



New Hampshire Health Alert Network

Health.Alert@nh.gov

Status: Actual
Message Type: Alert
Severity: Severe
Sensitive: Not Sensitive
Message Identifier: NH-HAN #20121004 Fungal Meningitis
Delivery Time: 12 hours
Acknowledgement: No
Originating Agency: NH Department of Health and Human Services, Division of Public Health Services

DATE: October 4, 2012 **TIME:** 1600 EDT

TO: Physicians, Physician Assistants, Nurses, Infection Control Practitioners, Infectious Disease Specialists, Hospital Emergency Departments, Hospital CEOs, Laboratory Response Network, Manchester Health Department, Nashua Health Department, NHHA, NH School Nurses and Administrators, Community Health Centers, DHHS Outbreak Team, DPHS Investigation Team, Ambulatory Surgical Centers, Public Health Network, and DPHS Management Team

FROM: Sharon Alroy-Preis MD, State Epidemiologist

SUBJECT: Fungal Meningitis Outbreak Following Epidural Steroid Injection.

New Hampshire DHHS, Division of Public Health Service (NH DPHS) recommends:

- Awareness of a rapidly evolving national meningitis outbreak
- Check the drug supplies and discontinue use of all products distributed by the New England Compounding Center (NECC) of Massachusetts.
- Consideration of fungal etiology in **any** patient with CNS symptoms (meningitis, brain abscess or stroke), with recent epidural medication injection since July 1st, 2012 (especially methylprednisolone), even if symptoms are subtle.
- Awareness of appropriate diagnostic and therapeutic measures for this outbreak.
- Timely reporting to NH DPHS of any suspect cases that may be related to this outbreak.
- Additional surveillance: report to NH DPHS any case of mold infection from a sterile site.

Background:

The Centers for Disease Control and Prevention (CDC) in collaboration with the Food and Drug Administration (FDA) are working on an active outbreak of fungal meningitis in patients post epidural steroid injection. Aspergillus, a type of mold, has been isolated from CSF in a confirmed case but other fungal and bacterial organisms may be involved as well.

The currently implicated product (methylprednisolone Acetate) was compounded at the New England Compounding Center (NECC), a Massachusetts pharmacy. Twenty-three states have received the product, which has already been recalled, including NH. Testing of sealed product by FDA has confirmed foreign elements suspicious for fungus and identification of those is in process. In an abundance of caution it is recommended to discontinue use of all medications compounded by NECC.

NH Specific Information:

In New Hampshire the product was shipped and used in 2 facilities of Pain Care LLC: the Somersworth and Merrimack locations only. Those facilities are in the process of contacting the patients who received the recalled product (approximately 186 patients had epidural injection of the recalled product) to recommend evaluation if individuals have any symptoms.

Clinical Information:

A HAN from CDC, with more detailed information, is forthcoming and will be shared with you once available. It is important to note that some of the national cases have very mild symptoms (such as mild headache with no fever or stiff neck) and some only presented with stroke. A few cases were only identified through active surveillance and never sought care for their mild symptoms. It is recommended to have a low threshold for lumbar puncture for any patient who has symptoms (even subtle) following epidural steroid injection since July 1st, 2012.

Aspergillus has been isolated in a confirmed case-patient. Another mold has also been isolated and is in the process of being identified. The contamination may be polymicrobial.

Case Definition:

- 1: A person with meningitis¹ of sub-acute onset (1-4 weeks) following epidural injection after July 1, 2012.
- 2: A person with basilar stroke 1-4 weeks following epidural injection after July 1, 2012² who did not undergo lumbar puncture.
3. A person with evidence of spinal osteomyelitis or epidural abscess at the site of an epidural injection diagnosed 1-4 weeks after epidural injection after July 1, 2012.

¹clinically diagnosed meningitis meaning 1 or more of the following symptoms: HA, fever, stiff neck, or photophobia **and** a CSF profile consistent with meningitis (elevated protein/low glucose/pleocytosis)

²These people, if possible, should have an LP.

