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Review

Microbiological Characteristics of *Corynebacterium striatum*, an Emerging Pathogen

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C. striatum is part of the normal skin and mucous membrane flora in humans and is widely disseminated in the environment. Traditionally, these strains have been considered contaminants. However, *C. striatum* has been linked to respiratory infection, bacteremia, and endocarditis; and it is strongly related to nosocomial outbreaks. At present, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) is the most accurate routine identification method. Many *C. striatum* strains are multi-drug resistant, being susceptible only to vancomycin and linezolid. We should survey the antimicrobial susceptibility results regularly to monitor its resistance and consider it a possible pathogen.

Key words: *Corynebacterium striatum*; Emerging pathogen; Resistance

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INTRODUCTION

Corynebacterium is a gram-positive bacillus that is widely distributed in the environment [1]. It consists of more than 80 species and is common in the normal flora of human skin and mucous membranes [1]. These organisms traditionally have been considered contaminants and are ignored when they are detected in clinical specimens. However, the association of *Corynebacterium* species with disease is increasing, and we should consider them true pathogens when they are isolated from usually sterile specimens or invasive indwelling devices and in patients who have received long-term antimicrobial therapy.

In recent years, *Corynebacterium striatum* has been isolated frequently from clinical specimens, and multi-drug-resistant strains are common. We need to know more precisely about the general characteristics of this organism, its clinical features, an accurate identification method, and antimicrobial resistance. We review the characteristics of *C. striatum*, an emerging pathogen, focusing on these points.

1. Epidemiology and Clinical Features

Corynebacterium striatum is part of the normal flora of the skin and mucous membranes in humans and is widely disseminated in the environment. It has generally been regarded as a contaminant when isolated from clinical specimens. However, it can have pathogenicity in both immunocompromised and immunocompetent hosts [2] and can colonize various medical devices. Since *C. striatum* was first reported as a causative pathogen of pleuropulmonary infection in 1980 [3], it has been associated with diverse infections and nosocomial outbreaks. Thus, the organisms have been responsible for respiratory infection [4], infectious endocarditis [5,6], arthritis [7], cellulitis [8,9], catheter-related bloodstream infection [10,11], meningitis [12], skin infection [13], osteomyelitis [14], abscess [15], and wound infection [16]. An important aspect of several of these infections, including infectious endocarditis, sepsis, or meningitis, caused by *C. striatum* is an association with a nosocomial risk factor such as med-

ical devices [11,17] and underlying immunosuppressive conditions. Also, it can cause clinically significant infections at multiple sites and exhibited behavior consistent with an emerging pathogen in several studies [18,19]. Belmares et al. reported infections with this organism, which was the most common among *Corynebacterium* species [17], to have a mortality rate of 78.6%. There have been occasional reports of *C. striatum* nosocomial outbreaks in patients with chronic obstructive pulmonary disease (COPD) [20] and those in intensive care units [21]. These studies showed that the most common comorbidity in infected patients is COPD, which means that chronic pulmonary disease with long-time use of respiratory equipment can contribute to respiratory infection or colonization by *C. striatum*. Furthermore, *C. striatum* has pathogenicity in specific conditions such as repeated exposure to antibiotics or invasive procedures. Also, several studies have reported that *C. striatum* can be transmitted from patient to patient via the hands of medical personnel [21,22]. Thus, enforcing hand hygiene and applying short-period therapeutic devices or antibiotics are significant factors recognized as preventative of nosocomial infection. However, these strains commonly were isolated in outpatient settings, so we can presume that they originated in the community [23].

Corynebacterium striatum infection can occur at any age and in various sites, but it is more common in male patients because the greater sebum output on the skin of males can support the survival of lipophilic diphtheroids such as *C. striatum* [12,24,25]. Virulence factors associated with *C. striatum* are limited. However, skin barrier damage, a medical device, use of broad-spectrum antibiotics, underlying disease, and poor immune status may influence the occurrence of infection. *Corynebacterium striatum* is known to be resistant to many antimicrobial treatments. To prevent such infections, it is recommended to remove any artificial device if possible and not to use long-term antimicrobial agents [26,27]. Therefore, repeated isolation of *C. striatum* is significant and should not be underappreciated, as it may contribute to the death of some patients [28].

