Reflections on the approach to treatment of a mycologic disaster

David A. Stevens

Div. of Infectious Diseases, Dept. of Medicine, Sta. Clara Valley Med. Ctr. and Stanford University Medical School, San Jose & Stanford, CA, and Calif. Inst. for Medical Research, San Jose, CA

Address: Dr. DA Stevens, Div. Infectious Dis., Dept. Med., Sta. Clara Valley Med. Ctr., Rm. 6C097, 751 So. Bascom Av., San Jose, CA 95128-2699
Tel. 408-885-4302
Fax 408-885-4306
e-mail: stevens@stanford.edu

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On Sept. 18, 2012 health authorities began to react to a multistate outbreak of fungal meningitis of unprecedented magnitude, traceable to 3 lots of preservative-free methylprednisolone compounded in one pharmacy [1]. The steroids had been mostly used for epidural injection, largely causing fungal meningitis (91%), although cases of spinal osteomyelitis/epidural abscess and septic arthritis/osteomyelitis were also reported. On Oct. 24th, the Associated Press reported 308 cases and 23 deaths, and a later report suggested the cases had already reached 620 and deaths had reached 39. Forty-seven patient isolates had been determined to the species level: 45 as the dematiaceous genus Exserohilum, 1 as Cladosporium (another dematiaceous fungus), 1 as Aspergillus fumigatus (the index case) [T. Chiller, presentation to the Infectious Disease Society of America, October 2012]. Rhodotorula laryngis, a yeast, and Rhizopus stolonifer, a zygomycete, both not known human pathogens, were also isolated from unopened vials of the lots [Chiller, op. cit.]. Faced with a rapidly evolving disaster, the CDC’s initial recommendations for therapy of affected cases were to use systemic voriconazole and liposomal amphotericin B for therapy [later expanded to use of voriconazole as primary therapy, and the combination for patients with severe disease or not responding] [2], not to routinely use intrathecal amphotericin, and not to use antifungal chemotherapy for prophylaxis or for empiric therapy of symptomatic patients with normal CSF exams [1]. It is useful to discuss these approaches. In what follows, I will address the central issue of CNS infections, leaving aside the less common orthopedic complications of the contaminated material. I will try to offer sufficient documentation to show there are alternative approaches worthy of consideration. With the benefit of time, and persistent tracking of the outcome of cases treated with the CDC recommendations (or other regimens if used), it will be important, at a later evaluation point, to assess the success rate in treated cases.

In vitro susceptibility. Starting with in vitro susceptibilities, as a beginning guide to drug choice, voriconazole and itraconazole of the azoles, along with amphotericin B, are suggested to have the broadest spectrum against the dematiaceous fungi (see
Table 2 in ref. [3]), although it was noted that what data is available about posaconazole indicates comparable activity against the species tested [3]. Extensive studies document consistent potent activity of itraconazole [4-6], and the comparable in vitro activity of voriconazole and itraconazole against these fungi [5, 7, 8], although some have suggested voriconazole is the more potent of the two [9, 10] and others the reverse [5]. Frequent resistance of clinical isolates to voriconazole has also been reported [11]. There is also ample data about good [12, 13], even superior [14], posaconazole activity in vitro against dematiaceous fungi. Resistance of some isolates to amphotericin has been noted [4, 15]. A recent paper [16] specifically reporting susceptibility results on E. rostratum indicated equivalent, potent activity of itraconazole, posaconazole and amphotericin, and, to a lesser extent, voriconazole.

All 3 of the azoles, and amphotericin B, are active against Aspergillus fumigatus in vitro [17], though we showed amphotericin, and to a lesser extent, itraconazole, could not inhibit a minority of isolates at a clinically achievable concentration [18]. Voriconazole and itraconazole [19], and posaconazole and voriconazole [20], were shown similar in in vitro activity against this pathogen; both the latter drugs were a bit more potent than itraconazole in the latter study [20]. A possible concern is the development of spreading A. fumigatus azole resistance in some geographic areas, apparently as a result of azole agricultural fungicide-induced mutations; of the 3 azoles, itraconazole is most affected by the cross-resistance and posaconazole least [21].

