

# **A Pathologist's Perspective on Naegleria Fowleri Meningoencephalitis(PAM)**

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**PAM was diagnosed in only 27% of patients before death.**

**Capewell LG, Harris AM, Yoder JS et al. J Ped Infect Dis (2014)doi:  
10.1093/jpids/piu103**

**Are there opportunities to improve  
the yield of the present diagnostic  
process?**

# Diagnostic Process

- **Clinical**
- **Laboratory**

# Clinical Diagnostic Process

- **Through history and physical examination define a category of diseases**
- **Design a strategy to sort the diagnostic possibilities**

# History

- **Water Exposure – sensitive but non-specific**
- **Nature of the water exposure – helpful in some cases**

# 28% of PAM Patients Presented with Flu like Symptoms

- Headache
- Nausea/vomiting
- Fever
- Fatigue
- Earache

Capewell LG, Harris AM, Yoder JS et al. J Ped Infect Dis (2014)doi:  
10.1093/jpids/piu103

**In the United States, about 4,100 cases of bacterial meningitis, including 500 deaths, occurred each year between 2003–2007.**

**Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Emerging Infections Programs Network. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med.* 2011;364:2016-25.**

**In 2005 there were approximately  
40,000 hospitalizations for viral  
meningitis in the US.**

Holmquist L, Russo CA, Elixhauser A. Meningitis-Related Hospitalizations in the United States, 2006: Statistical Brief #57. Healthcare Cost and Utilization Project (HCUP). Rockville, MD: Statistical Briefs; 2006

**From 1937 to 2013, 142 patients with PAM were reported in the United States.**

**Capewell LG, Harris AM, Yoder JS et al. J Ped Infect Dis (2014)doi:  
10.1093/jpids/piu103**

# CSF Laboratory Findings to the Clinician

- **Cell count & differential**
- **Glucose & Protein**
- **Gram stain**

# CSF Finding in PAM

- Cell count and differential 2400/ $\mu$ L(range 5 – 26,000), 83% neutrophils(range 21% - 98%)
- Protein – 365 mg/dL(range 24 – 1210)
- Glucose – 23 mg/dL( range 1 – 92)
- *The above values are similar to those usually found in bacterial meningitis*
- *Antibiotics were used in 94% of patients*

# Concentration of *Naegleria fowleri* in a given CSF Sample

- Not known with certainty
- 38 of 39 antemortem identifications were by hematocytometer (Capewell LG et al)
- Case report with csf findings of 310 RBCs and 300 WBCs with 83 % neutrophils
- Hematocytometer - 118 motile amoeba/mm<sup>3</sup>

Duma RJ, Ferrell HW, Nelson EC, Jones MM. Primary Amebic Meningoencephalitis. N Engl J Med 1969; 281:1315-1323  
DOI:10.1056/NEJM196912112812401

# Detection of amoeba by motile cells in CSF

- Capewell et al - only 47 patients had cell count data.
- Motility is commonly seen in body fluid specimens – ciliated respiratory epithelium in pulmonary lavage fluid so technologists should recognize it
- May not be seen because motile organisms are few in number or the organisms lose motility for a variety of reasons

# Detection of amoeba by motile cells in CSF

- 18 year old Orlando high school student
- Initial CSF- WBCs – 20,000/mm<sup>3</sup>, 88% neutrophils, motility not observed
- Twelve hours later CSF – WBCs 15,200/mm<sup>3</sup>. After “...warming with a hot penny...active directional amebas were seen.”

Butt CG, Primary Amebic Meningoencephalitis N Engl J Med 1966; 274:1473-147, DOI: 10.1056/NEJM196606302742605

# Detection of Amoeba by Wright Stain

- **Case report with csf findings of 310 RBCs and 300 WBCs with 83 % neutrophils**
- **Wright stain - 10 amoeba/100 WBCs\***
- **Recall the average csf cell count data was 2400/ $\mu$ L(range 5 – 26,000), 83% neutrophils (range 21% - 98%)(Capewell LG et al)**
- **The above implies most specimens with csf neutrophilic pleocytosis should have amoeba visible on the Wright stained slides**

\*Duma RJ, Ferrell HW, Nelson EC, Jones MM. Primary Amebic Meningoencephalitis. N Engl J Med 1969; 281:1315-1323  
DOI:10.1056/NEJM196912112812401

# Why not seen on Wright stained slide?

- **Outnumbered by inflammatory cells.**
- **Superficial resemblance to inflammatory cells**
- **Neutrophilic pleocytosis associated with a more common diagnosis**
- **Slides are discarded after 7 days**