2. Laboratory Diagnosis

Corynebacterium species are gram-positive, slightly curved, typically club-shaped bacilli. Generally, *Corynebacterium* can be isolated on 5% sheep blood agar-based selective medium at 37°C. The biochemical identification of various species can be difficult because of their biochemical variability. For routine identification, micromethods such as API Coryne strip (bioMérieux, Marcy l'Étoile, France) and RapID® CB Plus or several automated identification systems are commonly used in the clinical microbiology laboratory.

API Coryne strip can be used for suspect colonies, which are tiny grayish, mostly translucent, coryneform organisms. The device consists of 20 microtubes that test carbohydrate fermentation or enzymatic activity. Unfortunately, the device cannot distinguish *C. striatum* from *C. amycolatum* because these species have similar phenotypic characteristics. Moreover, the final identification is based on the statistical use of multiplicity. Therefore, the accuracy is relatively low.

Various automated identification systems for *Corynebacterium* are used routinely. VITEK®2 (bioMérieux) with an anaerobe and *Corynebacterium* (ANC) identification card employs kinetic analysis utilizing fluorescence, turbidity, and colorimetric technology based on the metabolic processes of the microorganisms. Rennie et al. reported that the correct identification rate of the Vitek2 ANC identification card for *Corynebacterium* species was 80% to 100% [29]. The Microscan system (Beckman Coulter, Brea, CA, USA) and BD Phoenix system (Becton Dickinson, Franklin Lakes, NJ, USA) also are commercially available for *Corynebacterium* identification.

The reliable identification techniques include matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and 16S rRNA sequencing. MALDI-TOF MS, which is based on the protein composition of microorganisms, has been used in clinical laboratories to identify *Corynebacterium* species. Vila et al. reported that MALDI-TOF MS analysis is a rapid and consistent system for identification of *Corynebacterium* at the species level within 15 min [30]. Rong Bao et al. reported the MALDI-TOF identification rate for *Corynebacterium* as 92% compared with *rpoB* gene sequencing [31]. Other studies showed similar identification rates, ranging from 92.3% to 100% [32-35]. Therefore, MALDI-TOF may be a more useful diagnostic method than biochemical assay and can be a primary identification tool.

Various molecular methods have been applied for identification of *Corynebacterium* species, including 16S rRNA sequencing, *rpoB* gene sequencing, and restriction fragment-length polymorphism (RFLP), DNA–DNA hybridization, and real-time polymerase chain reaction (PCR). Because the 16S rRNA gene of *Corynebacterium* shows low intra-genus polymorphism, nearly complete 16S rRNA sequencing (approximately 1,500 bp) is required to identify to the species level. The *Rpo B* gene also can be used to discriminate *Corynebacterium* species. Khamis reported that the *rpoB* gene is polymorphic enough to identify *Corynebacterium* species [36]. Alibi et al. suggested PCR restriction analysis using the *rpoB* gene to differentiate *C. striatum* from other *Corynebacterium* species [32]. We do not need to use these molecular methods as routine tests, but they can be used as a confirmatory tool when we need to check the final results because of an inappropriate phenotypic method.

