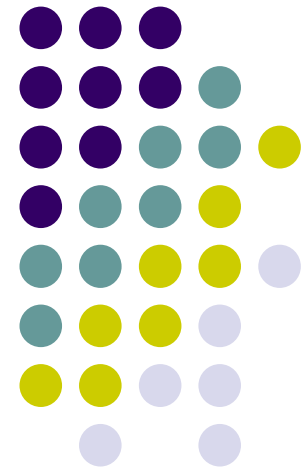


Steroid-related fungal meningitis outbreak, 2012, USA

衛生署 疾病管制局
中區傳染病防治醫療網
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Causes of fungal meningitis



- Fungal meningitis is rare and usually the result of spread of a fungus **through blood to the spinal cord**. Although anyone can get fungal meningitis, people with **weak immune systems**, like those **with AIDS** or **cancer**, are at higher risk.
- The most common cause of fungal meningitis for people with weak immune systems is ***Cryptococcus***. This disease is one of the most common causes of adult meningitis in Africa.

事情的起源



- As the tally from a **deadly meningitis outbreak** rose Friday, health officials identified the medical clinics across the country that received **steroid shots for back pain** now linked to the illnesses.

美國醫療主管機關採取的動作



1. Authorities took the step to **help identify everyone who may have gotten sick – or may still get sick – in the outbreak.**

美國醫療主管機關採取的動作



2. "All patients who may have received these medications need to be **tracked down immediately**," said Dr. Benjamin Park of the Centers for Disease Control and Prevention.

美國醫療主管機關採取的動作



3. "It is possible that if patients with **infection are identified soon** and **put on appropriate antifungal therapy**, lives may be saved," he said in a statement.

美國醫療主管機關採取的動作



4. The CDC said the number of cases of the rare fungal meningitis reached **nearly 50 cases**, and spread to a **seventh state** Friday. The number of **deaths** in the outbreak remained **at five**.

