Austrian Syndrome Caused by Highly Penicillin-Resistant *Streptococcus pneumoniae*

The finding of pneumococcal meningitis and pneumonia in an alcoholic patient requires that the diagnosis of endocarditis be excluded. This tetrad was first described by Osler but is also known as the Austrian syndrome. Nowadays, this entity is uncommon, since the incidence of *Streptococcus pneumoniae* endocarditis has significantly decreased (from 10%–15% of endocarditis cases in the preantibiotic era to 1%–3% now). Penicillin-resistant strains of *S. pneumoniae* account for 44%–58% of cases in some European countries and for 24% in the United States [1], and are a matter of concern worldwide. Herein we report what we believe is the first case of an alcoholic patient with infective endocarditis, meningitis, and pneumonia caused by *S. pneumoniae* resistant to penicillin and cefotaxime.

A 53-year-old alcoholic man with fever, headache, and impaired consciousness level was admitted to the hospital. Physical examination revealed a temperature of 39°C, confusion (Glasgow score of 9), and meningeal signs. A lumbar puncture showed the following values: glucose, 9–103 g/dL in blood; protein, 259 mg/dL; and WBCs, 1300/mm³ (90% neutrophils). A chest radiograph showed an upper-left-lobe infiltrate.

He was admitted to the intensive care unit, intubated, and treated with cefotaxime (3 g every 4 h), ampicillin (3.5 g every 6 h), dexamethasone (0.4 mg/kg iv every 12 h for 2 days), phenytoin, and mannitol. Cranial CT findings were within normal limits. Blood and CSF cultures were positive for *S. pneumoniae* (MICs: penicillin, 2 μg/mL; cefotaxime, 1 μg/mL; and vancomycin, <0.5 μg/mL). Intrathecal (3 doses) and iv vancomycin was added to the therapeutic regimen, and ampicillin was withdrawn. The CSF became culture-negative after 72 h of therapy.

On day 5 a systolic mitral murmur became evident. An echocardiogram disclosed a mitral vegetation with moderate valve insufficiency. The patient was still intubated in the intensive care unit and in poor condition. On day 17, his hemodynamic status deteriorated and the rupture of a tendinous cord was diagnosed. Emergency valve substitution was performed, revealing a destroyed valve and purulent pericarditis.

After surgery, multiple complications arose (multifactorial renal failure, *Pseudomonas aeruginosa* pneumonia, and *Clostridium difficile* diarrhea). He was discharged 4 months after admission in good condition. He received therapy with cefotaxime for 10 days and with vancomycin for 5 weeks.

Only 3 cases of pneumococcal endocarditis caused by a penicillin-resistant pneumococcus have been described previously [1–3] (table 1). Pneumococcal endocarditis classically affects middle-aged men with chronic underlying diseases (alcoholism in 28% of cases). Its course is usually acute and very aggressive, with a high rate of local and systemic complications. Endocarditis may become evident after apparent recovery from pneumonia or meningitis. The mortality rate ranges from 59% to 63%, and combined medical-surgical treatment seems the best option.

### Table 1. Characteristics of patients with endocarditis caused by *Streptococcus pneumoniae* that was highly resistant to penicillin.

<table>
<thead>
<tr>
<th>Age in y, sex [reference]</th>
<th>Underlying disease</th>
<th>Clinical presentation</th>
<th>MIC, μg/mL</th>
<th>Heart valve involved</th>
<th>Therapy (duration, w)</th>
<th>Surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>63, F [1]</td>
<td>None</td>
<td>Otitis</td>
<td>6</td>
<td>Aortic Vancomycin + rifampin (6)</td>
<td>No</td>
<td>Cured</td>
<td></td>
</tr>
<tr>
<td>53, M [PR]</td>
<td>Alcoholism</td>
<td>Meningitis, pneumonia</td>
<td>2</td>
<td>Penicillin  2</td>
<td>Cefotaxime + vancomycin (5)</td>
<td>Yes</td>
<td>Cured</td>
</tr>
</tbody>
</table>

NOTE: F, female; M, male; PR, present report.

* Imipenem, cefuzonam, and ampicillin were administered one after the other.
Fluconazole-Resistant Cryptococcus neoformans Isolated from an Immunocompetent Patient without Prior Exposure to Fluconazole

Fluconazole has been shown to be an effective alternative to amphotericin B in the treatment of cryptococcal meningitis [1–4] and is the most commonly used antifungal agent in maintenance therapy for this disease [5, 6]. A few cases of meningitis due to Cryptococcus neoformans resistant to fluconazole have been reported, all of which occurred in patients with AIDS who were previously treated with fluconazole [5–9]. Herein, we describe a case of meningitis due to fluconazole-resistant C. neoformans in an immunocompetent patient without prior exposure to fluconazole.

A previously healthy 32-year-old Philippine male employed as a nurse in Israel was admitted to the hospital with a 5-day history of headache, nausea, vomiting, and dizziness. Physical examination revealed only right-sided optic neuritis. Brain CT was unremarkable. During lumbar puncture, the opening pressure was 50 cm H2O. Analysis of CSF revealed the following: glucose level, 50 mg/dL; protein level, 85 mg/dL; and WBC count, 149/mm3 (96% lymphocytes). India ink capsule staining was negative. Cryptococcal antigen was present in CSF and blood. A cryptococcal antigen titer in CSF decreased to 1 : 100. After 5 weeks, fluconazole treatment was discontinued, and therapy with oral fluconazole (400 mg/d) was initiated. Nine days later, headache, dizziness, and diplopia appeared, and left abducens nerve paralysis was found. Therapy failure was suspected, and treatment with amphotericin B combined with flucytosine was given for another 5 weeks with significant clinical improvement. The patient was well during a follow-up 1 month later. The patient denied ever having taken antifungal drugs, and his employer confirmed this.

MICs determined by Etest (AB BIODISK, Solna, Sweden) with use of RPMI medium–4-morpholinepropanesulfonic acid were as follows: fluconazole, ≥256 μg/mL; ketoconazole, 0.38 μg/mL; itraconazole, 3.0 μg/mL; and amphotericin B, 0.5 μg/mL. Resistance to fluconazole was also confirmed at the National Institute of Allergy and Infectious Diseases (Bethesda, MD). Although CSF remained sterile after the onset of treatment, clinical deterioration after the start of oral fluconazole therapy is highly suggestive of treatment failure and is in accord with the high MIC of fluconazole for the isolate.

All previously reported cases of meningitis due to Cryptococcus neoformans resistant to fluconazole occurred in patients with AIDS who had been treated with fluconazole [5–9]. Putter et al. [9] showed heterogeneity in susceptibility when only 1% of cryptococci were resistant to fluconazole at the beginning of therapy, whereas 35% of isolates were resistant after the sixth episode of meningitis in the same patients.

To the best of our knowledge, this is the first reported case of meningitis due to fluconazole-resistant Cryptococcus neoformans in an immunocompetent patient who had never been exposed to azoles. The increasingly wide use of azoles might cause an increase in resistance to these agents. Fluconazole susceptibility testing...