



Corynebacterium Species Rarely Cause Orthopedic Infections

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ABSTRACT *Corynebacterium* spp. are rarely considered pathogens, but data on *Corynebacterium* spp. as a cause of orthopedic infections are sparse. Therefore, we asked how often *Corynebacterium* spp. caused an infection in a defined cohort of orthopedic patients with a positive culture. In addition, we aimed to determine the species variety and the susceptibility of isolated strains to define potential treatment strategies. We retrospectively assessed all bone and joint samples that were collected between 2006 and 2015 from an orthopedic ward and that were positive for *Corynebacterium* spp. by culture. The isolates were considered relevant to an infection if the same *Corynebacterium* sp. was present in at least two samples. We found 97 orthopedic cases with isolation of *Corynebacterium* spp. (128 positive samples). These were mainly *Corynebacterium tuberculostearicum* ($n = 26$), *Corynebacterium amycolatum* ($n = 17$), *Corynebacterium striatum* ($n = 13$), and *Corynebacterium afermentans* ($n = 11$). Compared to the species found in a cohort of patients with positive blood cultures hospitalized in nonorthopedic wards, we found significantly more *C. striatum*- and *C. tuberculostearicum*-positive cases but no *C. jeikeium*-positive cases in our orthopedic cohort. Only 16 out of 66 cases (24.2%) with an available diagnostic set of at least two samples had an infection. Antibiotic susceptibility testing (AST) showed various susceptibility results for all antibiotics except vancomycin and linezolid, to which 100% of the isolates were susceptible. The rates of susceptibility of corynebacteria isolated from orthopedic samples and of isolates from blood cultures were comparable. In conclusion, our study results confirmed that a *Corynebacterium* sp. is most often isolated as a contaminant in a cohort of orthopedic patients. AST is necessary to define the optimal treatment in orthopedic infections.

KEYWORDS *Corynebacterium*, *Corynebacterium striatum*, orthopedic infections, biofilms, susceptibility testing

Orthopedic infections, including septic arthritis of a native joint, periprosthetic joint infections (PJI), and osteomyelitis, are typically treated in specialized orthopedic centers. Most of these infections are chronic, and they are difficult to diagnose and to treat due to biofilm formation (1). A definitive criterion for orthopedic infections is growth of the same pathogen in at least two diagnostic samples or the presence of a sinus tract in implant-associated infections (2, 3). The significance of a single positive sample for skin commensals, such as coagulase-negative staphylococci, *Cutibacterium* species (formerly *Propionibacterium* species), or *Corynebacterium* species, is not fully clear. Often, skin commensals are considered sample contaminants.

The spectrum of human infections with corynebacteria is broad, ranging from community-acquired infections, such as conjunctivitis, pharyngitis, genitourinary tract infections, prostatitis, skin and soft tissue infections, and breast abscess, to nosocomially acquired infections, such as cerebrospinal fluid shunt infections, pneumonia,

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intravenous catheter-related bloodstream infections, endocarditis, postsurgical infections, urinary tract infections, and peritoneal dialysis-related peritonitis (4–12). The spectrum of *Corynebacterium* sp. orthopedic infections has not been described so far. In this study, we report on the spectrum of *Corynebacterium* isolates from patients with suspected orthopedic infections and compare it with the spectrum of species isolated from patients hospitalized in nonorthopedic wards with suspected bloodstream infections. We discriminated between infections and contaminants based on clinical and microbiological criteria and present antibiotic susceptibility data to describe treatment options.

MATERIALS AND METHODS

Orthopedic study population. The orthopedic hospital Balgrist University Hospital in Zurich, Switzerland, is a 140-bed orthopedic center in which approximately 5,000 orthopedic procedures are performed annually. In this single-center study, we retrospectively identified patients with at least one sample from synovial fluid, deep tissue/bone, or sonication fluid from implants removed between January 2006 and December 2015 that was culture positive for *Corynebacterium* spp. Bacteria labeled “coryneform bacteria,” i.e., aerobic *Actinomyces* spp., *Brevibacterium* spp., *Dermabacter hominis*, *Lactobacillus* spp., *Cutibacterium* (*Propionibacterium*) spp., and other Gram-positive rods, which were not further characterized, were excluded from our analysis. The latter were found only in single samples in a small amount or in mixed cultures. Cases with a lack of clinical data were excluded for our investigation (Fig. 1).

