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ISSN 2544-1361 (online); ISSN 2544-2406
doi: 10.15584/ejcem.2019.2.9

http://www.ejcem.ur.edu.pl/en/
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2019; 17 (2): 157–161

REVIEW PAPER

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The role of opportunistic *Corynebacterium* spp. in human infections

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ABSTRACT

Introduction. The non-diphtherial corynebacteria (diphtheroids, "coryneform" bacteria) have been increasingly recognized as causative agents of human infections.

Aim. To provide an overview of the role of non-diphtherial *Corynebacterium* species in human infections.

Material and methods. Analysis of the literature data found in the PubMed database.

Results. The role of diphtheroids - inherently low-virulent microorganisms considered members of the human microbiota – as potential pathogens has been linked to specific risk factors including immunosuppression, implantation of biomaterials and invasive medical procedures. Their pathogenic potential is primarily associated with frequent multidrug resistance, the ability to adhere to biotic and abiotic surfaces and/or to form biofilm as well as with internalization, intracellular survival and persistence within human cells. The most common infections include bacteremia, sepsis, endocarditis, meningitis, urinary tract infections, respiratory tract infections, wound and skin infections, and endophthalmitis. The leading species are *C. jeikeium*, *C. striatum, C. urealyticum, C. amycolatum,* and *C. pseudodiphtheriticum*.

Conclusion. Opportunistic corynebacteria can be responsible for a wide range of infections which can be expected to increase in frequency in the future due to an enlarging population of patients with predisposing risk factors but also due to the increasing problem of antibiotic resistance in this group of bacteria.

Keywords. coryneform, diphtheroids, opportunistic corynebacteria

Introduction

The non-diphtherial corynebacteria (also known as diphtheroids, or "coryneform" bacteria) have been increasingly recognized as causative agents of opportunistic and nosocomial infections within recent years.[1-7] The bacteria are considered members of the human microbiota.[5-7]

Aim

The aim of this review is to discuss the role of non-diphtherial corynebacteria as potential human pathogens.

Description of the subject literature

The review was prepared by the analysis of the literature data found in the PubMed data base using the following

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Participation of co-authors: A – Author of the concept and objectives of paper; B – collection of data; C – implementation of research; D – elaborate, analysis and interpretation of data; E – statistical analysis; F – preparation of a manuscript; G – working out the literature; H – obtaining funds

Received: 3.01.2019 | Accepted: 12.02.2019
Publication date: June 2019

Olender A, Bogut A, Bańska A. *The role of opportunistic "Corynebacterium" spp. in human infections.* Eur J Clin Exp Med. 2019;17(2):157–161. doi: 10.15584/ejcem.2019.2.9

keywords: diphtheroids, coryneform, opportunistic corynebacteria, *Corynebacterium jeikeium*, *Corynebacterium striatum, Corynebacterium amycolatum Corynebacterium minutissimum, Corynebacterium urealyticum, Corynebacterium pseudodiphtheriticum*, antibiotic resistance. This literature analysis spans the years 1990 to 2019.

Literature analysis

The role of non-diphtherial corynebacteria - inherently low-virulent microorganisms - as potential pathogens has been predominantly linked to specific risk factors. The compromise of the host immune system is considered the leading predisposing factor. Immunosuppression is observed in many patient groups including patients with the bone marrow suppression, malignancies, in transplant recipients, those who are treated with corticosteroids and in heavily antibiotic-experienced patients. The development of opportunistic infections is also favored in patients suffering from debilitation, diabetes, extensive trauma, wounds, burns, and HIV infection. Implantation of vascular grafts, prosthetic heart valves, and joint endoprosthesis also increases the risk of infection development. Invasive medical procedures posing a risk of the introduction of the skin and/or mucosal microbiota into sterile body sites are considered an additional risk factor.[4,5,8,9]

In addition to host factors, microbial determinants of pathogenicity contribute to the increasing role of diphtheroids as medically relevant microorganisms. Although the pathogenesis of non-diphtheriae *Corynebacterium* infections remains poorly understood and little is known about their virulence factors, there are several aspects linked to their increasing pathogenic potential. The leading aspect of this potential is a frequent multidrug antibiotic resistance of coryneform bacteria. The ability to adhere to biotic and abiotic surfaces and/or to form biofilms in which bacteria are protected both against antimicrobial agents and the host immune responses are also considered an important strategy promoting the involvement of bacteria in both medical devices- and tissue-associated chronic infections.[2,3,5,7,9-15] Moreover, recently, the *in vitro* pattern of adherence, internalization, intracellular survival and persistence of *C. pseudodiphtheriticum* within human epithelial cells has been demonstrated.[16]

