



Worldwide survey of *Corynebacterium striatum* increasingly associated with human invasive infections, nosocomial outbreak, and antimicrobial multidrug-resistance, 1976–2020

Giorgio Silva-Santana^{1,2,3,4} · Cecília Maria Ferreira Silva^{1,2} · Julianna Giordano Botelho Olivella^{1,2} · Igor Ferreira Silva^{1,2} · Laís Menegoi Oliveira Fernandes^{1,2} · Bruna Ribeiro Sued-Karam^{1,2} · Cíntia Silva Santos^{1,2} · Cassius Souza^{1,2} · Ana Luíza Mattos-Guaraldi^{1,2,3,4}

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Abstract

Corynebacterium striatum is part of microbiota of skin and nasal mucosa of humans and has been increasingly reported as the etiologic agent of community-acquired and nosocomial diseases. Antimicrobial multidrug-resistant (MDR) *C. striatum* strains have been increasingly related to various nosocomial diseases and/or outbreaks worldwide, including fatal invasive infections in immunosuppressed and immunocompetent patients. Although cases of infections by *C. striatum* still neglected in some countries, the improvement of microbiological techniques and studies led to the increase of survival of patients with *C. striatum* nosocomial infections at different levels of magnitude. Biofilm formation on abiotic surfaces contributes for the persistence of virulent *C. striatum* and dissemination of antimicrobial resistance in hospital environment. Besides that, empirical antibiotic therapy can select multi-resistant strains and transfer intra and interspecies genes horizontally. In this study, a worldwide survey of *C. striatum* human infections and nosocomial outbreaks was accomplished by the analysis of clinical–epidemiological and microbiological features of reported cases from varied countries, during a 44-year period (1976–2020).

Keywords Biocides · Biofilm · *Corynebacterium striatum* · Multidrug-resistance · Neglected pathogen · Nosocomial outbreak

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✉ Giorgio Silva-Santana
bio.sant@hotmail.com

- ¹ Laboratory of Diphtheria and Corynebacteria of Clinical Relevance, Faculty of Medical Sciences, University of the State of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
- ² The Collaborating Centre for Reference and Research on Diphtheria/National Health Foundation/Ministry of Health, Rio de Janeiro, Brazil
- ³ Health Sciences Center, Institute of Microbiology Paulo de Góes, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
- ⁴ Centro de Ciências da Saúde (CCS), Universidade Federal do Rio de Janeiro, Instituto de Microbiologia Professor Paulo de Góes, Cidade Universitária, Ilha do Fundão, Rio de Janeiro, Brazil

Introduction

The *Corynebacterium* genus, described by Lehmann and Neumann (1896), belongs to Actinobacteria class, Actinomecetales order, and Corynebacteriaceae family (Lehmann and Neumann 1896). Nowadays, *Corynebacterium* genus has more than 132 highly diversified species and 11 subspecies, with at least 50 species already recognized of medical, veterinary, and biotechnological relevance (Parte 2014; Zasada and Mosiej 2018). Although non-diphtherial *Corynebacterium* spp. may be part of the human microbiota (amphibionics), varied species have been currently reported as the etiologic agent of human infections (Funke and Bernard 2011; Baio et al. 2013; Bernard et al. 2013; Zasada and Mosiej 2018). For many decades, the pathogenic potential of non-diphtherial *Corynebacterium* species was neglected, mainly for the difficulty in identification and distinction between colonization and infection (Camello et al. 2003; Martins et al. 2009). However, *Corynebacterium* species

identified during laboratorial procedures remain frequently considered as contaminants of clinical specimens and/or underestimated by a variety of health professionals in many countries (Baio et al. 2013; Bernard et al. 2013; Zasada and Mosiej 2018).

A growing number of reports have demonstrated the relevance of *Corynebacterium* pathogens in the etiology of a variety of infectious processes, in both immunocompromised and immunocompetent patients. Some species have been also described different corynebacterial species as causal agents of infections with high morbidity and mortality rates. Data reflect a tendency towards infection or colonization of patients who have undergone surgical/invasive procedures and a long subsequent hospitalization period, advanced age, neoplastic diseases, organ transplantation, Acquired Immunodeficiency Syndrome (AIDS), diabetes, prolonged antibiotic therapy, as well as procedures such as catheterization, heart valves and prosthetic implants (Martins et al. 2009; Carvalho et al. 2018).

Diphtheria outbreaks and atypical cases of diphtheria localized, and systemic infections cases have been reported in both industrialized and developing countries due to diphtheria toxin (DT)-producing and non-DT-producing *C. diphtheriae* and *C. ulcerans*, a zoonotic pathogen (Schröder et al. 2012; Simpson-Lourêdo et al. 2019). Moreover, potentially DT-producer *C. pseudotuberculosis*, a zoonotic pathogen, have been mainly related to cases of contagious chronic disease, named Caseous Lymphadenitis (CLA) in ruminants (Azevedo Antunes et al. 2018).

Clinical implications due to expression of multidrug-resistance (MDR) profiles by non-DT-producing *Corynebacterium* species have been reported among hospitalized patients infected with *C. afermentans*, *C. amycolatum*, *C. jeikeium*, *C. pseudodiphtheriticum*, *C. striatum*, and *C. urealyticum* (Renom et al. 2007; Martins et al. 2009; Carvalho et al. 2018). Clones presenting natural and/or acquired resistance to antimicrobials have been identified, such as *C. macginleyi*, *C. minutissimum*, and *C. xerosis*, both in and out of hospitals' environments (Renom et al. 2007; Reddy et al. 2012). Studies have shown that the prevalence of those MDR clones depends on geographic location, beyond the constant acquisition of genes from other species, that grant resistance phenotypes to new antimicrobials (Zasada and Mosiej 2018; Ramos et al. 2019).

In this study, a worldwide survey of *C. striatum* human infections and nosocomial outbreaks was accomplished by the analysis of clinical–epidemiological and microbiological features of reported cases from varied countries, during a 44-year period (1976–2020).

***Corynebacterium striatum* infections features and nosocomial outbreaks**

Corynebacterium striatum exhibiting MDR profiles have been isolated from the respiratory tract of patients with community-acquired infections and nosocomial diseases. Since *C. striatum* is a participant in microbiota of the skin, and nasal mucosa of humans, this pathogen also remains recognized as contaminant and systematically disregarded during clinical and laboratory diagnosis in many opportunities (Lee et al. 2005; Bernard et al. 2013). An increasing number of cases of invasive infections by *C. striatum* are reported in immunocompromised and immunocompetent individuals, including: bacteremia and sepsis (Renom et al. 2007; Wong et al. 2010), septic arthritis (Cone et al. 1998; Scholle 2007), endocarditis, meningitis (Weiss et al. 1996; Oliva et al. 2010), osteomyelitis (Fernández-Ayala et al. 2001; Scholle 2007), sinusitis (Heidemann et al. 1991), pulmonary infection (Renom et al. 2007; Wong et al. 2010), and synovitis (Cone et al. 1998; Scholle 2007). It has also been identified as etiologic agent of liver abscesses (Stone et al. 1997) and in mammary gland (Boltin et al. 2009; Martins et al. 2009), keratitis (Heidemann et al. 1991), wounds in skin and surgical (Moore et al. 2010), intrauterine infections (Boltin et al. 2009; Campanile et al. 2009), peritonitis (Bhandari et al. 1995), and in patients affected by AIDS, cancer, and transplanted (Tarr et al. 2003; Martins et al. 2009).

