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Stan Deresinski, Section Editor

In the Literature

Hot Spring Hazard–Microsporidial Keratitis

Fan NW, Wu CC, Chen TL, Yu WK, Chen CP, Lee SM, Lin PY. Microsporidial keratitis in patients with hot springs exposure. J Clin Microbiol 2011; 50:414–8.

Fan et al in Taipei retrospectively analyzed the cases of 9 immunocompetent adults with microsporidial keratitis who had bathed in hot springs. None of the patients had a history of ocular trauma, ocular exposure to soil or mud, or contact lens use. Their initial symptoms included red eye, pain, blurred vision, epiphora, and lid swelling. The best corrected visual acuity of one patient with advanced glaucoma was counting fingers, whereas it ranged from 20/20 to 20/200 in the other 8.

All 9 patients had mild to severe conjunctivitis that was nonpurulent. Slit-lamp biomicroscopy in 8 revealed characteristic multiple whitish, round, or bizarre-shaped slightly raised epithelial lesions of variable size and without significant involvement of the stroma. One patient had atypical diffuse, whorl-like fine and coarse punctate lesions. Oval gram-positive organisms were seen in corneal scrapings, whereas brightly acid-fast spores were seen with modified Kinyoun's stain. Reverse-transcription polymerase chain reaction examination of the last 6 cases seen demonstrated the presence of microsporidial DNA, which had 98%–100% identity to that of *Vittaforma corneae*.

The epithelial lesions were debrided with 26-gauge needles or number 64 blades, and residual or recurrent lesions were removed with a cotton swab. Antibacterial agents were applied topically to prevent secondary infection, and fluorometholone and/or lubricant eye drops were also administered. The epithelial lesions resolved within 2–12 days (median, 6 days) without further recurrence. No compromising visual sequelae were observed at follow-up examination.

Microsporidial keratitis has been reported to occur in patients with AIDS, usually with stromal involvement, and in healthy individuals who have recognized risk factors, such as use of contact lenses, LASIK surgery, use of topical corticosteroids, and exposure to soil, mud, or dirty water. This study provides circumstantial evidence of an association with exposure to water from thermal springs.

The microbial contents of hot springs are rich with thermophilic bacteria, archaea, viruses, and fungi. Recreational hot springs in Taiwan are monitored for *Escherichia coli* contamination (and pH), but not for the presence of other potential pathogens. Microsporidia retain infectiousness at temperatures ≥50°C (122° F). Water in hot tub spas may often be circulated through a filter, but some may not prove a barrier to *V. corneae*, whose spores are only 3.3 × 1.4 μm in size. The organism has, in fact, been detected in wastewater effluent that has been passed through such filters.

Other pathogenic organisms that thrive in water from thermal springs include Legionella and free-living amoeba, including Naegleria, Balamuthia, and Acanthamoeba (which may, in turn, harbor Legionella and other organisms). As a Californian, I am fully aware of the pleasure associated with bathing in thermal springs, and so, despite the aforementioned risks, I guess I will keep taking a chance.

Can Linezolid be Safely Used in Patients Receiving Serotonergic Drugs?

Butterfield JM, Lawrence KR, Reisman A, et al. Comparison of serotonin toxicity with concomitant use of either linezolid or comparators and serotonergic agents: an analysis of Phase III and IV randomized clinical trial data. J Antimicrob Chemother 2012; 67:494–502.

Linezolid is a nonselective weak reversible inhibitor of monoamine oxidase (MAO) with greater affinity for MAO-B (K_i 0.71 μM) than for MAO-A (K_i 56 μM). The former is mostly responsible for oxidation of benzylamine, dopamine, and β-phenylethylamine, whereas the latter primarily oxidizes epinephrine, norepinephrine, and serotonin. Tyramine is metabolized by both. As a consequence of its inhibitory activity, linezolid has the potential for causing serotonin toxicity in patients also receiving potentially interacting drugs.

Lawrence et al reviewed spontaneous reports to the US Food and Drug Administration (FDA) from 1997 through 2003 of serotonin toxicity in linezolid recipients [1]. They identified 29 cases that met their case definition, the majority of which were being treated with serotonin reuptake inhibitors (SSRIs). Only 3 of these, however, met a standardized set of criteria (modified Hunter Serotonin Toxicity Criteria). Most other reports of serotonin toxicity in patients receiving linezolid consist only of case reports or small case series that allow neither a determination of the incidence of this complication, nor comparison to a control group.

