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Multiresistance and endemic status of *Corynebacterium striatum* associated with nosocomial infections: A critical situation in ICU and varied wards of a tertiary care hospital, Rio de Janeiro metropolitan area, Brazil

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Abstract

Nowadays, *Corynebacterium striatum* has been reported as etiologic agent of mild to severe hospital-acquired infections, including patients undergoing endotracheal intubation with fatal outcome. A continuous survey of infections due multidrug-resistant (MDR) *C. striatum* in South American countries remains necessary. This retrospective and prospective study aimed to analyze clinical-microbiological features of *C. striatum* clinical isolates from patients attended at a Brazilian tertiary care hospital, during a nine-year period. *C. striatum* strains (n=130) were isolated from infected patients attended at twenty nosocomial wards, mainly of tracheal aspirate (n=53) and blood and/or intravenous catheter (n=21/n=13). Notably, original cases of nosocomial infections due to *C. striatum* were verified in children making use of invasive devices, including one fatal neonatal case, in addition to a fatal respiratory infection in patient with cystic fibrosis, as well as urinary tract infections of kidney transplant recipients. Most of *C. striatum* strains expressed MDR profiles (88.46%). Emergence of vancomycin (1.90%) and linezolid (7.41%) resistance was verified among MDR and non-MDR-strains. In conclusion, endemic condition with wide dissemination among hospital wards of varied types of infections due to MDR and non-MDR *C. striatum* strains expressing heterogenic virulence potential and genetic features may occur in hospital units.

Keywords: *Corynebacterium striatum*; Multidrug resistance; nosocomial infections; virulence; endemic.

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Introduction

Currently, a growing number of reports have demonstrated *Corynebacterium* spp. as etiologic agents of a variety of infectious processes in both immunocompromised and immunocompetent patients. At least fifty *Corynebacterium* species have been recognized of medical, veterinary, or biotechnological relevance, including diphtheria toxin (DT)-producing *Corynebacterium diphtheriae, Corynebacterium ulcerans, Corynebacterium pseudotuberculosis, Corynebacterium belfanti* and non-DT-producing *Corynebacterium* spp. participants of human microbiota.[1-3] The increasing number of reports concerning infections related to different and new *Corynebacterium* species were favored by genotyping and taxonomy studies, laboratorial identification techniques, and/or immunocompromised patients survival conditions.[4-6] Although, diphtheria vaccination programs have been implemented in many countries, diphtheria outbreaks, atypical cases of diphtheria, and cases of invasive infections, including immunized individuals caused by DT-producing and non-DT-producing *C. diphtheriae* and *C. ulcerans* zoonotic pathogen have been reported, including Brazil.[6,7] Consequently, microbiologists must not promptly discard colonies of irregular Gram-positive rods (IGPRs) from cultures, even when grown associated with one or more poten-

tially pathogenic clinical isolate, especially in cases of infections in tropical and/or developing countries.[1,6,8,9]

Corynebacterium striatum was firstly considered as part of the skin and mucous membranes of healthy normal persons unable of causing disease. However, further studies have increasingly recognized *C. striatum* as etiologic agent of a variety types of infections that can range from mild signs and symptoms to severe illness and even death of patients. *C. striatum* expressing multidrug-resistant (MDR) profiles have been also related to nosocomial infections and outbreaks in different countries, especially in long-term hospitalized patients with prolonged exposure to broad-spectrum antibiotics and admitted in intensive care units (ICUs) or surgical wards using continuous or prolonged medical devices and respiratory recuperation.[4,10,11] An increasing number of studies demonstrated variations in clinical sites among patients with *C. striatum* infections: bacteremia, sepsis and catheter-related infections,[4,12] endocarditis, meningitis,[13,14] septic arthritis,[15] osteomyelitis[16] and pulmonary infections.[4,12] *C. striatum* strains have also been identified as etiologic agents of breast abscesses,[6] skin lesions and surgical wounds,[17] urinary tract and intrauterine infections[18] including patients affected by AIDS and cancer.[6]

Multidrug-resistant (MDR) *C. striatum* strains have been increasingly reported as pathogens of nosocomial infections and outbreaks in different continents of industrialized and developing countries, including China, Japan, United States, Canada, Belgium, Italy, Spain, Tunisia, and Brazil.[19,20] During the year 2009, a nosocomial outbreak caused by *C. striatum* strains was initially verified in a Brazilian university hospital located at Rio de Janeiro metropolitan area.[1] Pulsed field gel electrophoresis (PFGE) analysis indicated the presence of four profiles, including two predominant and related MDR clones (PFGE-types I and II) that were mainly isolated from patients undergoing endotracheal intubation procedures from ICUs and surgical wards. Subsequently, cases of bloodstream and catheter-related infections caused by *C. striatum* isolates were progressively certified.[21]

Therefore, investigation of clinical, epidemiological, and microbiological features of nosocomial infections caused by *C. striatum* is necessary to prevent future problems and guarantee continued vigilance by researchers, bacteriology laboratory and medical professionals concerning community, nosocomial infections, and outbreaks due to MDR emergent pathogens.[8,9] The aim of this study was to assess the diversity, dissemination, and persistence of *C. striatum* strains isolated from patients attended in a Brazilian tertiary care hospital – located at Rio de Janeiro metropolitan area, during a nine-year period (2009-2018).

Materials and methods

Study design and origin of bacterial isolates

This retrospective and prospective investigation demonstrated and characterized the presence of *C. striatum* strains among clinical isolates recovered from patients with signs and symptoms of bacterial infections as part of medical care procedures in different wards, during a nine-year period (August 2009 – August 2018) of Hospital Universitário Pedro Ernesto (HUPE) – a tertiary care hospital of Rio de Janeiro State University – UERJ, located at the metropolitan area of Rio de Janeiro, RJ, Brazil.

Clinical strains of Irregular Gram-Positive Rods (IGPRs) were previously detected by using regular diagnostic cultures in the Bacteriology Laboratory (LABAC/UERJ) and routinely sent for further analysis in the Laboratory of Diphtheria and Corynebacteriosis of Clinical Importance (LDCIC/FCM/UERJ). All *Corynebacterium* strains were stored in Trypticase Soy Broth (TSB) with 20% glycerol at -80ºC in LDCIC collection.