# Lab section visited for problematic bacterial meningitis cases

- **Microbiology**
- **Gram stain may or not be reviewed.**
- **Organisms seldom seen on gram stain.**
- **Wright stain slide in hematology section is generally seen by the hematology technologist only**

# PAM & CSF Pleocytosis

- **May not be neutrophilic**
- **One of three cases in the initial US description PAM was a 10 year old boy who presented with mild nuchal rigidity, occasional vomiting and low grade fever – WBCs – less than 5/mm<sup>3</sup> and glucose, 70 mg/dL. 24 hours later repeat LP showed 27,000/mm<sup>3</sup> with 73% neutrophils. Motile amoeba were identified.**

Butt CG, Primary Amebic Meningoencephalitis N Engl J Med 1966; 274:1473-147, DOI: 10.1056/NEJM196606302742605

# PAM & CSF Pleocytosis

- **8 year old male presented with frontal headaches, nausea, fever and vomiting**
- **Admission CSF – 17 RBCs/ $\mu$ L, 19WBCs/ $\mu$ L with 74% PMNs**
- **Died three days after admission – diagnosis made at autopsy**

Stephany JD, Pearl GS, Gonzalez O. Arch Pathol Lab Med, 2004; 128:e33-e34.

**A seven year old female is admitted to Children's,  
with probable bacterial meningitis...**

# History

- **Well until two days prior to admission.**
- **Complained of headaches and neck pain.**
- **Developed fever to 39.2<sup>0</sup>C.**
- **Seen at an urgent care clinic the day before admission and is reported to have had a positive rapid strep test.**

# History

- **Received an IM dose of penicillin at urgent care clinic and was discharged home.**
- **Over the subsequent 12 hours her condition deteriorated, she became unresponsive to her parents and was brought to the Children' s ER.**

# CT Scan

- **"Normal brain parenchyma. Normal size and configuration of the ventricles.**
- **Normal size and symmetry of suprasellar cistern and basilar cistern, no evidence of midline shift, or mass effect.**
- **No evidence of intraparenchymal or intraventricular bleeding..."**

# CSF

- **8150 WBC' s/uL(normal range 0 - 10).**
- **CSF cell count - 90 percent neutrophils, 4 percent lymphocytes and 6 percent monocytes.**
- **Glucose - less than 6(40 -70) mg/dL.**
- **Protein - 461(15 - 40) mg/dL.**
- **Gram stain - 4+ WBC' s; no organisms.**

# Presumptive diagnosis: bacterial meningitis

- **Cefotaxime 1.5 gm IV q6h.**
- **Vancomycin 600 mg IV q6h.**
- **Possibly due to Streptococcus pyogenes(positive rapid Strep test in physician's office)**

# Further History

- **Very involved in gymnastics class.**
- **History of swimming in area waters.**
- **No pets or animal exposures besides at county fair several weeks earlier.**
- **Deer tick exposures earlier in summer.**
- **No history of travel outside Minnesota - Wisconsin.**

# Day 2 Study Results

- **CSF latex antigen studies for H influenzae and N. meningitidis – negative.**
- **CSF bacterial culture - negative**

## Day 3

- **Dilated pupils; No pupillary reflex obtained bilaterally.**
- **No gag reflex present**
- **No corneal reflex present. No reaction to painful stimuli.**
- **No spontaneous movement.**
- **Gram stain reviewed afternoon of day 3 and negative**
- **Death at 2330 hours, day 3.**

# What do we know about Group A Streptococcus Meningitis?

# Invasive Group A Streptococcal Disease

- **Bacteremia without focus**      **147(22%)**
- **Skin or soft tissue**                      **196(30)**
- **Necrotizing fasciitis**                      **104(16)**
- **Pleuropulmonary**                          **71(11)**
- **Postpartum**                                      **32(5)**
- **Intra-abdominal**                              **24(4)**
- **Septic arthritis**                              **59(9)**
- **Osteomyelitis**                                **22(3)**
- **Other**    **48(7)**