A possible consideration in a recommendation based only on in vitro susceptibility is that more species than known at the time of the exposure might turn up involved at a later time. If so, perhaps the best choice would have been posaconazole, because it is the broadest spectrumazole [3, 22], or an amphotericin B preparation, our most fungicidal broad-spectrum agent [17]; not only because of their activity against the dematiaceous fungi and A. fumigatus cited above, but because of their activity against some of the most resistant of fungi, the zygomycetes. Rhodotorula species
also are susceptible to amphotericin, and of the azoles, posaconazole is most active, itraconazole less so, and voriconazole most variable [23]. It is this desire to recommend a broad-spectrum agent, at least until the pathogens in an individual case are identified, that precludes discussion of agents such as the echinocandins, which are active against *Aspergillus*.

What could have been informative at the outset was rapidly disseminated information, even preliminary information, regarding in vitro susceptibility of the outbreak *Exserohilum* isolates, eventually with results from several laboratories for comparison. Testing of the isolates would reduce the need for inferences about susceptibility of the pathogens isolated by examinations of data sets about other fungi in the same fungal group or same species. The testing done could have included drug interaction studies between the azoles and amphotericin against the isolates, to assess possible synergy or antagonism, the latter a sometimes occurrence and long-held concern regarding azoles and polyenes [24]. There is not a universally accepted methodology for drug interaction studies [25].

*Animal model studies.* What is more relevant, in my view, than in vitro results is in vivo results, and a starting place is animal model studies. These can be particularly illuminating, because study conditions can be standardized (e.g., age, sex and genetic background of hosts, stage of disease, etc.), and undesired co-morbidities and their therapies, as in patients, aren’t variables to cloud interpretations of outcomes [26]. Their value is particularly important in CNS mycoses, because the number of clinical cases doesn’t easily lend these diseases to randomized clinical trials.

There is relevant experience in the present situation. Posaconazole has been shown to be effective in therapy of murine models of infection with dematiaceous fungi, either disseminated [27, 28] or soft issue [29]. More to the point, posaconazole has been shown effective in models of dematiaceous infection where the key target is the CNS [28, 30, 31]. There are few data about voriconazole in murine models, because of concern about inducible and accelerated metabolism of this drug in
rodents, though therapy can be studied, once it was shown that the P450 system, in the gut and liver, can be blocked by the ingestion of grapefruit juice [32]. In other models that focus on CNS mycoses, we have shown that voriconazole [33], as well as posaconazole [34] and itraconazole [35], all have activity against cerebral aspergillosis, as does liposomal amphotericin (AmBisome)[33] and amphotericin in the ribbon-like lipid delivery system, Abelcet [36]. In fungal meningitis models, we have demonstrated good itraconazole activity in coccidioidal meningitis in rabbits [37] and mice [38], as well as that of AmBisome [39, 40] and Abelcet [40, 41]. To the point of concern about possible azole-amphotericin antagonism [24], voriconazole-amphotericin synergy in vivo was shown [33, 36] against cerebral aspergillosis. This would be a time to develop animal models of Exserohilum CNS infection, for therapeutic (and prophylactic) studies.

Pharmacology. Critical to judgments about human efficacy is information about pharmacology in humans, though the therapeutic studies in animals must not be forgotten. Those animal results summate not only inhibitory or cidal drug activity as can be assessed in vitro, but also pharmacology, including tissue penetration, especially into infected (and possibly necrotic) tissues, fungal killing in the presence of organic matter (present in vivo but not in vitro), and toxicology (particularly in the presence of infection). These latter issues are not usually addressed in pharmacologic studies in man, most often done in healthy volunteers. Much has been made of the variability in absorption of oral itraconazole tablets in man, explaining the development of the more reliable liquid preparation [42], but absorption of oral voriconazole or posaconazole is also very variable. For example, our clinical laboratory, a reference laboratory in Northern California, has noted 57% of 215 serum voriconazole levels, and 67% of 147 posaconazole levels, determined for therapeutic drug monitoring, to be below 2.05 and 0.7 mcg/mL, respectively, levels that have been indicated to correlate with drug efficacy [43, 44]. All 3 azoles also have a large number of drug-drug interactions that can complicate therapy [17].
A factor considered in formulating the CDC drug recommendations was "penetration into the CNS" [1]. One must be careful here to distinguish between penetration into the CSF as opposed to "the CNS". There is actually scant data about penetration of any of the antifungals into brain or cord parenchyma, and none about penetration into the meninges, which is probably an even more important compartment, particularly in meningitis. Writers most commonly do not specify to which compartment they are referring, when referring to "penetration into the CNS".