Briefly, clinical strains of IGPRs were selected for further identification when cultures were grown in any quantity from normally sterile body fluid or when IGPR strains were isolated in significant numbers or in pure culture from other specimens obtained at clinical sites where infection was suspected. *Corynebacterium*-like (coryneform) colonies were selected for identification when grown in significant numbers (>15 colonies) or in pure culture from blood or catheter samples, as recommended by Maki's semi-quantitative method to distinguish infection (>15 colonies) from contamination of catheter-tips. Microorganisms were identified from the urine cultures and considered to be potential pathogens, as follows: bacterial growth $>10^4$ CFU $mL^{[-1]}$ as the only isolate; $>10^5$ CFU $mL^{[-1]}$ as the predominant isolate; $>10^3$ CFU $mL^{[-1]}$ in cases of nephropathies. Clinical samples yielding more than three organisms were regarded as contaminated and discarded in most opportunities, except in cases of urine samples of patients submitted to renal transplantation, with procedures established in accordance with LABAC and LDCIC units.[1,8]

This study was developed in compliance with the Brazilian Government's Ethical Guidelines for research

involving human beings (resolution of the National Health Council/Ministry of Health) and approved by the Research Ethics Committee of the Hospital University Pedro Ernesto of Rio de Janeiro city (CAAE 44674314.3.3001.5091). The consent to participate was not required because all the investigated *C. striatum* clinical isolates were taken as a part of standard care (diagnostic purposes) and no identifiable human data were used.

Culture conditions and identification procedures of *C. striatum* clinical isolates

Clinical isolates identified as IGPRs were inoculated onto Columbia agar base with the addition of 5% sheep's blood and incubated at 37 ºC in a 3-5% CO_2 atmosphere and monitored for 72 h. Phenotypic analysis of IGPRs clinical strains included colonial morphology, pigmentation, motility, hemolysis, lipolytic, catalase and DNase activities; CAMP reaction by using beta-lysin-producing. *Staphylococcus aureus* strain, among other screening, phenotypic and molecular procedures regularly achieved in LDCIC unit. During August 2009 – August 2018, identification and/or reidentification of *C. striatum* strains were done by phenotypic and molecular procedures, as previously described: (i) commercially available semi-automated identification API-Coryne System 3.0 (bioMérieux) with the API web decoding system (www.apiweb.biomerieux.com) (all possibility >90%); (ii) MALDI-TOF (Matrix Assisted Laser Desorption Ionization Time-Of-Flight, Bruker Daltonics™).[3] Each bacterial colony were tested in duplicate onto a 98-target plate to verify reproducibility and achieve proper identification. Identification criteria recommended by equipment manufacturer were as follows: score ≥2.000, species-level; 1.700 - 1.999, genus level ; ≤ 1.700, no identification; (iii) 16S rRNA and *rpoB* gene amplification and sequencing assays for one strain.[1,21] The 16S rRNA gene sequences were compared with National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov) using BLAST algorithm and Ribosomal Database Project (RDP-II) (http://rdp.cme.msu.edu/html). The *rpoB* gene sequences were compared at GenBank database.[1,21-23]

Antimicrobial susceptibility testing and characterization of MDR profiles

Antimicrobial susceptibility profiles were described by making use of the disk diffusion method in Mueller-Hinton agar supplemented with 5% sheep blood, according to CLSI document M20. Vancomycin susceptibility testing was interpreted in accordance with criteria defined for *Staphylococcus* spp. and *Enterococcus* spp.[24] The antimicrobial agents (Oxoid SA, Spain) tested included: penicillin (10 UI), ampicillin (30μg), cefotaxime (30 μg), imipenem (10 μg), erythromycin (15 μg), clindamycin (2 μg), gentamicin (10 μg), ciprofloxacin (5 μg), tetracycline (30 μg), rifampin (5 μg), linezolid (30 μg), vancomycin (30 μg). MDR profiles were defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[23,25]

Pulsed field gel electrophoresis assays

Thirty-seven *C. striatum* strains were previously submitted to analysis of genetic diversity by using Pulsed field gel electrophoresis (PFGE) assays, as previously described. PFGE profiles were characterized by roman numerals and subtypes were identified by roman numerals followed by a letter. The similarities were determined by Dice correlation coefficient. Similarity coefficient ≥85% were considered genetically related.[21]

Results

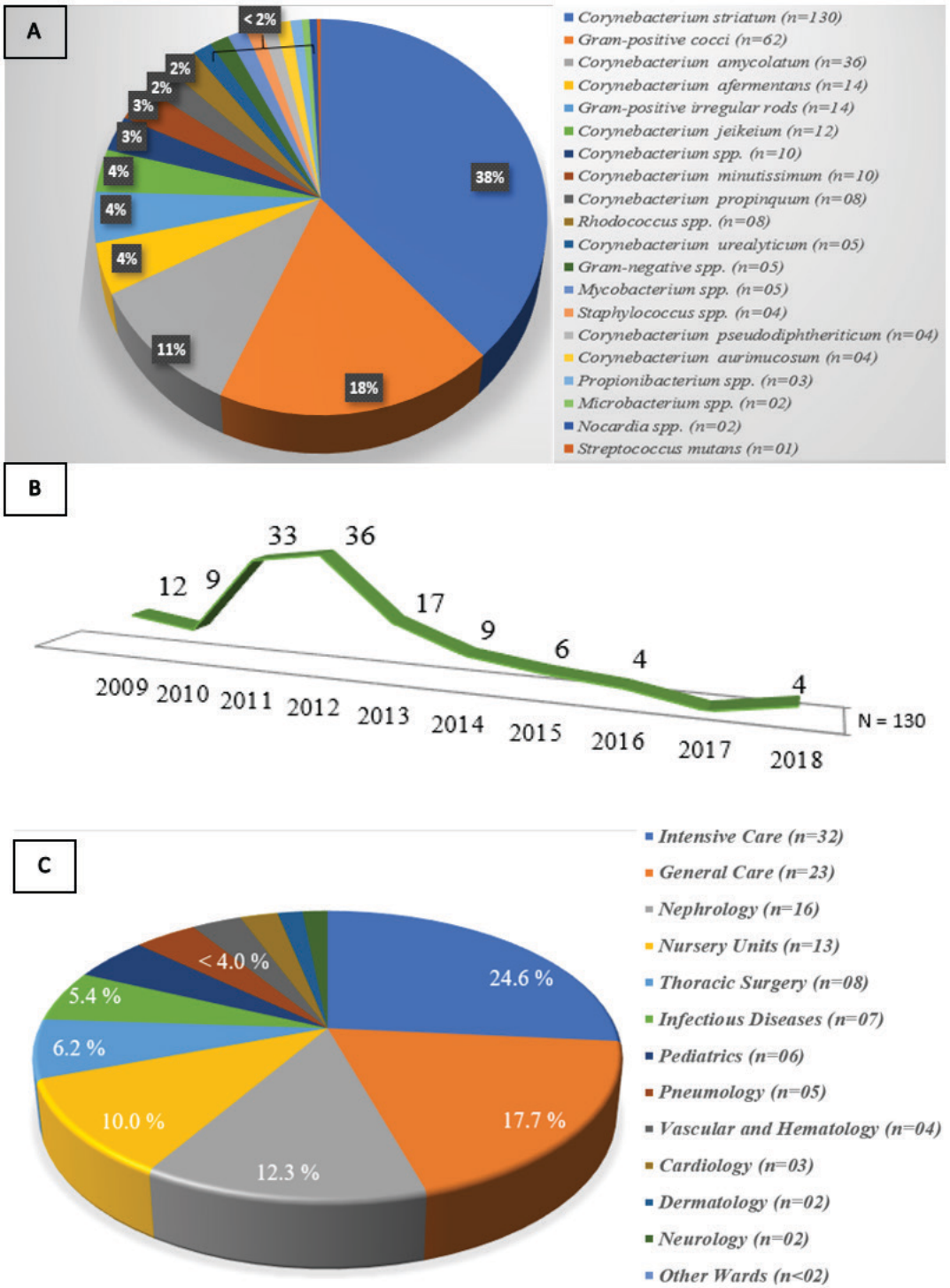
C. striatum and other *Corynebacterium* spp. isolated from clinical samples:

