Virology & Mycology
ISSN: 2161-0517

Kotwal and Chein, Virol-mycol 2015, 4:1
DOI; 10.4172/2161-0517.1000e108

Editorial Open access

Facing the Increasingly Looming Challenges from Environmental Fungal (Molds and Yeast) Contamination

Girish J. Kotwal and Sufan Chien

Department of Surgery, University of Louisville School of Medicine, and Noveratech, Louisville, KY, USA

Corresponding author: Girish J. Kotwal, InFlaMed Inc. and Kotwal Bioconsulting, LLC, Nucleus, Med. Center 3, Louisville, KY, 40202, USA, Tel: 502 327 7466; E-mail: gjkotw01@gmail.com

Received date: February 23, 2015, **Accepted date:** February 23, 2015, **Published date:** February 23, 2015

Fungal Meningitis Outbreak, Arrest of the Personnel at The NECC, and what could have been done Differently

In an unprecedented and extraordinary case of a deadly multi-state meningitis outbreak in the fall of 2012, 64 people died and 751 cases were treated across 20 states within the USA, according to the Centers for Disease Control and Prevention (CDC)[1]. *Exserohilum rostratum*, a fungus commonly found in the environment, was identified as the predominant organism in the patients with meningitis and was associated with the growth in the meninges [2]. One of the early patients from the outbreak was infected with *Aspergillus fumigatus* [2].

"In December 2014", 14 former workers, including the owners, from the New England Compounding Center (NECC), a pharmacy in Framingham Massachusetts, were arrested in connection with the outbreak [3]. "As alleged in the indictment, these employees knew they were producing their medication in an unsafe manner and in unsanitary conditions, and authorized it to be shipped out anyway, with fatal results," said Attorney General Eric Holder. "With the indictment and these arrests, the Department of Justice is taking decisive action to hold these individuals accountable for their alleged participation in grievous wrongdoing. Actions like the ones alleged in this case display not only a reckless disregard for health and safety regulations, but also an extreme and appalling indifference to human life. American consumers have a right to know that their medications are safe to use, and this case proves that the Department of Justice will always stand resolute to ensure that right, to protect the American people, and to hold wrongdoers accountable to the fullest extent of the law [3]."

Let us now connect the dots and try to understand the association between the meningitis deaths and what led to the arrests, in order to learn what could have been done differently per the existing guidelines at that time. In future, this kind of major tragedy should be avoidable if what we propose is considered for implementation and is enforced by the regulatory agencies like the FDA and National Association of Boards of Pharmacy (NABP).

NABP had jurisdiction over the compounding labs such as NECC in 2012. The outbreak of fungal meningitis occurred after patients were injected into the spine (epidural) with a contaminated preservative-free methylprednisolone acetate, a steroid prescribed for pain management.

The spinal cord is encased in a membrane that forms a barrier similar to the blood-brain barrier and is thereby an immunoprivileged site. This means that any entry of a microbe into the cerebrospinal fluid meets with no immune resistance. Therefore, any medication delivered into the spinal cord should be sterile (germ/microbe free and free of prions). Airborne microorganisms such as *Exserohilum* and *Aspergillus*, which are normally nonpathogenic, can become deadly when allowed to cross the blood-CNS barrier surrounding the spinal cord and the brain.

A month after the outbreak first came to light in September 2012, the Massachusetts Health Department declared that the MECC had serious deficiencies and significant violations of pharmacy law and regulations. NECC promptly recalled 3 lots of their product in September, but their contaminated product had already been in the supply chain of 20 states. The NECC filed for bankruptcy over expected lawsuits (400+ of them did follow) and tried to partially blame the "once-a-month" cleaning service it used, but the authorities found this excuse to be without merit. The 14 arrested people are facing a range of charges from adulterated drugs to second-degree murder (a charge laid against the president and the supervisory pharmacist).

What could have been done differently besides keeping clean premises? In our opinion, a clean environment should have included a weekly surveillance of the air in the facility, similar to that described by Prasla et al.[5] and Landa et al. [6] in order to check for the presence of microbes. No shipment should be allowed out of the facility until no contamination is detected for a 72-hour period post sampling.

The precise rules that the regulatory agencies expected NECC to follow and be in compliance with are unclear. Should there not have been surprise inspections? Had NECC been warned that a reckless disregard to possible serious consequences was evident prior to the beginning of the outbreak? It seems that there was no clarity.

The nebulous nature of this entire episode has to be remedied by imposition of clear guidelines indicating the exact expectations of the critical pain management product being shipped. An absolute requirement of any product is that it be free of any and all microorganisms. This is of paramount importance; therefore, the establishment of a quality control unit to monitor the absence of microbes in the air and in the product should be mandatory.

Our own experience with identification of yeast contamination

At one time, we also encountered some irregularity regarding our own testing drugs. Our attempts to troubleshoot and get to the root cause of possible irregularities led to the launch of several studies. One of these focused on testing the batches of drug preparations for the presence of either bacteria or fungi by culture on nutrient agar and Sabouraud's agar, using a process similar to that described by Prasla et al.[5] Heavy contamination was found in one batch, as evidenced by growth in both the nutrient agar and Sabouraud's agar. Further

identification of the molds followed, using procedures similar to those described by Landa et al [6].

The staining procedure suggested that the contaminant was structurally most similar to *Sporothrix schenckii*, a cigar-shaped yeast commonly found in the environment. *S. scheckni* is not a major systemic pathogen; however, if it pierces the skin, it can cause a lesion that, if left untreated, can result in spread of the organism via the lymphatics. This experience should be a wakeup call for every laboratory that is developing a product for ultimate administration in humans. It is absolutely essential to have quality control measures, such as those described by Witt et al. [4] from very earlier on in development, to begin to assess potential sources of contamination.