Please contact the NH DPHS Infectious Disease Investigation and Surveillance Sections at 603-271-4496 (after hours 1-800-852-3345, x5300) to report suspect or confirmed cases and coordinate shipment of specimens to CDC for further testing in patients meeting this case definition. Please refer to the attached documents for talking points diagnostic protocol and treatment protocol for suspected cases.

This outbreak is evolving and NH DPHS will continue to provide updates as new information is learned.

Attachments: Talking Points, Outbreak Diagnostic Protocol, Treatment Options.

For any questions regarding the contents of this message, please contact NH DHHS Infectious Disease Investigation and Surveillance Sections at 603-271-4496. After hours or toll free (In NH) at 800-852-3345, ext. 4496 or 603-271-5300 and ask for the public health professional on call.

DEFINITION OF TERMS AND ALERTING VOCABULARY

Message Type

Alert: Original alert
Update: Prior alert has been updated and superseded
Cancel: Prior alert has been cancelled
Error: Prior alert has been retracted

Status

Actual: Refers to a live event
Exercise: Designated recipients must respond to the communication or alert
Test: Related to a technical and/or system test

Severity

Extreme: Extraordinary threat to life or property
Severe: Significant threat to life or property
Moderate: Possible threat to life or property
Minor: Minimal threat to life or property
Unknown: Unknown threat to life or property

Sensitive

Sensitive: Indicates the alert contains sensitive content
Not Sensitive: Indicates non-sensitive content

Message Identifier

A unique alert identifier that is generated upon alert activation

Delivery Time

Indicates the time frame for the delivery of the alert

Acknowledgement

Indicates whether an acknowledgement on the part of the recipient is required to confirm that the alert was received, and the time frame in which a response is required.

Originating Agency

A guaranteed unique identifier for the agency originating the alert.

Alerting Program

The program sending the alert or engaging in alerts and communications using PHIN Communication and Alerting (PCA) as a vehicle for their delivery.

You have received this message based upon the information contained within our emergency notification database.

If you have a different or additional e-mail or fax address that you would prefer to be used, please contact:

Denise M. Krol, MS
NH HAN Coordinator
Denise.Krol@dhhs.state.nh.us

Business Hours: 8 AM – 4 PM
Tel: 603-271-4596
Fax: 603-271-0545

Colleagues

On Thursday, October 4th, CDC and FDA will be hosting a press conference to give updates on the multistate outbreak of meningitis following epidural steroid injection. In the interim, we are providing the following talking points, which will also be addressed in the press conference, for your use with reporters and the public. We thank you for your assistance in this investigation.

CDC's Staff in the Division of Foodborne, Waterborne, and Environmental Diseases and the Division for Healthcare Quality Promotion

Talking Points on meningitis and stroke associated with potentially contaminated product – 10/3/2012

Summary

The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration are coordinating a multi-state investigation of meningitis among patients who had received epidural steroid injection. Many of these patients have also had strokes that are believed to have resulted from their infection. At least four deaths have been reported. Fungal meningitis, which is not transmitted from persons to person, from a potentially contaminated product is suspected to be the cause of the outbreak. Investigation into the exact source is still ongoing. However, interim data show that all infected patients received injection with preservative-free methylprednisolone acetate (80mg/ml) prepared by New England Compounding Center, located in Framingham, MA. The lots of medication that were used on infected patients have been recalled. The lots are:

- Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #05212012@68, BUD 11/17/2012
- Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #06292012@26, BUD 12/26/2012
- Methylprednisolone Acetate (PF) 80 mg/ml Injection, Lot #08102012@51, BUD 2/6/2013

Background

On September 21, 2012, CDC was notified by the Tennessee Department of Health of a patient with the onset of meningitis approximately nineteen days following epidural steroid injection at a Tennessee ambulatory surgical center (ASC). All initial cultures of cerebrospinal fluid (CSF) and blood were negative; subsequently the patient had *Aspergillus fumigatus* isolated from CSF by fungal culture. On September 28, 2012, investigators identified a case outside of Tennessee, possibly indicating contamination of a widely-distributed medication. As of October 3, 2012, a total of twenty-seven cases in five states, as listed below, have been identified. Fungus has been identified in specimens obtained from three of these additional patients, one of whom also had *Propionibacterium acnes*, of unclear clinical significance, isolated from a post-mortem central nervous system specimen.

