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# Fatal Fulminant Pneumonia Caused by Methicillin-Sensitive *Staphylococcus aureus* Negative for Major High-Virulence Factors Following Influenza B Virus Infection

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Patient:** Male, 32  
**Final Diagnosis:** MSSA pneumonia  
**Symptoms:** Cough • dyspnea • fever  
**Medication:** Meropenem • levofloxacin • vancomycin • peramivir  
**Clinical Procedure:** Diagnosed based on CT images • sputum culture • PCR  
**Specialty:** Infectious Diseases

**Objective:** Rare disease  
**Background:** Increasing evidence has indicated that *Staphylococcus aureus* pneumonia complicated with influenza virus infection is often fatal. In these cases, disease severity is typically determined by susceptibility to antimicrobial agents and the presence of high-virulence factors that are produced by *Staphylococcus aureus*, such as Panton-Valentine leukocidin (PVL).





**Case Report:** We describe a rare case of fatal community-acquired pneumonia caused by methicillin-sensitive *Staphylococcus aureus* (MSSA), which did not secrete major high-virulence factors and coexisted with influenza type B infection. The 32-year-old previously healthy male patient presented with dyspnea, high fever, and cough. His roommate had been diagnosed with influenza B virus infection 3 days earlier. Gram-positive clusters of cocci were detected in the patient's sputum; therefore, he was diagnosed with severe pneumonia and septic shock, and was admitted to the intensive care unit. Despite intensive antibiotic and antiviral treatment, he died of multiple organ failure 5 days after admission. His blood culture from the admission was positive for MSSA, and further analysis revealed that the strain was negative for major high-virulence factors, including PVL and enterotoxins, although influenza B virus RNA was detected by PCR.

**Conclusions:** Physicians should pay special attention to patients with pneumonia following influenza and *Staphylococcus aureus* infection, as it may be fatal, even if the *Staphylococcus aureus* strain is PVL-negative and sensitive to antimicrobial agents.

**MeSH Keywords:** Influenza, Human • Leukocidins • Pneumonia, Staphylococci

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## Background

Community-acquired pneumonia (CAP) due to *Staphylococcus aureus* usually follows influenza virus infection [1]. In these cases, the virulence of the *Staphylococcus aureus* infection is often related to a variety of factors, including coagulase, enterotoxin, toxic-shock syndrome toxin, and Panton-Valentine leukocidin (PVL) [2]. PVL is a bicomponent leukotoxin that induces the lysis of leukocytes, particularly neutrophils [3]. Furthermore, PVL-positive *Staphylococcus aureus* strains have often been reported in cases of fulminant pneumonia, where they are implicated in PVL-mediated leukocyte destruction and tissue necrosis, particularly among immunocompetent young adults [4,5]. In contrast, PVL-negative *Staphylococcus aureus* strains generally induce non-specific *Staphylococcus aureus* pneumonia, which is less fulminant and typically occurs in older adults (age  $\geq 60$  years) with underlying diseases [5,6]. We report a rare case of fatal fulminant pneumonia following infection with influenza type B and methicillin-sensitive *Staphylococcus aureus* (MSSA), which was negative for major high-virulence factors (including PVL), in a previously healthy young man.

## Case Report

In March 2012, a previously healthy 32-year-old Japanese man visited our emergency department with dyspnea, high fever, and a 5-day history of coughing. Three days before this visit, the patient's roommate had experienced fever and coughing, and was diagnosed with influenza B infection following a rapid influenza diagnostic test. Our patient had difficulty breathing and appeared unwell. His vital signs included a fever with a body temperature of 39.1°C, pulse rate of 120 beats/min, respiratory rate of 40 breaths/min, and blood pressure of 110/50 mmHg. Despite oxygen administration via a mask with a reservoir bag (10 L/min), his percutaneous oxygen saturation level was only 88%. We performed tracheal intubation with mechanical ventilation, and he was admitted to the intensive care unit. Physical examination revealed bilateral coarse crackles during lung auscultation and peripheral coldness in his limbs, which suggested septic shock due to severe pneumonia. Laboratory tests revealed liver dysfunction (aspartate aminotransferase: 1,111 IU/L, alanine aminotransferase: 826 IU/L, total bilirubin: 1.4 mg/dL) renal dysfunction (creatinine: 2.06 mg/dL), elevated inflammatory markers (C-reactive protein: 11.81 mg/dL, procalcitonin: >99.9 ng/dL), and low levels of endotoxin (<2.6 EU/mL).