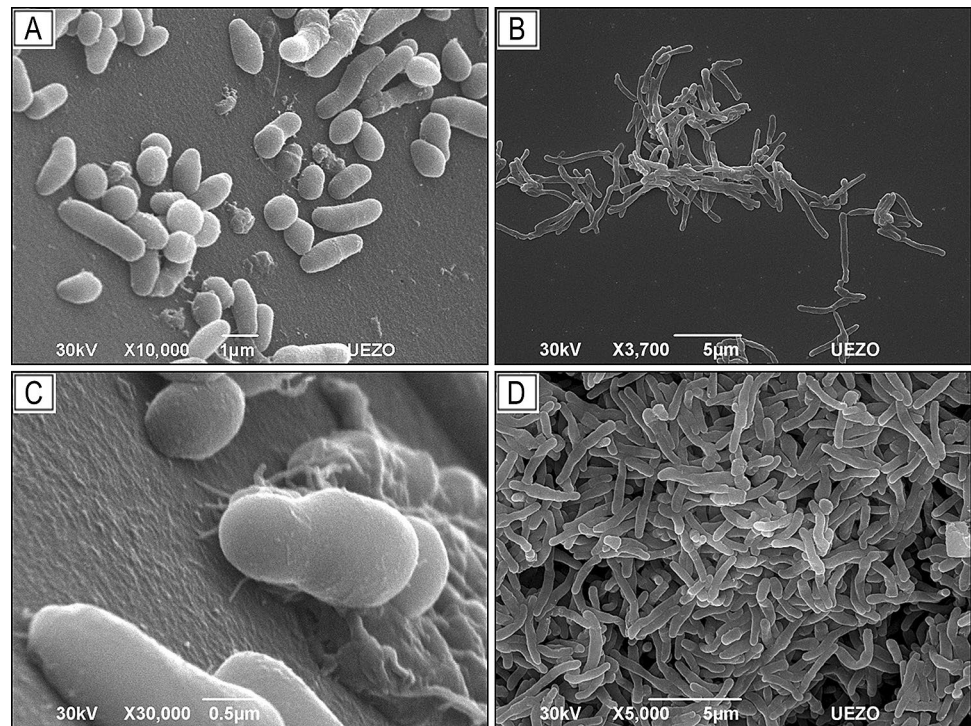
Phenotypic and genotypic typing methods of *C. striatum*

Corynebacterium spp. are characterized by the presence of arabinose, galactose, meso-diaminopimelic acid, and short chains of mycolic acid in the cell wall; they are aerobic, catalase-positive, not sporulated, and immovable, and can be observed with light microscopy such as irregular Gram-positive rods (with pleomorphic cell morphology, presenting coccoid, bacillary, or filamentous forms) (Fig. 1a), individualized or grouped in pairs and/or in the form of palisades (Fig. 1b). Some species can present corynomicolic acids and metachromatic granules as a reserve of high energy phosphate (e.g., *C. diphtheriae*) (Funke and Bernard 2011).

The identification of *C. striatum* can be performed using the conventional biochemical methods. The biochemical tests used to identify the species mentioned in this work are shown in Table 1. Phenotypic analysis may also be available in semi-automated systems (Camello et al. 2003; Pimenta et al. 2008; Jorgensen et al. 2015).

Nowadays, the identification of bacterial species by mass spectrometry offers quicker and more practical

Fig. 1 Scanning electron microscopy (SEM). Photomicrograph of adhesion by *Corynebacterium striatum* to polyurethane catheter surface. Pleomorphism, cells with coccoid, bacillary, and filamentous morphology (a); rods grouped together in a characteristic way “V”, “palisades”, “Chinese letters” (b); initial adhesion, with the presence of filamentous extracellular material (c); mature biofilm (d). The mechanisms that influence *C. striatum* ability to adhere to different abiotic surfaces and form biofilm remain unknown



protocols such as the MALDI (Matrix-Assisted Laser Desorption Ionization), followed by detection in a type analyzer time-of-flight (TOF) and mass spectrometry (MS) (MALDI-TOF MS) (Díez-Aguilar et al. 2013). Molecular methods such as sequencing 16S rRNA and *rpoB* genes are generally used in Reference Laboratories. Molecular technological advances have led to improvements in the survival of immunocompromised patients, as well as in identification, which enabled the increase of case reports in the literature on infections caused by DT-producing and non-DT-producing *Corynebacterium* species. Genomic analysis may reveal virulence and resistance genes and predominant clones spreading in the hospital environment (Trost et al. 2011; Torres et al. 2013; Wang et al. 2019).

Epidemiological features of *C. striatum* human infections and nosocomial outbreaks

C. striatum has been increasingly considered as potentially pathogenic microorganism during the last 5 decades. Until the present moment, a review of the available world literature revealed a total of 218 references related *C. striatum* to human infections and nosocomial outbreaks worldwide during the 44-year period of study (<https://pubmed.ncbi.nlm.nih.gov>). Table 2 and Fig. 2 illustrate the occurrence of a total of 254 cases of *C. striatum* human infections and/or outbreaks from different (Martins et al. 2009) continents and countries, including the first reported case in 1976—United States of America (USA) (Bowstead and Santiago 1980).

Similar to the first case of acute and fatal pulmonary infection, *C. striatum* infections were associated with underlying medical problems in varied reports. Most cases of *C. striatum* infection occurred in either immunocompromised or damaged skin conditions (Superti et al. 2009; Díez-Aguilar et al. 2013).

Since 2000 *C. striatum* has been associated with nosocomial infections, mainly in immunodepressed patients, that were hospitalized for long periods in Intensive-Care Units (ICU) due to invasive medical devices such as intravenous catheters. The use of multiple medical devices led to colonization of the upper respiratory tract, with subsequent invasive infection (Martins et al. 2009; Superti et al. 2009; Wong et al. 2010; Díez-Aguilar et al. 2013). During a nosocomial outbreak in Rio de Janeiro metropolitan area, *C. striatum* predominant genotypes were mostly isolated in pure culture from tracheal aspirates of patients undergoing endotracheal intubation procedures (Baio et al. 2013). Previous studies reported cases of *C. striatum* infection associated to various hospital materials used during respiratory and urological assistance, such as: bronchoscopes, catheters, colonoscopes, laparoscopes, and nasofibrosopes (Scholle 2007; Oliva et al. 2010). Therefore, *C. striatum* should receive special attention, especially when isolated from patients chronically debilitated and/or making use of invasive devices (Renom et al. 2007; Superti et al. 2009; Wong et al. 2010; Baio et al. 2013).

