

Biofilm Formation and Antimicrobial Susceptibility of Non-Diphtheriae *Corynebacterium* Strains Isolated from Blood Cultures: First Report from Turkey

Kan Kültürlerinden İzole Edilen Difteri-Dışı *Corynebacterium* Suşlarının Biyofilm Oluşturması ve Antimikrobiyal Duyarlılıkları: Türkiye'deki İlk Bildirim

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ABSTRACT

Objective: Non-diphtheriae *Corynebacterium* strains have been recognized as important pathogens after decades of confusion regarding their microbiological classification and clinical significance. The aim of this study was to identify non-diphtheriae *Corynebacterium* strains and the prevalence of biofilm formation and antimicrobial resistance.

Method: In total, 126 non-diphtheriae *Corynebacterium* strains were isolated from blood cultures of inpatients with bacteremia in our hospital between January 2015 and January 2020. Blood cultures were analyzed with the Bactec-9120 system. Strains were identified using MALDI-TOF MS (Bruker Daltonics, Germany). Antimicrobial susceptibilities were determined using the Kirby-Bauer disk diffusion method on a Mueller-Hinton agar and evaluated according to EUCAST standards. Biofilm formation was assessed with the Congo Red Agar method.

Results: *Corynebacterium striatum* and *Corynebacterium matruchotii* were the most prevalent with 29 and 26 isolates, respectively. Biofilm production was detected in 62.06% (18/29) of *C. striatum*, in 53.8% (14/26) of *C. matruchotii*, in 50% (9/18) of *Corynebacterium afermentans*, 50% (6/12) of *Corynebacterium amycolatum*, and in 46% (7/15) of *Corynebacterium jeikeium* strains. Among the five most prevalent strains, we found a high biofilm rate of 54%. The resistance rates to penicillin, clindamycin, ciprofloxacin, rifampicin, tetracycline, and gentamicin were 91.2%, 87.3%, 79.3%, 56.3%, 45.2%, and 39.6%, respectively. All 126 strains were susceptible to vancomycin and linezolid.

Conclusion: Non-diphtheriae *Corynebacterium* strains isolated from blood cultures of hospitalized patients with bacteremia may have multidrug resistance and the ability to produce biofilm. These results emphasize the importance of identifying strains and determining their antimicrobial susceptibility and biofilm production potential.

Keywords: *Corynebacterium striatum*, *Corynebacterium matruchotii*, *Corynebacterium afermentans*, *Corynebacterium amycolatum*, *Corynebacterium mucifaciens*, *Corynebacterium kutscheri*

ÖZ

Amaç: Difteri-dışı *Corynebacterium* suşları, mikrobiyolojik sınıflandırmaları ve klinik önemi ile onlarca yıllık kafa karışıklığının ardından önemli patojenler olarak kabul edilmiştir. Bu çalışmanın amacı, difteri-dışı *Corynebacterium* suşlarının tür tayinini yapılması, biyofilm oluşumu ve antimikrobiyal direnç prevalansını araştırmaktır.

Yöntem: Ocak 2015-Ocak 2020 tarihleri arasında hastanemizde yatarak tedavi gören bakteriyemili hastaların kan kültürlerinden difteri olmayan 126 *Corynebacterium* suşu izole edildi. Kan kültürleri Bactec-9120 sistemi ile analiz edildi. Suşların tanımlanması MALDI-TOF MS (Bruker Daltonics, Almanya) kullanılarak yapıldı. Antimikrobiyal duyarlılıklar Mueller-Hinton agarda Kirby-Bauer disk difüzyon yöntemiyle belirlendi ve EUCAST standartlarına göre değerlendirildi. Biyofilm oluşumu Congo Red Agar yöntemi ile değerlendirildi.

Bulgular: Difteri-dışı *Corynebacterium* suşları arasında *Corynebacterium striatum* ve *Corynebacterium matruchotii* sırasıyla 29 ve 26 izolata en yaygın suşlardı. Biyofilm üretimi *C. striatum* suşlarında %62,06 (18/29), *C. matruchotii* suşlarında %53,8 (14/26), *Corynebacterium afermentans* suşlarında %50 (9/18), *Corynebacterium amycolatum* suşlarında %50 (6/12) ve *Corynebacterium jeikeium* suşlarında %46 (7/15) olarak tespit edilmiştir. Çalışmanın en sık izole edilen ilk beş suşunda, %54 gibi yüksek bir biyofilm oranı bulduk. Penisilin, klindamisin, siprofloksasin, rifampisin, tetrasiklin ve gentamisine direnç oranları sırasıyla %91,2, %87,3, %79,3, %56,3, %45,2 ve %39,6 olarak tespit edildi. 126 suşun tamamı vankomisin ve linezolide duyarlıydı.

