Antimicrobial Resistance and Pathogenicity of *Corynebacterium Striatum* Clinical Isolates Collected from Three Tertiary Hospitals in China

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Research

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Abstract

Background

Antimicrobial resistance and patient-to-patient transmission of *Corynebacterium striatum* (*C. striatum*) clinical strains were frequently reported in recent years. Even worse, daptomycin resistant isolates were found in some studies and possible resistance mechanism was explored. Also, few investigations revealed the diversity of resistance feature and potential pathogenicity of *C. striatum* strains with different genotypes. However, less is known about the possible differences of resistance feature and pathogenicity of *C. striatum* clinical strains from different hospitals at a long distance.

Methods

C. striatum clinical strains were isolated and identified with VITEK-2 ANC card, MALDI-TOF microTyper and 16S rRNA sequencing technique. Broth microdilution method was used to detect the antibiotic susceptibility profiles of 420 *C. striatum* clinical isolates, and PFGE method was used to discriminate different clones. Furthermore, in vitro adherence assay and mouse toxicity assay were performed to assess the pathogenicity of the strains with different genotypes.

Results

420 *C. striatum* isolates were all sensitive to vancomycin, linezolid and daptomycin. Based on antibiotic resistance results, 420 strains were classified into 19 resistance patterns, when R1, R2 and R3 patterns accounted for 45.2%(190/420), 20.2%(85/420) and 22.4%(94/420), which were all multi-drug resistant patterns. PFGE typing results showed that 107 *C. striatum* strains were classified into 52 types (T01-T52), when 4 epidemic clones(T36, T28, T32, T14) accounted for 14.02% (15/107), 11.21%(12/107), 5.61%(6/107) and 3.73%(4/107), respectively. All of these 4 clones belonged to resistance patterns R1, R2 and R3. Among 27 *C. striatum* strains, 92.6%(25/27) strains showed moderate to strong in vitro adherence abilities, while only 7.4%(2/27) strains showed weak adherence ability on polystyrene surfaces. Furthermore, mouse lethality of different strains differed greatly, when non-dominant clone(Strain NMGYC339, T24) showed the strongest mouse lethality(90.0%).

Conclusions

The majority of *C. striatum* strains were multi-drug resistant and few dominant clones could persist for a long time in hospital environment. The in vitro adherence abilities and mouse lethality among different clones differed greatly. The resistance and pathogenicity of *C. striatum* clinical strains should be paid more attention to, especially for some specific clones at different hospitals.

Introduction

In recent years, more and more reports regarding *Corynebacterium striatum* (*C. striatum*) were published, since most of the *C. striatum* strains were found to be multi-drug resistant and the only effective antibiotics were limited to vancomycin, linezolid [1–3]. Even worse, daptomycin resistant isolates were recently reported and its resistance mechanism was explored, which pose a more knotty issue for clinicians [4–6]. Furthermore, some recent reports revealed that *C. striatum* can lead to multi-site invasive infections, such as bacteremia,

monomicrobial bone and joint infection, prosthetic valve endocarditis [7–9], which suggest that *C. striatum* may possess stronger pathogenicity, especially for the patients with specific risk factors [10, 11].

It is reported that *C. striatum* can colonize onto multiple environmental and bodily surfaces and could transmit within patients in specific wards [12, 13]. Also, the multi-drug resistant *C. striatum* clones seemed to be with stronger adhesion abilities^[14], which was consistent with one of our previous study [15], which may partly explain the reason why *C. striatum* can rapidly transmit within hospital environment. Moreover, Souza C et al [16] reported that *C. striatum* could lead to the death of *Caenorhabditis elegans*, and virulence potential varied among different *C. striatum* clones. The pathogenicity potential of *C. striatum* strains isolated from different origins need to be further investigated.

In this study, we aim to perform a further investigation with a larger number of *C. striatum* isolates from multi-centres to better understand the actual resistance and pathogenicity features of *C. striatum*. Here, *C. striatum* isolates were collected in three tertiary teaching hospitals in China from March 2013 to May 2019, and the antibiotic susceptibility features were tested. Furthermore, the potential pathogenicity of different clones with different genotypes were investigated.

