Short Communication

Latest outbreak news from ProMED-mail

Exserohilum and the compounding pharmacy: pushing the envelope of virulence

Larry I. Lutwic

Division of Infectious Diseases, Western Michigan University School of Medicine, 1000 Oakland Avenue, Kalamazoo, MI 49009, USA

A R T I C L E   I N F O

Article history:
Received 5 February 2014
Accepted 5 February 2014

Corresponding Editor: Eksild Petersen, Aarhus, Denmark

Keywords:
Exserohilum
Compounding pharmacy
Fungal meningitis
Pheohyphomycosis

S U M M A R Y

Microorganisms poorly pathogenic for man may become significant causes of morbidity and mortality when inadvertently inoculated into normally sterile sites. Compounding pharmacies in the USA, not strictly overseen by the US Food and Drug Administration but by individual states, have been implicated in a number of clusters of such events. Recognized in the fall of 2012, fungus-tainted corticosteroid manufactured by a Massachusetts compounding pharmacy has caused the largest outbreak of this kind, affecting 751 people with, to date, 64 deaths. The etiology of the cases of meningitis, perispinal infection and septic arthritis was found to be, mostly, Exserohilum rostratum, a very uncommon human fungal pathogen. Prevention of future outbreaks such as this one will require an overhaul of the control over these industrialized compounding pharmacies and, until then, making both clinicians and patients alike aware of this issue in order for them to make informed decisions about these products and the risk of their use.

© 2014 The Author. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

Open access under CC BY-NC-ND license.

1. Introduction

Progress, far from consisting in change, depends on retentiveness. When change is absolute there remains no being to improve and no direction is set for possible improvement: and when experience is not retained, as among savages, infancy is perpetual. Those who cannot remember the past are condemned to repeat it.

George Santayana
The Life of Reason

2. The Exserohilum fiasco

Several fungal meningitis cases that occurred mid-month were reported by the Tennessee State Department of Health to the US Centers for Disease Control and Prevention (CDC) in September 2012. Each of the patients involved had received one or more epidural injections of a corticosteroid. The first cases were posted by ProMED-mail on October 2, 2012 when there were 11 probable cases in Tennessee and at least one in North Carolina. Although the sentinel case in Tennessee was caused by an Aspergillus, the primary cause of the outbreak was subsequently found to be a mold rarely reported as a human pathogen, the phaeohyphomycotic (or dematiaceous) organism, Exserohilum rostratum. October 2, 2012 was 10 years to the day that ProMED-mail reported a small cluster of fungal meningitis cases caused by Exophiala dermatitidis, another dematiaceous mold.3

The source of the Exserohilum was quickly found to be the injected, pharmacy compounded corticosteroid, as it had been with the Exophiala cluster. The tainted drug was traced back to three lots of preservative-free methylprednisolone that had been manufactured by the New England Compounding Center in Framington, MA, USA. The affected lots were recalled on October 6, 2013; by that time 64 patients had been affected in nine states, with seven deaths.3

National and state public health officials quickly established that the three affected lots had been apportioned to 17 676 vials distributed to 23 states, and that 13 534 individuals had already been injected with the drug from these lots during the 4-month period prior to recall.3 Although many of the cases were of fungal meningitis, subsequent manifestations of infection related to the drug were paravertebral and epidural abscesses, with or without meningitis, as well as joint infections of either the sacroiliac or peripheral joints.
By October 15, 2012, CDC had recorded 214 cases in 15 states with 15 deaths; and by November 2, 2012, there were 404 cases in 19 states with 29 deaths. In early December, 3 months or so into the epidemic, 590 cases in 19 states with 37 deaths had occurred; and after a year, the totals were 751 cases, 20 states and 64 deaths. Among the cases, 233 (31%) were meningitis alone, 325 (43%) were spinal or paraspinal infections alone, 33 (4%) were peripheral joint infections alone and the rest were combination infections. Four hundred seventeen cases were in two of the affected 20 states, 264 (35%) in Michigan and 153 (20%) in Tennessee. The case fatality rate for non-peripheral joint infections, including all the central nervous system or surrounding infections, was 8.5%. There may be still more deaths from relapses or late complications of central nervous system infection.

3. Background warnings

As noted above, a small outbreak of fungal meningitis related to a tainted corticosteroid occurred in 2002 due to Exophiala dermatitidis. Staes et al. have reported on healthcare-associated infections linked to compounding pharmacies occurring over 13 years through 2012. Prior to the Exsorohilum epidemic, they cited 11 different outbreaks involving 207 patients with 17 deaths. The etiologies were primarily Gram-negative bacilli and the vehicle involved mostly intravenous or intravitreal injection, and these infections resulted in prolonged hospitalizations, with blindness and death in some cases. In these outbreaks, the infecting organism could be isolated from the associated compounded drug, which had been manufactured with poor quality control and inadequate sterility.