The most frequent infections caused by opportunistic *Corynebacterium* spp. include bacteremia, sepsis, endocarditis, meningitis, urinary tract infections, respiratory tract infections, wound, skin infections and endophthalmitis (Table 1). Based on the literature data, reporting cases of bacteremia in hospitalized patients, it can be concluded that the leading species involved in the etiology are *C. jeikeium*, *C. striatum,* and *C. amycolatum*.[17-19]

Treatment of bacteremia caused by *C. jeikeium* can be problematic due to its resistance to a variety of antibiotics including beta-lactams, macrolides, licosamides, tetracycylines, aminoglycosides. Nevertheless, bacterial strains belonging to this species tend to remain sensitive to vancomycin. Satisfactory therapeutic effects have also been observed following administration of daptomycin – a novel lipopeptide antibiotic, although daptomycin-resistant strains have already been identified.[20]

Bacteremia is also important in the development of infective endocarditis. Clinical manifestations of endocarditis caused by diphtheroids initially can be of low specificity and follow a chronic course. *C. jeikeium* is a species which deserves special attention when prosthetic valve endocarditis is concerned. In cases analyzed, the period between the onset of symptoms and the diagnosis of infectious endocarditis (defined as subacute) usually ranged between 1 to 3 months. In early endocarditis, in turn, the symptoms developed in more than half of the patients within 60 days after the prosthetic valve implantation; the mortality rate was 38%, whereas late endocarditis was associated with a mortality rate of 33%.[21]

C. striatum is another species involved in the etiology of prosthetic valve endocarditis. A long hospital stay has been identified as an important risk factor for the development of this type of infection. The association between placement of prosthetic valves and the isolation of *C. striatum* from the site of the infection was observed for 50% of analyzed patients. [22] Another important issue associated with endocarditis of this etiology, was the development of embolism in up to one third of patients.[1]

C. amycolatum can also be involved in the etiology of bacteremia and infective endocarditis. Due to a frequent multidrug resistance of this species, import information on the effective treatment is presented in the case report in which daptomycin was combined with rifampicin.[23]

Table 1. The most common sites of human infections caused by the opportunistic *Corynebacterium* species

Sites of infection	***Corynebacterium*** **species**
– bacteremia – endocarditis – infections with different locations	*C. jeikeium* *C. striatum* *C. amycolatum*
– urinary tract – infections with different locations	*C. urealyticum*
– respiratory tract – infections with different locations	*C. pseudodiphtheriticum*
– skin – infections with different locations	*C. minutissimum*

C. minutissimum is the frequent causative agent of life-threatening infections associated with bacteremia in neutropenic, HIV- infected patients, transplant recipients or in patients suffering from malignancies. Infections caused by this species can be invasive, and present as meningitis, glomerulonephritis, or cellulitis. In analyzed cases the portals of entry were most probably central venous catheters, peritoneal dialysis, hemodialysis. Most infected patients were effectively treated with vancomycin.[24,25]

C. coyleae, represents a diphtheroid species linked to bacteremia in immunocompromied patients; it is frequently isolated from the bloodstream of hospitalized patients. The predominant types of infections caused by this species include cellulitis, bacteriemia in adults and neonates, sepsis. *C. coyleae* strains can demonstrate MLS_B resistance phenotype (macrolide-lincosamides-group B streptogramins), conferred by the *ermX* gene.[26]

It should be noted that diphtheroid species identification is nowadays facilitated by molecular methods. Their implementation in the microbiological diagnostics allowed to identify new *Corynebacterium* species, mainly isolated from the blood and exemplified by *C. tuscaniae, C. ureicelerivorans, C. timonensez, C. falsenii,* and *C. musteale*.[27-31]

Opportunistic *Corynebacterium* ssp. can also be involved in the etiology of urinary tract infections (UTIs). The predominant species is a lipophilic *C. urealyticum* associated with UTIs in immunocompromised patients, patients who underwent urological procedures or those with previous episodes of UTIs. Infections caused by *C. urealyticum* are usually diagnosed in the hospital setting and it is assumed that they have an association with the previous colonization of the skin. Important hallmarks facilitating the recognition of this etiologic agent of UTI include the presence of the magnesium-ammonium phosphate (struvite) crystals in the urine which contribute to the formation of renal stones and alkaline urine pH resulting from the profuse production of bacterial urease.[32-35]