Additionally, *C. striatum* infections with evolution to bacteremia, recurrence of infection, and/or progression to septic

Table 1 Biochemical profiles of *Corynebacterium striatum* and other *Corynebacterium* species currently related to reported cases of human infections and nosocomial outbreaks during 44-year period (1979–2020)

Species	Biochemical profiles																	
	CAT	MET	LIP	NIT	ESC	GEL	URE	PYZ	FRUT	GAL	GLI	GLIC	MAL	SAC	CAMP	HEM	DNase	TYR
<i>C. afermentans</i>	+	O	V	-	-	-	-	V	-	+	-	-	-	-	V	V	-	ND
<i>C. amycolatum</i>	+	F	-	+	-	-	V	V	+	-	-	-	V	V	-	-	-	-
<i>C. diptheriae</i> subsp. <i>Beljanti</i>	+	F	V	V	-	V	-	-	ND	ND	+	V	+	V	-	-	+	ND
<i>C. diptheriae</i> subsp. <i>Gravis</i>	+	F	-	+	-	V	-	-	ND	+	+	+	+	V	-	V	+	ND
<i>C. diptheriae</i> subsp. <i>Intermedius</i>	+	F	+	+	-	V	-	-	ND	ND	+	-	+	-	-	-	+	ND
<i>C. diptheriae</i> subsp. <i>Mitis</i>	+	F	-	+	-	V	-	-	ND	ND	+	-	+	V	-	V	+	ND
<i>C. jeikeium</i>	+	O	+	-	-	-	-	+	-	+	+	ND	V	-	-	-	ND	ND
<i>C. macginleyi</i>	+	F	+	+	-	-	ND	-	ND	ND	+	ND	+	+	-	-	+	ND
<i>C. minutissimum</i>	+	F	-	-	-	-	-	+	+	ND	+	ND	V	V	V	-	V	+
<i>C. pseudodiphtheriticum</i>	+	O	-	+	-	-	+	+	ND	ND	-	ND	-	-	-	-	ND	-
<i>C. pseudotuberculosis</i>	+	F	-	V	-	V	+	-	-	ND	+	V	+	V	RR	+	-	ND
<i>C. striatum</i>	+	F	-	V	-	-	-	+	V	V	+	ND	-	V	V	-	ND	+
<i>C. ulcerans</i>	+	F	-	-	-	V	+	-	ND	+	+	V	+	-	RR	+	+	ND
<i>C. urealyticum</i>	+	O	+	-	-	-	+	+	ND	ND	-	ND	-	-	-	-	ND	ND
<i>C. xerosis</i>	+	F	-	V	-	ND	-	+	ND	V	+	ND	+	+	-	-	ND	ND

Acid production from fructose metabolism (FRUT), of Galactose (GAL), of Glucose (GLI), of Glycogen/starch (GLIC), of Maltose (MAL), of Sucrose (SAC), Catalase (CAT), Esculin hydrolysis (ESC), Fermentative (F), Gelatin hydrolysis (GEL), Hemolysis in nutritive medium containing sheep blood (HEM), Lipophilia (LIP) (grow well in culture medium containing 1% Tween 80), Metabolism (MET), Negative (-), Nitrate reduction NO₃- (NIT), Not defined (ND), Oxidative (+), Production of deoxyribonuclease (DNase), Pyrazinamidase activity (PYZ), Reverse reaction (RR), Synergistic hemolysis with β-hemolysin from *S. aureus* in sheep blood (CAMP), Tyrosine (TYR), Urease (URE), Variable (V), Weak positive (+) (Pimenta et al. 2008; Funke and Bernard 2011; ANVISA 2014)

Table 2 Presentation of partially reported cases of *Corynebacterium striatum* human infections and nosocomial outbreaks in different continents, from year 1976 to 2020

Year and Country	Number of cases	Gender/age	Prognostic	Clinical sample	Comorbidity	Diagnosis–Outcome (D/S)	References
<i>Multiple case report in health unit</i>							
1994–1995 Netherlands	14 (outbreak)	Not specified	Infection symptoms	Sputum and wound fluid	Not specified	Not specified	Brandenburg et al. (1996)
2004 UK	2	M 72	Weight loss, indisposition, sweating, dizziness, and arthralgia	Blood	Rheumatic fever and prosthetic mitral valve	Endocarditis—S1	Stoddart et al. (2005)
		F 61	Dizziness, nausea, backache, palpitations, lethargy	Blood	Cutaneous lupus erythematosus, pulmonary and heart disease	Endocarditis—S1	
2004–2005 Spain	21 (outbreak)	M and F 57–88	COPD exacerbation	Spontaneous sputum	Not specified	Not specified—D1	Renom et al. (2007)
2005–2007 Italy	36	Not specified	Wound infection, infectious tracheobronchitis, ventilator-associated pneumonia, catheter-related bacteremia	Not specified	Surgery and nosocomial procedures	Catheter-related pneumonia and sepsis—Not specified	Campanile et al. (2009)
2006 Italy	13 (outbreak)	M 16–73 F 16–80	Cranial trauma multiple fractures, hemorrhage, and brain metastasis	Blood and, bronchial aspirate and catheter-tip	Not specified	D3/S5	Iaria et al. (2007)
2009 Israel	3	M 71	Fever, respiratory infection symptoms and acute ischemic in the lower limbs	Blood	Diabetes mellitus (T2)	Sepsis with fulminant myocarditis—D1	Boltin et al. (2009)
		F 80	Fever and mass in right axilla	Blood, aspirated fluid	Not specified	Urinary tract infection and sepsis—D1	
		F 80	Fever, knee pain and swelling, bacteremia	Bone	Osteoarthritis	Not specified	
2009–2010 Brazil	14 (outbreak)	M 51–85 F 23–54	Infection symptoms	Tracheal aspirate, bronchoalveolar lavage, blood, cerebrospinal fluid and urine	Not specified	Respiratory, hematogenic, urinary tract infection and meningitis—D6/S4	Baio et al. (2013)
2010–2014 Japan	24	M and F 20–80	Bacteremia symptoms	Blood	Severe burns, heart disease, encephalopathy, transplant, neoplasia, hepatorenal insufficiency	D13/S11	Ishiwada et al. (2016)
2011 Belgium	24 (outbreak)	M 61–88 F 59–91	Infection symptoms	Respiratory tract fluids	Not specified	D1	Verroken et al. (2014)