Corynebacterium of varied species and other Gram-positive and Gram-negative pathogens isolated from clinical samples by using routine diagnostic procedures in LABAC/UERJ and sent for further analysis in LDCIC/FCM-UERJ during and/or post nosocomial outbreak, were displayed in Figure 1. A total of 339 IGPRs strains were isolated from patients with signs and symptoms of infection as part of medical care procedures in HUPE/UERJ throughout the nine-year period of study (August 2009 - August 2018). Most of *Corynebacterium* clinical isolates were identified as *C. striatum* (n=130; 38.34%). However, other *Corynebacterium* species were isolated from clinical samples of infected patients at lower quantities (<10%), including *Corynebacterium amycolatum*, *Corynebacterium aurimucosum Corynebacterium propinquum*, *Corynebacterium afermentans*, *Corynebacterium urealyticum*, and *Corynebacterium jeikeium* (Figure 1A).

Number of *C. striatum* clinical strains isolated per year

The annual number *C. striatum* strains isolated from infected patients attended in HUPE/UERJ (August 2009 - August 2018) was displayed in Figure 1B.

Figure 1. *Corynebacterium striatum* **and other** *Corynebacterium* **spp. in addition to varied Gram-positive and Gram-negative pathogens isolated from clinical samples by using routine diagnostic procedures in LABAC/UERJ and sent for further analysis in LDCIC/FCM-UERJ during a nine-year period of study (A); number of** *C. striatum* **strains isolated from infected patients attended in HUPE/UERJ from August 2009 to August 2018 (B); and dissemination of** *C. striatum* **pathogen among hospital wards (C)**



Source: The authors (2021).

During the nosocomial outbreak (August 2009 – May 2010) *C. striatum* strains (n=15) were recovered from representative clinical sites of 14 hospitalized adult patients with signs and symptoms of bacterial infection: 50% male; age ≥50 years-old and 50% with informed fatal outcomes (n=07). Thereafter, a total of 115 *C. striatum* strains were isolated during the post-outbreak period (nine-year; May 2010 - August 2018): 2010 (n= 06), 2011 (n=33), 2012 (n=36), 2013 (n=17), 2014 (n= 09), 2015 (n=06); 2016 (n=04), 2018 (n=04). The highest number of *C. striatum* strains isolated from infected patients were detected during the years 2011 and 2012. A decrease in number of *C. striatum* clinical isolates initiated in 2013.

Dissemination of *C. striatum* pathogen among hospital wards

During the period from August 2009-August 2018, *C. striatum* strains were isolated from infected patients attended at different wards of a 600-bed university hospital, as shown in Figure 1C, Tables 1 and 2. Present study verified that 130 *C. striatum* clinical samples were isolated from patients attended over twenty distinct hospital wards, mostly ICUs (24.6%), General Care (17.7%), Nephrology (12.3%) and Nursery Units (10%). During the nosocomial outbreak period (August 2009-April 2010), *C. striatum* strains (n=15) were isolated from patients of five different hospital wards, but mostly (n = 10) from inpatients admitted to ICUs and surgical wards. Data revealed a subsequent increase of intra-hospital dissemination during the post-outbreak period in HUPE/UERJ. Interestingly, *C. striatum* strains were also related to cases of infections in Pediatric and Adolescent Care wards and neonatal ICU (n=09), and Cystic fibrosis (n=01) units.

Antimicrobial susceptibility analysis

Percentages of antimicrobial resistant *C. striatum* strains (n=130) isolated from varied clinical samples in HUPE/UERJ were shown in Figure 2A. Most of *C. striatum* clinical isolates (88.46%) from infected patients attended at different nosocomial wards expressed multidrug-resistance (MDR) profiles. *C. striatum* nosocomial clinical strains exhibited diverse resistance arrangements when tested for twelve antimicrobial agents used to treat Gram-positive infections. Higher number of resistant *C. striatum* strains were verified for clindamycin (88.75%), erythromycin (85.96%), ciprofloxacin (76.52%) and penicillin (76.52%), followed by trimethoprim-sulfamethoxazole (76.29%). *C. striatum* strains were also found resistant at lower rates to gentamicin (58.16%), rifampicin (35.40%), and tetracycline (10.38%). In the present study, emergence of linezolid-resistance (7.41%) and vancomycin-resistance (1.90%) was certified among *C. striatum* strains isolated from varied clinical sites of infected patients attended at different nosocomial wards.

Predominance and variability of PFGE-types among *C. striatum* clinical isolates

PFGE profiles presented by *C. striatum* strains isolated from different clinical specimens of infected patients attended in distinct hospital wards were shown in Table 1. Eleven PFGE profiles were verified among *C. striatum* isolates and designated I, Ia, Ib, II, V, VI, VIa, VII, VIII, IX and X. The PFGE - type I, subtypes - Ia, and Ib and PFGE - type II were previously considered genetically related, as well as PFGE - type VI and subtype - VIa: with ≥ 85% and ≥ 90% similarity coefficients, respectively. All *C. striatum* strains of PFGE-type I were characterized as MDR and found to express different MDR profiles. Interestingly, a diversity of PFGE profiles (n=10) were verified among MDR *C. striatum* strains isolated from different clinical specimens of infected patients attended in distinct hospital wards: I, Ia, Ib, II, V, VI, VIa, VII, VIII, and IX. *C. striatum* clinical isolates comprising PFGE-types III, IV, X were characterized as non-MDR.