A recent publication from the Infectious Disease Society of America [45] and an initial review [46] emphasized the recommendations in this outbreak for voriconazole and AmBisome on the basis of "CSF penetration". With respect to the azoles, voriconazole does penetrate into CSF [47, 48], whereas itraconazole partitions into CSF very poorly [49]. Posaconazole also partitions into CSF generally poorly [50-52]. In terms of therapeutic outcome in fungal CNS infection (except possibly relevant to intrathecal administration), the one thing you can say with confidence about CSF levels, with systemically administered drugs, is that, while they're easy to measure and parenchymal levels are not easy to obtain or measure, CSF levels have nothing to do with outcome. This is shown by the similar efficacy of itraconazole vs. fluconazole (the azole with, by far, the greatest CSF penetration [53]) in rabbit cryptococcal meningitis [54], in rabbit [37] and murine [38] coccidioidal meningitis, in human coccidioidal meningitis [55, 56], and in acute treatment of human cryptococcal meningitis [57, 58], and also, most important, shown by the posaconazole dematiaceous CNS infections mentioned above [28, 30, 31] and below [59, 60]. Another drug that penetrates poorly into CSF is amphotericin B deoxycholate [17], and there is none better in treatment of human cryptococcal meningitis [57], and it is efficacious in human candidal meningitis [61].

Voriconazole does penetrate into infected parenchyma [48]. In the presence of inflammation, posaconazole levels in CNS abscesses and even CSF can exceed levels that can inhibit fungal pathogens in vitro [52].
The expanded version of the CDC recommendations were to use 6 mg/kg voriconazole in treatment, a higher dose than recommended in the package insert, presumably to increase drug levels in the “CNS”. The desired, elevated serum levels were achieved [62], but it could be predicted that such levels would be associated with side effects, such as confusion, hallucinations, and hepatotoxicity [63]. The initial side effect profile reported indicated 64% of patients receiving voriconazole experiencing hallucinations, and 32% with transaminases at least 3 times normal [62].

The CDC analysis stated AmBisome “is preferred over other lipid formulations because of better CNS penetration” [1]. However, we found AmBisome and Abelcet to give the same therapeutic results in murine CNS aspergillosis [33, 36, 64] and in rabbit coccidioidal meningitis [39-41], although others found Abelcet inferior in rabbit Candida CNS infection [65]. Our histopathologic studies [64] suggested it is the anatomic distribution of the amphotericin from these preparations within the brain that will correlate with outcome, an assessment that drug determinations performed on whole experimental brains or chunks of parenchyma can miss.

**Human experience.** Perhaps the most relevant data in considering therapy is what human data is available. There are a number of reports of fine outcomes in infections by dematiaceous fungi treated with posaconazole [66, 67], including soft tissue infection [68] and sinonasal disease [69], supporting the relevance of the animal model studies referred to above. Most relevant are reported responses to CNS infection [59, 60]. Reports of several clinical responses in dematiaceous fungal infections have also been reported withitraconazole [6], and voriconazole [70-72], including CNS infection [73], as well as voriconazole failure [74].

Studies of voriconazole [75], itraconazole [76, 77], posaconazole [78], AmBisome [79], and Abelcet [80] have produced gratifying results of responses in clinical invasive aspergillosis. There is room for improvement, combinations have not yet been convincingly shown to be advantageous, and none of the agents discussed have
been compared to another for efficacy in a randomized clinical trial. Itraconazole (at high doses) [81] and voriconazole [82] have the largest reports of successful experience in clinical CNS aspergillosis. Focusing instead on other CNS mycoses, note the favorable experiences with itraconazole in human cryptococcal [57, 58] and coccidioidal [56] meningitis, and voriconazole in coccidioidal meningitis [83]. In choosing between AmBisome and Abelcet, the greater toxicity of Abelcet would be a consideration [84].

**Intrathecal therapy.** Intrathecal therapy of coccidioidal meningitis with amphotericin was the only effective treatment for coccidioidal meningitis before the azoles became available, and cured as many as one third of patients [85]. The azoles replaced this treatment, because of the appeal of oral agents with markedly reduced side effects by comparison. However, it became clear that azoles do not cure this disease [86], and we have returned to the use of intrathecal therapy for the most severe cases and those who have failed azoles. Intrathecal therapy should be considered for cases in the present epidemic that fit the criteria in the preceding sentence, and we need also keep in mind the lack of cure with azoles in some fungal meningitides. Intrathecal therapy is complicated and can be dangerous, and not many have experience and confidence in this form of therapy; we have tried to share our experience in managing it [87]. Imaging the area of injection before initiating intrathecal therapy may be needed, as cases of epidural abscess and perispinal inflammation (which might be in the path of the therapy needle) have been recorded in this outbreak.