Table 2 (continued)

Year and Country	Number of cases	Gender/age	Prognostic	Clinical sample	Comorbidity	Diagnosis–Outcome (D/S)	References
2011–2014 Tunisia	63	Not specified	Skin, ear, urinary, catheter, pulmonary, eye, blood, vaginal, and seminal infections	Tracheal aspirate, wound, vagina, ear, and eyes fluids; sperm, blood, venous and urinary catheters	Not specified	Cellulitis, leucorrhoea, otitis, intrauterine and urinary infection, pneumonia, tracheobronchitis, congenital infection ocular, catheter-related infection, sepsis, and sterility—Not specified	Alibi et al. (2017)
<i>Single case report in health units</i>							
1976 USA	1	M 79	Anorexia, fatigue, and dyspnea	Blood and pleural fluid	Acute pneumonia	D	Bowstead and Santiago (1980)
1986 UK	1	M 22	Multiple bone fractures	Tracheal fluid	Not specified	Not specified	Barr and Murphy (1986)
1989 USA	1	F 64	Not specified	Blood	Diabetes mellitus and neoplasia	S	Dall et al. (1989)
1990 USA	1	M 76	Acute aortic valve insufficiency and severe pulmonary edema	Blood	Cardiac insufficiency	Endocarditis—D	Markowitz and Coudron (1990)
1992 UK	1	M 69	Chronic airway obstruction, dyspnea	Sputum	Not specified	Not specified—S	Cowling and Hall (1992)
1992 Spain	1	M 27	Intracerebral hemorrhage, fever, and mucopurulent rhinorrhea	Pleural fluid	Not specified	Cardio-respiratory arrest—S	Martínez-Martínez et al. (1994)
1994 USA	1	M 54	Fever, cough, and dyspnea	Blood	Hypertension and hemorrhoid	Endocarditis—S	Rufael and Cohn (1994)
1995 Canada	1	M 23	Headache, nausea, vomit, photophobia	Blood, and cerebrospinal fluid	Pseudomeningocele and paralysis of the right arm	Meningitis—S	Weiss et al. (1996)
1996 Canada	1	M 68	Anorexia, fatigue, dyspnea, fever and atrial fibrillation	Blood	Diabetes mellitus, congestive heart failure, and pulmonary insufficiency	Endocarditis—S	Juurink et al. (1996)
1996 UK	1	F 41	Nipple sensitive protuberance	Surgical debridement and microscopy of tissue	Not specified	Necrotic abscess—Not specified	Stone et al. (1997)
1998 USA	1	Not specified	Pain, edema, fever, erythema on left elbow	Not specified	Accidental scalp injury	Septic synovitis—Not specified	Cone et al. (1998)
2000 Netherlands	1	Not specified	Enterocutaneous fistula, fever, lethargy, and confusion	Blood	Graft with aorto-femoral prosthesis, hyperthyroidism and hypertension	Diverticulitis, intestinal perforation and graft infection, endocarditis with death by another pathogen—D	Keijman et al. (2000)

Table 2 (continued)

Year and Country	Number of cases	Gender/age	Prognostic	Clinical sample	Comorbidity	Diagnosis–Outcome (D/S)	References
2001 Spain	1	M 60	Fever and backache	Blood	Lumbar spine fractures	Vertebral osteomyelitis—S	Fernández-Ayala et al. (2001)
2002 Spain	1	F 72	Hip fracture	Blood	Diabetes mellitus, cardiac insufficiency	Sepsis with hemodynamic instability—D	de Arriba et al. (2002)
2003 Spain	1	M 69	Fever, lower extremity chronic ischemia, injuries in fingers foot	Blood, skin biopsy and tissue culture	Thyroidectomy and tumor metastasis to the lungs	Pleural effusion and pneumonia—Not specified	Martín et al. (2003)
2005 USA	1	M 63	Abdominal pain	Hemoculture (GB and PC) and pancreatic aspirate	Not specified	Cholecystitis, gallstone pancreatitis and sepsis not defined—Not specified	Lee et al. (2005)
2006 Northern Ireland	1	F 77	Fever, anemia and septic embolism	Blood	Chronic arthralgia	Endocarditis—Not specified	Elshibly et al. (2006)
2007 USA	1	M 87	Pain, edema, and erythema in lower limbs extremities	Synovial fluid, blood	Osteoarthritis, cardiac insufficiency	Joint infection and pulmonary infiltrate—S	Scholle (2007)
2008 Taiwan	1	F 83	Loss of consciousness and sudden cardiac arrest	Blood, intravenous-catheter	Chronic kidney disease and cardiac insufficiency	Septic shock—D	Fu-Lun et al. (2012)
2009 Brazil	1	M 27	Ulcer, edema, and purulent secretion	Lymph node, biopsy of skin lesion	Not specified	Not specified—S	Superti et al. (2009)
2010 Italy	1	F 71	Fever, pain, and purulent secretion	Blood, smear of purulent secretion	Pacemaker replacement	Endocarditis (with device removal)—S	Oliva et al. (2010)
2011 Spain	1	F 47	Fever, dry cough and dyspnea	Bronchial aspirate secretion	HIV infection	Pneumonia—S	Roig-Rico et al. (2011)
2012 Spain	1	M 78	Fever and chronic kidney insufficiency	Not specified	Diabetes mellitus and pacemaker implant	Endocarditis—S	Fernández Guerrero et al. (2012)
2013 India	1	M 57	Dysphagia, and dysphonia	Not specified	Carcinoma	Laryngectomy—S	Biswal et al. (2014)
2013 India	1	M 37	Blunt trauma in left lower limb with diffuse edema	Ulcer secretion	Not specified	Necrotizing fasciitis—S	Gandham et al. (2013)
2014 USA	1	M 84	Pain in the right knee and fever	Aspirated fluid	Diabetes mellitus, cardiac insufficiency and deep venous thrombosis	Not specified—S	Westblade et al. (2014)
2014 Brazil	1	F 72	Pleuritic chest pain, cough with mucopurulent sputum, dyspnea	Lung biopsy	Coronary artery disease and hypertension	Multiple nodules and cavitary lung lesions—D	Severo et al. (2014)

Table 2 (continued)