美國醫療主管機關採取的動作

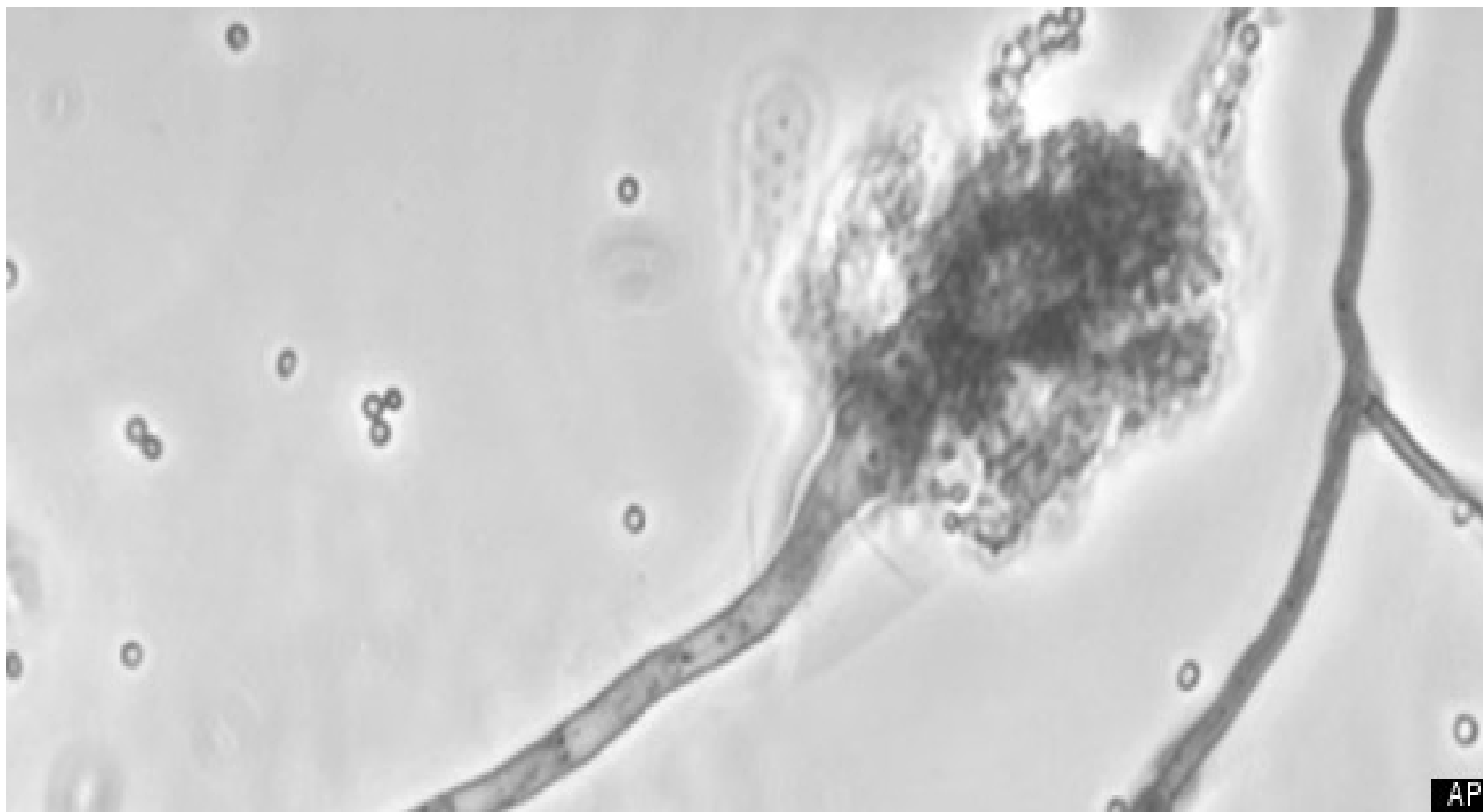


5. Investigators have focused on a **steroid medication** made by **a specialty pharmacy in Massachusetts**. All the outbreak patients had gotten **shots of the steroid for back pain**, a common treatment, and inspectors found **at least one sealed vial contaminated with fungus**.

美國醫療主管機關採取的動作



6. On Friday, officials said they have found fungal infections in **nine** sick patients. They weren't able to identify what types of fungus in every one of those patients, but did distinguish at least two types – **Aspergillus and Exserohilum.**



美國醫療主管機關採取的動作



7. In all, **47 people** have contracted fungal meningitis, the CDC said. **Michigan** became the **seventh state** to report cases, with **four**. **Tennessee's cases** now total **29**; **Virginia, six**; **Indiana, 3**; two each in Maryland and Florida and one in North Carolina.

美國醫療主管機關採取的動作



8. Three people have died in Tennessee and one in Virginia and Maryland.

美國醫療主管機關採取的動作



9. The **first known case** in the meningitis outbreak was diagnosed about two weeks ago in **Tennessee**, and the steroid was **recalled last week** by the pharmacy, **New England Compounding Center** in Framingham, Mass.

美國醫療主管機關採取的動作



10. About **17,700 single-dose vials of the steroid** were covered in the recall. On Friday, the government released the names of about **75 facilities in 23 states** that got recalled doses between July and September.

美國醫療主管機關採取的動作



11. It's not clear **how many were sent to clinics, how many were used,** or even whether everyone who got one will get sick. **Once infected, it can take as long as a month for symptoms to appear.**

美國醫療主管機關採取的動作



12. At the prompting of government officials, clinics are notifying all the patients who got shots from the recalled lots.

美國醫療主管機關採取的動作



12. "There's a **massive effort to contact all the patients,**" said Marsha Thiel, the chief executive officer of MAPS, a company that owns surgery center clinics in Minnesota.

美國醫療主管機關採取的動作



13. She added, "If there's any question at all, they're being directed to go to their physician."

美國醫療主管機關採取的動作



14. As a precaution, the FDA urged doctors **not to use any of the company's products**, and released a list Friday that **included other steroids, anesthetics and a blood pressure medicine**. The company, which is now **closed**, said in a statement Thursday that despite the FDA warning, **"there is no indication of any potential issues with other products."**

美國醫療主管機關採取的動作



15. The steroid is known as **preservative-free methylprednisolone acetate**, which the compounding pharmacy creates by **combining a powder with a liquid**.

美國醫療主管機關採取的動作



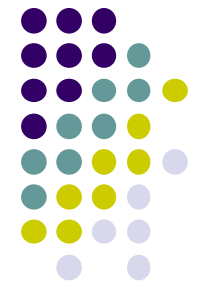
16. There are **FDA-approved versions** of the drug, sold by the brand name Depo-Medrol, in good supply. So patients who need the medicine should **not encounter a shortage**, the FDA said Friday.

美國醫療主管機關採取的動作



17. Most of the anxiety now involves patients who got **steroid shots for back pain** and are worried about becoming seriously ill.