**No prophylaxis or empiric therapy of undiagnosed symptomatic cases?** Now we come to the most problematic area. These recommendations suggested an infectious disease specialist be consulted in all possible cases [1]. Each of us will need to consider whether a patient we see who was injected intrathecally with one of the contaminated lots would not be wise to take prophylaxis (not to mention, in the presence of relevant but undiagnosed symptoms and signs, empiric therapy), after a procedure that has resulted in an impressive proportion of infections, with a high
lethality (in addition to lethality, some of the nonfatal cases have experienced stroke), against diseases that are difficult to treat. This needs consideration, even with an attack rate so far of only about 4%. For many, drugs started in the absence of clinical disease would really be early therapy, not prophylaxis, and innumerable animal model studies have demonstrated therapeutic results are always better when you’re treating a smaller inoculum. Prophylaxis is aggressively studied in immunocompromised host populations, where the attack rate is not dissimilar; e.g., the attack rate of proven fungal infections in the placebo arm of a large prophylaxis study was 4% [88].

A problem is the scale of prophylaxis needed, as there may be 14,000 persons so exposed [Chiller, op. cit.]. To perform mass prophylaxis on this scale may result in logistic issues that could rival that which would be conceived for a localized bioterrorist attack, but less complicated than preparing, testing, manufacturing, distributing and striving for universal vaccination with a new vaccine against what was anticipated recently to be a pandemic of a novel influenza virus. If subsets of patients at higher risk could be established from the epidemiological data - e.g., more cases from one lot than the others, persons who have received larger volume or repeated injections - prophylaxis might be prioritized. The duration of use would need to be guessed, but would be finite, and the longest time from intrathecal steroid to appearance of a case not receiving prophylaxis could be one basis for an endpoint chosen. In a previous outbreak of fungal meningitis caused by steroids contaminated by the dematiaceous fungus *Exophiala*, cases appeared with a latent period as long as 6 months [73]. Duration is an important issue to ponder, because it is possible prophylaxis/early therapy would prevent disease while given but not be curative, and disease could emerge once drug(s) was withdrawn.

However, I have given above some alternative agents that also could be considered in therapy decisions. More alternatives could alleviate local supply problems in mass prophylaxis. Itraconazole (see citations 2-10, 33, 34, 37, 38 in ref. [42]), posaconazole [89, 90], and voriconazole [91] all have had extensive safety
documentation when used for prophylaxis in immunocompromised patients, could be conveniently given orally, and as seen above, have been useful even in treatment of established CNS mycoses. The already uncommon side effects of these agents are likely to be less in the present patients at risk than in neutropenic immunocompromised patients with mucositis, because of fewer co-morbidities in the former, and fewer concomitant drugs. Voriconazole appears to have more side effects to consider [92]. Intermittent intravenous AmBisome has also been used for prophylaxis and empiric treatment [93], but intravenous administration presents much greater logistic issues.

If I were advising any patient who had been injected intrathecally or into a space adjacent to the intrathecal sac with material from one of the known contaminated lots, I would recommend taking chances with the known, uncommon, and usually inconsequential side effects of the oral drugs (and even more certainly if empiric therapy became an issue), and try to prevent onset of a serious and lethal disease, one which steroids would likely worsen, even given the lack of any data proving whether such prophylaxis would be effective. The precariousness of the situation is emphasized by a predominance of older patients with pre-existing co-morbidities [46]. I’m assuming in this the impossibility of establishing a randomized trial of prophylaxis, given the time frame available. Faced with a problem of staggering size, complexity and potential total cost, and considering measures of unproven benefit, public health authorities may arrive at choices that could be different than for a physician facing his/her exposed patient, and weighing possible individual risks vs. benefits. An objection to prophylaxis has been raised [46] regarding development of resistance while disease was only suppressed, but the setting for resistance development is usually when the microbial population is high (as would occur in treatment of disease), not when the microbial burden is low (as would be the case if prophylaxis/early treatment was started when few organisms were present, in the absence of disease).
All amphotericin B preparations are only available for intravenous use, voriconazole is available for oral or intravenous use, and the other two azoles are only available orally. Concomitant other drugs the patient is already receiving could also be a factor in the choice of which agent to use, avoiding known drug-drug interactions. Therapeutic drug monitoring would then be helpful, with dose adjustment or drug switch as needed.
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