Materials And Methods

C. striatum isolation and identification

The hospitals enrolled in this study include Affiliated hospital of Inner Mongolian medical University (hospital A, 3000 beds), Shandong Provincial QianFuoShan Hospital(hospital B, 2813 beds) and Bayannaoer People's Hospital (hospital C, 1700 beds), China. From March 2013 to May 2019, all of *C. striatum* strains isolated from aseptic sites were collected and identified. The sputum samples were enrolled if they were evaluated to be qualified based on the numbers of leukocytes and epithelium using microscopy [13]. All of the cultures suspected to be *C. striatum* were routinely identified with VITEK-2 ANC card(Biometrieum, France), MALDI-TOF microTyper (Tianrui, China) and 16S rRNA sequencing technique. Only one *C. striatum* strain from the same patient was selected in this study, while the repeated ones were excluded.

Antibiotics susceptibility test

The antibiotic susceptibility test was performed using broth microdilution method, and the antibiotics tested include ceftriaxone, imipenem, erythromycin, clindamycin, gentamycin, tetracycline, vancomycin, ciprofloxacin, sulfamethoxazole, rifampin and daptomycin. The operation of susceptibility test and results analysis were performed according to Clinical and Laboratory Standards Institute guidelines (CLSI) [17].

Pulsed-Field Gel Electrophoresis (PFGE)

In general, the whole genomic DNA chromosome of the *C. striatum* was extracted, and macrorestriction digestion (Swal) and PFGE (CHEF-DR II apparatus; Bio-Rad, Hercules, CA, USA) were performed as previously reported [15]. Macrorestriction patterns were analysed using Dice coefficient with Bionumerics software (Applied Maths,

Kortrijk, Belgium, Version 5.0). The classification criteria for PFGE analysis was subjectively designated and the clones with similarity index 100% was classified to be a single type and named with a single capital letter.

In vitro adherence assay

In vitro adherence abilities on polystyrene surfaces of different *C. striatum* strains were detected quantitatively in 96-well flat-bottomed microtitre plates with a commonly used method described previously [15]. Generally, aliquots of 200 μ L of bacterial suspensions [0.2 optical density (OD) at $\lambda = 620$ nm] were added to the microplate wells and incubated for 24 h at 35 °C. After the suspension content removed, the remaining attached bacteria in each well were fixed with 99% methanol and stained with 2% crystal violet. The negative controls contained LB liquid medium only. Then 33% glacial acetic acid was used to dissolve bound crystal violet and the OD of the solution was determined ($\lambda = 620$ nm) using an enzyme immunosorbent assay reader (Tecan, Sunrise). The cut-off OD (OD_c) was defined as the mean OD of the negative control. The adhesion abilities was classified as nonadherent, weakly, moderately and strongly according to Souza C et al [14].

Mouse lethality assay

Six different strains with PFGE types and ATCC6940 standard strain were selected to do mouse lethality assay. Generally, overnight cultures of bacteria were washed twice with sterile PBS by centrifugation, and approximately 10^7 CFUs of bacteria for each strain were then added into 200 ml of PBS for inoculation. Eight-week-old BALB/c mice were intraperitoneally injected with the inoculums. The survival rates of mice were monitored for 7 days. Moribund mice were anesthetized and sacrificed prior to death. Mice were housed and monitored daily at the Animal centre of Chinese Center For Disease Control And Prevention, Beijing.

Results

Isolates distribution and Antibiotic resistance feature

For the 420 isolates analyzed in this study, 329 isolates (78.3%) were collected from hospital A, 44 isolates (10.5%) from hospital B and 47 isolates (11.2%) from hospital C.

Antibiotics susceptibility testing showed that all of the strains were sensitive to vancomycin, linezolid and daptomycin. The total resistance rates to vancomycin, linezolid and daptomycin were all 0.0%, and those to penicillin, cefepime, meropenem, ciprofloxacin, erythromycin, tetracycline, gentamicin, clindamycin, sulfamethoxazole and trimethoprim were 97.6% (410/420), 97.1% (408/420), 86.9% (365/420), 99.0% (416/420), 97.6% (410/420), 69.5% (292/420), 51.4% (216/420), 97.6% (410/420) and 95.2% (400/420), respectively, as shown in Table 1.

