In 2012 the medical community in the United States faced an unprecedented outbreak of fungal meningitis caused by *Exserohilum rostratum* associated with injections of contaminated lots of methylprednisolone acetate. Rapid response by public health authorities led to the identification of the cause of the outbreak and the epidemic quickly abated, even though new cases were still being reported many months later. Although the cause of the outbreak is known there are many uncertainties regarding the management of infected individuals and the long term risk for those who were exposed to this organism. The epidemic of *E. rostratum* infections illustrates how an organism that normally has low pathogenic potential for humans can transform into a very dangerous pathogen when conditions are changed such that skin barriers are breached while it is simultaneously delivered with an immunosuppressive drug. Furthermore, this epidemic highlights the potential threats to human and animal health from the fungal kingdom.

In late 2012 the medical community in the United States was confronted by an outbreak of meningitis cases caused by an organism that only very rarely caused disease in humans, a fungus known as *Exserohilum rostratum* (*Kainer et al., 2012; Kauffman et al., 2013; Kerkering et al., 2013; Smith et al., 2013*). The cause of the epidemic was eventually traced to the use of methylprednisolone acetate (MPA) injections contaminated with *E. rostratum* (telomorph *Setosphaeria*) as a result of poor manufacturing practices at the New England Compounding Center (*Lockhart et al., 2013*). Cases were reported in 20 of the 23 states where the product was used. By mid-2013 the epidemic had abated as the contaminated MPA vials were withdrawn from clinical practice. However, as of July 1, 2013 the total case count stood at 749 with 61 deaths and new cases continued to be reported, with three deaths in June 2013, many months after initial infection. This episode constitutes the largest iatrogenic fungal outbreak in the United States. Hence, this outbreak has a known cause and may not repeat itself but this tragic episode provides us with new insights into the potential for fungi to cause disease and the conditions where fungal infection can progress to disease. Incidentally, the 2012–2013 fungal epidemic from contaminated drugs was not the first time that such an iatrogenic disaster had occurred. Over a decade ago several cases of *Exophiala (Wangiella) dermatitides* fungal meningitis occurred in individuals given injectable steroids contaminated with fungal spores (*Anonymous, 2002*) and outbreak of Aspergillosis followed the use of a contaminated spinal anesthetic in Sri Lanka (*Rodrigo et al. 2007*). Decades ago outbreaks of zygomycosis were associated with the use of contaminated bandages (*Antoniadou, 2009*). These episodes highlight the enormous potential of contaminating fungi to cause disease when inadvertently introduced into the human host as part of contaminated therapies. In fact, as of May 2013 the Centers for Disease Control (CDC, Atlanta, GA) was investigating a new outbreak of fungal meningitis associated with a different compounding pharmacy (*Kuehn, 2013*).

In the United States there are over half a million epidural injections each year and infection is a rare complication that is usually caused by skin bacteria (*Cooper and Sharpe, 1996; Hooten et al., 2004*). In contrast, the overall case rate for infection with *E. rostratum* was near 4% of more than 13,500 exposed individuals, of which over 90% were exposed through an epidural, paraspinal, or spinal injection, with the remainder having joint or peripheral infections. Hence, the majority of the clinical manifestations observed during the *E. rostratum* outbreak reflected the mode of infection, which involved direct inoculation of the fungal cells into normally sterile body sites. The distribution of clinical presentations was as follows: 391 (52%) cases of meningitis, 323 (43%) cases of local paraspinal infections, 60 (15%) cases of arachnoiditis and 33 (4%) cases of septic arthritis. The total percentage exceeds 100% because some individuals had more than one condition. The early cases mostly involved meningitis complicated by poster-
ior circulation stroke in 10% of affected individuals. Histological analysis of post-mortem specimens demonstrated that *E. rostratum* was angioinvasive and elicited an inflammatory response with neutrophil predominance (Bell and Khabbaz, 2013). The incubation period for the onset of meningitis after MPA injection ranged from 1 to 120 days (mean 23 days), with the longest times being comparable to those described for the earlier *Exophiala* outbreak. As the outbreak has evolved later cases tended to present more commonly with infection of local tissues and these included a large number of paraspinal and epidural infections with a significantly smaller number of joint and bone infections. For patients with paraspinal infections the media number of days from injection to MRI diagnosis was 52 days for those that received one injection and 43 for those that received several (Kontoyiannis et al., 2013). It is noteworthy that the time between infection and disease for the soft tissue infections was significantly longer than that observed with the meningitis cases, which may reflect differences in local immunity between the CNS and soft tissues and/or tissue damage leading to symptomatology. The patients ranged in age from 16 to 92 years with a mean age of 64. Older age (> 60) was associated with 4-fold higher risk of disease (11.8% vs 2.9%) suggesting the possibility that senescent immune system was less likely to control infection, especially in the presence of high concentrations of corticosteroid in tissue (Kainer et al., 2012).