Year and Country	Number of cases	Gender/age	Prognostic	Clinical sample	Comorbidity	Diagnosis—Outcome (D/S)	References
2015 Korea*	1	M 64	G-tube replacements and fever	Blood	Hypertension, diabetes mellitus and encephalopathy	Bacteremia and urinary tract infection—S	Yoo et al. (2015)
2016 Colombia	1	M 13	Triplane ankle fracture	Purulent secretion	Chronic post-operative injury	Wound healing—S	Beltrán-Arroyave et al. (2016)
2016 Greece	1	M 76	Fever, cough, and severe respiratory infection	Blood and urine	Smoking, myelodysplastic syndrome, atopic dermatitis / eczema	Severe sepsis—D	Chatzopoulou et al. (2016)
2016 Korea	1	M 55	Fever and lethargy	Blood	Traumatic subdural hemorrhage	Endocarditis—S	Hyo-Lim et al. (2016)
2016 India	1	M 27	Lower-limb edema	Not specified	Pansystolic at apex	Rheumatic heart disease and infectious endocarditis—S	Jagadeeshan et al. (2016)
2016 Tunisia	1	M 28	Cranial polytrauma and fever	Cerebrospinal fluid	Not specified	Meningitis, ventilator-associated pneumonia and urinary tract infection—Not specified	Kammoun et al. (2016)
2017 USA	1	M 62	Fever, bacteremia	Blood	Severe cardiopathy	Not specified—S	Ajmal et al. (2017)
2017 Spain	1	M 84	Fever, acute monoarthritis of knee with microcrystalline arthropathy and functional involvement	Aspirated fluid	Pulmonary disease and cardiac insufficiency, and nephrectomy	Not specified—S	Collada et al. (2018)
2017 Japan	1	F 49	Dyspnea due to severe left ventricular insufficiency and disseminated intravascular coagulation	Blood and, intravenous-catheter	Cardiac insufficiency treated with pacemaker implant	Not specified—D	Daisuke et al. (2017)
2018 USA	1	M 68	Skin lesions and graft versus host disease (pancytopenia on bone marrow)	Blood and biopsy	Hepatitis C, cirrhosis, hepatocarcinoma and transplant	Not specified—D	Gehlhausen et al. (2018)
2019 Japan	1	M 68	Fever, abdominal pain, intraperitoneal lesion in the peri-duodenal adipose tissue (suggestive of abscess)	Blood biochemistry, and culture	Diabetes mellitus and pancreas-kidney transplantation	Not specified—S	Hagiya et al. (2019)

Table 2 (continued)

Year and Country	Number of cases	Gender/age	Prognostic	Clinical sample	Comorbidity	Diagnosis–Outcome (D/S)	References
2020 China	1	M 57	Chest pressure and dyspnea (in hemodialysis)	Blood, sputum, pleural fluid and catheter tip	Diabetes mellitus, chronic kidney disease pulmonary infection and cardiac insufficiency	Septic shock—D	Ge et al. (2020)
2020 USA	1	M 78	Pain in the left knee	Aspirate culture (left knee joint)	Diabetes mellitus, osteoarthritis, and prostate cancer	Septic arthritis bone destruction—Not specified	Hollnagel et al. (2020)

*First case of *C. striatum* infection in Korea. In years 1977–1985, 1987, 1988, 1991, 1993, and 1999, they were not found infection records by *C. striatum* in the literature
 COPD chronic obstructive pulmonary disease, D dead, F female, GB gallbladder, HIV human immunodeficiency viruses, M male, PC peritoneal cavity, S survivor, T type, UK United Kingdom, USA United States of America

arthritis were also described for pediatric oncology patients from the St Jude Children Research Hospital (Tennessee, USA) (Adderson et al. 2008); the first case of infection in urinary tract by *C. striatum* in outpatient patient, without predisposing factors (López et al. 2009).

Susceptibility to antimicrobial agents

The incidence antimicrobial-resistant bacterial pathogens isolated from community-acquired or nosocomial infections is a Public Health problem worldwide, including Commissions for Control and Prevention of Hospital Infections in many health institutions, Brazilian Health Regulatory Agency (ANVISA), Centers for Disease Control and Prevention (CDC/USA), and World Health Organization (WHO) (Oliveira et al. 2009).

Antimicrobial resistance has evolved rapidly, leading to therapeutic failure and, consequently, limitations on treatment options; for this reason, the discovery of new drugs with bactericidal properties becomes even more necessary. In the last 40 years, only two drugs were introduced on the market: linezolid and daptomycin (Caumo et al. 2010).

The dissemination of MDR pathogens in hospital environment has been of concern due to increase in rate of acquired resistance to β -lactam antimicrobials, clindamycin, erythromycin, ciprofloxacin, and gentamycin by *Corynebacterium* species. Currently, vancomycin, teicoplanin, and linezolid are the most active in vitro drugs against *Corynebacterium* (Yoon et al. 2011; Reddy et al. 2012). Except for the effective activity of vancomycin against *Corynebacterium*, the variability in resistance acquisition of other classes of antimicrobials highlights the need for continuous surveillance of resistance profiles in these species (Weiss et al. 1996).

During the last decades that selective pressure exercised by previous treatments with antimicrobials, induced the growth of *C. striatum* as the second most prevalent coryneform microorganism in immunocompromised patients (Adderson et al. 2008; Campanile et al. 2009; Souza et al. 2020). Nevertheless, the criteria for evaluation of susceptibility to antimicrobials for *Corynebacterium* still are not standardized; some authors suggest that cases of total antibiotic resistance should be reported, that is, absence of any zone (halo) of inhibition in Antimicrobial Susceptibility Test (AST), by the disk-diffusion method in Mueller–Hinton agar medium (MHA), to understand the behavior of different species of this genus under exposure to the drugs in the treatment of infections (Díez-Aguilar et al. 2013). Data emphasize the need for a continuous survey of antibiotic susceptibility for *Corynebacterium* spp., especially in tropical and developing countries where diphtheria is endemic and invasive infections may occur, as already done for decades in the Brazilian Laboratory of Diphtheria and Corynebacteria



Fig. 2 Worldwide distribution of 254 reported *Corynebacterium striatum* cases of human infections and/or nosocomial outbreaks from year 1976 to 2020: Canada (1), United States of America (2), Colombia (3), Brazil (4), Netherlands (5), Belgium (6), United Kingdom (7), Northern Ireland (8), Italy (9), Spain (10), Greece (11), Tunisia (12), Israel (13), India (14), China (15), Korea (16), Japan (17), and Taiwan (18). Cases and/or outbreaks were reported in Europe ($n=124$), Africa ($n=64$), Asia ($n=36$), South America ($n=17$), and

North America ($n=13$). Nosocomial outbreaks were reported in Belgium ($n=24$), Spain ($n=21$), Brazil ($n=14$), Netherlands ($n=14$), and Italy ($n=13$). Multiple and single cases were reported in health units China ($n=1$), Colombia ($n=1$), Greece ($n=1$), Netherlands ($n=1$), Northern Ireland ($n=1$), Taiwan ($n=1$), Brazil ($n=2$), Canada ($n=2$), Korea ($n=2$), India ($n=3$), Israel ($n=3$), United Kingdom ($n=5$); Spain ($n=7$); United States ($n=11$); Japan ($n=26$); Italy ($n=37$), and Tunisia ($n=64$)

of Clinical Relevance (LDCIC) (Camello et al. 2003; Martins et al. 2009; Baio et al. 2013; Souza et al. 2019).