Table 1
Antibiotics susceptibility profiles of 420 *C. striatum* strains

Antibiotics	MIC(μ g/ml)			Percentage of resistant isolates,% (n/420)
	MIC ₅₀	MIC ₉₀	Range	
Penicillin	≥ 8	> 64	$\leq 1, \geq 4$	97.6(410/420)
Cefepime	≥ 8	> 64	$\leq 1, \geq 4$	97.1(408/420)
Meropenem	≥ 32	> 64	$\leq 4, \geq 16$	86.9 (365/420)
Ciprofloxacin	≥ 8	64	$\leq 1, \geq 4$	99.0 (416/420)
Erythromycin	32	64	$\leq 0.5, \geq 2$	97.6 (410/420)
Tetracycline	≥ 32	> 64	$\leq 4, \geq 16$	69.5 (292/420)
Gentamicin	8	≥ 32	$\leq 4, \geq 16$	51.4 (216/420)
Clindamycin	16	> 32	$\leq 0.5, \geq 4$	97.6 (410/420)
Sulfamethoxazole and trimethoprim	$\geq 8/152$	$\geq 8/152$	$\leq 2/38, \geq 4/76$	95.2 (400/420)
Linezolid	< 0.5	< 0.5	≤ 2	0(0.0)
Daptomycin	< 0.5	< 0.5	≤ 1	0(0.0)
Vancomycin	< 0.5	< 0.5	≤ 2	0(0.0)

Based on the susceptibility testing results, 420 *C. striatum* strains can be classified into 19 resistance biotypes, designating as pattern R1-R19. Among these biotypes, four biotypes (R1, R2, R3 and R4) were the dominant biotypes and were resistant or intermediate resistant to most of the antibiotics tested in this study, except vancomycin, linezolid and daptomycin. The resistance features of the 19 resistance biotypes changed diversely, as shown in Table 2. 329 isolates collected from hospital A belonged to 18 resistance biotypes, and the majority of the isolates belonged to R1(44.4%,146/329), R2 (23.4%, 77/329) and R3 (22.5%, 74/329). 44 isolates collected from hospital B were divided into 10 different resistance biotypes, and 23 isolates (52.3%), 7 isolates (15.9%) and 5 isolates (11.4%) belonged to R1, R2 and R4, respectively. 47 isolates collected from hospital C were classified into 4 resistance biotypes, and 21 isolates (44.7%), 18 isolates (38.3%) and 7 isolates (14.9%) belonged to R1, R3 and R7, respectively.

Table 2
Resistance biotypes of 420 *C. striatum* strains

Resistance biotypes	No. of Isolates(n)	Antibiotics											
		VAN	DAP	LNZ	P	FEP	CIP	SXT	E	CLI	IPM	TE	GEN
R01	190	S	S	S	R	R	R	R	R	R/I	R/I	R/I	R/I
R02	85	S	S	S	R	R	R/I	R	R	R/I	R/I	R/I	S
R03	94	S	S	S	R	R	R	R	R	R	R/I	S	R/I
R04	18	S	S	S	R	R	R	R	R	R	S	R	R
R05	8	S	S	S	S	S	R	S	R/I	R/I	S	S	S
R06	6	S	S	S	R	R	R	R	R/I	R	R	S	S
R07	3	S	S	S	R	R/I	R	S	R	R/I	R	S	S
R08	2	S	S	S	R	R	R	S	R	R	R	R	I
R09	2	S	S	S	R	R	R	S	R	R	R	R	S
R10	2	S	S	S	R	R	R	R	S	S	R	R/I	S
R11	2	S	S	S	R	R	R	S	R	R	R	S	I
R12	1	S	S	S	R	R	R	R	S	R	R	R	R
R13	1	S	S	S	R	R	R	R	R	R	S	R	S
R14	1	S	S	S	R	R	R	R	R	R	S	S	R
R15	1	S	S	S	R	S	S	S	R	R	S	S	S
R16	1	S	S	S	S	S	S	R	R	R	S	S	S
R17	1	S	S	S	S	R	R	S	S	I	S	S	S
R18	1	S	S	S	S	S	S	S	R	R	S	S	S
R19	1	S	S	S	S	S	S	S	S	I	S	S	S
Note: VAN, vancomycin; DAP, daptomycin; LNZ, linezolid; P, penicillin; FEP, cefepime; CIP, ciprofloxacin; SXT, sulfamethoxazole and trimethoprim; E, erythromycin; CLI, clindamycin; IPM, imipenem; TE, tetracycline; GEN, gentamicin.													