Variation of *Corynebacterium* species in suspected orthopedic infections compared to bloodstream infections outside orthopedic wards. We compared the various *Corynebacterium* spp. isolated from orthopedic origins with isolates recovered from blood cultures (from January 2006 to December 2015) from patients with suspected bloodstream infections hospitalized in nonorthopedic wards of the University Hospital Zurich, Zurich, Switzerland, with a wide range of medical specialties (e.g., ophthalmology, urology, gynecology, neurosurgery, vascular and heart surgery, dermatology, internal medicine, oncology).

Clinical diagnosis. All samples from the same patient, the same hospitalization period, and the same infection site were considered one diagnostic set. The number of samples with *Corynebacterium* spp., the sample type, and the results of antibiotic susceptibility testing (AST) were analyzed using the database of the Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland. According to the current guidelines of the Infectious Diseases Society of America (IDSA) (2), we classified a bacterium as a relevant pathogen when the same species was cultured in ≥ 2 samples and as a contaminant when a species was detected in only 1 of ≥ 2 samples (2). Cases with only one sample per diagnostic set were excluded for further analysis, as a distinction between infection and contamination was not possible in those cases. The patients' clinical and demographic parameters and medical history, including the time of diagnosis and follow-up, were investigated using the clinical database of the orthopedic hospital and the database of the Infectious Diseases Consultation Service of the University Hospital Zurich. We grouped patients with an infection into two groups, as follows: (i) those with a monobacterial *Corynebacterium* sp. infection and (ii) those in whom the *Corynebacterium* sp. was part of a polymicrobial infection (a *Corynebacterium* sp. and at least another pathogen in ≥ 2 samples). The clinical parameters of the symptoms, such as fever, redness, swelling, and the presence of a sinus tract at the infection site, were reviewed. Patients with an infection were grouped into those with infections associated with joint arthroplasty (PJI) or another orthopedic implant (implant-associated infection), a foot or pressure ulcer with or without osteomyelitis, septic arthritis without foreign material, or a deep soft tissue infection associated with surgery. Osteomyelitis was defined when histopathology confirmed acute osteomyelitis (the presence of neutrophils) or chronic osteomyelitis (the presence of bone necrosis or sequester), when bone biopsy specimens showed the growth of a *Corynebacterium* sp., or when osteomyelitis was assumed by magnet resonance imaging (MRI).

In the control group with bloodstream infections, we diagnosed an infection when either ≥ 2 blood cultures were positive with the same *Corynebacterium* sp. or only 1 blood culture plus a vascular catheter was positive and sepsis criteria were fulfilled.

The study was performed in line with the current ethical guidelines and approved by the Institutional Review Board in Zurich, Switzerland (KEK no. 2016-00145).

Microbiological methods. Prediagnostic and diagnostic processing was done as previously described (13). From 2006 to 2011, Gram-positive rods were identified by an in-house standard scheme by means of biochemical methods (14). From 2012 on, strains were identified using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) using a Bruker MALDI Biotyper as described elsewhere (15). Reference database V.3.3.2.0 (3,995 entries) or later database versions were applied with a species cutoff of 1.7 (15, 16). If no or ambiguous identification was achieved by biochemical characterization or MALDI-TOF MS and a Gram-positive rod was isolated from more than one sample or from a normally sterile fluid, the identification was confirmed by 16S rRNA gene sequence analysis (17). *Corynebacterium* spp. that could not be assigned to the species level due to the high degree of homology of the 16S rRNA gene sequences were identified to the genus level as a *Corynebacterium* sp. (18).