Epidural injection



Edward H. Livingston, MD



- A recent outbreak of fungal meningitis cases has been followed by the US CDC. **Three lots of injectable steroids**, derived from the New England Compounding Center (NECC), appear to be responsible for these cases. Although nearly all patients exposed to the contaminated steroid injection have been notified of their exposure, any patients who received an epidural or joint injection of steroids **since May 21, 2012**, should check with their physician regarding the risk for complications related to contaminated steroids.

Information for Clinicians



- **Four clinical syndromes** are associated with contaminated steroid injections: (1) subacute meningitis, (2) basilar stroke, (3) spinal osteomyelitis or epidural abscess, and (4) septic arthritis. **Ninety-one percent** of all cases attributable to the contaminated steroid material were **meningitis**. Because these disorders are caused by fungal contamination, they **present very differently** than their bacterial or viral counterparts. The **disease onset is slow**, and symptom development is more **insidious**.

Characteristics of Patients (N = 70) With Fungal Infections Following Epidural Steroid Injection of Methylprednisolone Acetate From NECC, 2012,



Compared With Summary of Signs and Symptoms From Attia et al

Signs/Symptoms	Attia et al %	Current CDC case %
Headache	50	81
Fever	85	34
Nausea	30	30
Photophobia	NR	10
Meningeal Signs	70	14
Gait disturbance	NR	4
Falls	NR	11
Stroke	NR	17



臨床症狀總結

- Steroid injection fungal meningitis has an **insidious onset**, averaging about 15 days after the fungal exposure to develop.
- Signs and symptoms of meningitis are more **subtle** than those observed in bacterial or viral meningitis.
- **Fevers** are frequent with conventional meningitis, whereas **headache** is more prevalent with the current fungal disease.



後續的動作

- Any patient who received epidural injections from the **contaminated lots of steroids** should be **carefully observed**.
- Any sign or symptom consistent with meningitis should result in a **diagnostic lumbar puncture**.

美國FDA的動作



- The US Food and Drug Administration (FDA) issued an **advisory on October 15, 2012**, regarding fungal contamination **of other NECC products**. These include **triamcinolone** and **cardioplegia** solutions. Most of the prior cases were associated with **injectable methylprednisolone**. These additional concerns have led the FDA to advise physicians to **closely monitor all patients who received any NECC product**.

致病元凶



- Although **the first case** report of fungal meningitis related to steroid injections was caused by *Aspergillus fumigatus*, most cases were caused by *Exserohilum rostratum*. *Exserohilum* is a **pigmented** plant fungus that usually does not cause human disease. As noted above, presentation of this **unusual fungal meningitis** differs from that for bacterial disease. The CDC and FDA frequently **update their websites** regarding the identification and treatment of steroid injection–associated meningitis as new information becomes available. It is recommended that physicians refer to these websites for the most current information regarding this unusual form of meningitis.

事件給我們的啟示



- The recent outbreak of meningitis resulting from epidural steroid injections raises concerns about the **safety of medications** used in hospitals and ambulatory surgical centers. Physicians and patients should be aware of where medications originate when used in hospitals and outpatient clinics. **Methylprednisolone**, a steroid used for epidural injections for back pain, **was obtained from a compounding pharmacy that was not following acceptable standards for preparing medications**. As a result, injectable medications were contaminated by fungus that caused meningitis in a number of patients.

什麼是compounding pharmacy?



- The company responsible for this outbreak was operating as a **compounding pharmacy** rather than as a **manufacturer**. Compounding pharmacies mix drugs in preparations customized for individual patients. This is done when the drug cannot be administered by commercially available preparations from drug manufacturers. Compounding pharmacies and manufacturers are **regulated in very different ways**. Compounding pharmacies, like all **local pharmacies**, are licensed by individual states and fall within state regulations for monitoring their operations. They should adhere to United States Pharmacopeia (USP) <795> (Pharmaceutical Compounding—Nonsterile Preparations) and <797> (Pharmaceutical Compounding—Sterile Preparations) standards. These standards provide sufficient protection for individual patients receiving medications custom made for them.

Drug manufacturer



- Drug manufacturers make, package, and distribute drugs in large quantities. They are regulated by the FDA. FDA regulations and standards are rigorous and designed to protect the public from large-scale exposure to defective or contaminated medications as occurred in the current meningitis outbreak. **Compounding pharmacies can be registered by the FDA.** When this occurs, the FDA monitors their activities as they would a drug manufacturer. Drug manufacturers are governed by rigorous FDA Good Manufacturing Practice (GMP) regulations that detail expectations for manufacturing processes, equipment, facilities, personnel, and associated considerations.