Sonuç: Bu sonuçlar, hastanede yatan bakteriyemili hastaların kan kültürlerinden izole edilen *Corynebacterium* suşlarının biyofilm oluşturma yeteneğiyle birlikte çoklu-ilaç direnci gösterdiklerini ve kontaminasyon olarak göz ardı edilmemesi için, tür tayini ve antibiyotik duyarlılığının belirlenmesinin önemini vurgulamaktadır.

Anahtar kelimeler: *Corynebacterium striatum*, *Corynebacterium matruchotii*, *Corynebacterium afermentans*, *Corynebacterium amycolatum*, *Corynebacterium mucifaciens*, *Corynebacterium kutscheri*

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INTRODUCTION

Corynebacterium is a genus of aerobic, Gram-positive, non-motile bacteria called “diphtheroids” or “coryneform”. *Corynebacterium* spp. are typically club-shaped and nonsporulating rods. *Corynebacterium* spp. are divided into two groups: *Corynebacterium diphtheriae* and non-diphtheriae *Corynebacterium*^{1,2}.

Previously, *C. diphtheriae* was considered an agent that caused serious infections, whereas other non-diphtheriae *Corynebacterium* strains were dismissed as contaminating bacteria when isolated from clinical specimens. Recently, non-diphtheriae *Corynebacterium* spp. have been recognized as important pathogens after decades of confusion regarding their microbiological classification and clinical significance. Non-diphtheriae *Corynebacterium* spp. are normal flora bacteria in human skin and mucous membranes. When isolated from clinical specimens they cause serious infections and nosocomial outbreaks in critically ill immunocompromised patients, for example in those with end-stage cancer, hematologic malignancy, or who have prosthetic devices or stayed for prolonged periods in a hospital or nursing homes³⁻⁵. Nosocomial outbreaks, especially due to *Corynebacterium striatum*, are increasing in both industrialized and developing countries. *C. striatum* is associated with pulmonary infections, sepsis, endocarditis, meningitis, osteomyelitis, arthritis, sinusitis, skin wounds, and intrauterine infection⁶.

The ability to form biofilm plays a pivotal role in the pathogenesis of nosocomial infections, whether or not they are associated with devices. Biofilm makes it easier for opportunistic pathogens to adhere to catheters, implanted medical devices, and build multidrug resistance. Biofilm-associated infections are increasingly reported due to the growing elderly population and the use of implantable medical devices⁶⁻⁸. The aim of this study was to identify non-diphtheriae

Corynebacterium strains and the prevalence of biofilm formation and antimicrobial resistance.

MATERIAL and METHOD

The study was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects” (amended in October 2013). Informed consent was obtained from the patients who participated in the study with their clinical specimens.

In total, 126 non-diphtheriae *Corynebacterium* strains were isolated from patients’ blood cultures between January 2015 and January 2020. The strains were isolated from routine clinical samples of inpatients with bacteremia in intensive care units and in other departments of İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine Hospital. Only patients with at least two positive blood cultures were included. *Corynebacterium diphtheriae* and contaminated strains were excluded.

Blood cultures of 8-10 mL samples obtained from each patient were inoculated into BD BACTEC vials and incubated in the Bactec 9120 (Becton Dickinson, MD, USA) automated blood culture system. When Gram-positive pleomorphic bacilli were seen, colonies were identified using the matrix-assisted laser desorption/ionization time-of-flight method with MALDI-TOF MS (Bruker Daltonics, Germany). Antimicrobial susceptibilities were determined by the Kirby-Bauer disk diffusion method on Mueller-Hinton agar and evaluated according to the criteria of EUCAST (The European Committee on Antimicrobial Susceptibility Testing)⁹.

To qualitatively assess biofilm formation, we used the Congo Red Agar method following Ramos et al.¹⁰ (2019). Black colonies were considered strong biofilm producers and red colonies as non-biofilm producers.

RESULTS

Eighty-two (65%) patients were from internal medicine wards, and 44 (35%) were from intensive care units (ICUs; Table 1).