Although his clinical course was highly suggestive of influenza infection, the rapid test for influenza type A and B was negative at the time of admission. However, chest radiography revealed diffuse bilateral pulmonary infiltrates (Figure 1A), and

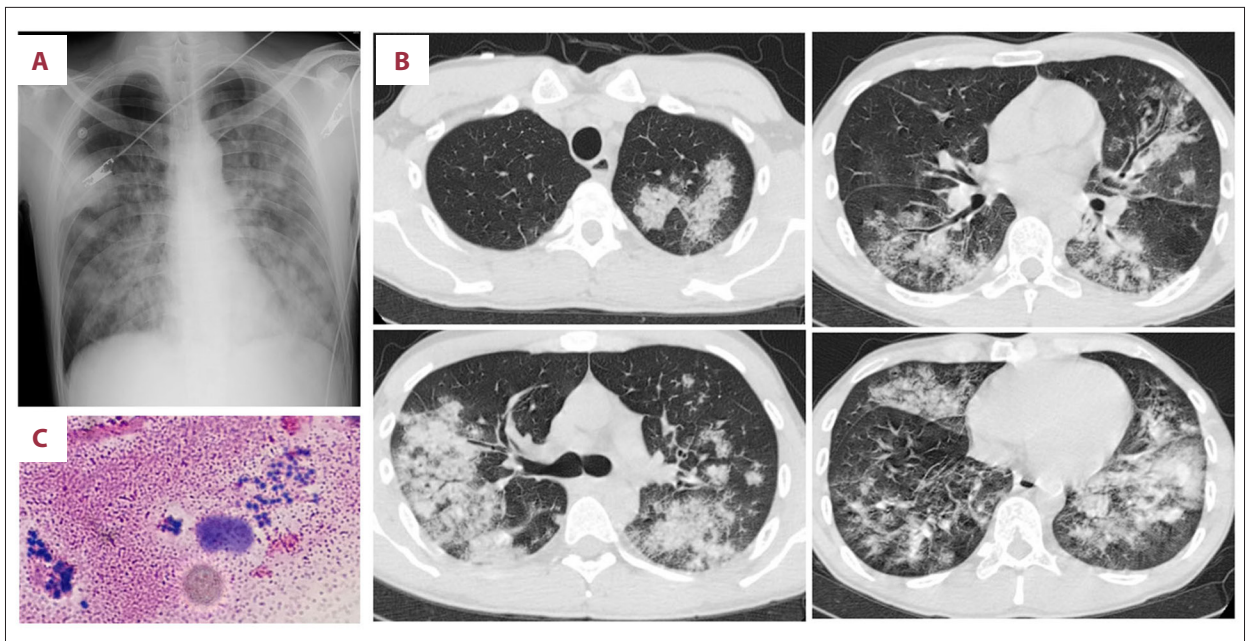
computed tomography revealed extensive multilobar infiltrates (Figure 1B). Furthermore, Gram-positive cocci were detected in his sputum at admission, which was highly suggestive of Staphylococcal infection (Figure 1C).

Based on this information, the patient was diagnosed with severe pneumonia and septic shock due to suspected acute influenza and Staphylococcal infection. We initiated treatment with intravenous meropenem (1000 mg every 8 h), levofloxacin (500 mg per day), vancomycin (500 mg every 12 h), and peramivir (600 mg per day) (Figure 2A). However, chest radiography revealed that the bilateral pulmonary infiltrates had progressively worsened following admission (Figure 2B). Ten hours after admission, 2 independent blood cultures, which had been initiated at the time of admission, confirmed *Staphylococcus aureus* infection. Twelve hours after admission, he developed right pneumothorax and a chest tube was inserted, which further aggravated his condition. Thirty hours after admission, hypoxemia had progressed and he required extracorporeal membrane oxygenation. Two days after admission, the bacterium that we isolated from the patient's blood and sputum was confirmed to be MSSA, and we switched from vancomycin and meropenem to ampicillin and sulbactam (3000 mg every 6 h), based on the results of the antimicrobial susceptibility test. Intravenous immunoglobulin (5000 mg per day) was also administered. However, despite the intensive care, the patient developed disseminated intravascular coagulation at 2 days after admission, and subsequently died of multiple organ failure on day 5 of admission (105 h after admission).