C. striatum strains were isolated from multiple clinical specimens. The majority of the *C. striatum* strains were isolated from sputum (72.1%,303/420) and BALF specimens (17.1%,72/420), and 1.2% (5/420) strains were isolated from blood specimens. Moreover, 52.4% (220/420) specimens were pure cultured with *C. striatum*, and 47.6% (200/420) specimens were polymicrobial, as shown in Table 3.

Table 3
Microbiological characteristics of 420 samples with *C. striatum* isolation

Parameters	
Specimens	Number(%)
Sputum	303(72.1)
Bronchoalveolar lavage fluid(BALF)	72(17.1)
Whole blood	5(1.2)
Hydrothorax and ascites	6(1.4)
Cerebrospinal fluid	2(0.5)
Urine	4(1.0)
Pus	5(1.2)
Central venous catheters	3(0.7)
Wound secretion	20(4.8)
Simultaneously isolated strains from the same specimen, n(%)	
<i>C.striatum</i> (pure culture)	220(52.4)
<i>Klebsiella pneumoniae</i>	46(11.0)
<i>Acinetobacter baumannii</i>	63(15.0)
<i>Pseudomonas aeruginosa</i>	42(10.0)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	33(7.9)
<i>Enterococcus</i> species	5(1.2)
<i>Achromobacter xylosoxidans</i>	2(0.5)
<i>Candida</i> species	13(3.1)
<i>Stenotrophomonas maltophilia</i>	17(4.0)
<i>Aspergillus fumigatus</i>	2(0.5)

PFGE results

A total of 107 *C. striatum* strains with different resistance patterns were selected to do PFGE typing and 52 different PFGE types were identified, among which type T36 (R3), type T28 (R1), type T32 (R1) and type T14 (R1) were the dominant clones, accounting for 14.02% (15/107), 11.21% (12/107), 5.61% (6/107), 3.74% (4/107), respectively. Moreover, the 4 clones presented similar antibiotic susceptibility feature and were all multi-drug resistant. These four clones were mainly distributed in neurosurgery unit and intensive care unit. For T36 clone, it prevailed in hospital A (40.0%, 6/15) and hospital B (60.0%, 9/15). T28 clone and T32 clone were only isolated in hospital C (100.0%,18/18), while T14 clone distributed in hospital A (50.0%, 2/4) and hospital C (50.0%,2/4) separately. No isolate from hospital B belonged to above four dominant clones.

In vitro adherence assay

Totally, 27 *C. striatum* clinical isolates with different PFGE types were selected to test their in vitro adherence abilities (Table 4). 92.6% (25/27) isolates could form moderate to strong in vitro adherence abilities on polystyrene surfaces, and the most adhesive isolates were QFS022 (R1,T24), QFS028 (R1,T21), QFS027 (R1,T40), NMFYC225 (R2,T04) and NMFYC339 (R1,T42), all of which were multi-drug resistant strains and only sensitive to vancomycin, linezolid and daptomycin. Only two isolates (NMFYC220 [T15] and NMFYC132 [T44]) showed weakly biofilm formation abilities.

Table 4

In vitro adherence abilities of 28 *C. Striatum* strains with different PFGE types