An increasing number of reports of nosocomial infections due to MDR *C. striatum* clones have been documented in several countries such as Italy, Spain, The Netherlands, USA, China, and Japan (Adderson et al. 2008; Boltin et al. 2009; Campanile et al. 2009; Wong et al. 2010). However, in developing countries, including Latin America, notifications MDR *C. striatum* infections remain occasional, possibly due to the need for qualified professionals in performing accurate isolation and identification of slow-growing Gram-positive irregular rods microorganisms. Additionally, the requirement of many phenotypic tests and the necessity of costly, sophisticated procedures make it difficult or even impossible to identify coryneform species in laboratories with scarcity of resources (Camello et al. 2003; Pimenta et al. 2008; Superti et al. 2009; Torres et al. 2013).

In Japan, *C. striatum* strains demonstrated variable susceptibility rates to β -lactams and aminoglycosides, in addition to high levels of resistance for erythromycin,

tetracycline, rifampicin, and ciprofloxacin, and 100% susceptibility to vancomycin. Pulsed-field Gel Electrophoresis (PFGE) analysis of *C. striatum* characterized 14 pulsotypes A, D, and E PFGE types associated with nosocomial outbreaks of respiratory origin and subtypes A1, A2, D2, and E with resistance to a wide variety of antimicrobial agents (Otsuka et al. 2006). In Spain, all *C. striatum* strains isolated from nosocomial outbreaks showed resistance to three or more antimicrobials from different classes and were described as MDR, of which 65% were resistant to four or five classes of antibiotics; 6.9% susceptible only to imipenem and vancomycin and 11% susceptible only to vancomycin (Renom et al. 2007).

In South America, cases of *C. striatum* infections and nosocomial outbreaks were only reported in Brazil. *C. striatum* strains were isolated from different colonization sites, including the upper and lower respiratory tract, and surgical wounds of cancer patients from a reference center located in Rio de Janeiro (Martins et al. 2009). In 2009, *C. striatum* strains also triggered an outbreak in a care hospital located at

the Rio de Janeiro metropolitan area, Brazil; where *C. striatum* strains were isolated in ICUs and surgical wards, mainly from tracheal aspirates of patients undergoing endotracheal intubation procedures and were mostly MDR. About 87% of the strains belonged to PFGE-types I and II and were related to the death of five infected patients. Surprisingly, only adult patients were colonized by MDR *C. striatum* strains and 50% had age higher than 50 years. Infections by these MDR *C. striatum* clones were frighteningly correlated to death (Baio et al. 2013).

There is still limited database available for *C. striatum*, such as PulseNet (<http://www.cdc.gov/pulsenet>) that allows the comparison of standards of PFGE observed in different nosocomial outbreaks in different countries. Studies performed during a nosocomial outbreak in Italy evidenced profiles such as SwaI-PFGE with band size varying between 48.5 and 533.5 kb (Campanile et al. 2009). In Brazil, MDR *C. striatum* strains isolated during an outbreak expressed PFGE-profiles such as SwaI-PFGE of *C. striatum* with band size varying between 97.0 and 533.5 kb (Baio et al. 2013). Comparative analysis between the Italian and Brazilian outbreaks revealed the absence of band sizes suggesting differences among MDR strains (Campanile et al. 2009; Baio et al. 2013). Moreover, phenotypic analysis of MDR *C. striatum* strains isolated during outbreaks in Brazil and in The Netherlands were found to express different biotypes: nitrate/pyz-positive and sucrose-negative, respectively (Brandenburg et al. 1996). The mechanisms of resistance to antimicrobial agents and tolerance to antiseptic and disinfectants of *C. striatum* strains need further investigation; however, it is known that the low-permeability external wall, the great lipid content, and the capacity of forming biofilm can contribute to tolerance to various antimicrobial agents (Souza et al. 2019, 2020).

Control of *C. striatum* dissemination in hospital environment

Hospital infections are of epidemiological relevance in both nosocomial and Public Health assistance due to raise in morbimortality rates, and increase time of permanence of patients in hospitals, with irreparable economically and socially consequences. Usually, higher index of infection occurs in ICUs than in the other hospital areas, partially due to immunodeficiency conditions of patients and interaction with pathogens present in contaminated surfaces (ANVISA 2000). There is a worldwide concern with control nosocomial environmental conditions due to recurrent outbreak and varied types of infections caused by MDR pathogenic species. Control of nosocomial outbreaks require cautious environmental decontamination mainly dependent of specific routines procedures and particular technical training. Moreover, antimicrobial therapies with a rational use of

antibiotics of hospitalized patients with infectious diseases should be also taken into consideration (ANVISA 2004, 2014). Hospital Infection Control Commission (HICC) is responsible for standardization of routine and protocols with employee training, selection of chemical decontaminating agents, application of updated techniques of cleaning, decontamination, and disinfection, with the constant evaluation of the effectiveness of antimicrobial agents via Brazilian standardized protocols. Clinical invasive procedures performed in children and adult's attendance in nosocomial units, especially in critical sectors, may contribute to Infections Related to Health Care (IRHC), including surgical treatment and insertion of medical-invasive devices (ANVISA 2004, 2014).

Despite advanced sterilization and asepsis techniques, hospital-acquired infection due to invasive procedures remain a problem, partially due to enhancement of resistance to antimicrobial agents of bacterial pathogens (Renom et al. 2007). Constant reports of transmission of infectious agents during invasive procedures are arising from inefficiency in cleaning and disinfecting surgical environments, but mainly from inappropriate decontamination of hospital materials (Howie et al. 2008). Several chemical agents have been used to control bacterial growth in hospital environments, both in the presence as well as in the absence of organic matter. However, the choice of the appropriate chemical agents for each different type of disinfection as well as the disinfection method used for each type of surface is essential to obtain a controlled hospital environment with minimal risk of infections (Rutala and Weber 2008; Vermelho et al. 2008).

Glutaraldehyde (GA) stands out for its broad spectrum, among the components that can be used as disinfectants in the hospital environment, acting against Gram-positive and Gram-negative pathogens, mycobacteria (especially, *Mycobacterium tuberculosis*), as well as some viruses, fungi, and their spores that can cause hospital infections. The microbicidal activity of this agent comes from the alkylation of sulfhydryl, hydroxyl, carboxyl, and amino groups of microorganisms, changing DNA, RNA, and protein synthesis, with consequent inhibitory action on transport and enzyme systems, where the access of the substrate to the enzyme is compromised. Sporicidal activity of glutaraldehyde is related to interaction with the spore surface, provoking the hardening of external layers. In many hospitals, non-corrosive glutaraldehyde 2% solution at pH 8.0 (activated glutaraldehyde/alkaline), has been used to disinfect materials with surgical purposes in critical and semi-critical environments, but cannot be subjected to heat (rubber and plastic). Unfortunately, the use is limited high-level disinfection due to glutaraldehyde toxicity (Lorena et al. 2009).