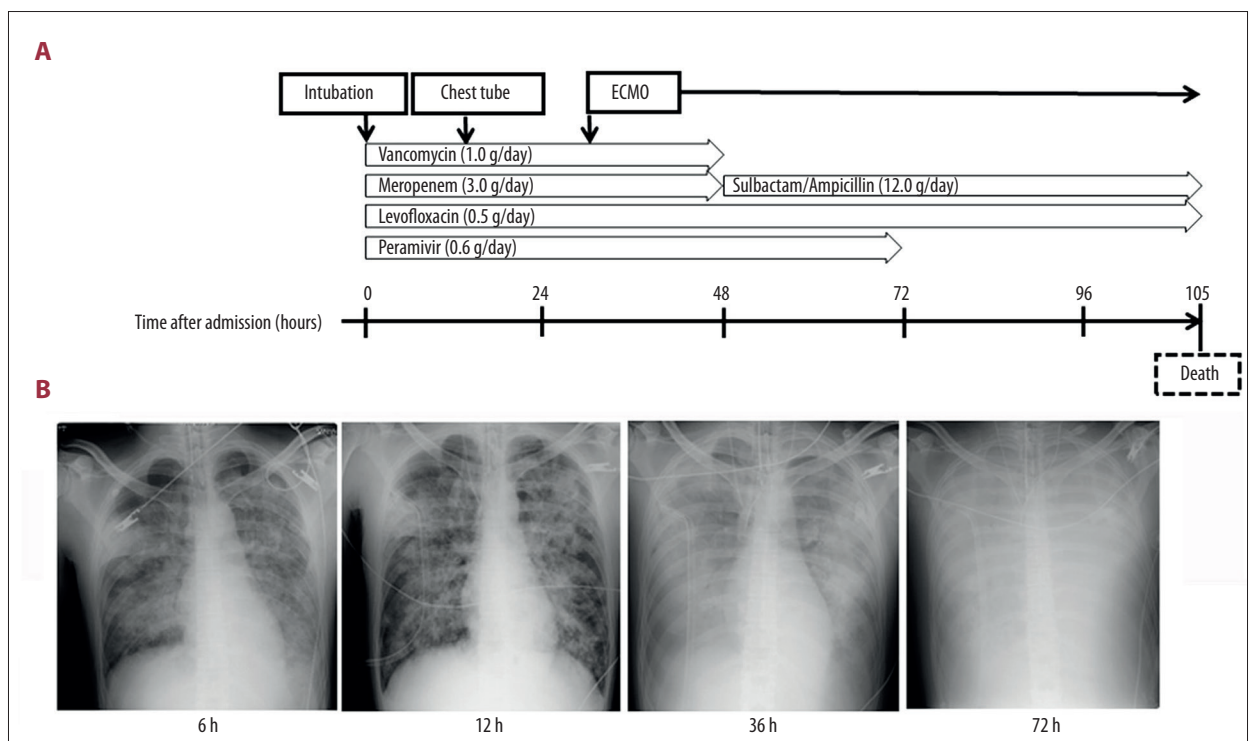
Postmortem PCR revealed that his sputum was positive for influenza type B viral RNA. In addition, the MSSA that isolated from his admission blood sample did not carry the PVL genes (Figure 3). The primer sequences of the PVL gene were as follows: forward: 5'-ATGCTGGACATGATCCAA, reverse: 5'-AACTATCTGCGCATATGGT [7]. After amplification for 30 cycles (30 s of denaturation at 94°C, 30 s of annealing at 55°C, and 1 min of extension at 72°C), the PCR products were resolved by electrophoresis through 1.5% agarose gels, according to the previous report [7]. The latex agglutination method, using a Staphylococcal superantigen detection kit (Denka Seiken, Tokyo, Japan), did not detect any major virulence factors, including enterotoxins (*sea*, *seb*, *sec*, *sed*), exfoliative toxins (*eta*, *etb*), or toxic shock syndrome toxin-1 (*tst*).

## Discussion

In this report we describe a rare case of fatal CAP caused by MSSA, which was negative for major high-virulence factors, following influenza B infection in a previously healthy 32-year-old man. At the time of his admission, large amounts of clustered Gram-positive cocci were detected in his sputum



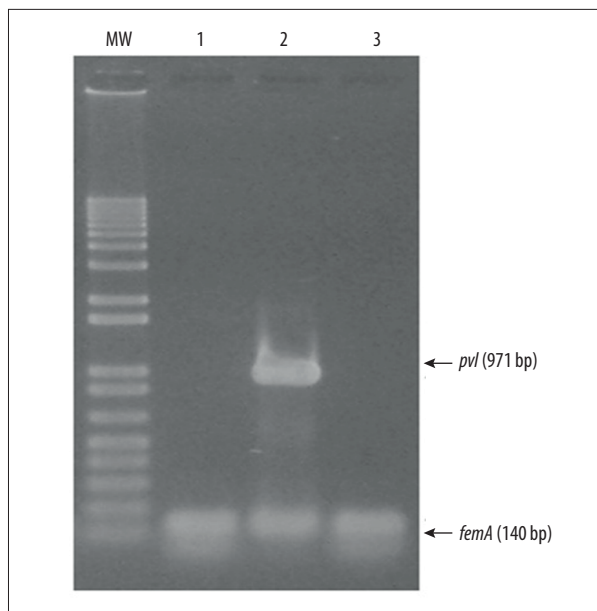
**Figure 1.** (A) Chest radiography and (B) high-resolution computed tomography of the lungs on admission. (C) Microscopic examination of Gram-stained sputum specimens on admission.