From August 2009-April 2010, PFGE-type I was the most frequently genotypic profile observed among *C. striatum* strains isolated from infected patients (71.42%). *C. striatum* strains isolated from tracheal aspirate of patients with ventilator-associated respiratory tract infection or pneumonia were mostly of PFGE type I. *C. striatum* comprising PFGE-type I isolates were also isolated from bronchoalveolar lavage (BAL) (n = 1), cerebrospinal fluid (CSF) (n = 1), surgical wounds (n = 1), urine (n = 1) and blood (n=1) samples. Interestingly, analysis from Jan 2009-February 2013 showed that *C. striatum* strains were increasingly isolated from blood (n=13) and catheter (n=10) samples: 2009 (n = 02), 2010 (n = 04), 2011 (n = 10), 2012 (n = 06) and 2013 (n = 01). *C. striatum* comprising a diversity of genetically related and/or distinct PFGE-types (n=11) were isolated from patients with hematogenic infections: I, Ia, Ib, II; V; VI, VIa; VII; VIII; IX; X. PFGE profile I was also found predominant among patients with hematogenic infections.

Table 1. Pulsed-field gel electrophoresis retrospective analysis and clinical-microbiological features of *Corynebacterium striatum* strains (n=38) isolated from infected patients attended at the university hospital - HUPE/ UERJ, Rio de Janeiro, Brazil

PFGE-types-sub-types	Antimicrobial-resistance Profiles	Date/year	Number of strains			Clinical Samples Hospital	
			Total	Outbreak Aug 09 April 10	Post-Outbreak	Sites	Wards
I	MDR	2009, 2010, 2011, 2013, 2014	20	12	08	Tracheal aspirate, Bronchoalveolar lavage, Blood, Intravenous catheter, Cerebral spinal fluid, Urine, Surgical wound	General ICU and ICU II, Thoracic and Coronary Surgery units, General Care, Cardiology, Nephrology, Nursery, Hematology, Orthopedy, and Infectious Diseases
Ia	MDR	2011	02	-	01	Intravenous catheter	Pneumology
Ib	MDR	2012	01	-	01	Intravenous catheter	General Care
II	MDR	2009, 2012	03	02	01	Tracheal aspirate, Blood	General ICU, Thoracic Surgery, Infectious Diseases
III	Non-MDR	2009	01	01	-	Urine	Infectious Diseases
IV	Non-MDR	2009	01	01	-	Surgical wound	Thoracic Surgery
V	MDR	2010	01	-	01	Blood	Dermatology
VI	MDR	2011, 2012	03	-	03	Blood	General and Cardiac ICUs
VIa	MDR	2012	01	-	01	Intravenous catheter	General Care
VII	MDR	2011	01	01	-	Intravenous catheter	Pediatrics
VIII	MDR	2010	01	-	01	Intravenous catheter	Infectious Diseases
IX	MDR	2012	02	-	02	Blood, Intravenous catheter	Hematology, Pediatrics
X	Non-MDR	2012	01	-	01	Intravenous catheter	Neonatal ICU

Legend: PFGE: Pulsed-field gel electrophoresis; ICU: Intensive care Unit; MDR: Multidrug-resistance.[1,21]
Source: The authors (2021).

Diversity of clinical sites and correspondent frequency of *C. striatum* strains

Since *C. striatum* infections were not restricted to ICUs, but had also emerged in surgery units, dispersion throughout hospital wards was considered a matter of concern. Epidemiological and clinical-microbiological features of (130) *C. striatum* strains isolated from infected patients attended at HUPE/UERJ analyzed in the present study were displayed in Figure 2B and Table 2. Remarkably, *C. striatum* pathogen was present right from the beginning until the end of the study period, occurring in over twenty distinct wards, and fifteen different clinical specimens. Data showed that *C. striatum* strains were found as the etiologic agent of nosocomial infections in different clinical sites, predominantly of lower respiratory tract and bloodstream of several patients: tracheal aspirate; bronchoalveolar lavage and sputum; blood samples and intravenous catheters; urine; surgical wounds; cerebrospinal fluid; peritoneal fluid; bone fragment; hallux tendon, skin ulcer; nasopharynx/oropharynx swabs; eye secretion.

Table 2. Epidemiological and clinical-microbiological features of *Corynebacterium striatum strains* (n=130) isolated from infected patients attended at Hospital Universitário Pedro Ernesto (HUPE/UERJ), located at Rio de Janeiro city, Brazil, during a nine-year period (August 2009 - August 2018)

Clinical samples/ Hospital wards	Number of strains in wards	Year (number of strains) and Antimicrobial resistance profiles	
Tracheal aspirate		Total =53	MDR (n=53)
Intensive Care Units-ICUs	13	2009 (n=03) */pa and pb ; 2010 (n=02)*; 2011 (n=02); 2012 (n=01); 2013 (n=01); 2014(n=01); 2015 (n=01); 2016 (n=01); 2018 (n=01)	
Thoracic Surgery	04	2009 (n=01) */#; 2010 (n=01) *; 2011 (n=01); 2014 (n=01)	
Nursery units	07	2009 (n=01) *; 2010 (n=01); 2011 (n=03); 2015 (n=01) ##; 2018 (n=01)	
Nephrology	02	2009 (n=01) *; 2012 (n=01)	
General Care	16	2010 (n=01); 2011 (n=03); 2012 (n=07); 2013 (n=02); 2014 (n=03)	
Pediatric	03	2011 (n=01); 2018 (n=02)	
Coronary Care	02	2012 (n=02)	
Infectious Diseases	02	2013 (n=02)	
Pneumology / Cystic fibrosis	04	2014 (n=01); 2015 (n=01); 2016 (n=01/01##)	
NI	01	2011 (n=01)	
Additional data: General (n=10), Cardiac (n=01); ICU II (n=01); PFGE-types I, and II; Van - R (n=02); Lzd - R (n=04); Registered fatal cases (n=04); Outpatient (n=02) ## + K pneumoniae(n=01) #;'			
Bronchoalveolar lavage -BAL/ Sputum		Total = 04 (02/02)	MDR (n=04)
Nursery units	02	2009 (n=01) */ #; 2012 (n=01)	
Nephrology	01	2012 (n=01)	
General Care		2012 (n=01)	
Additional data: PFGE-type I; BAL-Registered fatal case#;			
Blood		Total = 21	MDR (n=19) /non- MDRS (n=02)
General ICU	05	2009 (n=01) *; 2011 (n=03); 2013 (n=01) S	
Thoracic Surgery	01	2012 (n=01)	
Cardiac ICU	04	2011 (n=01); 2013 (n=02); 2014 (n=01)	
General Care	01	2012 (n=01)	
Nursery units	02	2011 (n=01); 2012 (n=01)	
Infectious Diseases	03	2009 (n=02) */pb ## ; 2010 (n=01)	
Hematology	01	2011 (n=01) #	
Orthopedic	01	2011 (n=01) #	
Dermatology	01	2010 (n=01)	
Pediatric	01	2012 (n=01)	
Adolescent		2014 (n=01) S	
Additional data: PFGE-types I, II, V, VI, IX; Van- R (n=01); Registered fatal cases# (n=02); + CNS (n=01) ##			
Central venous catheter		Total =13	MDR (n=12) / non-MDRS (n=01)
General ICU	03	2011 (n=02); 2012 (n=01)	
General Care	04	2012 (n=03); 2013 (n=01)	
Neonatal ICU	01	2012 (n=01) S	
HMJ - Pediatric	01	2011 (n=01)	
Infectious Diseases	01	2010 (n=01)	
Pneumology	01	2011 (n=01) #	