Among non-diphtheriae *Corynebacterium* strains, *Corynebacterium striatum* was the most prevalent isolate (n:29; 23.01%), followed by *C. matruchotii* (n:26; 20.63%), *C. afermentans* (n:18; 14.28%), *C. jeikeium* (n:15; 11.9%), *C. amycolatum* (n:12; 9.52%), *C. mucifaciens* (n:6; 4.76%), *C. kutscheri* (n:5; 3.96%), *C. pseudodiphtheriticum* (n:3; 2.38%), *C. xerosis* (n:3; 2.38%), *C. imitans 1* (n:2; 59%), *C. minutissimum* (n:2; 1.59%), and *C. singulare*, *C. aguaticum*, *C. aurimucosum*, *C. propinquum*, *C. bovis* (for each n:1; 0.8%).

Biofilm formation by non-diphtheriae *Corynebacterium* strains were determined as 50.8%. Biofilm production was detected in 62.06% (18/29) of *C. striatum*, in 53.8% (14/26) of *C. matruchotii*, in 50% (9/18) of *C. afermentans*, in 50% (6/12) of *C. amycolatum*, and in 46% (7/15)

Table 1. The distribution of the 126 non-diphtheriae *Corynebacterium* strains by hospital wards.

	2015	2016	2017	2018	2019	Total (%)
Internal Medicine	7	8	19	21	17	72 (57.1)
Pediatric Internal Medicine	1	1	5	2	1	10 (8)
Intensive Care Units	6	5	15	6	6	38 (30.1)
Pediatric Intensive Care Units	-	2	3	1	-	6 (4.8)
Total	14	16	42	30	24	126 (100)

of *C. jeikeium* strains (Table 2). *C. singulare*, *C. aguaticum*, *C. aurimucosum*, *C. propinquum*, and *C. bovis* were identified as non-biofilm producing isolates. Biofilm production rates of the

Table 2. Distribution of biofilm-forming non-diphtheria *Corynebacterium* spp.

Bofilm production	N	%
<i>C. striatum</i>	18/29	62.0
<i>C. matruchotii</i>	14/26	53.8
<i>C. afermentans</i>	9/18	50.0
<i>C. jeikeium</i>	7/15	46.0
<i>C. amycolatum</i>	6/12	50.0
<i>C. mucifaciens</i>	3/6	50.0
<i>C. kutscheri</i>	3/5	60.0
<i>C. pseudodiphtheriticum</i>	1/3	33.3
<i>C. xerosis</i>	1/3	33.3
<i>C. imitans</i>	1/2	50.0
<i>C. minutissimum</i>	1/2	50.0
<i>C. singulare</i>	0/1	-
<i>C. aguaticum</i>	0/1	-
<i>C. aurimucosum</i>	0/1	-
<i>C. propinquum</i>	0/1	-
<i>C. bovis</i>	0/1	-
Total	64/126	50.8

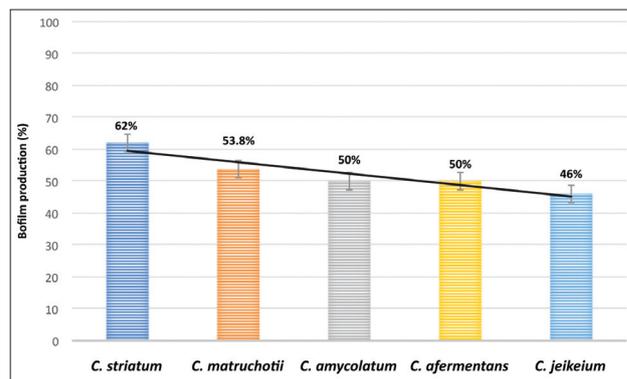


Figure 1. Biofilm production rates of top-five prevalent strains in the study.

Table 3. Distribution of antimicrobial resistance among non-diphtheriae *Corynebacterium* strains by years.

	2015		2016		2017		2018		2019		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Penicillin	11/14	78.5	14/16	87.5	39/42	92.8	28/30	93.3	23/24	95.8	115/126	91.2
Clindamycin	11/14	78.5	13/16	81.2	39/42	92.8	27/30	90	20/24	83.3	110/126	87.3
Ciprofloxacin	9/14	64.2	12/16	75	35/42	83.3	26/30	86.6	20/24	83.3	100/126	79.3
Rifampicin	9/14	64.2	10/16	62.5	23/42	54.7	18/30	60	11/24	45.8	71/126	56.3
Gentamicin	6/14	42.8	6/16	37.5	19/42	45.2	14/30	46.6	12/24	50	50/126	39.6
Tetracycline	4/14	28.5	6/16	37.5	19/42	45.2	14/30	46.6	11/24	45.8	57/126	45.2
Linezolid	0/14	0	0/16	0	0/42	0	0/30	0	0/24	0	0/126	0
Vancomycin	0/14	0	0/16	0	0/42	0	0/30	0	0/24	0	0/126	0

five most prevalent strains (more than 10 isolates) are shown in Figure 1. Among these strains, we found a high biofilm forming rate of 54%.