Screening for antimicrobial susceptibility was performed by disc diffusion tests on Mueller-Hinton agar (Becton, Dickinson, Cockeysville, MD) supplemented with 5% sheep blood before 2011 and on

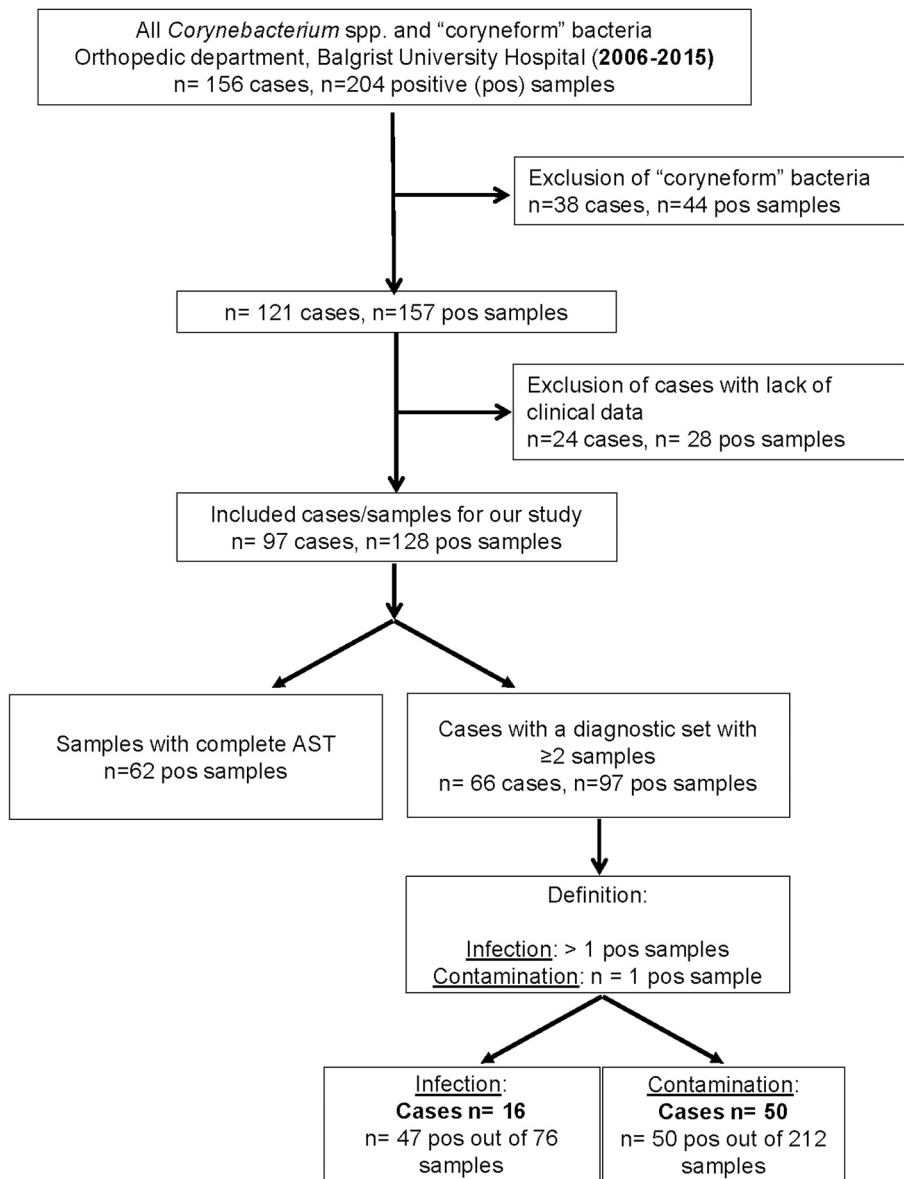


FIG 1 Flowchart of 97 cases and 128 positive (pos) samples in which *Corynebacterium* spp. were isolated, describing the variation of different species in suspected orthopedic infections, the number of samples analyzed by antibiotic susceptibility testing (AST), and the clinical characteristics of the infections.