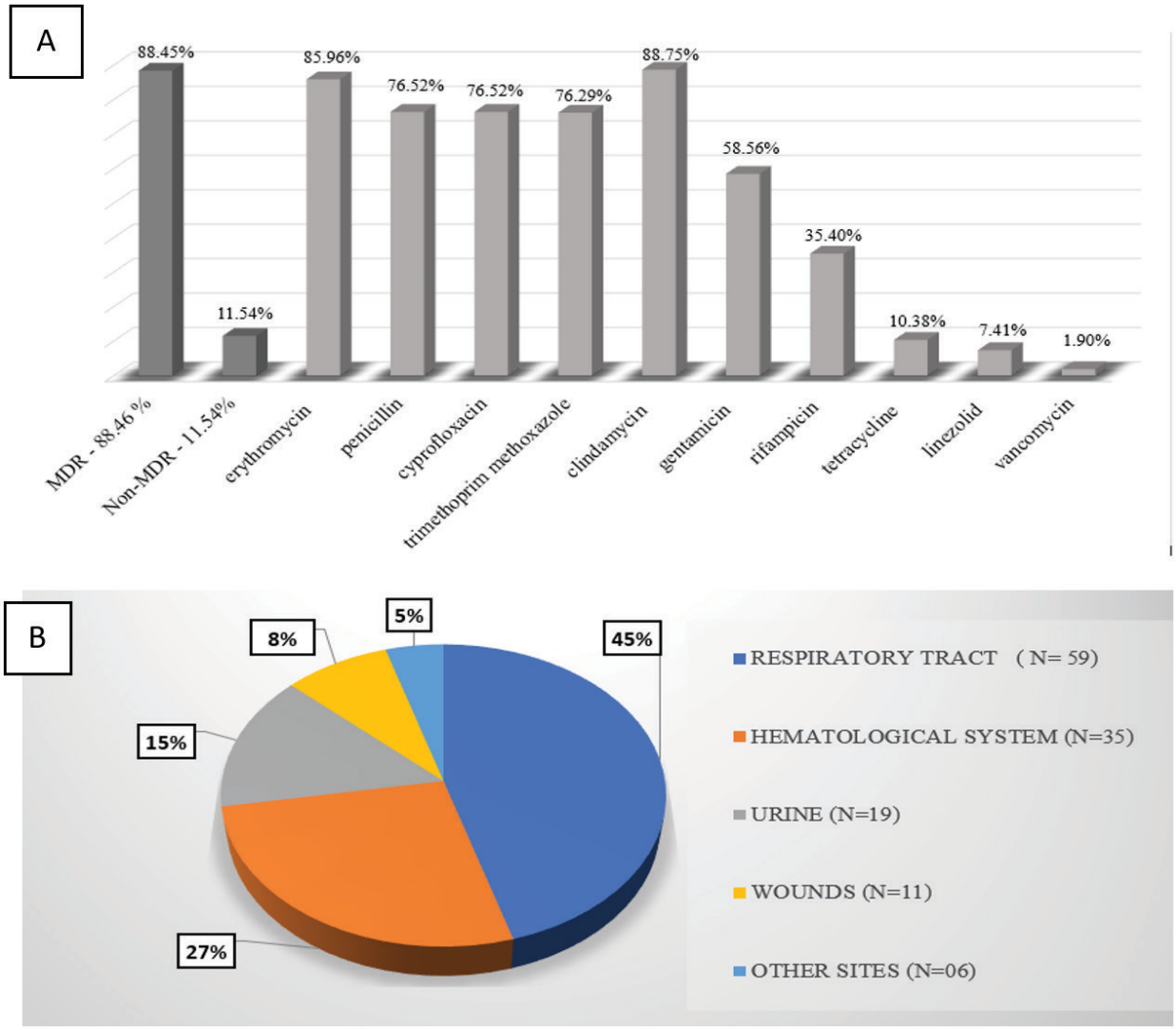
Table 2 (cont.). Epidemiological and clinical-microbiological features of *Corynebacterium striatum strains* (n=130) isolated from infected patients attended at Hospital Universitário Pedro Ernesto (HUPE/UERJ), located at Rio de Janeiro city, Brazil, during a nine-year period (August 2009 - August 2018)