The resistance rates to penicillin, clindamycin, ciprofloxacin, rifampicin, tetracycline, and gentamicin were 91.2%, 87.3%, 79.3%, 56.3%, 45.2%, and 39.6%, respectively. All 126 strains were susceptible to vancomycin and linezolid (Table 3). According to our results, there is an increasing rate of resistance to clindamycin, ciprofloxacin, rifampicin, gentamicin, tetracycline, and especially penicillin (Figure 2).

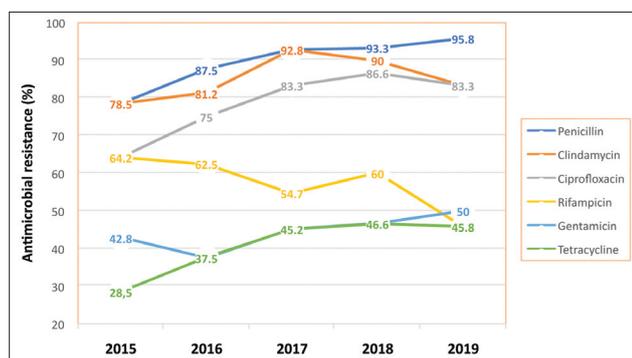


Figure 2. Trends of antimicrobial resistance to penicillin, clindamycin, ciprofloxacin, rifampicin, gentamicin, and tetracycline between 2015-2019.

DISCUSSION

Corynebacterium spp. are common in the environment and as part of the normal skin flora and mucous membranes. The pathogenic potential of coryneform bacteria has long been underestimated. Long considered as a contaminant, they were ignored as a cause of infection when isolated from clinical specimens in microbiology laboratories¹¹. However, owing to the increasing number of immunocompromised patients, *Corynebacterium* spp., which are usually found as opportunistic pathogens in patients with immune deficiency, have become clinically relevant. In recent years, various non-diphtheriae *Corynebacterium* spp. have been increasingly reported to be infectious agents in inpatients and have caused outbreaks in ICUs^{3,5,10}. Yoldas et

al.¹² showed that more than 10% of the microbial growth in clinical cultures were Gram-positive bacteria cultured from ICU patients.

Recent studies have increasingly reported that the following strains are important causes of infection: *C. striatum*, *C. jeikeum*, *C. amycolatum*, *C. urealyticum*, *C. afermentans*, *C. ulcerans*, *C. minutissimum*, *C. propinquum*, and *C. pseudodiphtheriticum*³. Studies investigating various clinical specimens have indicated that between 44% and 71% of patients with *Corynebacterium* bacteremia have true infections¹³⁻¹⁵. When coryneform bacteria are isolated from sterile samples such as blood, it is difficult for microbiologists to identify their clinical significance¹¹.

However, the lack of single definition of true infection and contamination hinders accurate conclusions regarding the incidence of true *Corynebacterium* infections¹⁵. For diagnosing true infection, some researchers use only one bacteriological criterion based on the presence of two or more positive blood cultures, while many studies have reported that time to positivity can be used to distinguish between contamination and bacteremia^{13,14,16-18}. Zhang et al.¹⁶ reported that the time to positivity was <36 h in 98% of bacteremia caused by Gram-positive bacteria. In the present study, positivity was detected within 24 h for all bacteremia cases. In other studies, patients' clinical conditions were taken into consideration and intravascular catheters were accepted as risk factors for true *Corynebacterium* infection^{15,19,20}.

In the present study, non-diphtheriae *Corynebacterium* strains that grew in the blood cultures between 2015-2020 (with at least two positive blood cultures) were included if they were compatible with the patients' clinical features. The most common isolated strain was *C. striatum* (23%) followed by *C. matruchotii* (21%).

C. striatum strains are rarely isolated from the blood, however they have often been reported as a cause of catheter-associated bloodstream infections and endocarditis^{3,4,21,22}. In the present study, we saw that our strains were isolated mainly from samples sent from internal medicine and ICUs.

Although opportunistic infections caused by these microorganisms are mostly endogenous, epidemiological studies have revealed that bacterial transition from patient to patient is possible in ICUs. Hospital staffs play an important role as carriers with their contaminated hands in this transition, according to some studies^{11,21}.