Mueller-Hinton agar (Becton, Dickinson) supplemented with defibrinated horse blood and 20 mg/liter beta-NAD (MH-F) from 2011 on; zone diameters were interpreted according to CLSI guidelines for staphylococci as the closest surrogate for corynebacteria before 2011 (19), according to EUCAST breakpoints for staphylococci from 2011 to 2013, and according to EUCAST guidelines for corynebacteria from 2014 on (20). For this study, zone diameters obtained during the period from 2011 to 2013 were reinterpreted retrospectively according to the latest EUCAST guidelines for corynebacteria (20). MIC testing by Etest was done for relevant *Corynebacterium* isolates and single drugs to confirm the results of the disc diffusion tests and for strains with poor growth throughout the study period (data not shown).

Statistical analysis. Categorical data were tested for differences using Fisher’s exact test or the chi-square test, as appropriate, whereas continuous variables were tested using Wilcoxon rank sum tests. Two-tailed *P* values of <0.05 were considered statistically significant.

RESULTS

***Corynebacterium* strains and variation.** We identified 128 *Corynebacterium* sp. isolates in 97 cases at the orthopedic hospital Balgrist University Hospital between 2006 and 2015 (Fig. 1). The median age of all included patients was 66 years (range, 9 to 86 years), with a predominance of men (67%); among the patients with an infection, the

TABLE 1 Variation of *Corynebacterium* strains isolated from 97 patients with suspected orthopedic infections and *Corynebacterium* strains recovered from blood cultures from 70 patients with suspected bloodstream infections^a

Species	No. (%) of patients with positive orthopedic isolates ^b (n = 97)	No. (%) of patients with positive blood cultures (n = 70)	P value	No. of orthopedic infections (n = 16)	No. of bloodstream infections (n = 17)
<i>C. accolens</i>	1 (1.0)	1 (1.4)	1.0	0	1
<i>C. afermentans</i>	11 (11.4)	8 (11.4)	1.0	0	0
<i>C. amycolatum</i>	17 (17.5)	11 (15.7)	0.8	3	7
<i>C. aurimucosum</i>	2 (2.1)	3 (4.3)	1.0	1	0
<i>C. diphtheriae</i> bv. mitis	1 (1.0)	0 (0)		1	0
<i>C. glucuronolyticum</i>	1 (1.0)	1 (1.4)		0	0
<i>C. imitans</i>	0	2 (2.9)		0	0
<i>C. jeikeium</i>	0	14 (20.0)	0.0001	0	7
<i>C. macginleyi</i>	0	1 (1.4)		0	0
<i>C. minutissimum</i>	1 (1.0)	4 (5.7)	0.162	0	1
<i>C. mucifaciens</i>	1 (1.0)	4 (5.7)		0	0
<i>C. pseudodiphtheriticum</i>	1 (1.0)	0 (0)		0	0
<i>C. propinquum</i>	0	1 (1.4)		0	0
<i>C. simulans</i>	5 (5.2)	2 (2.9)	0.700	1	0
<i>C. striatum</i>	13 (13.4)	2 (2.9)	0.026	3	1
<i>C. tuberculostearicum</i>	26 (26.8)	3 (4.3)	0.001	3	0
<i>C. ureicelerivorans</i>	2 (2.1)	0 (0)		1	0
<i>Corynebacterium</i> sp.	13 (13.4)	13 (18.6)		1	0
Polymicrobial ^c	2 (2.06)	0		2	0

^aOf the 97 patients with suspected orthopedic infections, the infection was proved in 16, and of the 70 patients with suspected bloodstream infections, the infection was proved in 17. n, total number of isolates in each category.

^bThe most commonly isolated orthopedic strains are labeled in bold.

^cIsolation of two different *Corynebacterium* strains (one case with *C. aurimucosum* and *C. amycolatum* and one case with *C. auris* and *C. aurimucosum*).

median age was 54.5 years (range, 25 to 83 years), and 56.3% of them were men. Most commonly, *Corynebacterium tuberculostearicum* (n = 26), *Corynebacterium amycolatum* (n = 17), *Corynebacterium striatum* (n = 13), or *Corynebacterium afermentans* (n = 11) was found as the single pathogen in 97 cases with suspected orthopedic infections (Table 1). In 13 cases, identification of *Corynebacterium* to the species level was not available. In two cases, two different *Corynebacterium* spp. were cultivated in the same diagnostic set.