Large amounts of the produced struvite crystals can be deposited on the wall of the bladder which can subsequently lead to the development of encrusting cystitis which frequently follows a chronic course, and is associated with interference in urine flow, dysuria, suprapubic and flank pain, and hematuria. Fever develops only in 25-50% of infected patients. The diagnosis is based on the examination of area and thickness of calcifications on the surface of the bladder mucosa. In reported cases, infected patients had been previously subjected to the diagnostic or therapeutic urinary procedures which facilitated transmission of *C. urealyticum* for the skin. The encrusting cystitis or pyelonephritis were recognized between 5 days and 3 years after the aforementioned urological procedure.[31,35]

C. urealyticum can demonstrate different antibiotic resistance profiles including multidrug resistance. Nevertheless, it is commonly sensitive to vancomycin and teicoplanin which is effectively used in the treatment of infections caused by this species.[34,35]

Respiratory tract infections (RTIs) are most commonly caused by *C. pseudodiphtheriticum* – a member of the normal microbiota of the human nasopharynx. It tends to cause RTIs in immunocompromised patients and in cystic fibrosis patients. It can also cause nosocomial infections in patients with tracheal intubation. In the reported cases of infections caused by *C. pseudodiphtheriticum* particular attention has been drawn to the predisposing factors including congestive heart failure, chronic renal insufficiency, diabetes, malignancy, obstructive pneumonia, previous infection with *Chlamydia pneumoniae*. In one thirds of infected patients the diphtheroid infection was accompanied by the rise in the body temperature > 37°C and an acute course. *C. pseudodiphtheriticum* has been isolated from the sputum but not from the bloodstream.[37,38]

The second most frequent diphtheroid species involved in the etiology of RTIs, especially in the hospitalized patients, undergoing long courses of antibiotic therapy, is *C. striatum*. This species includes 14 genotypes. Strains representing types A, D, and E have been predominantly associated with hospital-acquired infections. Subtypes A1, A2, D2, and E tend to be resistant to erythromycin, tetracycylines, rifampicin, ciprofloxacin, and they present a varied degree of resistance against beta-lactams and aminoglycosides. Similarly to other diphtheroid species, in turn, *C. striatum* remains sensitive to vancomycin. *C. striatum* is considered an important multidrug resistant pathogen which is transmitted between hospitalized patients and medical personnel. Its involvement in human infections is also frequently associated with catheterization, intubation and immunosuppression.[39,40]

It has been estimated that *Corynebacterium* species inhabiting the human skin account for more than half of microorganisms constituting the skin microbiota devoid of significant pathogenic potential. Skin infections can be caused by *C. minutissimum* – the causative agent of erythrasma. This species leads to development of scaly lesions in the axilla which can be misdiagnosed as a fungal infection. Nevertheless, this diphtheroid can also cause mixed infections along with dermatophytes and *Candida albicans*. Moreover, *C. minutissimum* can be transferred from the erythrasma foci and, particularly in immunocompromised individuals, it can lead to development of bacteremia, meningitis, endocarditis, cellulitis, or pyelonephritis.[24,41,42]

Pitted keratolysis is another example of the skin infections caused by diphtheroids. This type of infection does not involve deeper layers of the skin which was evidenced by the observation of clinical samples under the electron microscope. The presence of bacteria was

detected within keratinocytes, and granular changes of keratohyalin were associated with the proteolytic activity of bacteria. Other corynebacteria species involved in the development of skin lesions include *C. striatum* (extensive, erythema lesions with irregular edges), *C. pseudodiphtheriticum* (ulcers). The non-diphtherial corynebacteria can additionally be involved in the development of chronic wound infections.[43,44]

Implant and prosthetic joint infections are indicative of adherence capabilities of *Corynebacterium* spp. It has been reported that *C. massiliense* isolated from the synovial fluid was associated with the prothetic joint infection, whereas *C. xerosis* was involved in the etiology of the cardioverter-defibrillator implant and led to the development of bacteremia.[29,45,46]

Opportunistic corynebacteria also constitute a significant problem in ophthalmology. Literature data present cases of endophtalmitis associated with this group of bacteria.[47-50] For example, Ferrer et al. have discussed a case of postoperative *C. macginleyi* endophtalmitis. This microorganism was identified with the use of the PCR assay and the analysis of the 16rRNA gene sequence with the lack of growth in the conventional culture.[47] Quin et al., in turn, reported a case of posttrabeculectomy bleb-related infection associated with *Corynebaterium macginleyi*.[51]

Conclusions

Based on the literature, the non-diphtheria corynebacteria can be responsible for a wide range of human infections which can be expected to increase in frequency in the future due to an enlarging population of patients with predisposing risk factors but also due to the increasing problem of antibiotic resistance in this group of bacteria.

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