Peracetic acid has been suggested as an alternative to replace glutaraldehyde in disinfection of materials in critical

and semi-critical environments, for its effectiveness against several pathogens, as well as its bactericidal, tuberculicidal, virucidal, fungicidal, and sporicidal action, even in the presence of organic matter, Peracetic acid has high oxidizing power in cellular components, acting on the cytoplasmic membrane and deactivating the physiological functions, including the osmotic barrier. However, some disadvantages include reduced time of action post-dilution (a solution at 1% loses activity in 6 days by hydrolysis or oxidation in the presence of iron and copper), low stability in stock, and the need for specialized handling, due to its corrosive activity that can cause skin irritation (Block 2001; Sattar and Springthorpe 2001; McDonnell 2007).

Sodium hypochlorite (NaClO) use is limited to abiotic surfaces and other materials that do not come into direct contact with the patient due to a high corrosive power. NaClO is a salt of hypochlorous acid, in equilibrium with the hypochlorite anion that has high oxidizing power due to the neutral charge and diffuses easily through the cell wall of bacteria (Andrade 1988).

Potassium monopersulfate is a new chemical agent, which acts through oxidizing sulfhydryl groups present in proteins, thus eliminating microorganisms. The most important characteristic is the activity in the presence of organic matter, besides not being corrosive to metals. However, it has been more used in materials in the non-critical environment (medical office, pharmacy; that is, where there is no risk of transmission of infection as well as no patients), due its low effectiveness in mycobacteria, the loss of activity after 7 days of activation, the necessity of technically qualified professionals for dilution maintaining their color, as reduction of intensity in color means decreased effectiveness (Rutala et al. 1996; Silva et al. 2013).

The ortho-phthalaldehyde was initially considered a high-level disinfectant by the Food and Drug Administration (FDA), for interacting with proteins and amino acids of microorganisms. The benefits when compared with glutaraldehyde includes toxicity, odor, and good stability in pH ~ 3.0–9.0, not causing irritation to the eyes nor to the airways and it is non-teratogenic and non-mutagenic nature. However, it has the disadvantages of staining the skin, mucosa, and other surfaces exposed to the environment, as well as causing hypersensitivity in patients with repeated exposure and having a higher cost than glutaraldehyde, while having low sporicidal activity (Psaltikidis et al. 2014).

The glucoprotamine comes from a conversion reaction of the amino acid L-glutamic acid with cocosamine, a substance extracted from the coconut. Although the mechanism of action remains unclear, the effectiveness is proven, and correlation with the oxidation of vital substances of microorganisms is a possibility. Glucoprotamine has ecologically important advantages, since it is biodegradable and its disposal does not damage the environment, making

neutralization unneeded. Moreover, glucoprotamine presents a high spectrum of action against microorganisms, a noncorrosive activity in addition to affinity with most metals, such as stainless steel, brass, aluminum, and others (Widmer and Frei 2003).

Only a few studies were found available in the literature concerning the effects of biocidal agents in *Corynebacterium* spp. pathogens. *Corynebacterium* species are included among as the most resistant pathogenic species expressing resistance during analysis of efficiency of disinfection protocols used in health care instruments and environments, especially *C. striatum* and *C. amycolatum*. Previous research detected *Corynebacterium* species after gastrointestinal endoscopes submitted to disinfection with 2% peracetic acid or 2% glutaraldehyde solutions, during periods of exposure up to 30 min. Comparative analysis among different biocidal agents showed in vitro microbicidal activity of 5% povidone iodine, 4% chlorhexidine digluconate and 0.01% hypochlorous acid solutions for *C. striatum* and *C. amycolatum* strains, indicating efficiency in preoperative antisepsis (Anagnostopoulos et al. 2018). Chlorhexidine 0.05–0.5% solutions have been used as a skin cleanser for surgical scrubs, as a cleanser for skin wounds, for preoperative skin preparation, germicidal hand rinses, ocular conjunctiva, and varied mucosal surfaces, in addition to treatment of umbilical cord. Recently, a comparative analysis of disinfection efficiency between two associations of biocides (0.5% chlorhexidine and 70% ethyl alcohol versus 1% iodine and 70% ethyl alcohol solutions) used in orthopedic surgeries, showed that *Corynebacterium* pathogenic species were included among the group microorganisms mostly isolated from skin surface after surgical procedure (Shadid et al. 2019). Therefore, treatment with chlorhexidine during preoperative procedures led to a significant inhibition of *Corynebacterium* spp. growth condition; however, it did not exert microbicidal effect on biotic (skin) surfaces in vivo, as expected (Gili et al. 2018).

Nowadays, infections related to health services (HAIs) due to MDR and multidrug-susceptible (MDS) *C. striatum* should not be underestimated, including patients using invasive medical devices. Disinfection and antisepsis are of primary importance in controlling nosocomial infections and outbreaks by pathogens expressing multiple resistance to antimicrobial agents used in therapy. Several studies reported the efficacy of disinfectants and antiseptics agents and correlation with technical procedures mostly on abiotic surfaces. Phenotypic and genotypic properties of microorganisms, including mechanisms of survival and resistance to antimicrobial agents, should be also a matter of concern, considering the efficacy of disinfectants and antiseptics agents. A recent study verified the ability of biofilm formation by *C. striatum* strains on abiotic substrates, including steel surfaces, and survival of sessile forms in the presence

of GA. Moreover, bovine serum albumin (BSA), organic substance, increased the survival of planktonic and sessile forms in the presence of GA. Data demonstrated that hospital staff should be aware of dissemination and eradication of HAIs by *C. striatum* presenting resistance to biocides, including high-level disinfectants, such as GA (Souza et al. 2020).

