# Increased Patient Survival: Miltefosine for Treatment of Free-living Ameba Infections Caused by *Acanthamoeba*, *Balamuthia,* and *Naegleria*

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## BACKGROUND

### Granulomatous amebic encephalitis (GAE)

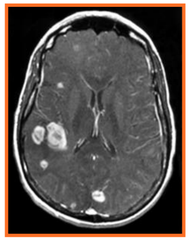
- Subacute to chronic central nervous system infection
- Caused by the free-living amebae (FLA) *Balamuthia mandrillaris* and *Acanthamoeba* spp.
- Often fatal

### Symptoms of GAE

- Personality and behavioral changes
- Depressed mental status
- Fever
- Photophobia
- Seizures
- Cranial nerve dysfunction
- Visual Loss

### Brain imaging

- Single or multiple ring-enhancing lesions



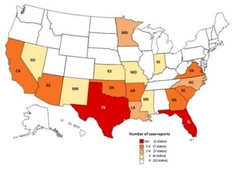
Magnetic resonance imaging (MRI) of patient with *Balamuthia* GAE

### Primary amebic meningoencephalitis (PAM)

- Acute central nervous system infection mimicking bacterial meningitis
- Caused by the FLA *Naegleria fowleri*
- Nearly always fatal (>99%)

### Symptoms of PAM

- Severe headache
- Fever
- Nausea and vomiting
- Stiff neck
- Seizures
- Altered mental status



**Number of *Naegleria fowleri* cases by state in U.S., 1962–2012. (N=128)**

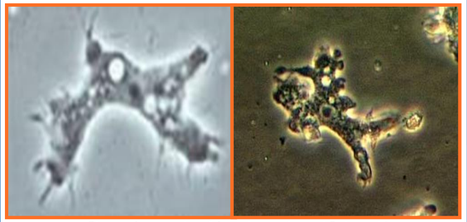
### Changing epidemiology of PAM

- Geographic distribution expanding into northern states
- Novel transmission routes and exposures (e.g., neti pots, ritual ablution)

## METHODS

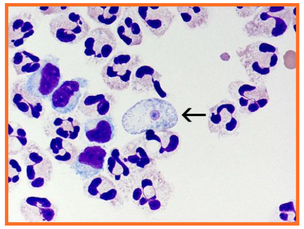
- Reviewed the literature and case reports submitted to CDC
- Determined treatment regimens, including miltefosine use, and mortality for case patients with *B. mandrillaris* infection, non-keratitis *Acanthamoeba* spp. infection, and *Naegleria fowleri* infection
- Analyzed proportions using Fisher's exact test

***Acanthamoeba*** ***Balamuthia mandrillaris***



Photomicrographs of *Acanthamoeba* and *Balamuthia* trophozoites

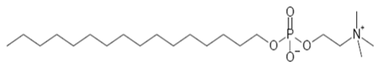
***Naegleria fowleri***



Cytospin of fixed, Wright-Giemsa stained CSF showing a *Naegleria fowleri* trophozoite (arrow). Nucleus and nucleolus can be seen within the trophozoite. Magnification: 1000x.

### Miltefosine

- Alkylphosphocholine drug with antineoplastic and antiparasitic activity
- Used to treat leishmaniasis
- Precise mechanism of action unknown. Inhibits the metabolism of phospholipids in cell membranes of parasites
- Not currently licensed in U.S. for any indication
- Manufacturer seeking licensing for leishmaniasis indication
- Structure of miltefosine (below)



## RESULTS

### Survival in Patients Who Received Miltefosine vs. Patients Who Did Not Receive Miltefosine

| | N | Received Miltefosine* Survived/Total (%) | Did Not Receive Miltefosine Survived/Total (%) | *P*-value |
|---|---|---|---|---|
| Non-keratitis *Acanthamoeba* infections (1955–2012) | 63 | 5/7 (71) | 9/56 (16) | 0.005 |
| *Balamuthia* infections (1974–2012) | 60 | 6/14 (43) | 6/46 (13) | 0.05 |
| *Naegleria* infections (1962–2013) | 69 | 2/4 (50) | 1/65 (1.5) | 0.02 |

*** Miltefosine is given in combination with other antibiotics and antifungals such as:**

| | | |
|---|---|---|
| Amphotericin B | Macrolides | Sulfadiazine |
| Azoles | Flucytosine | |
| Rifampin | Pentamidine | |

### Age and Gender of Patients Who Received Miltefosine

| | N | Median age in years (range) | Gender (% male) |
|---|---|---|---|
| *Acanthamoeba* miltefosine patients | 7 | 53 (2–64) | 71.4 |
| *Balamuthia* miltefosine patients | 9 | 24 (4–67) | 66.7 |
| *Naegleria* miltefosine patients | 4 | 8 (4–12) | 75.0 |

## CONCLUSIONS

- Number of *Acanthamoeba*, *Balamuthia,* and *Naegleria* infections treated with a miltefosine-containing regimen is small.
- Miltefosine-containing treatment regimen does offer a significant survival advantage for these often fatal infections.
- CDC should provide drug to clinicians for FLA infections under an expanded access IND until it becomes commercially available in the United States.

## CDC's Free-living Ameba Program Activities

- Providing 24/7 diagnostic services and clinical guidance to health professionals, including provision of miltefosine when indicated
- Tracking, investigating, and reporting infections and disease outbreaks
- Leading CDC health promotion and communication activities
- Testing the efficacy of promising drugs against amebae in the laboratory setting
- Developing new methods for detection of FLA in clinical and environmental samples

**For 24/7 diagnostic assistance, specimen collection guidance, shipping instructions, and treatment recommendations, including how to obtain miltefosine from CDC, please contact the CDC Emergency Operations Center at 770-488-7100.**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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



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