Butterfield et al have attempted to address this deficiency by examining the locked databases of 20 phase III and IV comparator-controlled clinical trials evaluating the relative efficacy of linezolid in the treatment of a variety of infections. The comparators were all β-lactam or glycopeptide antibiotics. Of the 10 484 patients enrolled in these trials, 4265 (40.7%) were receiving at least 1 serotonergic drug and are the subject of the analysis.

There were no investigator-initiated reports of serotonin toxicity. The presence of serotonin toxicity was also determined by the investigators in a treatment-blinded review, using standardized criteria (Sternbach Criteria and the Hunter Serotonin Toxicity Criteria). Of the 2208 patients receiving linezolid who also received at least 1 serotonergic medication, 9 (0.41%) met the Sternbach criteria, and among comparator recipients, 3 (0.15%) of the 2057 met them (risk ratio, 2.79; 95% confidence interval: .76–10.31). Among patients also receiving serotonergic agents, the Hunter Serotonin Toxicity Criteria were met by 3 (0.14%) linezolid recipients and 1 (0.05%) of recipient of a comparator (risk ratio, 2.79; 95% confidence interval, .29–26.85). No patient met both sets of criteria.

Thus, the incidence of apparent serotonin toxicity among patients also receiving serotonergic agents, although numerically greater, did not significantly differ between patients receiving linezolid and those receiving a comparator antibiotic. Nonetheless, some degree of risk does exist and must be considered by the clinician. The FDA has, over the years, published cautions such as: "Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, ZYVOX should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: SSRIs, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, and buspirone" [2]. Although the FDA warns that linezolid should generally not be given to patients taking serotonergic drugs, it states the following: "However, there are some conditions that may be life-threatening or require urgent treatment with linezolid such as when:

- Linezolid is used to treat vancomycin-resistant *Enterococcus faecium* (VRE) infections.
- Linezolid is used to treat infections such as nosocomial pneumonia and complicated skin and skin structure infections, including cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA)."

Another consideration for the clinician is that serotonergic medications possess highly variable risk, something that cannot be teased out from the article reviewed here. The variability is acknowledged by the FDA in its recent warnings in which they have attempted stratification, with the drugs in the following table having the greatest risk [3]:

Serotonergic psychiatric drugs implicated in the adverse event reporting system cases of serotonin syndrome with linezolid:

1. Selective Serotonin Reuptake Inhibitors

Generic Name	Found in Brand Names
Paroxetine	Paxil, Paxil CR
Fluvoxamine	Luvox, Luvox CR
Fluoxetine	Prozac, Symbyax
Sertraline	Zolort
Citalopram	Celexa
Escitalopram	Lexapro
vilazodone[a]	Viibryd

[a]Although the US Food and Drug Administration has not received cases of serotonin syndrome to date involving vilazodone, the pharmacology of this drug places it in the selective serotonin reuptake inhibitor (SSRI) category and suggests that it possesses a risk comparable to that of the SSRIs.

2. Serotonin Norepinephrine Reuptake Inhibitors

Generic Name	Found in Brand Names
Venlafaxine	Effexor, Effexor XR
Desvenlafaxine	Pristiq
Duloxetine	Cymbalta

It should be further noted that discontinuing these agents at the time of initiating linezolid therapy does not solve the problem, at least with regard to SSRIs. Rapid discontinuation of an SSRI may lead to severe withdrawal symptoms. In addition, members of this class of drugs have prolonged elimination half-lives and complete elimination may take weeks.

Thus, the use of linezolid with serotonergic agents comes down to a confluence of the available data and expert dinical judgment. The clinician must balance the limited, but existent, risk with the potential benefits of treatment with linezolid relative to treatment with alternative antibiotics.

References

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2. FDA. Zyvox (linezolid): drug safety communication - serious CNS reactions possible when given to patients taking certain psychiatric medications. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm265479.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=linezolid&utm_content=2. Accessed 30 May 2012.
3. FDA. Drug safety communication: updated information about the drug interaction between linezolid (Zyvox) and serotonergic psychiatric medications. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm276251.htm. Accessed 30 May 2012.

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