B (Linam et al., 2015). One 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 (Cope & Ali, 2016).

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

Johns Hopkins All Children's Hospital

Emergency Department: Primary Amoebic Meningoencephalitis (PAM) Clinical Pathway



Abbreviations: ED: Emergency Department; IR: Interventional Radiology; LP: lumbar puncture; re: with regard to; QNS: quantity not sufficient

Admission Criteria:

Admission criteria include suspected or confirmed meningitis, detection of the amoeba *N. fowleri,* or a clinical condition that warrants close monitoring while awaiting CSF results. Contact the Pediatric Intensive Care Unit (PICU) for patient admission.

References:

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Cincinnati Children's Hospital Medical Center. (2015). *Best Evidence Statement development process manual*. https://www.cincinnatichildrens.org/-/media/Cincinnati-Childrens/Home/service/j/anderson-center/evidence-based-care/legend/BESt-Development-Manual.pdf

Cope, J. R., & Ali, I. K. M. (2016). Primary amebic meningoencephalitis: What have we learned in the last 5 years? *Current Infectious Disease Reports, 18*(10), Article 31. https://doi.org/10.1007/s11908-016-0539-4

Linam, W. M., Ahmed, M., Cope, J. R., Chu, C., Visvesvara, G. S., da Silva, A. J., Qvarnstrom, Y., & Green, J. (2015). Successful treatment of an adolescent with *Naegleria fowleri* primary amebic meningoencephalitis. *Pediatrics, 135*(3), e744–e748. https://doi.org/10.1542/peds.2014-2292

Outcome Measures:

- Turnaround time between the order for CSF amoeba testing and results reported to the ordering physician

Clinical Pathway Stakeholders:

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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 diagnosing, managing, or preventing specific diseases or conditions. The provider must make the ultimate judgment regarding the care of a particular patient in light of the patient's individual circumstances.

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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˚celcius [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 microliters (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 lab protocols. Look for the *N. fowleri* trophozoite, which can be differentiated from leukocytes by the nucleus that has a large, centrally placed nucleolus.

Sending CSF to the CDC for *N. fowleri* PCR:

For 24/7 diagnostic assistance, specimen collection guidance, shipping instructions, and treatment recommendations, contact the CDC Emergency Operations Center at 770-488-7100.

Appendix B: Clinical Management

Monitor and manage cerebral edema with hyperventilation (goal partial pressure of carbon dioxide [$PaCO^2$] 30-35 millimeters of mercury [mmHg]), hyperosmolar therapy (3% saline, mannitol), induced moderate hypothermia (32-34˚C), and a prophylactic anticonvulsant (Linam et al., 2015). Consider an induced pentobarbital coma. The intracranial pressure goal is <20 mmHg. A nasogastric tube should be placed for miltefosine administration.

Table 1: Medications for Primary Amoebic Meningoencephalitis

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 days
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 days
Azithromycin	10 mg/kg/day once daily	IV/PO	500 mg/day	28 days
Dexamethasone	0.6 mg/kg/day in 4 divided doses	IV	0.6 mg/kg/day	4 days
Miltefosine***	Weight <45 kg: 50 mg BID Weight ≥45 kg: 50 mg TID	PO	2.5 mg/kg/day	28 days
Nitroxoline****	**Contact the CDC for dosing.**	-	-	-
Posaconazole**	10 mg/kg/day q12h for two doses, followed by 10 mg/kg/dose once daily	IV/PO	300 mg/DOSE	28 days
Rifampin	10 mg/kg/day once daily	IV/PO	600 mg/day	28 days

Note. Table 1 and medication information below were adapted from *Clinical Care of Naegleria fowleri Infection*, by the Centers for Disease Control and Prevention, 2025 (https://www.cdc.gov/naegleria/hcp/clinical-care/index.html).

*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 less effective in the mouse model and in vitro than the more toxic form of AMB. AMB methyl ester was also found to be less effective in the mouse model. Because the prognosis of *Naegleria fowleri* infection is extremely poor, consider aggressive treatment.

**Posaconazole has been found to have superior in vitro activity and may be more effective than fluconazole, which has been historically recommended and used in the treatment regimen for 3 of 4 U.S. survivors. Isavuconazole has also shown in vitro activity, though studies are limited. Consider azole selection on an individual basis.

Due to limited availability, limited data, and variable absorption for some posaconazole formulations, intravenous (IV) and delayed-release tablet (DRT) enteral formulations are preferred. Immediate-release suspension is not recommended. Posaconazole dosing must be monitored and adjusted according to the institution's therapeutic drug monitoring protocols.

***The standard miltefosine dosing recommended for the treatment of leishmaniasis is presented in Table 1. Oral preparation is the only available formulation. Higher doses may cause nausea, vomiting, diarrhea, or other side effects. Miltefosine can increase serum creatinine, but dosing generally does not require adjustment in patients with impaired renal function. Because little data are available on the effective dose for amebic infection, the risk of nephrotoxicity should be balanced against the risk of death from amebic infection. Miltefosine is available from the JHACH inpatient pharmacy.

Nursing instructions: Capsules may be opened and the powder placed into an enteral tube, followed by a sterile water flush.

****Nitroxoline is an investigational drug that may be effective for *Naegleria fowleri* infections. It is not FDA-approved in the United States but is available for treatment of free-living amoeba infections through CDC's expanded access Investigational New Drug program. Contact the CDC Emergency Operations Center at 770-488-7100 for more information.

Table 2: Evidence Levels

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 3: Recommendation Strength

Strength	Definition
"Strongly recommended"	There is consensus that benefits clearly outweigh risks and burdens (or vice versa for negative recommendations).
"Recommended"	There is consensus that the risks and burdens closely balance the benefits.
No recommendation made	There is a lack of consensus to direct development of a recommendation.

Dimensions: When determining the strength of a recommendation, the development group makes a considered judgment through a consensus process that incorporates critically appraised evidence, clinical experience, and the following dimensions.

1. Grade of the body of evidence
2. Safety/Harm
3. Health benefit to the patient (direct benefit)
4. Burden to the patient of adherence to recommendation *(cost, hassle, discomfort, pain, motivation, ability to adhere, time)*
5. Cost-effectiveness to the healthcare system *(balance of cost/resource savings, 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 or problem, intervention, comparison, outcome])*
7. Impact on morbidity and/or mortality, or quality of life

Note. Tables 2 and 3 are reproduced from *Best Evidence Statement Development Process Manual*, by Cincinnati Children's Hospital Medical Center, 2015 (https://www.cincinnatichildrens.org/-/media/Cincinnati-Childrens/Home/service/j/anderson-center/evidence-based-care/legend/BESt-Development-Manual.pdf).