Infected patients have presented approximately one to four weeks following their injection with a variety of symptoms including: fever, new or worsening headache, nausea, and/or new neurological deficit (consistent with deep brain stroke). Some of these patients' symptoms were very mild in nature. Cerebrospinal fluid (CSF) obtained from these patients has typically shown elevated white cell count (with a predominance of neutrophils), low glucose, and elevated protein.

Active Surveillance Update – As of October 3, 2012

State	Cases* (deaths)
TN	18 (2)
NC	1 (0)
FL	2 (0)
VA	4 (1)
MD	2 (1)
Total	27 (4)

***Case Definition**

- 1: A person with meningitis¹ of sub-acute onset (1-4 weeks) following epidural injection after July 1, 2012.
- 2: A person, who has not received a lumbar puncture, with basilar stroke 1-4 weeks following epidural injection after July 1, 2012².
3. A person with evidence of spinal osteomyelitis or epidural abscess at the site of an epidural injection diagnosed 1-4 weeks after epidural injection after July 1, 2012.

¹Clinically diagnosed meningitis meaning 1 or more of the following symptoms: HA, fever, stiff neck, or photophobia **and** a CSF profile consistent with meningitis (elevated protein/low glucose/pleocytosis)

²These people, if possible, should have an LP.

What should physicians be doing?

Physicians should contact patients who have had any injection (e.g., spinal, joint) using any of the three lots of methylprednisolone acetate listed above to determine if they are having any symptoms.

For patients who received epidural injection and have symptoms of meningitis or basilar stroke, a diagnostic lumbar puncture (LP) should be performed, if not contraindicated. Because presenting symptoms of some patients with meningitis have been mild and not classic for meningitis (e.g., new or worsening headache without fever or neck stiffness), physicians should have a low threshold for LP. While CDC is only aware of infections occurring in patients who have received epidural steroid injections, patients who received other types of injection with methylprednisolone acetate from those three lots should also be contacted to assess for signs of infection (e.g., swelling, increasing pain, redness, warmth at the injection site) and should be encouraged to seek evaluation (e.g., arthrocentesis) if such symptoms exist.

For guidance on diagnostic testing that should be performed on patient specimens, refer to the diagnostic protocol developed by CDC for this outbreak, which will be posted on the CDC website on October 4, 2012.

Clinicians are also requested to report any suspected adverse events following use of these products to FDA's MedWatch program at 1-800-332-1088 or www.fda.gov/medwatch.

What should patients be doing?

If you have received a steroid injection, and you are experiencing symptoms such as new or worsening headache, fever, neck stiffness, or pain at the injection site, contact your physician to determine if you have received one of the recalled products and to receive further evaluation.

Instructions for Clinical Teams Regarding Diagnostic Testing – Outbreak of Unknown Meningitis

As of October 3, 2012

The etiology of this cluster of meningitis has not yet been determined. Potential infectious causes may include fungal pathogens as well as less commonly identified bacteria. The following algorithm has been developed to help guide clinicians in their diagnostic work-up of a patient with meningitis of unknown etiology who meets the outbreak definition.¹ These instructions are meant to supplement routine laboratory and microbiologic test deemed necessary by the clinical team and should not replace existing diagnostic protocol.