J Clin Microbiol, 2011;49(12):4094 -4100

# Group A Streptococcal Meningitis

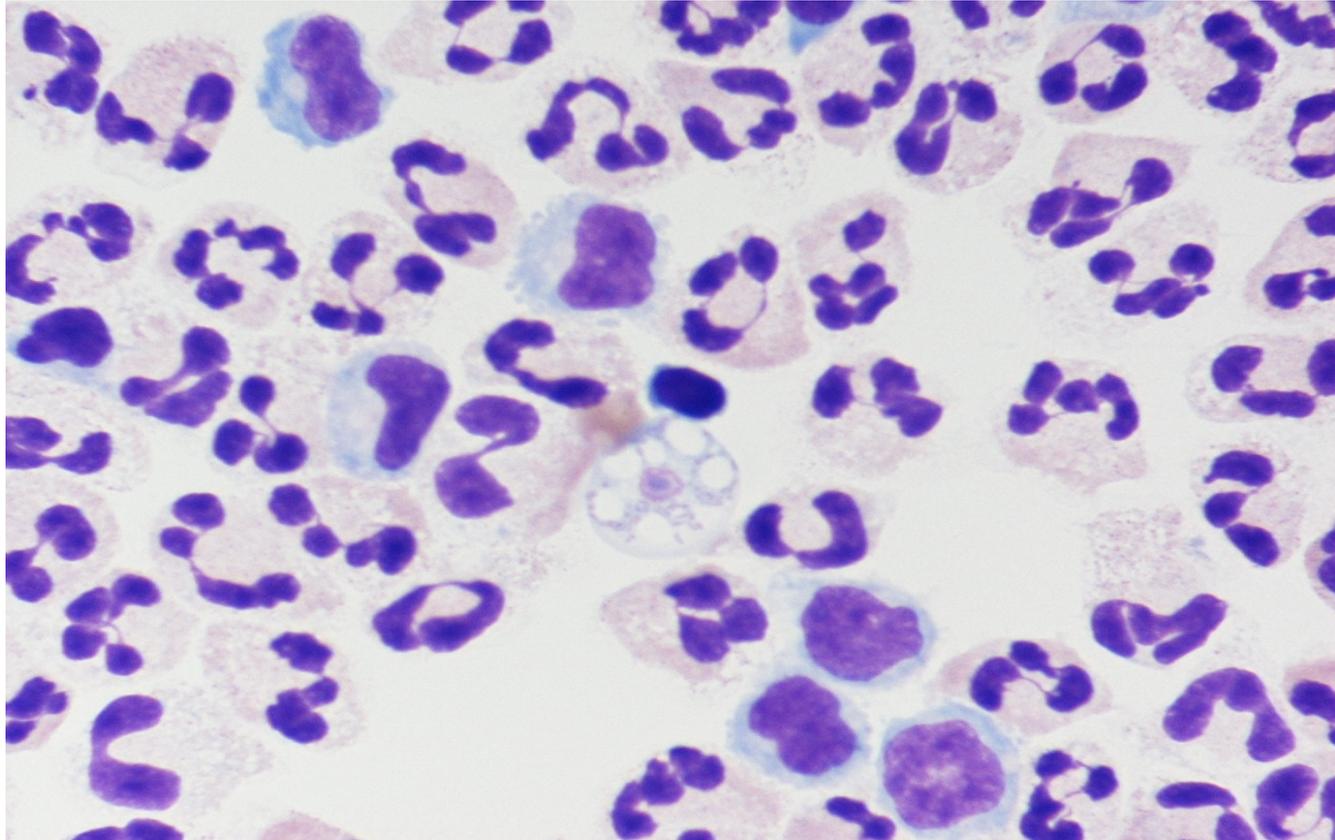
**“Group A streptococcus is an uncommon cause of meningitis in children. We report a single case of Group A streptococcus meningitis, in an apparently healthy 6-week-old infant. Twenty-five cases in the English-language literature in the last 25 years and our case are reviewed...”**

Perera N, Abulhoul L, Green MR, Swann RA. Group A streptococcal meningitis: case report and review of the literature. *J Infect.* 2005 Aug;51(2):E1-4.