4. The compounding pharmacy

Before 1937 there was little federal regulatory control ensuring the safety of new drugs. In that year, a pharmaceutical company produced sulfanilamide using diethylene glycol as a solvent, and called the preparation ‘Elixir Sulfanilamide’. The solvent is poisonous to humans and other mammals, but the company’s chief pharmacist and chemist was not aware of this. Flavoring was added to the dissolved sulfonamide and the company marketed the product. Although animal testing should have been routine in most drug company operations, none were performed and there were no regulations requiring premarket safety testing of new drugs. At least 100 people died. Later on, again in a time of crisis related to the thalidomide tragedy, additional legislation was passed in the USA in 1962 to make sure that new drugs or formulations were produced under ‘Good Manufacturing Practices’, and also that specific sterility requirements were adhered to.

After a hiatus of several decades, in particular beginning in the 1980s, there was a growing call for formulations that were not Food and Drug Administration (FDA)-approved, such as oral suspensions, ointments, and preservative-free formulations. As a result, an upsweep of these so-called compounding pharmacies began, regulated by state rules and regulations and not the FDA. The FDA has struggled to regulate compounding on an ‘industrial scale’, but has been stymied by ‘First Amendment’ rights. Because of this, issues of potency and sterility remain.

5. The virulence interface

As is the case for many of the fungal infections associated with compounding pharmacy manufacturing, Exsorohilum is uncommon as a human pathogen and is generally considered to have low virulence potential for man. It is found in soil and water and is a phytopathogen of some grasses. As pointed out in the seminal writings of Arturo Casadevall and colleagues, virulence depends not only on the invading organism itself, but also on the interaction of the organism and the host, which they refer to as the ‘damage–response framework’. In the outbreak beginning in October 2012, this basically non-human pathogen became highly virulent by virtue of its introduction into normally sterile sites with limited immunological responsiveness, like the central nervous system, and the fungus was further helped by the immunosuppressive corticosteroid. Exsorohilum is thermo-tolerant allowing it to grow at human body temperatures. An attack rate of 751/13 534 overall, 5.5%, reflects a combination of factors including the size of the inoculum and variable inocula between different lots.

6. Time’s awasting

Since the Exsorohilum incident began, the US FDA has attempted to gain better control of the compounding pharmacy industry. During this time, another outbreak of fungal infections associated with compounded pharmaceuticals has occurred; in 2013 subcutaneous abscesses containing mixed fungal and bacterial organisms were reported in at least 24 people in four states, linked to a compounded corticosteroid. Additionally, another cluster of endophthalmitis was reported from a compounded drug.

7. Conclusion

It is 77 years since the sulfanilamide disaster precipitated the Food, Drug and Cosmetic Act aimed at protecting the American public from such incidents. Without aggressive legislation to ensure that the compounding pharmacy industry can produce medications with the expected sterility and potency, over- and understoing illnesses, blindness, and deaths will continue to occur. This is particularly true of ‘industrialized’ compounds, which manufacture large quantities of supposedly sterile medications that are distributed widely.

As stated by Mikosz et al. in a report on fungal endophthalmitis linked to compounded products, “Clinicians should be aware that the availability of a compounded medication in the United States is not a guarantee of its quality or of FDA approval. Disclosure of a medication’s FDA approval status should be encouraged at all stages of purchase and use. This information might enable clinicians to make informed decisions about the medications they purchase for patient use and to educate patients about the status of medications to which they are exposed. Maintenance of the safety and integrity of sterile compounded drugs in the United States demands a thorough review and improvement of compounding pharmacy regulatory practices.”

Conflict of interest: None.

References

1. ProMED-mail. Aspergillus meningitis—USA: (Tennessee, North Carolina) contaminated drug; 2012-10-02. 20121002.1320024.
3. ProMED-mail. Aspergillus meningitis—USA (04): more cases, 2nd fungus; 2012-10-07. 20121007.1328893.
6. ProMED-mail. Fungal infection, contaminated drug—USA (15); 2012-12-14. 20121214.1439451.
7. ProMED-mail. Fungal infection, contaminated drug—USA (14); 2013-09-09. 20130909.1931179.


17. ProMED-mail. Fungal infection, contaminated drug—USA: mixed cultures. 2013-06-16. 20130616.1773872.