給醫院的建議(一)



- Hospitals and clinics obtain medications through their pharmacies. Depending on the organization, responsibility for purchasing pharmaceuticals and associated hospital supplies may be handled in different ways and with different levels of evaluation. **Given recent events, it would be best to acquire medications from major, recognized drug manufacturers.** If medications are obtained from compounding pharmacies processing large volumes of medications, **these pharmacies should be FDA registered.** In contrast, **pharmaceutical manufacturers have a very rigorous supplier qualification program to evaluate their sources of drugs and excipients, packaging supplies, and other purchased materials.**

給醫院的建議(二)



- When **prescribing injectable medications** or **performing procedures** in a hospital or clinic, physicians should **ensure the medications used originate from a safe source**. In hospitals, quality is governed by the **medical executive committee**. Physicians should work through this committee to ensure a hospital's medication supply derives from safe sources.

Steroid Injections for Back Pain: I



- About 14□000 people undergoing epidural injections for back pain were exposed to contaminated steroid, resulting in more than 400 cases of fungal meningitis. This outbreak highlights the importance of assessing risks of procedures, even if they are remote. Since complications are always possible following procedures, it is essential that interventions are only done for the appropriate indications.
- A recent Cochrane review of epidural injections for back pain highlighted the very limited evidence to support the use of this procedure. To date, very few properly controlled clinical trials investigated outcomes for these procedures. Given the limited evidence, it is generally recommended that these injections be used on a limited basis for patients with nerve pain caused by impingement or inflammation of spinal nerves.

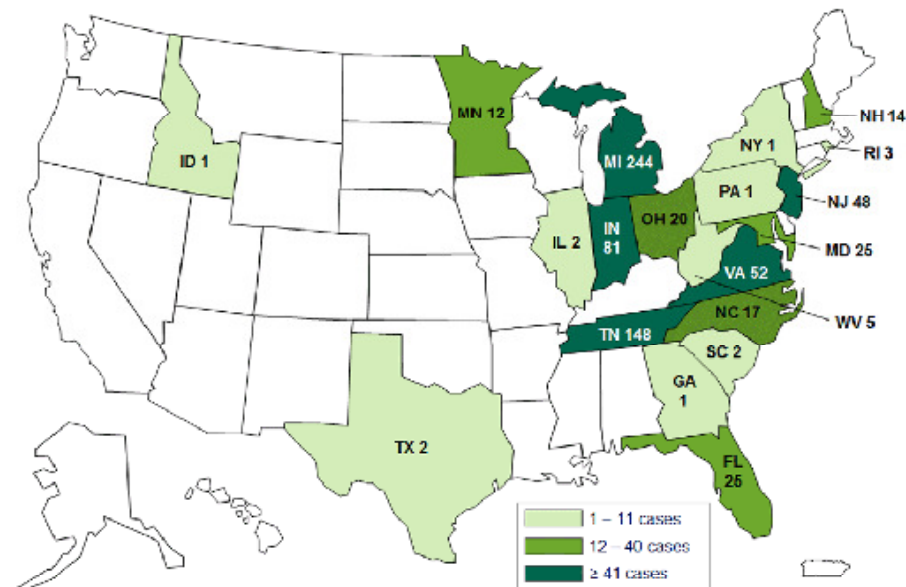
Multistate Fungal Meningitis Outbreak Investigation



Multi-State Meningitis Outbreak - Current Case Count

Persons with Fungal Infections Linked to Steroid Injections, by State

FEBRUARY 11, 2013 4:30 PM EST



CDC continues to receive reports of patients presenting with paraspinal/spinal infections (e.g., epidural abscess, phlegmon, discitis, vertebral osteomyelitis, or arachnoiditis at or near the site of injection). These syndromes have occurred in patients with and without evidence of fungal meningitis.



Steroid Injections for Back Pain: II



- It is not appropriate to inject epidural steroids for back pain without nerve involvement. Pain relief can be expected **only for a few weeks**. These injections **should not replace** permanent solutions to nerve compression such **as surgery**. Patients **should not have more than about 3 injections in the course of a year**. Beyond those first few injections, no further benefit from these injections can be anticipated.

懇請賜教