**Figure 2.** (A) Overview of the clinical course and treatment from admission to death. The patient received broad-spectrum antimicrobials, intubation, chest tube insertion, and extracorporeal membrane oxygenation (ECMO). (B) Chest radiographs at the indicated time points following admission.

smear, which was finally confirmed to be *Staphylococcus aureus* via blood and sputum culture. Therefore, we believe that both the influenza infection and the Staphylococcal infection

contributed to the immunopathogenesis of severe pneumonia in the present case.



**Figure 3.** PCR of the Pantone-Valentine leukocidin (PVL) gene from *Staphylococcus aureus* that was isolated from the patient's admission blood culture (Lane 1). The positive control was MRSA strain MW2 (971 bp, Lane 2) and the negative control was MRSA strain N315 obtained from another patient (Lane 3).

Concomitant influenza and bacterial infection often results in fatal outcomes [8], although the reason for this poor prognosis is not fully understood. Previous reports have suggested various pathogenic mechanisms, including the hypothesis that epithelial cell injury caused by the influenza virus can facilitate secondary bacterial invasion [9]. Other hypotheses include decreased bacterial phagocytosis among alveolar macrophages [10,11], downregulation of Toll-like receptors [9], and inhibition of neutrophil recruitment by type I interferon that is produced following influenza infection [12]. Furthermore, hyperactive immune cells (T cells) may be involved in acute lung injury due to influenza virus infections, which could help facilitate secondary bacterial invasion [13].

Co-infection with the influenza virus was most commonly by *Streptococcus pneumoniae* in the 1918–1919 influenza pandemic [14]. However, recent reports have suggested that *Staphylococcus aureus* is emerging as a cause of fatal pneumonia when associated with the influenza virus [5,15], as in the present case. The virulence of *Staphylococcus aureus* is often associated with antimicrobial resistance to methicillin (ie, MRSA) and the expression of toxin genes such as PVL [16]. In addition, necrotizing pneumonia caused by PVL-positive *Staphylococcus aureus* has a poor prognosis, with a reported mortality rate of nearly 75% [5]. The PVL toxin is typically produced by MRSA, which is typically a community-acquired strain, and is infrequently produced by MSSA [17]. However, a previous

report has indicated that methicillin resistance does not determine the severity of PVL-producing *Staphylococcus aureus* pneumonia, as the prognosis is comparable between patients with community-acquired MSSA and MRSA pneumonia [18].

In the present case, fulminant pneumonia was caused by a PVL-negative *Staphylococcus aureus* strain, which typically induces non-specific *Staphylococcus aureus* pneumonia and is often less severe than pneumonia that is induced by PVL-positive *Staphylococcus aureus* strains [5,6]. For example, a recent study from the United States has reported that 56 of 62 cases (90%) of histologically confirmed fatal necrotizing pneumonia were caused by influenza and PVL-positive *Staphylococcus aureus* co-infection [16]. In contrast, only 3 of 62 cases were caused by PVL-negative MSSA and influenza B co-infection, as observed in the present case. To the best of our knowledge, ours is the first report of fatal fulminant pneumonia caused by influenza B and PVL-negative MSSA infection in a country other than the United States.

A previous study has demonstrated that toxic shock syndrome toxin-1 and enterotoxin B contributed to toxic shock syndrome subsequent to pneumonia that is caused by influenza B and *Staphylococcus aureus* [19]. Therefore, as the present case was PVL-negative, we assessed whether other toxins, including enterotoxin (*seb* and *sec*) and exfoliative toxin (*etb*), contributed to the fatal outcome. However, none of these toxins were detected.

Corticosteroids were not administered in the present case, and the efficacy of corticosteroid therapy for severe pneumonia due to influenza virus infection remains controversial, as various reports have described beneficial effects [13,20] and no beneficial effects [21–23]. However, very recent reports have suggested that early corticosteroid therapy for severe CAP can provide beneficial effects [24,25]. Therefore, it is possible that early use of antibiotics or antivirals, combined with systemic immune modulators (e.g., corticosteroids and/or high-dose intravenous immunoglobulin) may help prevent the rapid progression of pneumonia and/or allow for rapid resolution of the pulmonary lesions in influenza pneumonia and reduce the risk of subsequent bacterial pneumonia [13,20]. Thus, in cases of severe CAP due to influenza and bacterial infection (such as the present case), early initiation of immune modulators during the initial stage of respiratory distress might improve the patient's prognosis.

## Conclusions

Pneumonia following influenza and *Staphylococcus aureus* infection can be fatal, regardless of whether the *Staphylococcus aureus* strain carries major high-virulence factor genes or is



resistant to methicillin. Physicians should pay special attention to cases of pneumonia following influenza and *Staphylococcus aureus* infection.

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## Conflicts of interest

The authors declare that there are no conflicts of interest.