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Corynebacterium pseudodiphtheriticum as a pathogen in bacterial co-infection in COVID-19 patients with mechanical ventilation

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Abstract

Many studies have been conducted on ventilator-associated complications (VACs) in COVID-19 patients. However, in these studies, the causative organisms were similar, and there are no reports on VAC corresponding with Corynebacteria. Coryneforms are frequently cultured in polymicrobial infections and are usually considered contaminants in respiratory specimens. However today, *Corynebacterium pseudodiphtheriticum* or *striatum* is known to be a pathogen in lower respiratory tract infection. We report three cases of VAC probably due to *Corynebacterium pseudodiphtheriticum* in COVID-19 patients. If purulent lower respiratory specimens showed coryneform predominantly via Gram staining, empirical therapy should be started. Furthermore, species identification and drug susceptibility testing should be performed.
Coryneform bacteria are characterized as irregularly shaped, non–spore-forming, aerobic, Gram-positive rods. Coryneforms are frequently cultured in polymicrobial infections and are usually considered contaminants in respiratory specimens. However, *Corynebacterium pseudodiphtheriticum* or *striatum* is known to be a pathogen in lower respiratory tract infections (1,2).

The COVID-19 pandemic caused by SARS-CoV-2 has a high incidence of severe acute respiratory syndrome (SARS). Many of the affected patients require admission to an intensive care unit (ICU) for invasive ventilation and are at high risk of developing secondary ventilator-associated complications (VACs). Studies on VACs have already been conducted in COVID-19 patients (3–6). However, in these studies, the causative organisms were similar, and there are no reports on VAC corresponding to corynebacteria. Herein, we report three cases of VACs probably due to *Corynebacterium pseudodiphtheriticum* in COVID-19 patients.

*Case 1*

A 65-year-old woman was admitted to our hospital with general fatigue, high-grade fever, and cough. On the same day of admission, the antigen quantitative test results for SARS-CoV-2 were positive. On admission, computed tomography of the lungs showed diffuse ground-glass opacities and consolidations with bilateral bronchial dilation. She required 3-L/min oxygen therapy, and oral dexamethasone (6 mg/day) was administered immediately. Intravenous remdesivir was also administered on day 3. Although fever was relieved, oxygenation gradually deteriorated. On day 5 after admission, she was intubated and transferred to the intensive care unit (ICU). Lower tract
secretions were collected soon after intubation, which contained almost no cellular components and only a few gram-positive cocci. On day 9, the ventilator settings required to maintain oxygenation were escalated. She had frequent cough reflexes and an increase in purulent intratracheal viscous secretion. Gram staining of the secretion was classified as Geckler 5, and coryneform gram-positive small rods were observed predominantly in all fields of view (Figure 1A). Phagocytosed small rods were also confirmed in many fields. Intravenous vancomycin treatment was introduced. Subsequently, intratracheal secretions were no longer purulent, and ventilator settings could be de-escalated daily. Two days later, the gram-positive rod was identified as *Corynebacterium pseudodiphtheriticum* by API coryne® (Biomerieux, France), and drug susceptibility testing performed by the broth microdilution method using an Eiken dry plate (Eiken, Japan) showed susceptibility to narrow-spectrum beta-lactams (Table 1). Thus, the antimicrobial agent was changed to cefazolin. She left ICU on day 25, and she finally discharged to home on day 50.

Case 2

A 78-year-old woman was admitted to our hospital with persistent fever and hypoxia. She was diagnosed with COVID-19 four days before admission. On admission, she required 4 L/min of oxygen therapy. Oral dexamethasone, intravenous remdesivir, and subcutaneous heparin (5000 U, twice daily) were administered. However, oxygenation gradually deteriorated, and on day 4 after admission, she was intubated and transferred to the intensive care unit (ICU). At the time of ICU admission, computed tomography of the lungs showed bilateral diffuse ground-glass opacities and consolidation. Lower
tract secretions were collected soon after intubation and were found to contain almost no cellular components. On day 6, the ventilator settings to maintain oxygenation were escalated, and purulent intratracheal viscous secretion was observed. Gram staining of the secretion was classified as Geckler 5, and coryneform gram-positive small rods were observed in all fields of view along with phagocytosis (Figure 1B). Thus, intravenous vancomycin treatment was introduced empirically. Subsequently, the quality and quantity of intratracheal secretions improved, and ventilator settings were de-escalated on day 7. On day 8, purulent intratracheal viscous secretion was observed again, and Gram staining revealed an increase in small gram-negative bacilli considered *Haemophilus*. Intravenous ceftriaxone was also administered. On day 10, *Serratia marcescens* was cultivated with *Haemophilus influenzae* from day-8 intratracheal secretion, and gram-positive rods were identified as *Corynebacterium pseudodiphtheriticum* by API coryne® (Biomerieux, France). Drug susceptibility testing was performed by the broth microdilution method using an Eiken dry plate (Eiken, Japan) (Table 1). Antibiotics were changed to cefepime to fully target these organisms. Unfortunately, she was died of the progression of COVID-19 on day 57.

