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Case Series

Corynebacterium spp. Pneumonia in ICU, A Case Series

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Abstract:

Background: *Corynebacterium* are a gram-positive genus of bacteria famously known for his member *C. diphtheriae*, the primary cause of diphtheria. They are part of the normal skin microbiota and mucous membranes. These well-known contaminants of clinical materials have been increasingly recognized as causing opportunistic infections. Non-diphtheria *Corynebacterium spp.* have been implicated in community-acquired, hospital-acquired and ventilator-associated pneumonia in immunocompromised patients or whose upper airways were bypassed (e.g., mechanical ventilation, tracheostomy).

Cases: Between January 2019 and March 2021, we identified a total of nine *Corynebacterium spp.* isolated in respiratory samples from seven patients.

Results: We reported three cases of ventilator-associated pneumonia (VAP), two cases of hospital-acquired pneumonia (HAP) and three colonizations. One patient had a VAP caused by two different *Corynebacterium spp*. and one patient was diagnosed with two *C. striatum* VAP during hospital stay. There were no isolations classified as infections from January 2019 until April 2020, prior to COVID-19 pandemic: all infections reported were diagnosed in patients admitted for SARS-CoV-2 pneumonia.

***Keywords:** Corynebacterium, ICU, pneumonia, COVID-19*

Introduction

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are two of the most common hospital-acquired infections in critically ill patients[1]. The pathogenesis and etiology depend on the host immune response, being the primary route of infection, microaspiration[2]. Common pathogens may differ from community-acquired[1] but prevalence of certain pathogens may be underestimated because special culture techniques are required to identify them.

Progress in medicine has resulted in the growth of the immunocompromised population. Besides the common pathogens, these patients are also at risk for opportunistic and multi-drug resistance pathogens[14].

Corynebacterium spp. are prominent contaminants of clinical materials, although occasionally relevance is hard to evaluate[3,4]. They are increasingly being recognized as opportunistic agents in immunocompromised or long-term hospitalized patients [3].

The present case series describes all *Corynebacterium* identifications made between January 2019 and March 2021 in a Portuguese Intensive Care Unit (ICU).

Cases

Demographics, primary evaluation, and microbiological isolations are summarized in Table 1.

Table 1 – Demographics, primary evaluation, and microbiological isolations of the cases.