A retrospective study conducted by Yanai et al.¹⁴ demonstrated that *C. striatum* was the most common strain detected in bacteremia patients and infections of more than 50% of bacteremic patients were catheter-associated. This route of infection has been reported in many studies^{18,23,24}.

Forty-four (35%) strains were isolated from inpatients who used catheters or other foreign bodies in ICUs. Traditionally, skin commensal bacteria have relatively low virulence. However, biofilm-forming ability can be a high-virulence factor for multidrug-resistant *C. striatum*. Previous studies reported that *C. striatum* causes nosocomial outbreaks associated with biofilm formation^{4,8}.

During a nosocomial outbreak in a hospital in Rio de Janeiro, Brazil, the ability of various clones of multidrug-resistant and multidrug-sensitive *C. striatum* strains to form biofilm on the surfaces of foreign materials was investigated. The *C. striatum* type I-multidrug-resistant strain was shown to have the greatest ability to adhere to biotic and abiotic surfaces. This clarified the relationship between biofilm-forming ability, antimicrobial multi-resistance, and clonality^{6,10}. All isolates were multidrug-resistant. Since biofilm-forming isolates are limited, we could not assess it statistically.

Biofilm production in non-diphtheriae *Corynebacterium* strains isolated in blood cultures was first reported by Qin et al.¹⁹. To the best of our knowledge, this is the first report on biofilm-forming non-diphtheriae *Corynebacterium* in blood culture isolates in Turkey. In our study, 51% of the strains were biofilm producers. Biofilm-forming ability was above average for *C. striatum* strains at a rate of 62%. Similarly, Qin et al.¹⁹ reported a biofilm production rate of 64.3% in *C. striatum* strains isolated from blood cultures in Japan.

Previously, non-diphtheriae *Corynebacterium* strains were susceptible to many antibiotics, but recent studies have reported they are multidrug-resistant. Given the increasing use of broad-spectrum antibiotics, multidrug resistance also occurs in non-diphtheriae *Corynebacterium* strains^{4,18,25}. Some studies have shown that antimicrobial resistance rates in biofilm-forming isolates were higher than in non-biofilm producers²⁶.

The present study assessed antimicrobial resistance rates over five years, which showed that strains have become more resistant to penicillin, clindamycin, ciprofloxacin, rifampicin, and tetracycline. We found the highest resistance to penicillin in 91.2%, followed by clindamycin in 87.3% of our isolates. Asgin et al.²⁵ also reported a resistance rate of 87.7% to clindamycin in 81 *C. striatum* strains in Turkey. All isolated strains were susceptible to vancomycin and linezolid. So far, no vancomycin or linezolid resistance has been reported.

The resistance rates are in line with some recent studies^{11,20}. Especially high penicillin resistance rates were detected in many studies^{4,16,19}. In both present and previous reports, vancomycin has been proposed as an empirical therapy for severe infections caused by non-diphtheriae-*Corynebacterium* species^{3,11}. However, the management of antimicrobial treatment for these infections is still fraught with controversies. In

in vitro susceptibility tests have shown that linezolid and tigecycline are effective against coryneform bacteria³.

Many studies have recommended vancomycin as the first treatment option when invasive *C. striatum* infection was suspected, because none of the *Corynebacterium* strains have been reported to have in vitro resistance to vancomycin. If the patient was allergic to vancomycin, linezolid or daptomycin has been recommended^{4,11,20,27}. Successful treatment in these cases depends on long-term, high-dose antimicrobial therapy and the removal of foreign body material⁸. These results suggest that non-diphtheriae *Corynebacterium* strains from inpatients with bacteremia are multidrug-resistant and increasingly have the ability to form biofilms.

CONCLUSION

Non-diphtheriae *Corynebacterium* spp. should not be overlooked when isolated from blood cultures, as it may actually be the cause of infection, especially considering their virulent biofilm-forming abilities.

To implement advanced control strategies to reduce non-diphtheriae *Corynebacterium*-associated infections in hospitals, it is important to perform effective infection control measures focused on non-diphtheriae-*Corynebacterium* colonization. It is especially important that healthcare workers comply with hand hygiene and cleaning medical equipment and hospital surfaces with appropriate disinfectants.

Surveillance studies on non-diphtheriae *Corynebacterium* should also be performed in hospitals to increase awareness of *C. striatum* and other non-diphtheriae *Corynebacterium* that cause bloodstream infections and to prevent biofilm-related infections. The results of this study are based on a small sample, so further studies need to be done with greater number of patients.

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