Strains	PFGE type	Resistance pattern	OD(620 nm)	Adhesion ability
ATCC6940	-	-	1.114	+++
QFS 022	T24	R01	2.044	+++
QFS 028	T21	R01	1.927	+++
QFS 027	T40	R01	1.643	+++
NMFYC 225	T04	R02	1.313	+++
NMFYC339	T24	R01	1.129	+++
NMFYC 338	T43	R01	1.100	+++
NMFYC177	T05	R01	0.986	+++
NMFYC 363	T47	R02	0.952	+++
NMFYC464	T49	R01	0.875	+++
QFS 026	T08	R02	0.865	+++
NMBM003	T36	R03	0.809	+++
NMFYC 236	T45	R03	0.767	+++
QFS 015	T41	R03	0.675	++
QFS024	T50	R01	0.641	++
NMBM010	T28	R03	0.618	++
NMFYC007	T32	R01	0.609	++
QFS 007	T13	R01	0.576	++
NMFYC207	T48	R02	0.537	++
NMFYC451	T14	R01	0.523	++
QFS023	T01	R15	0.480	++
NMFYC477	T38	R01	0.479	++
NMFYC412	T15	R01	0.452	++
NMFYC457	T36	R01	0.450	++
NMFYC454	T40	R02	0.424	++
NMFYC108	T45	R02	0.402	++
NMFYC220	T15	R01	0.296	+
NMFYC132	T44	R01	0.260	+

Mouse lethality assay

After intraperitoneal injection *C. striatum* (10^7 CFUs), mice died from day 1 to day 4. As shown in Table 5, seven strains showed different mouse lethality. The non-dominant clone (Strain NMGYC339, T24) showed the strongest mouse virulence (90% lethality) and strong in vitro adherence ability, which was isolated from wound secretion. No death was observed in the groups of strain NMFYC177 and strain NMFYC477.

Table 5
Mouse lethality of 7 different *C. striatum* strains

Strains	No. of mice	Date of Intraperitoneal infection with C. Striatum						Death rate(%)
		Day 0	Day 1	Day 2	Day 3	Day 4	Day 5–7	
ATCC6940	1	A	A	D	-	-	-	40%
	2	A	A	A	D	-	-	
	6	A	D	-	-	-	-	
	7	A	A	D	-	-	-	
NMGYC220	1	A	D	-	-	-	-	40%
	4	A	D	-	-	-	-	
	7	A	A	D	-	-	-	
	9	A	A	D	-	-	-	
NMGYC339	1	A	A	D	-	-	-	90%
	2	A	A	D	-	-	-	
	3	A	A	A	D	-	-	
	4	A	D	-	-	-	-	
	5	A	A	D	-	-	-	
	6	A	A	D	-	-	-	
	7	A	A	D	-	-	-	
	8	A	A	D	-	-	-	
	9	A	A	A	D	-	-	
QFS023	3	A	A	A	D	-	-	40%
	7	A	D	-	-	-	-	
	8	A	A	A	D	-	-	
	10	A	A	A	D	-	-	
NMFYC177	1–10	A	A	A	A	A	A	0%
NMFYC477	1–10	A	A	A	A	A	A	0%
NMFYC457	1	A	D	-	-	-	-	30%
	4	A	A	A	A	D	-	
	10	A	A	A	D	-	-	
Note: A, alive; D, Dead.								

Discussion

As a potential pathogen for hospitalized patients in recent years, *C. striatum* was found to be isolated from almost all types of clinical samples [18–20], especially for sputum, whole blood, cerebrospinal fluid. In this study, the 420 *C. Striatum* were mainly isolated from lower respiratory tract (89.2%, 375/420), and 52.4% samples (220/420) were purely cultured with *C. striatum*. Five *C. striatum* strains were isolated from whole blood samples, and one of the strains were repeatedly isolated from an immunosuppressed patient with infective endocarditis. Some common multi-drug resistant bacteria were simultaneously isolated with *C. striatum* in the same sample (53.1%, 223/420), including *Acinetobacter baumannii*, Methicillin-Resistant *Staphylococcus Aureus* (MRSA), ESBLs or carbapenemase producing *Klebsiella pneumoniae*. This study highlights the higher prevalence of *C. striatum* from the long stay patients, especially for the ones with specific risk factors [14, 15, 21].

Consistent with the majority of the investigations previously published [1–3], the *C. striatum* strains detected in this study were all sensitive to vancomycin and linezolid, but no daptomycin resistant isolate was observed. The resistance rates of 420 *C. striatum* strains to penicillin, cefepime, ciprofloxacin, erythromycin, sulfamethoxazole and trimethoprim and clindamycin were all higher than 95%. Moreover, it is reported that the usage of parenteral antimicrobial drugs could promote *C. striatum* acquisition [22] and the resistance rate of *C. striatum* strains to meropenem reached up to 86.9% (365/420) in this study, which suggested that prescription of carbapenems or other non-sensitive antibiotics should be carefully considered, especially for the patients with risk factors for *C. striatum* acquisition or infection.