Demographics			Admission			Corynebacterium Isolation		
Case No Date	Age| Gender	Relevant medical history	Admission diagnosis	Organ dysfunction at admission	Inflammatory markers at admission	Isolated agent	Other exams	Evolution
1 Apr 2019	44 F	SLE, APS, TMA, CKD-HD Chronic antimalarial and corticosteroid therapy	Haemorrhagic Stroke	Previous renal and hematologic dysfunctions. Neurologic dysfunction compromising respiratory and cardiovascular failure. APACHE II 20; SAPS II 64 IMV 17days (Tracheostomy D12)	WBC 3.70x10^9/L (89.7%N, 6.5%L), C-RP 0.19mg/dL	D15 (D15 IMV) bronchoalveolar lavage	D15: WBC 0.7x10^9/L /45.7%N, 27.1% L)	Assumed VAP by S. maltophila. Treated with Ceftazidime. C. striatum discarded as colonizing.
2 Nov 2019	82 F	T2D, HTN, PAD	Ischemic Stroke	Neurologic dysfunction compromising respiratory failure. APACHE II 24; SAPS II 51 IMV 9 days	WBC 13x10^9/L (6.3%L, 86.9% N), C-RP 0.45mg/dL	D4 (D4 IMV) Tracheal Aspirate	D4: WBC 9.7x10^9/L (76.4%N, 12.9%L), C-PR 28.1mg/dL,	Clinical resolution without antimicrobial therapy. Assumed colonization + central fever.
3 Apr 2020	76 M	T2D, CKD-HD	SARS-CoV-2 Pneumonia	Previous renal dysfunction. Septic Shock: Cardiovascular, renal and respiratory dysfunction. APACHE II 27; SAPS II 55 IMV 20 days	WBC 7.8x10^9/L (84.7%N, 9.4%L) C-RP 14.3mg/dL, PCT 0.61ng/mL	D12 (D12 IMV) bronchoalveolar lavage	D12: WBC 12.5x10^9/L (85.0%N, 7.0% L).	Assumed C. striatum VAP. Medicated with Vancomycin. Clinical deterioration resulting in death at D 20.
4 Jan 2021	82 F	HTN, RA, Hypothyroidism chronic corticosteroid therapy	SARS-CoV-2 Pneumonia	Septic shock: Cardiovascular, neurologic, renal and respiratory dysfunction. APACHE II 17; SAPS II 53 IMV 7days	WBC 6.0x10^9/L (80.3%N, 12.8%L), C-RP 19.2mg/dl	D4 (D1 IMV) bronchoalveolar lavage	D4: WBC 20.9x10^9/L (91.1%N, 4.0% L). C-RP 29.0mg/dL (D4 0.48mg/dL),	Assumed HAP by C. propinquum. Directed therapy with piperacillin-tazobactam with clinical resolution.
5 Jan 2021	69 M	HTN Ischemic and valvular cardiopathy, HTN, CKD, T2D, Chronic AF	SARS-CoV-2 Pneumonia	Sepsis: Respiratory dysfunction. APACHE II 17, SAPS II 40 IMV 16 days	WBC 14.5x10^9/L (49.8%N, 47.8%L), C-RP 37.2mg/dL, PCT 0.6ng/mL	D8 (D7 IMV) bronchoalveolar lavage	D8: WBC 21.7x10^9/L (54.2%N, 43.0% L), C-RP 30.1mg/dL	Assumed VAP by H. Influenza. Directed therapy with Ampicilin with clinical resolution. C. pseudodiphtherticum discarded.
6 Jan 2021	77 M	Ischemic and valvular cardiopathy, HTN, CKD, T2D, Chronic AF Admitted for Salmonellosis.	Nosocomial SARS-CoV-2 Pneumonia	Previous renal dysfunction. Sepsis: Respiratory dysfunction. APACHE II 14, SAPS II 36 IMV 26days + 7days (reintubation) + 9days (reintubation)	WBC 5.6x10^9/L (86.2%N, 6.7%L), C-RP 9.2mg/dL, PCT 0.07ng/mL	D14 (D3 IMV) bronchoalveolar lavage D42 (D1 IMV)	D14: WBC 7.7x10^9/L (85.2%N, 8.0% L), C-RP 15.1mg/dl, PCT 0.12ng/mL D42: WBC 9.4x10^9/L (78.9%N, 10.6%L),	Assumed VAP by C. striatum, treated with 7- day course vancomycin. Reintubated due to aspiration pneumonia with C. striatum and S. cholerasusis isolated. Treated with Linezolide and Ampicilin.
7 Feb 2021	71 F	Depressive syndrome	SARS-CoV-2 Pneumonia	Sepsis: Respiratory dysfunction. ICU admission at D3 APACHE II 15, SAPS II 37 IMV 24days	WBC 8.3x10^9/L (88.8%N, 5.8%L),C-RP 11.7mg/dl, PCT 0.12ng/mL	D11 (D6 IMV) Tracheal Aspirate	D11: WBC 9.7x10^9/L (76.4%N, 13.0%L),	Assumed VAP by C. accolens + C. pseudodiphteriticu m, treated with Vancomycin.

Abbreviations: Past medical history: APS – antiphospholipid syndrome, CKD-HD –chronic kidney disease under haemodialysis, HTN – Arterial Hypertension, ITP – immune thrombocytopenia, T2D – Type 2 diabetes, TMA – Thrombotic microangiopathy, SLE – Systemic Lupus Erythematosus.

Organ dysfunctions: APACHE II - Acute Physiology And Chronic Health Evaluation II , SAPS II - Simplified Acute Physiology Score II, D – Hospital day, IMV – Invasive mechanical ventilation,

Lab: WBC – white blood count, N – neutrophils, L - lymphocytes, C-RP – C-reactive protein, PCT – procalcitonin.

Demographics

Nine *Corynebacterium spp.* were isolated in seven patients during a period of 27 months. One patient had two different *Corynebacterium spp*. isolated in a single tracheal aspirate (C. accolens and C. pseudodiphtheriticum) and in one patient, C. striatum was isolated twice from bronchoalveolar lavages separated by a adequate 7-day antibiotic course. The mean age was 71 years, and four patients were female.

