Bacteremic Pneumonia Caused by Extensively Drug-Resistant
Streptococcus pneumoniae

Cheol-In Kang, 1* Jin Yang Baek, 4 Kyeongman Jeon, 2 So Hyun Kim, 4 Doo Ryeon Chung, 1
Kyong Ran Peck, 1 Nam Yong Lee, 3 Jae-Hoon Song 1,4

1 Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School
of Medicine, Seoul, Republic of Korea

2 Division of Pulmonary and Critical Care Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

3 Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan
University School of Medicine, Seoul, Republic of Korea

4 Asia Pacific Foundation for Infection Diseases (APFID), Seoul, Republic of Korea

*Address correspondence to Cheol-In Kang, MD

Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School
of Medicine, Irwon-ro 81, Gangnam-gu, Seoul 135-710, Republic of Korea

Email: collacin@hotmail.com

CI Kang and JY Baek contributed equally to this study.
Running title: XDR pneumococcal bacteremia

Keywords: *Streptococcus pneumoniae*; Bacteremia; Pneumonia; Drug Resistance, Bacterial

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health & Welfare, Republic of Korea (A102065).

Word count: 1,059  References: 18

Figures: 0  Tables: 1
The emergence of antimicrobial resistance threatens the successful treatment of pneumococcal infections. Here we report a case of bacteremic pneumonia caused by an extremely drug-resistant strain of *Streptococcus pneumoniae*, non-susceptible to at least one agent in all classes but vancomycin and linezolid, posing an important new public health threat in our region.

**Case Report**

An 81-year-old man who had been in a long-term care facility was admitted to the Emergency Department (ED) of Samsung Medical Center, Seoul, Korea with a high fever and decreased consciousness of one day’s duration, on April 25, 2012. He had undergone surgery for stomach cancer three years previously and took anti-tuberculosis (Tb) medication for Tb pleurisy with cure a year prior to presentation. Three months before admission, he had a traffic accident that caused hemoperitoneum, and he was mechanically ventilated in the intensive care unit (ICU). He also received piperacillin-tazobactam and levofloxacin treatment for ventilator-associated pneumonia during the course of ICU care with improvement, and was transferred to a long-term care facility one month before admission to the ED.

On admission, he was febrile (39.3°), with a pulse rate of 130 beats/min, blood pressure of 93/59 mmHg, and respiratory rate of 34 breaths/min. Physical examination showed vesicular breath sounds with crackles in the right lower lung field. Laboratory tests showed 2,250 leukocytes/μL, hemoglobin 10.9 g/dL, and platelets 144,000/μL. Other
laboratory values included serum BUN 53.2 mg/dL, creatinine 1.88 mg/dL, glucose 105 mg/dL, sodium 144 mM/L, and lactic acid 5.4 mM/L. Arterial blood gas analysis showed pH 7.438, pCO₂ 28.1 mmHg, pO₂ 54.0 mmHg, and SaO₂ 88.0% on room air. His chest radiograph demonstrated pneumonic consolidation in the right lower lung zone.

Vancomycin and meropenem were empirically administered based on a diagnosis of healthcare-associated pneumonia. On the day of admission, his condition rapidly deteriorated and he was transferred to the ICU. He received ventilator support after intubation due to respiratory failure. Gram stain of the respiratory specimens showed many gram-positive cocci and gram-negative bacilli, and a urinary antigen test for *Streptococcus pneumoniae* was positive. Blood culture grew *S. pneumoniae*, susceptible only to vancomycin and linezolid, while sputum culture grew methicillin-resistant *Staphylococcus aureus* and extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*. The meropenem was discontinued and he recovered after vancomycin treatment lasting for two weeks.

This pneumococcal isolate, SMC1205-93, was serotype 11A as determined by the standard quellung method (Statens Serum Institut, Copenhagen, Denmark). Antimicrobial susceptibility testing was performed by broth micro-dilution according to CLSI guidelines (2). This isolate was non-susceptible to all tested antimicrobial agents but tigecycline, vancomycin, and linezolid (Table 1). To investigate the genotype of SMC1205-93, multilocus sequence typing (MLST) was performed as previously described (4), which revealed the ST8279, a double-locus variant of ST156 closely related to the PMEN global clone Spain9V-3 (http://www.sph.emory.edu/PMEN/pmen_criteria.html). Most isolates of this lineage including ST166, single-locus variant of ST156, have been circulating in South Korea (16). Analysis of penicillin binding protein (PBP) genes (pbp1a, pbp2b, and pbp2x; GeneBank
accession no. JX560510 to JX560512) of this isolate showed highly divergent sequences compared with those of *S. pneumoniae* R6 (25.9%, 14.1%, and 15.1% for nucleotide sequences and 17.1%, 9.3% and 11.1% for amino acids sequences, respectively). The *pbp1a*, *pbp2b*, and *pbp2x* sequences of the isolate were very similar to those of prototype Spain9V-3ST156 strain, which likely contributed to the high level of resistance to penicillin (86.5%, 99.4% and 93.0% for nucleotide sequence and 92.9%, 98.9% and 96.3% for amino acid sequences, respectively). The amino acid sequences of PBP1A, PBP2B, and PBP2X of this isolate were 85.1% to 94.5%, 93.6% to 99.2%, and 96.8% to 98.1% identical to those of other penicillin resistant isolates, respectively.