Clinical samples/ Hospital wards	Number of strains in wards	Year (number of strains) and Antimicrobial resistance profiles	
Neurology	01	2012 (n=01)	
Cardiology		2012 (n=01)	
Additional data: Catheter-tips (n=06); PFGE-types I, Ia, Ib, VIa, VII, VIII and XS; + CNS (n=01) #01			
Urine		Total = 19	MDR (n=12) / non-MDR S (n=07)
General ICU	01	2009 (n=01) *	
Nephrology	12	2010 (n=01); 2011 (n=05) S; 2012 (n=03) S; 2015 (n=02); 2013 (n=01) S	
Thoracic Surgery	01	2013 (n=01)	
General Care	01	2013 (n=01) #	
Infectious Diseases	01	2009 (n=01) * S	
PCP - Clinic	01	2013 (n=01)	
NI	02	2011 (n=02) S	
Additional data: PFGE-types I and III S; Lzd-R (n=02); Nephrology ward - Renal transplant (n= 10) hospitalized and/or outpatients (12); + CNS/ K pneumoniae (n=01) #02			
Surgical wound		Total = 07	MDR (n=05) /non-MDR S (n=02)
Thoracic Surgery	02	2009 (n=01) */ S; 2015 (n=01)	
General ICU	01	2013 (n=01)	
Nursery	01	2011 (n=01)	
Infectious Diseases	01	2013 (n=01) S	
Pediatric	02	2011 (n=01); 2014 (n=01)	
Additional data: PFGE-types I, and IV S; Lzd-R (n=01)			
Cerebrospinal fluid		Total = 01	MDR (n=01)
ICU II	01	2010 (n=01) */pa #	
PFGE-type I; Registered fatal case #01			
Peritoneal fluid		Total = 02	MDR (n=02)
General ICU	01	2012 (n=01)	
Gastroenterology	01	2012 (n=01) ##	
Additional data: Outpatient ##			
Bone / Tendon material		Total = 02	MDR (n=01) / non-MDR S (n=01)
Vascular	01	2012 (n=01)	
NI	01	2011 (n=01) S	
Additional data: Hallux tendon S			
Skin ulcer		Total = 01	MDR (n=01)
Dermatology	01	2013 (n=01)	
Nasopharynx / Oropharynx swabs		Total = 02	(01/01) MDR (n=02)
Psychiatric	01	2011 (n=01) ##	
General ICU	01	2013 (n=01)	
Additional data: Outpatient ##			
Eye secretion		Total = 01	MDR (n=01)
Vascular	01	2012 (n=01)	

*, Nosocomial outbreak period, (n=15); HMJ, Hospital Menino Jesus/HUPE ward; PCP, Piquet-Carneiro Policlinic/ HUPE ward; pa and pb, two C. striatum strains isolated from one patient a and patient b; MDR, Multidrug resistance-profile; S, non-multidrug resistant strains; Van-R, Vancomycin-Resistance; Lzd-R, Linezolid-Resistance.

Source: The authors (2021).

Figure 2. *Corynebacterium striatum* **strains (%) expressing heterogenic multidrug resistance and non-multidrug resistance profiles identified as Brazilian nosocomial pathogens (A); Diversity and frequency of** *C. striatum* **strains isolated from clinical specimens of infected patients attended at tertiary care hospital (HUPE/UERJ) located in Rio de Janeiro metropolitan area during August 2009 to August 2018 (B)**



Source: The authors (2021).

During the nosocomial outbreak period (2009-April 2010), MDR *C. striatum* strains expressing PFGE-type I profiles were most frequently (78.57%) observed, especially among inpatients admitted to the ICUs and surgical wards (n = 10). *C. striatum* infections were observed in the General ICU (n = 4), cardiac ICU (n = 1), ICU II (n = 2), Thoracic surgery (n = 3), Nursery 18 (n = 2), Infectious Diseases (n = 2) and Urology (n = 1) wards. *C. striatum* nosocomial pathogens isolated from tracheal aspirate specimens obtained from patients undergoing endotracheal intubation or pneumonia were mostly of PFGE-type I. Later, MDR *C. striatum* presenting PFGE-type I were also isolated from infected patients of other hospital wards: Hematology, Orthopedic and Infectious Diseases, including patients with bloodstream and/or catheter-related infections. An increased number of bloodstream and catheter-related nosocomial in-

fections caused by *C. striatum* strains of varied PFGE-types was verified, mostly expressing MDR profiles: PFGE-types I, II, V, VI, IX; PFGE-types I, Ia, Ib, VIa, VII and VIII X, respectively. PFGE profile X was related to a case of catheter-related infection in a three-month-old patient from Neonatal ICU. Non-MDR *C. striatum* strains of two distinct PFGE-profiles types III, and IV strains were isolated from urine (PFGE-type III), and surgical wound (PFGE-type III) of two patients attended at Infectious Diseases unit.

Current data reinforced the endemic condition of *C. striatum* as a nosocomial pathogen and dissemination among hospital wards of *C. striatum* strains expressing different antimicrobial susceptibility profiles and isolated from different clinical sites of infection of both hospitalized and outpatients. Interestingly, *C. striatum* strains were verified as pathogens of kidney transplant recipients (n=10) included at-risk populations, and predominantly isolated from urine samples of outpatients (n=09). Moreover, a total of *C. striatum* strains (n=19) expressing MDR (n=12) and non-MDR (n=07) profiles were isolated from urine samples of infected patients from other HUPE-wards in addition to Nephrology: General ICU, Thoracic Surgery, General Care, Infectious Diseases and PCP-Clinic. Additionally, most of *C. striatum* strains expressing MDR (n=08) profiles were isolated from urine samples of non-hospitalized infected patients attended at Nephrology ward while non-MDR *C. striatum* strains were also associated with nosocomial infection of urinary tract origin in some other wards.

Current analyses of pediatric data from the Brazilian tertiary teaching hospital demonstrated that nine *C. striatum* clinical strains were isolated from infected children of different ages, including one adolescent patient: blood (n=02), intravenous catheter (n=02), tracheal aspirate (n=03), and surgical wound (n=02). Most of the cases in the Pediatric unit (n=07) had been associated with invasive devices (n=05). Bloodstream infections making use or not of intravenous catheter devices were the main site of infection (n=04), and *C. striatum* strains expressing MDR profiles were isolated from pediatric samples in most cases (n=07). *C. striatum* strain expressing non-MDR profile was also isolated from blood samples of an adolescent patient. Moreover, a non-MDR *C. striatum* strain of PFGE-type X isolated from the intravenous catheter of a three-month-old patient from Neonatal ICU.

During the period of study, outcomes of patients were partially informed and fatal cases mostly occurred when *C. striatum* strains were grown in pure culture and from tracheal aspirates of hospitalized patients. In two opportunities, MDR *C. striatum* strains were isolated from distinct clinical sites or samples of patients with severe invasive diseases and fatal outcome: (a) tracheal aspirate and blood samples (PFGE-Type I strains / ICU II); (b) two blood samples (PFGE-Type II strains/Infectious Diseases ward). In January 2016, a case of an infected patient with a MDR *C. striatum* strain isolated from tracheal aspirate of attended at Cystic fibrosis ward with fatal outcome was verified.