Admission

All patients included before 2020 (2 patients) were hospitalized due to an acute cerebrovascular event and after (7 patients), due to SARS-CoV-2 pneumonia. Two patients were admitted from the internal medicine ward: one patient was admitted for SARS-CoV-2 pneumonia and transferred due to worsen respiratory insufficiency; one patient was admitted for Salmonellosis and contracted SARS-CoV-2 during hospitalization. All patients required invasive mechanical ventilation and three required renal replacement therapy (including two patients with previous renal disease).

ICU mortality scores (SOFA, APACHE II, SAPS II) were calculated and registered in table 1. Three patients had a SOFA score ≤6, three patients had a score ≥7 and ≤9 and one patient had a score ≥10 and ≤12. Two patients died during hospital stay.

Risk Factors

Known risk factors including malnutrition or concomitant immunosuppressive drug use were present at admission in two patients but, all except one, had lymphopenia at day 1. Chronic kidney disease was described in three patients.

All samples were collected after >72hrs of hospital stay and all were under mechanical ventilation at the time of sampling. One patient had a tracheostomy.

Corynebacterium Isolation

All pathogens were identified in respiratory tract samples: six in bronchoalveolar lavages and three in tracheal aspirates.

Polymicrobial isolation was present in four samples (*S*. maltophila, H. parainfluenza, S. cholerasuis and another Corynebacterium). No Corynebacterium were isolated in blood cultures.

Three Corynebacterium were classified as colonizers: in two patients, infection was attributed to another pathogen and in another patient, sepsis was discarded.

Two patients were diagnosed with HAP due to *Corynebacterium spp.,* both with <48h of mechanical ventilation, and three patients with VAP. One patient had two VAP episodes due to C. striatum: in the first episode C. striatum was isolated and treated with vancomycin, the patient improved and was extubated, but later he deteriorated, and aspiration was suspected; reintubation was performed and C. striatum was isolated again alongside with *S. cholerasuis*.

Antimicrobial susceptibility is expressed in Table 2.

Discussion

An increasingly number of *Corynebacterium spp*. identification has been reported in our ICU. Through a retrospective analysis we identified two cases in 2019, a single case in 2020, but six isolations in the first three months of 2021, including all five reported pneumonias.

Corynebacterium spp. are gram-positive, facultative anaerobic, facultative intracellular bacteria. They are pleomorphic throughout their life cycle and may have “club-shaped” thickenings, giving it the “coryneform” denomination.

According to the List of Prokaryotic Names Validly Published, a total of 125 Corynebacterium species have been identified[6]. C. diphtheriae, the primary cause of diphtheria, remains well known although it essentially disappeared form developed countries due to universal vaccination. C. ulcerans and C. pseudotuberculosis are also capable of producing diphtheria toxin and have been implicated in diphtheria-like disease[3].

Table 2 – Antimicrobial susceptibility patterns of isolated spp.

Case no	Agent	Sensitivity	Classification
1	C. striatum	Resistant to tetracyclines, fluroquinolones, aminoglycosides, penicillins. Sensible to Vancomycin	Colonizing agent
2	C. propinquum	Sensible to tetracyclines and penicilins, resistant to aminoglycosides	Colonizing agent
3	C. striatum	Resistant to tetracyclines, fluroquinolones, aminoglycosides, penicillins. Sensible to Vancomycin	VAP
4	C. propinquum	Sensible to tetracyclines and penicilins, resistant to aminoglycosides	HAP
5	C. pseudodiphtheriticum	Sensible to tetracyclines, resistant to aminoglycosides and penicilins	Colonizing agent
6	C. striatum	Resistant to tetracyclines, fluroquinolones, aminoglycosides, penicillins. Sensible to Vancomycin	VAP
7	C. striatum	Resistant to tetracyclines, fluroquinolones, aminoglycosides, penicillins. Sensible to Vancomycin	HAP
8	C. pseudodiphtheriticum	Sensible to tetracyclines, resistant to aminoglycosides and penicilins	VAP
9	C. accolens	Sensible to tetracyclines and penicilins, resistant to aminoglycosides	VAP

Non-diphtheria agents, collectively referred to as diphtheroids, are usually found as normal microbiota of skin, mucosae membranes and respiratory tract. Among this group, a growing number of species have been identified as responsible for opportunistic and nosocomial infections[3,4,5].