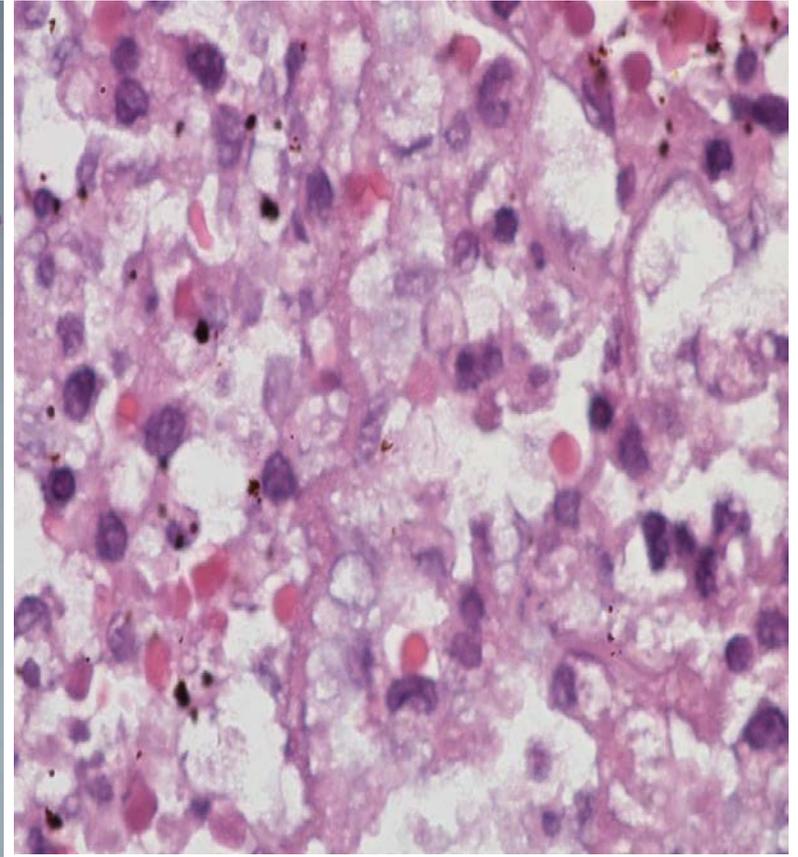
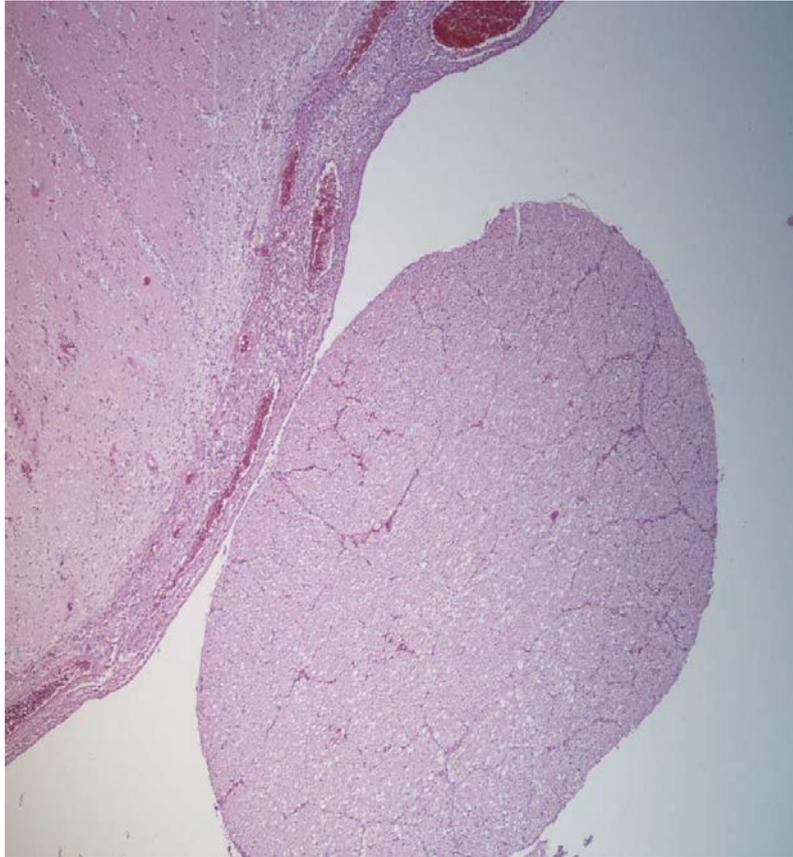
# Prior to Autopsy

- Reviewed Gram stain on last day of life – no organisms seen. Wright stain not sent with gram stain
- Day of autopsy – reviewed history; examination of gross anatomy
- Obtained Wright-Giemsa stained slide of CSF from admission