Detection of mold in the sterile water supply

Another recent experience we would like to share, to emphasize the need for vigilance and surveillance, is the finding of a few molds in the water pan placed at the bottom of a carbon dioxide incubator. Researchers were surprised that a pan with sterile distilled water could support fungal growth of an airborne contaminant. Once again, a search was conducted to determine the possible entry point of nutrients into the distilled water supply. The culprit was ultimately determined to be pipes that were installed years earlier, as fungal growth was observed at the joints. When the water was autoclaved, the fungal spores were destroyed but the contents were released and provided nutrition for incoming aerial contamination.

This problem was resolved by thoroughly washing the pan with a disinfectant, covering it with aluminum foil, and autoclaving it. The distilled water was autoclaved separately and a quaternary ammonium compound solution was added to the water. Holes were made in the foil to allow the necessary hydration to occur. A determination was also made that the water would have to be changed more frequently than had originally been done.

Surveillance of labs on the floor of a building commissioned in the first half of the last century

Another possible hypothesis that required testing was whether the mold count was too high in the laboratory air and whether the air filtration system was loaded with molds resulting in easy contamination. By following procedures similar to those described by Prasla et al. [5] the air was determined to have no significant mold count and both the air filtration and the floor cleaning procedures in place were deemed quite adequate.

How to prevent household molds from spoiling fresh produce

The studies described by Prasla et al. [5] pointed out quite clearly that among the public places where foodstuffs were sold, the vegetable market had the highest microbial spore count. The spoilage even of fresh produce kept in refrigerators was quite common within a few days. The deeper penetration of molds into fruits like papaya illustrated the extent of the invasiveness of the molds [5]. A number of ways can be considered for prolonging the shelf life of vegetables and fruits [7]. One is to wash the surface of the produce with soap upon entry onto the premises, and then wrapping it and refrigerating it for short-term storage. Alternatively, for longer-term storage, cooking the food or freezing it would be advisable.

The situation described by Prasla et al. [5] was restricted to the tropical Island of St. Kitts, but even in developed countries, produce is quite often left in the refrigerator for over a week and exhibits fungal growth. The inhabitants of Western countries can afford to throw away moldy produce, but the populations in tropical countries can face serious economic losses due to frequent contamination, which might force the inhabitants to minimize their consumption of fresh produce.

In summary, a whole spectrum of harm has been increasingly observed from airborne molds in recent years. The effects range from serious illness and death due to fungal meningitis to mold contamination of the food we consume as seen in the figure 1 of an Onion with mold growth. These types of contamination reinforce the urgent need to generate global maps of fungal diversity and quantitative presence in the air we breathe and that surrounds us, so that our pharmaceutical formulations, fruits and vegetables, and crops are protected from dangerous molds and yeasts.

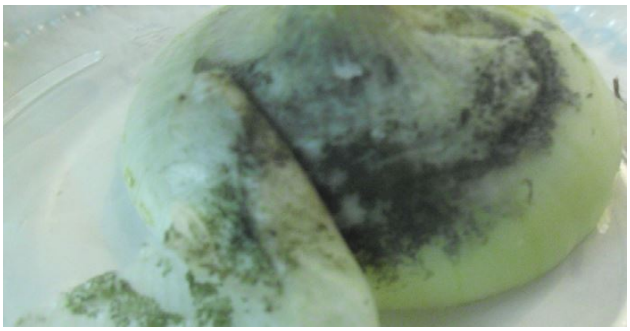

Figure 1: Mold growth on an onion held at 18 °C for a couple of weeks during the winter season in the USA

Acknowledgement

This study was supported in part by SBIR awards HL 114235, GM106639, DK 104625 from the NIH and in part from the Kentucky Cabinet for Economic Development, Office of Entrepreneurship, under the Grant Agreement KSTC-184-512-12-138, KSTC-184-512-14-174 with the Kentucky Science and Technology Corporation. The authors thank Ms Sarah Gardner of the Price Institute in the Department of Surgery at the University of Louisville School of Medicine, Louisville, KY, USA for insightful discussion

References

1. Multistate Outbreak of Fungal Meningitis and Other Infections-Case Count. http://www.cdc.gov/hai/outbreaks/meningitis-map-large.html
2. Multistate Outbreak of Fungal Meningitis and Other Infections http://www.cdc.gov/hai/outbreaks/meningitis.html
3. http://www.justice.gov/opa/pr/14-indicted-connection-new-england-compounding-center-and-nationwide-fungal-meningitis
4. Witt M, Kotwal GJ , Pathak Y (2011) Complying with FDA Regulations for the Manufacture and Quality Control of Nutraceuticals: Do What You Say, Say What You Do. In: Yashwant Pathak (ed.) Handbook of Nutraceuticals volume II: Scale Up, Processing, and Automation.
5. Prasla (2013) Significant Heterogeneity in Airborne Mold Quantities on the Caribbean Island Of St. Kitts: Health Implications and Impact on Food Preservation. Virology and Mycology 3:1 http://omicsonline.org/open-access/significant-heterogeneity-in-airborne-mold-quantities-on-the-

caribbean-island-of-st-kitts-health-implications-and-impact-on-food-preservation-2161-0517.1000123.pdf

6. Landa E, Gugnani HC, Burman A, Duman K, Ciochetto Z et al (2015). Virol Mycol 3: 139.doi:4172/2161-0517.100139.

7. Natural way to treat household Molds. https://homes.yahoo.com/news/natural-ways-to-treat-mold-in-your-home-191515766.html