Non-diphtheria Corynebacterium spp. have been implied in community-acquired, hospital-acquired, and ventilator-associated pneumonia. Yang et al. reported that the great majority of the cases had occurred in patients whose upper airways were bypassed (eg. ventilated patients, laryngectomy, tracheostomy), with impaired airway clearance (COPD, cystic fibrosis), or with an immunocompromising status. The presentation associated did not differ from other bacterial pneumonia[5].

All Corynebacterial pneumonia diagnosis were made in patients previously infected by SARS- CoV-2, which has been implicated with higher rates of VAP as compared to patients with influenza and no viral infection[11]. All patients had their airways bypassed as congruent with Yang et al. and known immunocompromising factors were present in 5 patients (71.4%).

Lymphopenia was present in 6 patients and has been associated with increased risk of ICU-acquired infection and mortality in hypotensive patients[13]. However, it has also been associated with severe COVID-19 and no extrapolation can be made regarding lymphopenia and the risk for Corynebacterial pneumonia.

Four species were isolated in samples from our patients: C. pseudodiphtheriticum, C. striatum, C. propinquum and C. accolens. The most commonly Corynebacterium implicated in pneumonia described in the literature is C. pseudodiphtheriticum[5,7]. It has an ability to aggregate, form biolfims and to survive intracellularly avoiding the innate immune system[7]. In our series, C. pseudodiphtheriticum was only implicated in a minority of infections (20%).

C. striatum has emerged as multidrug-resistant pathogen among patients with significant underlying disease, including CKD. It is commonly co-isolated with S. aureus, coagulase-negative staphylococci and P. aeruginosa[8]. C. striatum was the most common organism isolated in our patients, all with previous known CKD.

C. propinquum is an emerging organism responsible for respiratory tract infection in hospitalized or immunosuppressed patients with underlying respiratory disease[9].

C. accolens, is a common benign nasal bacterium, shown to inhibits growth of S. pneumoniae in children[10].
Correct phenotypic identification of diphtheroid agents remains routinely problematic and identification with commercial systems is limited to species included into appropriate databases. However, correct identification is important for treatment purposes and toxin testing[3,4].

All reported agents were identified through matrix-assisted laser desorption ionization–time of flight analysis (MALDI-TOF). In all patients we performed blood cultures at the same time of respiratory tract sampling and all were negative. Accordingly, to Yang et al., only 7.5% of the patients with Corynebacterial pneumonia have been found to have positive blood cultures., suggesting that blood cultures may be of minimal utility for confirming any respiratory tract findings[5]. The prognostic utility of positive blood cultures is not known.

Many medically relevant species, including agents responsible for respiratory, urinary and catheter-related infections have been found to be resistant to multiple antibiotic classes and occasionally fatal, particularly in immunocompromised patients. According to the European Society of Clinical microbiology and infectious diseases (EUCAST), most Corynebacterium spp. have expressed resistance to penicillin and cephalosporins, and some strains to tetracyclines and fluroquinolones.

According to Olender, A.. 20% of strains causing infections are multidrug resistant, remaining susceptible to vancomycin, the drug of choice for invasive Corynebacterium infections[12].
Antibiotic susceptibility test (table 2) was routinely performed in all isolations: In our series, 4 agents were multidrug-resistant, accounting for 44% of strains isolated.

Comparing with Yang's series, we reported more multi-drug resistant strains, including isolated C. pseudodiphtheriticum and C. striatum. Sensitivity to vancomycin in vitro was universal in both series, although in one of our patients, C. striatum was re-isolated after a vancomycin 7-day course. There is no accepted duration of treatment.

Conclusion

An increased number of Corynebacterium pneumonia has been identified in our ICU during the COVID-19 pandemic in immunocompromised and ventilated patients. Pathogens included multiple Corynebacterium spp. usually discarded as contaminants, being C. striatum the most common isolated pathogen in our series. Antibiotic susceptibility also varies from other studies, with an increased number of multidrug resistance agents.

Conflict of Interest

The authors have no conflicts of interest to declare.

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