Analysis of quinolone resistance-determining regions (QRDRs) (12) revealed several amino acid substitutions in the *gyrA, parC, parE* genes: Ser81-Phe in *gyrA*, Ser79-Phe and Lys137-Asn in *parC*, and Ile460-Val in *parE*. In addition, PCR analysis to detect the *erm*(B) and *mef*(A) genes (10) showed that this isolate possessed only the *erm*(B) gene, contributing to the macrolide resistance.

**Discussion**

Despite decreasing rates of invasive pneumococcal disease caused by vaccine-serotypes, *S. pneumoniae* continues to present a global threat and is associated with substantial morbidity and mortality. The emergence and spread of drug-resistant *S. pneumoniae* are a major cause of concern related to pneumococcal infection in recent years (9). The emergence of antimicrobial resistance threatens the successful treatment of pneumococcal infections (14).
Several case reports have described patients with pneumococcal bacteremia or pneumonia in whom empiric treatment with β-lactams, macrolides, or fluoroquinolones failed (3, 5, 15, 17).

Although fluoroquinolone resistance rates remain low in *S. pneumoniae* in most countries, higher resistance rates have occasionally been reported in some countries (6, 8). In addition to the emergence of resistance to newer drug classes such as the fluoroquinolones, the evolution of strains with resistance to higher concentrations of antimicrobial agents is a cause for concern (14). The treatment of patients with suspected pneumococcal infections usually consists of a third-generation cephalosporin or fluoroquinolone. The spread of such highly-resistant strains in the community could lead to an increase in treatment failure and to the increased use of vancomycin in pneumococcal infections, including invasive diseases, which are the most disturbing.

For gram-negative bacteria, extensively drug resistance (XDR) is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (11). Similarly, we propose the term, “XDR *S. pneumoniae*,” non-susceptible to at least one agent in all categories except vancomycin and linezolid (1). The emergence of XDR pneumococci with very high-level penicillin resistance poses a further challenge to the medical community. Since the first multidrug-resistant (MDR) pneumococci emerged in a limited, nosocomial setting, MDR pneumococci have spread worldwide (18). Therefore, interventions and public health measures are required to prevent the uncontrolled spread of XDR among pneumococci.

The newly licensed pneumococcal conjugate vaccine may be effective at limiting the spread of very-high-level penicillin-resistant strains. A previous study showed that the majority of very highly resistant strains occurred in vaccine-induced serotypes (14). However,
our case was not caused by the heptavalent polysaccharide conjugate vaccine-serotype (1).

Vaccine escape of XDR pneumococci such as the one reported here poses significant therapeutic challenges. In addition, use of fluoroquinolones should be restricted in patients who are at increased risk of MDR pneumococcal infection, as prior use of fluoroquinolones was reported to be a significant risk factor for fluoroquinolone resistance among pneumococci (7, 9).

Herein, we reported a case of bacteremic pneumonia caused by XDR *S. pneumoniae*, non-susceptible to at least one agent in all classes, but vancomycin and linezolid. This strain poses an important new public health threat in our region. More information on the emergence and spread of this XDR strain will be necessary in order to prevent its spread.

### Acknowledgments

This study was supported by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health & Welfare, Republic of Korea (A102065). Bacterial isolates were obtained from the Asian Bacterial Bank (ABB) of the Asia Pacific Foundation for Infectious Diseases (APFID).

### Disclosure Statement

No competing financial interest exists.


TABLE 1 Antimicrobial resistance of *Streptococcus pneumoniae* isolate SMC1205-93

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC <em>a</em> (µg/mL)</th>
<th>Resistance <em>b</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>4</td>
<td>I</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>16/8</td>
<td>R</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>&gt; 32</td>
<td>R</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt; 64</td>
<td>R</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&gt; 32</td>
<td>R</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Tigeceycline</td>
<td>≤ 0.03</td>
<td>S</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt; 32</td>
<td>R</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>32/608</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Doripenem <em>c</em></td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.5</td>
<td>S</td>
</tr>
</tbody>
</table>

*Note: MIC = Minimum Inhibitory Concentration*
Ceftobiprole \(^d\) & 4 & I 
Vancomycin & 0.25 & S 

\(^a\) Minimum inhibitory concentration

\(^b\) R, resistant; I, intermediate; S, susceptible; NS, non-susceptible

\(^c\) MIC breakpoint of resistance to doripenem was \(\geq 2 \mu g/mL\) according to the EUCAST guidelines (http://www.eucast.org/clinical_breakpoints/).

\(^d\) MIC breakpoints for ceftobiprole were resistant, \(\geq 8 \mu g/mL\) and susceptible, \(\leq 2 \mu g/mL\) (13).