The presence of organic matter is related to the ineffectiveness of chemical agents, as some agents have reduced action in the presence of carbon chains. Assessing the influence of organic matter on the disinfection process is important, as the materials from the critical and semi-critical environments are in direct contact with organic substances such as pus, blood, serum, and others (Lewis and Arens 1995). Mechanical cleaning with soap and water, performed manually with a brush and individual protection equipment (IPE), aims to remove all organic material, and reduce the presence of microorganisms in surgical materials, so that there is no interference in antimicrobial activity of disinfectants, or does not lead to the formation a physical barrier of protection to microorganisms during disinfection and sterilization processes by physical and chemical means. The meticulous cleaning of surgical materials, before submitting them to disinfection or sterilization, is a unanimous and universal procedure (Souza et al. 1998). The cell wall of Gram-positive bacteria has a high concentration of several biochemical compounds such as lipopolysaccharide (LPS), lipids with a very intense hydrophobic profile, granting the favorable properties of tolerance to hydrophilic chemical agents and of adhesiveness to hydrophobic surfaces. Adhesion and persistence mechanisms presented by microorganisms, especially under stress conditions, such as adhesins and invasins, enzymes are also capable of neutralizing the oxidizing action and sequestering micronutrients and the ability to produce biofilm that collaborate to resist the action of biocidal agents (Costerton et al. 1999). In addition, other factors may also change the action of chemical agents in disinfection processes, such as the acquisition of resistance genes through genetic transfer, mechanisms of pumping chemical substances out of the bacterial cytoplasm (efflux pumps), high-molecular-weight proteins found in the outer membrane of bacteria (porin channels) (Costerton et al. 2003). Deficiencies in the porin channels (proteins exposed on the surfaces of the bacterial cell, which usually transport molecules like antibiotics and disinfectants to the cell interior) can also represent a mechanism of tolerance to chemical agents especially to aldehyde-based agents, like glutaraldehyde and ortho-phthalaldehyde (Svetlíková et al. 2009).

The increased recognition of the pathogenic potential of *C. striatum* by health professionals and researchers, and investigations of virulence and multidrug-resistance mechanisms have been currently considered (Oliva et al. 2010; Díez-Aguilar et al. 2013; Ramos et al. 2019; Souza et al.

2019, 2020). Recent publications reveal the ability of *C. striatum* to adhere to various abiotic surfaces and to form biofilms in catheter models in vitro, allowing for an association between the increase in biofilm formation, multi-resistance antibacterial, and clonality of strains. The clinical isolates of different types of PFGE expressed a high capacity to form biofilms on hydrophilic abiotic surfaces (glass; positive charge) and hydrophobic (polystyrene; negative charge), including polyurethane catheter surfaces (positive charge). Nowadays, dissemination among patients through contaminated hands of health professionals, abiotic surfaces, and invasive medical procedures is a matter of concern (Moore et al. 2010; Díez-Aguilar et al. 2013; Souza et al. 2015, 2020) (Fig. 1c, d). However, little is known about its virulence factors that can contribute for Health Care Related Infections (HCRI) (Souza et al. 2015; Ramos et al. 2019). Relevant contributing factors to *C. striatum* hospital infections, include resistance gene transfer, inappropriate, and irrational use of antimicrobials promoting the selection of resistant bacteria, inefficiency in cleaning, and decontamination of hospital surfaces and materials used in critical areas (such as the surgical and sterilization center, hemodialysis, lactation, burn treatment, mortuary, laboratory and expurgation) and semi-critical (wards, rooms, ambulances, and ambulatories) (Rutala et al. 1996; Vermelho et al. 2008).

Discussion

MDR strains have been a concern among epidemiologists and the entire medical community, due to being isolated both in the hospital environment and in the community (Santos 2004; ANVISA 2007). The search for strategies to reduce the dissemination of HCRI is currently a worldwide concern (Santos 2004; ANVISA 2007). The mechanisms involved in antimicrobial resistance are increasingly well understood. Resistance can be a natural property of a microorganism (intrinsic), or acquired by mutation, acquisition of plasmids, and transposons. Studies related to the development of multi-resistance in *C. striatum* have focused on the presence of genes of resistance, such as *erm(X)*, encoding resistance to erythromycin and clindamycin, *tetA* and *tetB*, encoding resistance to tetracycline, oxytetracycline, and oxacillin, *cmx* and *aphA1*, encoding resistance to aminoglycosides and chloramphenicol (Campanile et al. 2009). Many measures are being taken in Brazil to control the rise of MDR strains of *C. striatum* (Santos 2004; ANVISA 2007). There are many promises for the development of new antimicrobials and disinfection products for medical–surgical materials. However, many barriers must be overcome, as the benefits of implementing a new drug should outweigh the disadvantages. New studies have sought to investigate therapeutic alternatives

for infections caused by multi-resistant bacteria, like synergistic combinations of two or more antibiotics, increasing the effectiveness and decreasing toxicity of the medication (Soares 2001; Mitsugui et al. 2008).

Disinfectants and antiseptics are used extensively in hospitals and other healthcare institutions for a variety of topical applications and on various surfaces. They are an essential part of infection control practices and help prevent nosocomial infections. The widespread use of antiseptic and disinfectant products has led to some investigations on the development of microbial resistance, particularly a cross-resistance for antibiotics. Antimicrobial activity can be influenced by many factors, such as chemical formulation, presence of organic waste, temperature, drug dilution, and decontamination method (Rutala and Weber 2008; Vermelho et al. 2008). Biocides when properly used and in conjunction to other procedures in infection control are essential in combating HCRI and eradicating MDR microorganisms. If management is inefficient, improper use of biocides during cleaning processes in the hospital environment can contribute to the persistence and dissemination of opportunistic pathogens, both in hospitals and in the community (McDonnell and Russell 1999).

Therefore, *C. striatum* strains have been increasingly verified as a nosocomial pathogen of severe infections and outbreaks in different continents, but mostly in industrialized countries. Multidrug-resistant *C. striatum* clones may be related to varied types of infections, especially in long-term hospitalized patients with prolonged exposure to broad-spectrum antibiotics and admitted in ICU or surgical wards using continuous or prolonged medical devices and respiratory recuperation, including patients with advanced chronic respiratory disease (mainly among elderly male patients). *C. striatum* strains may be transmitted between patients, from person to person and via caretakers. Clinical bacteriology laboratories, *C. striatum* strains are still discarded as contaminants, including when isolated from blood samples. Considering MDR nosocomial *C. striatum* strains as contaminant is a serious error, especially when isolated from chronically impaired patients using invasive devices (Superti et al. 2009; Wong et al. 2010; Baio et al. 2013; Díez-Aguilar et al. 2013; Savini et al. 2013).

Future prospects

Reliable laboratory diagnosis and appropriate actions to control *C. striatum* environmental dispersion are required. Further studies remain necessary to investigate clinical, epidemiological, and microbiological features concerning *C. striatum* infections to prevent future problems and guarantee continued vigilance by laboratories and medical community.

Significance and impact of the study

In this investigation, *C. striatum* was described as a potentially multidrug-resistant (MDR) pathogenic microorganism that causes healthcare-associated infections (HAIs) and nosocomial outbreaks. Cases of severe invasive infections occur especially among immunocompromised patients who have experienced long hospital admissions, several courses of antibiotics, and/or those who made use of invasive medical devices. The present study reinforces increasing participation of *C. striatum* as etiologic agent of human diseases, in addition to accurate clinical and laboratorial diagnosis and antimicrobial susceptibility testing of *Corynebacterium* species by health professionals to prevent death of immunodeficient and immunocompetent patients.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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