**Case 3**

A 70-year-old man was admitted to our hospital with persistent fatigue, fever, and hypoxia. He was diagnosed with COVID-19 four days before admission. Soon after admission, his hypoxia became severe, and he was intubated and transferred to the intensive care unit (ICU). Computed tomography of the lungs showed diffuse ground-glass opacities and bilateral consolidation. Intravenous
dexamethasone was administered. On day 5, the ventilator settings to maintain oxygenation were escalated, and purulent intratracheal viscous secretion was observed. Gram staining of the secretion was classified as Geckler 5, and only coryneform gram-positive small rods were observed in all fields of view (Figure 1C). Phagocytosed small rods were also confirmed in many fields. Intravenous vancomycin treatment was introduced empirically. However, the ventilator settings used to maintain oxygenation could not be de-escalated. Gram staining of intratracheal secretion on day 7 showed a decrease in white blood cells and gram-positive rods, but an increase in gram-negative rods such as Enterobacteriaceae. Ceftriaxone was administered intravenously. On day 8, gram-positive rods and gram-negative rods were identified as Corynebacterium pseudodiphtheriticum (by API coryne® (Biomerieux, France)), and Klebsiella pneumoniae, respectively. Drug susceptibility testing for C. pseudodiphtheriticum was performed by the broth microdilution method using an Eiken dry plate (Eiken, Japan) (Table 1). On the same day, his blood examination showed elevation of liver enzymes, and antibiotics were changed to cefotaxime according to the drug susceptibility test. He left ICU on day 52, and transferred to the rehabilitation facility on day 73.

Mechanical ventilation exposes patients to the risk of ventilator-associated pneumonia (VAP). VAP was diagnosed based on the criteria adapted from the European Centre for Disease Prevention and Control (ECDC) recommendations (7). However, the diagnosis of VAP is challenging in COVID-19 patients. The definition of VAP consists of radiological findings, clinical features such as fever or
counts of leukocytes, and microbiological aspects. COVID-19 patients are usually admitted to the ICU because of pneumonia. Furthermore, dexamethasone administration is now recommended for the specific treatment of COVID-19; it has an antipyretic effect and affects white blood cells in the peripheral blood. We present three cases of VAC probably due to *Corynebacterium pseudodiphtheriticum*. All three patients were admitted to the ICU due to severe COVID-19 pneumonia and were prescribed dexamethasone. However, two of the three patients did not have high-grade fever, the oxygenation worsened, and new purulent sputum appeared. There are many reports on VAP in COVID-19 patients. Maes et al. compared the lung microbiome of ventilated COVID-19 and non–COVID-19 patients and concluded that the distribution of organisms causing VAP was similar between the two groups, and the organisms were mainly gram-negative bacilli, followed by gram-positive cocci, yeasts, and *Aspergillus fumigatus* (3). Rouze et al. described that gram-negative bacilli are responsible for a large proportion of VAC, followed by gram-positive cocci (4). Blonz et al. and Moretti et al. reported similar results (5,6). In these studies, there are no reports on VAC due to Corynebacteria.

A recent study showed that *Corynebacterium* could be causing pneumonia or VAP. Bittar et al. described an outbreak of *Corynebacterium pseudodiphtheriticum* infection in patients with cystic fibrosis (8). Clariot et al. described the clinical relevance of *Corynebacterium* spp. in respiratory specimens from ICU patients and concluded that *Corynebacterium* spp. seemed responsible for authentic pneumonia in mechanically ventilated patients (9). Akbiyik et al. listed *Corynebacterium*
*striatum* as the multidrug-resistant causative agent of VAP alongside *Pseudomonas aeruginosa* or *Acinetobacter baumannii* (10). In our cases, oxygenation improved in two of three cases by the introduction of vancomycin treatment. Furthermore, intratracheal secretions were improved in all cases. However, we did not perform quantitative culture, and the culture media of purulent lower respiratory tract specimens were filled with the same colonies. Thus, we concluded that these cases were VACs probably due to *Corynebacterium pseudodiphtheriticum*. In addition, two of three cases, Gram negative bacilli were increased in the intratracheal secretion following treatments for *Corynebacterium pseudodiphtheriticum*. Thus, we should evaluate intratracheal secretion or sputum microbiologically in the process.

In conclusion, *Corynebacterium* spp. could be an organism causing VAC in COVID-19 patients. If purulent lower respiratory tract secretions increase and gram-positive rods are predominant on Gram stain, empirical treatment should be performed. In addition, species identification and drug susceptibility testing should be performed for antimicrobial stewardship.
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Conflict interest: None to declare.

References


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**Figure legends:**

Figure 1: Gram stain of purulent intratracheal secretion (×1,000). Numerous coryneform gram-positive small rods in all fields of view in (A) case 1, (B) case 2, and (C) case 3
### Table 1: The results of the drug susceptibility testing of *Corynebacterium pseudodiphtheriticum* in each case. MIC: Minimum Inhibitory Concentration

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<th>case 3</th>
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