Discussion

Hospital-acquired infections are responsible for significantly higher mortality rates, length of stay and hospital costs, being an increasing cause for concern in healthcare worldwide.[26,27] *C. striatum* have been increasingly certified as a potentially pathogenic microorganism during the last decades. During a 44-year period, over 218 studies related to C. *striatum* human infections and nosocomial outbreaks were reported.[19] Nevertheless, routine procedures for laboratorial identification of *Corynebacterium* spp. remain uncommonly undertaken in many countries or IGPR clinical isolates are frequently considered as contaminants and/or underestimated by health professionals. [1,5,6,28]

In South America, reported cases of *C. striatum* infections and nosocomial outbreaks remain scarce and have been mostly reported in Brazil. Therefore, continuous survey of pathogenic *Corynebacterium* spp., in tropical and developing countries is essential, as already done for decades in the Brazilian LDCIC/FCM/UERJ laboratory.[1,5-8,19,21,23]

In Brazil, a low number of *C. striatum* strains isolated from representative clinical sites of hospitalized infected patients were formerly reported.[5,6,29] Interestingly, *C. striatum* strains expressing MDR profiles were isolated among wound/abscess (n=04) and urine (n=04) samples from infected patients attended at HUPE/UERJ from September 1993 to December 1998.[5] Eleven years later (2009-April 2010), the nosocomial outbreak was reported and fifteen *C. striatum* strains, mainly expressing MDR profiles, were isolated from infected patients of five different hospital wards, mostly from patients admitted to ICUs and surgical units.[1] The present investigation regarding nosocomial infections caused by *C. striatum* pathogen verified the endemicity status and the extensively dissemina-

tion among wards of 130 *C. striatum* strains, mostly expressing MDR profiles, during a nine-year period (2009-2018) in HUPE/UERJ, a Brazilian tertiary-care hospital located at Rio de Janeiro metropolitan area. Data showed an increase in the number of *C. striatum* clinical isolates from 2009 to 2012, with highest numbers during 2011 and 2012. During 2013, a decrease in number of *C. striatum* clinical isolates was noticed, possibly related to a reduction in number of attended patients at the hospital unit.

During the present study, MDR *C. striatum* strains were mostly isolated in pure cultures, but in some opportunities were also co-isolated with other pathogens in cultures from tracheal aspirate, blood, catheter tips or urine samples, as also verified in previous reports. Consequently, health professionals and specialists in clinical bacteriology laboratories cannot promptly discard *C. striatum* strains as contaminants, especially when isolated from chronically impaired patients and/or using invasive devices.[5,6,12,30,31]

In HUPE/UERJ, most of *C. striatum* strains expressing MDR profiles were isolated from tracheal aspirate samples of infected patients attended at ICUs, surgical and other hospital wards, including Pneumology, Cystic fibrosis, Nephrology, Pediatric and Adolescent units. Notified fatal outcomes, included a cystic fibrosis patient with MDR *C. striatum* infection. *C. striatum* strains expressing MDR profiles were mostly isolated from tracheal aspirate among hospitalized patients during post and nosocomial outbreak period, including intubated patients receiving mechanical ventilation.

Studies on nosocomial pneumonia are mainly related to the United States and European countries, whereas studies from around the world are missing.[32] In France, a recent research emphasized the fact of the clinical diagnosis of pneumonia in mechanically ventilated patients remains challenging and controversial acknowledge that despite reaching consensus, some cases may have been debatable. The study, focusing on critically ill patients showed that *Corynebacterium* spp. (n=13; 58% fatal outcome) to be responsible for pneumonia in mechanically ventilated patients attended at ICU, including *C. striatum* strains. Respiratory failure leading to acute respiratory distress syndrome, septic shock, multiorgan failure, and care withdrawal were the principal causes of ICU death. Impaired airway protection, decreased lung clearance, damaged lung structure, antibiotic exposure, primary immunocompromised conditions or acquired immunodeficiency after a prolonged stay in ICU were all conditions that can be encountered in ICU, and that may promote the onset of pneumonia caused by *Corynebacterium* spp.[33]

Nowadays, the risk of pneumonia is increased in the intubated patients receiving mechanical ventilation and the ventilator associated pneumonia nosocomial pneumonia due to mechanical ventilation procedures in mechanically ventilated patients is a matter of concern world wild, including Brazil.[34] Remarkably, current findings also indicated ventilator support as a risk factor for acquiring *C. striatum* infection. Therefore, *C. striatum* strains, especially when expressing MDR profiles, should be considered as clinically relevant when isolated in pure culture, and/or predominantly from patients with hospital acquired infections in the respiratory tract and/or ventilator-associated pneumonia, as previously reported for *Corynebacterium* spp. and other human pathogens.[12,29,33,32,35]

Moreover, MDR *C. striatum* strains were presently isolated from sputum of infected patients, as previously reported in other studies. Data from Canada verified *C. striatum* as the most frequent pathogen (26.2%) among non-diphtheriae *Corynebacterium* spp, and predominantly isolated from sputum (26%) and blood (14%) samples.[21] In Spain, a nosocomial outbreak due to *C. striatum* infection in patients with Chronic Obstructive Pulmonary Disease occurred with transmission from patients and via caretakers of patients. A total of 21 strains were isolated from sputum of infected patients during an 18 month-period.[4] In the Brazilian Southern region, a fatal case of multiple pulmonary nodules caused by a MDR *C. striatum* in an elderly immunocompetent patient was reported. *C. striatum* strain was isolated in pure culture from lung fragment of patient, but data of culture from sputum samples were not described.[29] Accordingly, analysis of the presence of *Corynebacterium* spp, in laboratorial cultures from sputum of patient is a relevant procedure that may also anticipate the diagnosis of severe infections in the respiratory tract, sometimes avoiding or postponing harmful invasive procedures for collecting clinical samples.

During the nine-year period of study in HUPE/UERJ, *C. striatum* pathogen was also isolated from a high number of blood (n=21) and intravenous-catheter samples (n=13) from patients with hematogenic infections, including a case of systemic infection caused by MDR *C. striatum* with fatal outcome. In a previous reported

study, MDR *C. striatum* strains isolated from patients presenting bloodstream (n=13) and catheter-related (n=10) nosocomial infections attended at HUPE/UERJ were mostly isolated in pure cultures (n=18) or in significant numbers (n=05).[21]

Since *C. striatum* is a potentially pathogenic species commonly found in human skin and nasal microbiota, the ability of colonization of unharmed epithelial surfaces may contribute to an increased risk of invasive infections, as previously described for *Staphylococcus aureus*.[6,12] In Japan, cases of nosocomial-acquired hematogenic infections due to MDR *C. striatum* strains (n=24) were confirmed in patients of adult age groups with underlying disease submitted to long hospitalization period. Most of patients with *C. striatum* bacteremia were using invasive medical devices, such as a central venous catheter.[36] In Sweden, cases of community-acquired bacteremia due to *C. striatum* strains (n=08) in older males with comorbidities were recently investigated. *C. striatum* caused infective endocarditis were diagnosed in two patients with heart valve prosthesis, one with fatal outcome.[37]