Based on the resistance biotypes of *C. striatum* to 12 types of antibiotics tested in this study, three dominant resistance biotypes were discriminated, which were all multi-drug resistant. To further analyze the potential differences of resistance patterns of *C. striatum* from different hospitals, 420 isolates from 3 different hospitals in China were enrolled and analyzed. The isolates from hospital A and hospital C were separately distributed into at least 10 different resistance biotypes, while the isolates from hospital B were intensively distributed in 4 biotypes. The resistance features of the isolates from different hospitals varied greatly based on the results of this study. However, owing to relatively few isolates from hospital B and hospital C, the actual differences of resistance patterns of *C. striatum* isolates among these 3 hospitals still need to be explored.

To further investigate whether some dominant clones prevailed in the same hospital, PFGE typing method was employed, which revealed that 2 dominant clones (T36 and T14) were isolated from different patients in hospital A and hospital C and lasted from 2016 to 2019, which suggested that some dominant clones could exist in hospitals for a long time. Consistent with our findings, Baio PV et al [23] reported that dominant *C. striatum* clones can rapidly spread among inpatients and can exist for a long period in the same hospital [2]. Also, it is revealed that *C. striatum* could transmit from person-to-person via the hands of healthcare personnel or medical environment [24–26]. Unfortunately, based on the current data we obtained, it is difficult to confirm whether these two clones originated from the same patient in these two hospitals at a long distance. For the remaining two dominant clones (T32 and T28), they were only isolated from hospital C and the two times of nosocomial outbreak were observed from April, 2019 to May, 2019 and both of the outbreaks occurred in intensive care unit (ICU). For specific wards such as ICU, more efficient infection control measures should be implemented to better control the transmission of *C. striatum*.

Souza C et al [14] reported that *C. striatum* clinical strains can tightly adhere to several kinds of environmental surfaces or implanted medical devices [27–29] and lead to several kinds of invasive infections. Consistently,

most of the *C. striatum* strains tested in this study showed moderate to strong biofilm abilities and differed greatly. It is also noteworthy that all of the 4 dominant PFGE clones showed moderate adherence abilities on polystyrene surface, while the most adhesive strains belonged to non-dominant clones and the top three strains were all collected from hospital B. More attention should be taken for preventing catheter-related infections by *C. striatum*, especially for the strains with strong adherence abilities. Furthermore, as far as we know, it is the first study to reveal the significant mouse lethality of *C. striatum*. Also, the consistency between in vitro adherence and in vivo mouse lethality of the *C. striatum* strains was not observed in this study. The actual pathogenicity of *C. striatum* strains and possible mechanism deserves to be further investigated.

Conclusions

Most of the *C. striatum* clinical strains analyzed in this study showed multi-drug resistant features and could exist in hospitals for a long period. The antibiotic resistance patterns of *C. striatum* strains differed greatly from different districts, and most of the *C. striatum* strains can present with moderate to strong in vitro adherence abilities on polystyrene surfaces and some clones could lead to significant mouse lethality. The pathogenicity mechanism of multi-drug resistant *C. striatum* should be further explored to better prevent and control acquisition or infection of *C. striatum*.

Declarations

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Ethics approval and consent to participate

The animal study was approved by the Laboratory Animal Welfare&Ethics Committee of Chinese Center For Disease Control And Prevention (Animal ethics approval no. 2018018).

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

None

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Authors' contributions

Xiaohong Shi, Jian Zhang and Yanqiu Han are responsible for the isolates isolation and identification. Yingying LV and Roushan Liu are responsible for in vitro susceptibility test and in vitro adherence abilities. Xiaoli Du and Yingying LV are responsible for PFGE typing experiment. Xuancheng Lu and Yuan Chai are responsible for animal lethality assay. Junrui Wang is responsible for experiment design, data analysis and manuscript writing.

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Figures

Figure 1