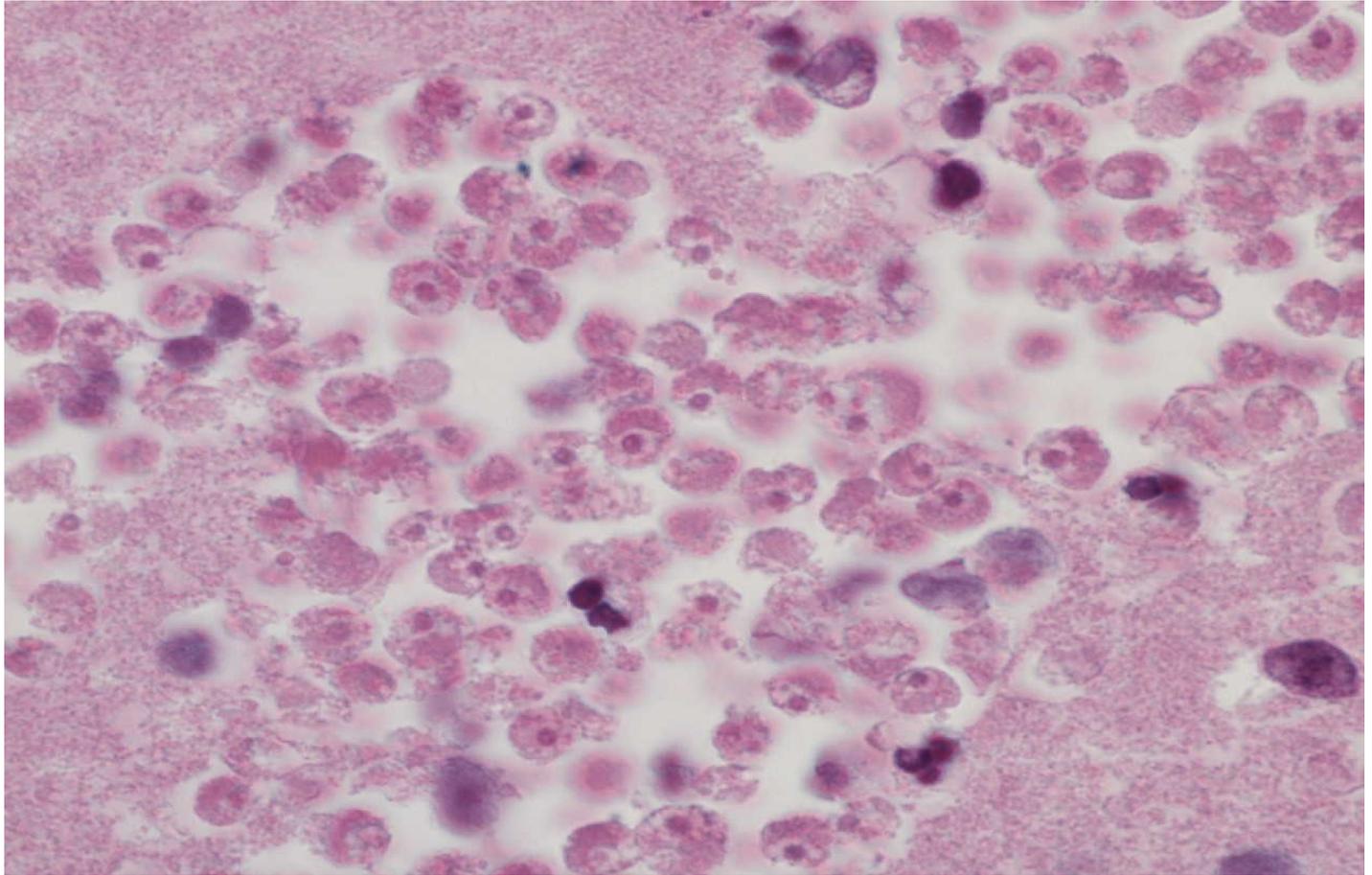
## Wright Stained CSF



## Area Adjacent to the optic chiasm



# Microabscess, right caudate/putamen nuclei



# Naegleria Meningoencephalitis

- **“...trophozoites proved to be difficult to identify on initial review of hematoxylin and eosin stained slides because of intense infiltrates by macrophages or the presence of necrotic debris...”**

# Diagnostic Modalities

- PCR
- Immunohistochemistry(CDC)
- Serology
- Light Microscopy

**Fatal Naegleria fowleri infection  
acquired in Minnesota: possible  
expanded range of a deadly  
thermophilic organism.**