In accordance with previous studies, current data emphasized that *C. striatum* strains, especially when expressing MDR profiles, isolated in pure culture or in significant number from blood and catheter segments, including catheter insertion sites, should be recognized as a true pathogen with ability of causing invasive infection rather than dismissed as a contamination from normal skin flora.[21]

Interestingly, MDR and non-MDR *C. striatum* strains were firstly demonstrated as etiologic agents of urinary tract infections from hospitalized kidney transplant recipients, mostly outpatients, attended at the Nephrology ward of HUPE/UERJ. In a previous research conducted at the Republic of Korea, MDR *C. striatum* strains were mostly recovered from urine samples of patients (35.8%), diagnosed with infections mainly characterized as nosocomial and community-acquired diseases. Comorbidities included cardiovascular, malignancy, renal, and transplantation.[30] Recently, a review of literature demonstrated the occurrence of individuals with end-stage kidney disease - ESKD on hemodialysis who developed *C. striatum* bacteremia.[31] In the Brazilian Cancer Reference Center – INCA/RJ, cases of infections in patients with neoplastic disease caused by MDR *C. striatum* strains in the respiratory tract (n=04) and surgical wounds (n=02) were also reported.[6] A case of infection by a non-MDR *C. striatum* strain in a malignant cutaneous lesion from a 27-year-old male patient was also reported in South region of Brazil.[38]

Moreover, a MDR *C. striatum* strain was currently isolated from eye secretion of an infected inpatient attended at the Vascular ward. *Corynebacterium* spp. were observed in the microbiome of the ocular surface from healthy adults. Over ten potentially pathogenic species, including *C. striatum*, have been reported as etiologic agents of severe and mild ocular infections.[35,39]

In HUPE/UERJ, most of *C. striatum* strains were obtained from tracheal aspirates (n=52), blood s (n=21), intravenous catheters (n=13), urine (n=19) and surgical wounds (n=07), among other clinical samples of infected patients. Higher virulence potential to human hosts was observed for some MDR and non-MDR *C. striatum* strains related to cases of severe illness and even death of patients, and survival against environmental stress conditions. Therefore, data reinforced the virulence potential of *C. striatum* strains expressing MDR profiles and non-MDR profiles within human hosts and increased mechanisms of protection and survival against environmental stress conditions, including resistance to antimicrobial agents used in therapy, antiseptics and disinfectants used in nosocomial environment.

During the last decades, the ability of biofilm formation has been increasingly recognized as an essential mechanism involved in the pathogenic potential of human causative agents of nosocomial and community-acquired infections associated (or not) with the use of medical devices. Biofilm formation has been shown to enhance virulence potential by contributing to bacterial adherence to abiotic and biotic surfaces, metabolite exchange, cellular communication, and protection of varied Gram-positive and Gram-negative pathogens against host immune defenses and antimicrobial agents.[36] Earlier studies also verified the ability of biofilm formation by diverse pathogenic *Corynebacterium* species, including *C. striatum*.[23,37-40]

Souza and co-workers demonstrated biofilm production by *C. striatum* of PFGE profiles I to IV associated with nosocomial outbreak in HUPE/UERJ on hydrophilic and hydrophobic abiotic surfaces, at different levels. The highest ability of biofilm formation was expressed by a MDR *C. striatum* strain representative of the predominantly PFGE-type I isolated during the nosocomial outbreak. Lately, MDR

C. striatum PFGE-type I clinical isolates from patients undergoing endotracheal intubation procedures as well as PFGE-type I strains were characterized as etiologic agents of bloodstream and catheter-related infections also exhibiting high ability of adherence, survival, and production of mature biofilms on catheter segments (polyurethane and/or silicone) and metal (steel) surfaces.[21,23]

In 2009, reported cases of *C. striatum* nosocomial infections were mostly associated with use of invasive medical devices, not only tubes or catheters, but also surgical wound wires. Interestingly, all *C. striatum* clinical isolates were described by that time in Italy, as vancomycin-resistant.[35] During the reported nosocomial outbreak in Spain during 2004 and 2005, MDR *C. striatum* strains were also found 89% vancomycin-resistant.[4,18] In Brazil, most (87%) of MDR *C. striatum* strains PFGE-types I and II were identified as susceptible to tetracycline, linezolid, and vancomycin during the HUPE/UERJ outbreak. Moreover, 76.2% of MDR *C. striatum* strains, independent of PFGE profiles, isolated from patients with bloodstream and catheter-related infections and 100% susceptible linezolid and vancomycin, daptomycin.[1,21] In the present nine-year period of study, demonstrated that most endemic *C. striatum* nosocomial isolates presented high resistance levels (≥ 80 %) to antimicrobials agents frequently used to treat Gram-positive infections, especially clindamycin, erythromycin, ciprofloxacin and penicillin. Worryingly, emergence of vancomycin-resistance and linezolid-resistance was observed among *C. striatum* strains expressing MDR profiles isolated from clinical isolates of infected patients attended in HUPE/UERJ.

Conclusion

Cases of nosocomial infections and outbreaks due to *C. striatum* pathogen, as well as endemicity and dissemination in hospital environments must remain a matter of concern among researchers, epidemiologists and the medical community in South America and other continents. Nowadays, health professionals must not promptly discard *C. striatum* strains as contaminants even when found associated with one or more potentially pathogenic strains in a clinical sample from hospitalized and outpatients, independently of age, gender, and comorbidities.

Nosocomial infections and outbreaks of MDR *C striatum* can have their origin in a single reservoir or in multiple contaminated sites. Patients may possibly acquire *C. striatum* from an environmental source or from other patients, as also reported for other pathogens. *C. striatum* strains of varied genetic types, expressing MDR and non MDR profiles were found endemic in nosocomial units and disseminated among infected patients of a wide-ranging hospital wards. Varied genetic types of MDR *C. striatum* strains were also isolated from nosocomial bloodstream and catheter-related infections in HUPE/UERJ. However, a common source and the mode of transmission could not be currently determined. Additional studies must be also conducted in this area to define the clonal nature and dissemination of MDR *C. striatum* pathogenic strains in hospital environment units in Brazil and other countries.

Strategies to control nosocomial infections caused by *C. striatum* strains, including analysis of virulence mechanism of multi-factorial nature involved in the ability to survive against host immune defenses, nosocomial stress conditions, as well as intrinsic and/or acquired mechanisms involved in antimicrobial resistance, including genes encoding resistance for varied antimicrobial agents will be further investigated.[9,21]

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Declarations:

Conflict of interest/Competing interest- The authors declare that they do not have conflict of interest.

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