CSF:

- When possible, collect large volume of CSF (10-20mL) for testing. Please save a minimum of 10 mL of CSF to send to state health departments and CDC for further testing.² This should be an unspun sample or a fresh unadulterated sample.
- In addition to routine gram stain and bacterial cultures (including aerobic and anaerobic), fungal and AFB smears and cultures should be obtained.
- All cultures should be held for at least 2-3 weeks prior to discarding
- Specifically for the work-up of possible fungal pathogens:
 - If patients have intraventricular shunts/drains, obtain large volume of CSF to culture for fungi from this source
 - Send CSF sample for Aspergillus galactomannan assay if available³

Serum:

- Send specimen for Aspergillus galactomannan assay

Other tests:

- In addition to routine blood cultures, consider obtaining fungal and AFB blood cultures
- Other potentially infected fluid collections should be sampled (e.g., aspiration of epidural abscess) and sent for microbiologic testing as described above for CSF specimens (including fungal smear).

Tissue specimens (including post mortem specimens):

- Any relevant tissue specimens sent for histopathology should be stained and reviewed for infectious agents, including fungi (silver stain). Please save specimens to send to state health departments and CDC for further evaluation².
- Please send available autopsy specimens to CDC for further evaluation. See attached guidance for specimen collection and processing².

¹A person with meningitis of sub-acute onset (1-4 weeks) following epidural injection after July 1, 2012. Meningitis is defined as having 1 or more of the following symptoms: HA, fever, stiff neck, or photophobia **and** a CSF profile consistent with meningitis (elevated protein/ low glucose/pleocytosis).

²Please contact the State Health Department and State Public Health Laboratory to coordinate shipment of specimens to CDC for further testing. Please refer to the attached documents for handling of specimens and shipment instructions.

³ The Aspergillus galactomannan assay (Platelia; BioRad) has been FDA approved only for serum. However there are some published case series reporting its utility in identifying cases of Aspergillus meningitis, where the test has been done on CSF samples on a research basis.

Interim Treatment Options – Outbreak of Unknown Meningitis

As of October 3, 2012

At present, the etiologic agent of this cluster of meningitis has not been clearly identified. However, a mold species has been isolated from CNS specimens from at least two patients linked to the outbreak, one of whom also had *Propionobacterium acnes* of unclear clinical significance isolated from a post-mortem CNS specimen. Two additional patients have preliminary histopathologic evidence of fungal infection. When treating patients with meningitis who meet the outbreak case definition,¹ clinicians should continue to follow routine treatment protocols for meningitis of unclear etiology, including covering for potential bacterial causes of meningitis. In addition, until the etiology is better defined, clinicians are encouraged to add empiric antifungal therapy to the treatment regimen because of the severe adverse outcomes of untreated fungal meningitis. CDC has consulted with national experts on the following guidance; these treatment options for fungal meningitis in patients associated with this cluster are interim, and may change as new information becomes available.

- Initiate empiric antifungal therapy using the following regimen:
 - At a minimum, all patients should receive voriconazole (if no contraindications), preferably at a dose of 6mg/kg every 12 hours (IV initially) and to continue on this high dose for the duration of treatment, if possible. Periodic monitoring of serum concentration is advisable.
 - Consider combination therapy with liposomal Amphotericin B (preferred over other lipid formulations), preferably at a higher dose of 7.5 mg/kg IV daily. If nephrotoxicity is a potential concern, particularly in older patients, the dose may be decreased to 5mg/kg IV daily. Administration of 1L normal saline prior to infusion may be considered to minimize risk of nephrotoxicity.
 - Avoid use of intrathecal amphotericin B, either the deoxycholate or the lipid formulations, due to limited data on its use and associated toxicities.
- There is currently no clear evidence for the use of adjuvant steroid therapy. If used, careful monitoring of clinical status is warranted.

Adequate duration of treatment is unknown but likely will require prolonged antifungal therapy (e.g., months) tailored by the clinical response to infection. Individual management decisions, including choice of long-term antifungal regimen, should be made in consultation with infectious disease physicians experienced in the treatment of fungal meningitis. Clinicians should be vigilant for potential relapse of infection.

¹A person with meningitis of sub-acute onset (1-4 weeks) following epidural injection after July 1, 2012. Meningitis is defined as having 1 or more of the following symptoms: HA, fever, stiff neck, or photophobia **and** a CSF profile consistent with meningitis (elevated protein, low glucose, and pleocytosis).