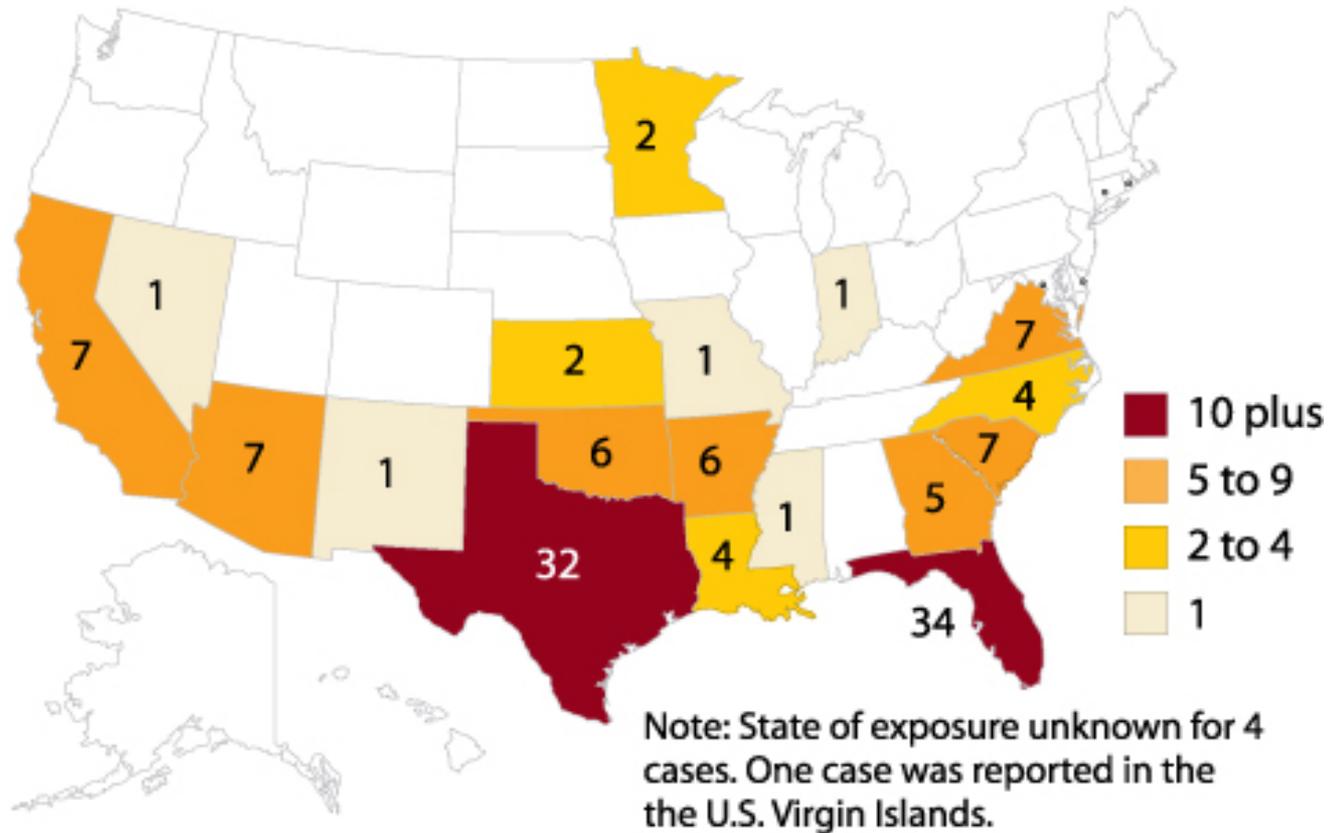
**Kemble SK, Lynfield R, DeVries AS, Drehner DM,  
Pomputius WF 3rd, Beach MJ, Visvesvara GS, da Silva  
AJ, Hill VR, Yoder JS, Xiao L, Smith KE, Danila R.  
Clin Infect Dis. 2012 Mar;54(6):805-9. Epub 2012 Jan 11.**

# Points to Remember

- **CSF neutrophilic pleocytosis without a positive gram stain should prompt review of the Wright Giemsa stained CSF slide to rule out PAM**
- **In cases of CSF neutrophilic pleocytosis with a negative gram stain and no significant medical history detailed history of freshwater exposures should be obtained**
- **Neutrophilic pleocytosis does not define all presentations of PAM**
- **Naegleria are not usually seen on gram stains**

# A rare parasite in the water

A total of 132 cases of primary amebic meningoencephalitis caused by *N. fowleri* were reported in the United States from 1962 through 2014, including 35 since 2005.



Source: Centers for Disease Control and Prevention

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# Freshwater Swimming Areas



## Area Adjacent to the optic chiasm