One praiseworthy aspect of this iatrogenic tragedy was the rapid recognition of the outbreak and the decisive action taken by public health authorities, which is apparent by the timeline of events. On September 21, 2012 several fungal meningitis cases were reported to the Center for Disease Control (Atlanta, Ga) and by October 4, 2012 that agency had associated the cases with MPA injections originating from the New England Compounding Center, two days later the manufacturer recalled all vials and by October 4, 2012 that agency had associated the cases with *E. rostratum* infections is evident from the long times between infection and disease after MPA injection reflects its deposition in normal sterile tissue sites in conjunction with an immunosuppressive drug in the form of MPA. In this regard, *E. rostratum* is not that different from other normally commensally organisms such as *Candida albicans*, which require a breakdown in tissue barriers or host defenses for pathogenicity. However a key difference in this outbreak was the delivery of the microbe in MPA, which was intended for local immunosuppression. Whether *E. rostratum* could have caused disease in the absence of MPA is unknown. Furthermore, the role of MPA on fungal virulence and metabolism is unknown. Some fungal pathogens, such as *Candida albicans*, express steroid receptors and *E. rostratum* could potentially respond to the class of compounds (Madani et al., 1994). Steroids have been shown to have protean effects on fungal physiology (Nosanchuk and Casadevall, 2006) and it is conceivable that long term exposure to MPA contributed to fungal changes that affected its virulence.

The *E. rostratum* outbreak illustrates another classical aspect of systemic fungal infections: chronicity. Unlike bacterial and viral infectious diseases fungal diseases are notorious for their indolence, chronicity, requirement for prolonged courses of therapy, and when fungi kill a host, this often occurs after a protracted period of time. Fungal infections cause damage to the host by direct action of fungal cells in tissue and by eliciting strong immune responses that damage tissue. For *E. rostratum* the relative proportion of damage caused by the microbe and host is unknown. Historical reports of neutrophilic infiltration in tissues infected with *E. rostratum* suggest that this organism elicits a strong inflammatory response that differs from the typical mononuclear responses associated with such fungal pathogens as *Cryptococcus neoformans* and *Histoplasma capsulatum*. Hence, some of the damage in *E. rostratum* infections may be the result of the host response. The chronicity of *E. rostratum* infections is evident from the long times between infection and disease and the protracted nature of the response...
to antifungal therapy. A recent report of recurrence of infection after 4.5 months of antifungal therapy suggests the possibility that many of the cases will need longer therapy that the currently recommended 3–6 months for parameningeal infection and up to 1 year for central nervous infection (Smith et al., 2013). In fact, this report combined with the experience for other types of fungal infections such as Coccioidioides spp. meningitis, raises the disturbing scenario that for some individuals very prolonged if not lifelong courses of antifungal agents may be needed to prevent recurrence of disease.

Little is known about virulence factors of E. rostratum except that it is a melanotic fungus and that it is thermophilic and capable of growth at mammalian temperatures. Melanin is well established virulence factor for other pathogenic fungi and, based on current knowledge, there is every expectation that it may be contributing to virulence by protecting the organism against host immune defenses such as phagocytic oxidative bursts (Nosanchuk and Casadevall, 2006). Melanin production has also been associated with acquired drug resistance to polyenes and echinocandins, but not to azoles (Nosanchuk and Casadevall, 2006), a fact that may explain the response to therapy observed with voriconazole. The ability of the fungus to survive in mammalian temperatures is a requirement for causing systemic disease and the relative paucity of pathogenic fungus for mammals has been attributed to their high temperatures that restrict the growth of most fungal species (Bergman and Casadevall, 2010; Robert and Casadevall, 2009). In fact, the E. rostratum outbreak illustrates the inherent potential of fungi capable of growing at mammalian temperatures for causing disease as a result of their thermostolerance and heightens the concern that adaptation of currently non-pathogenic fungi to higher temperatures as a result of global warming will bring new fungal diseases (Garcia-Solache and Izquierdo-Garcia, 2006).

In summary, the E. rostratum outbreak illustrates the potential threats to human and animal health from the fungal kingdom, which are largely unappreciated (Fisher et al., 2012). Virulence is a microbial property that is expressed only in a susceptible host. From this perspective it is clear that E. rostratum virulence expression required a host made susceptible by the iatrogenic breaching of barriers through percutaneous injection into deep tissues and/or the presence of MPA. Microbial virulence has been proposed to be an emergent property and as such, is not likely to be amenable to prediction (Garcia-Solache et al., 2013). This unpredictability is perhaps also illustrated in this sad episode where polymicrobial contamination of MPA during compounding resulted in the emergence of a predominant organism among several fungal contaminants with pathogenic potential. In recent years we have witnessed existential threats to amphibians and bats from new pathogenic fungi and that experience, combined with the emergence of a new type of fungal infection as a result of iatrogenic errors, illustrates the potential of the fungal kingdom to unleash new diseases with high mortality and morbidity for which treatment options are very limited.


References