3. Antimicrobial Susceptibility Test and Resistance

The Clinical and Laboratory Standards Institute (CLSI) published "Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria; Approved Guideline M45-A" in 2006. This guideline provides the information and interpretive criteria for broth microdilution susceptibility testing of *Corynebacterium* species. However, there are no interpretive criteria for disk diffusion testing. The testing conditions require lysed horse blood-supplemented Mueller-Hinton broth for adequate growth. Moreover, the medium should contain calcium 50 μg/mL for testing of daptomycin. The antimicrobial agents used are as follows: penicillin, cefotaxime (cefepime, ceftriaxone), imipenem (meropenem), vancomycin, daptomycin, gentamicin, erythromycin, ciprofloxacin, doxycycline (tetracycline), clindamycin, trimethoprim–sulfamethoxazole, quinupristin-dalfopristin, and linezolid. The interpretive criteria for penicillin and erythromycin are estimated from the minimum inhibitory concentrations (MICs) of *Corynebacterium* species. However, the interpretive criteria for cephalosporin, linezolid, and others are adapted from those for *Streptococcus*, *Enterococcus*, and *Staphylococcus* species published in CLSI document M100. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) provides a breakpoint table for interpretation of MICs and zone diameters for *Corynebacterium* species. Unlike CLSI, EUCAST includes the interpretive criteria for the disk diffusion method. The medium should have 5% defibrinated horse blood and beta-NAD 20 mg/L. The antimicrobial agents tested are benzylpenicillin, ciprofloxacin (moxifloxacin), gentamicin, vancomycin, clindamycin, tetracycline, linezolid, and rifampicin. It is not easy to perform routine antimicrobial susceptibility testing of *C. striatum* in the clinical laboratory because there is no commercial kit, and growth requires a special medium including horse blood.

Previous reports revealed that *C. striatum* generally is susceptible to several antimicrobial agents, including penicillin, cefazolin, imipenem, and vancomycin [28,37]. However, many more recent articles found an increase in multidrug resistance [21,23,38]. In Korea, Yoo et al. described bacteremia caused by multidrug-resistant *C. striatum* [39].

In 2006, *C. striatum* strains in Japan were all susceptible to vancomycin but showed high-level resistance to erythromycin, tetracycline, rifampin, and ciprofloxacin [40]. In one report from Brazil, 87% of *C. striatum* were resistant to most antimicrobial agents except vancomycin, linezolid, and tetracycline [41]. Vancomycin was consistently effective in most previous reports of *C. striatum* testing.

Daptomycin can be considered to treat gram-positive pathogens. Several reports show that *Corynebacterium* infections can be treated with daptomycin, for which the MICs are low [42,43]. However, daptomycin-resistant *C. striatum* is discussed in the literature [43,44]. Van Hal et al. reported that daptomycin resistance is highly correlated with higher MICs for vancomycin in *S. aureus* because cell-wall thickening can alter the charge of the outer membrane, which reduces daptomycin passage through the cell membrane [45]. However, others found no structural difference between daptomycin-susceptible and -resistant *Corynebacterium* strains [44,46]. McElvania TeKippe et al. [43] revealed a very interesting finding concerning daptomycin resistance. They demonstrated the acquisition of high-level resistance when the daptomycin-susceptible isolates were incubated with the drug. This implies the possibility of acquisition of daptomycin resistance in patients treated for a long time with the drug.

The other agent employed to treat *C. striatum* infection is linezolid because there have been no reports of resistance for *Corynebacterium* species. However, this drug carries a 34% to 80% rate of adverse effects that result in discontinuation of administration during long courses [47].

Ceftaroline has been explored for uncommon gram-positive pathogens, including *C. striatum* [48,49]. The efficacy was variable for *C. striatum* and other *Corynebacterium* species. On the other hand, McMullen et al. reported that *C. striatum* is nearly universally resistant to ceftaroline, although the extent of resistance is variable. They presumed that the resistance is attributable to the modification of penicillin-binding protein and concluded that ceftaroline is not adequate to use as a treatment. McMullen et al. [35] tested the activity of telavancin and revealed achievable MICs for *C. striatum* treatment.

CONCLUSION

Corynebacterium striatum is part of the normal flora of the skin and mucous membranes in humans. However, it can have pathogenicity in both immunocompromised and immunocompetent hosts. *C. striatum* has been associated with diverse infections and nosocomial outbreaks including skin infection, respiratory infection, and severe invasive infections. In addition, *C. striatum* is resistant to many antimicrobial treatments. We should identify *C. striatum* correctly to the species level and survey the antimicrobial susceptibility results regularly to monitor its resistance.

CONFLICTS OF INTEREST

The authors have no financial conflicts of interest.

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