For 31 out of the 97 cases, we could not distinguish between infection and contamination, as only one diagnostic sample was sent for microbiological analysis. Among the remaining 66 cases with ≥ 2 samples, we identified 16 cases (24.2%) with an infection due to a *Corynebacterium* sp.; in 50 cases, only one sample was positive by culture, and thus, the *Corynebacterium* sp. was considered a contaminant.

Of the 66 cases with ≥ 2 samples, the median number of analyzed samples per case was 4 (range, 2 to 11); in the cohort of 16 cases with infections due to a *Corynebacterium* sp., the median was 5 (range, 2 to 8), with a mean rate of positivity of 67.8% \pm 28.8% (standard deviation).

Infections were associated with a native joint (n = 1, 6.3%) or prosthetic joint (PJI, n = 4, 25%), an orthopedic implant other than a joint prosthesis (n = 5, 31.3%), a deep foot or pressure ulcer (n = 4, 25%), or a deep postsurgical soft tissue infection (n = 2, 12.5%) (see Table S1 in the supplemental material). All infection sites were found in the lower extremities (feet, n = 7; knee, n = 5; hip, n = 3; gluteus, n = 1). Knee arthroplasty was involved in 75% (n = 3) of the PJI cases.

Typical inflammatory signs, including redness, pain, or swelling, were present in the majority (n = 10, 62.5%) of the infections. Among the four cases diagnosed with PJI, all presented as chronic infections with a sinus tract after a prolonged wound healing. Within the four patients with a deep ulcer diagnosis, acute osteomyelitis was additionally diagnosed.

Nine out of 16 infections (56.3%) were diagnosed as polymicrobial infections, including in the four patients with an ulcer diagnosis. In addition to corynebacteria, staphylococci, streptococci, and *Enterobacteriaceae* were recovered most frequently from samples with polymicrobial infections. Monobacterial infections (n = 7) were caused by either *C. striatum* (n = 3), *C. tuberculostearicum* (n = 1), *C. amycolatum* (n = 1),

TABLE 2 AST of *Corynebacterium* spp. isolated between 2006 and 2015

Yr of isolation (no. of isolates)	CBP ^a	Sample origin	Susceptible isolates (%) ^b								
			ERY	GEN	PEN	TET	VAN	CIP	CLI	LZD	RIF
2006–2010 (26)	CLSI	Orthopedic	35	85	65	100	100	ND	ND	ND	ND
2011–2015 (36)	EUCAST	Orthopedic	ND	72	28	81	100	44	6	100 ^c	82 ^c
2006–2010 (36)	CLSI	Blood culture	22	64	47	92	100	ND	ND	ND	ND
2011–2015 (28)	EUCAST	Blood culture	ND	61	29	78	100	29	19	100 ^d	88 ^d

^aAST was performed by disc diffusion. Clinical breakpoints (CBP) from CLSI (19) were applied from 2006 to 2010, and CBP from EUCAST (20) were applied from 2011 to 2015.

^bERY, erythromycin; GEN, gentamicin; PEN, penicillin; TET, tetracycline; VAN, vancomycin; CIP, ciprofloxacin; CLI, clindamycin; LZD, linezolid; RIF, rifampin; ND, not determined.

^cAST data for linezolid and rifampin were available for 12 and 17 isolates, respectively.

^dAST data for linezolid and rifampin were available for 12 and 17 isolates, respectively.

Corynebacterium ureicelerivorans ($n = 1$), or a *Corynebacterium* sp. ($n = 1$) which could not further be specified even after sequencing of the strain. Table S1 summarizes all mono- and polymicrobial infections grouped according to infection diagnosis.

The majority of the infections were diagnosed while the patient was already taking antibiotics ($n = 9$). Antibiotic treatment widely differed, on the one hand, due to the different pathogens in the mostly polymicrobial infections but also, on the other hand, due to the different antimicrobial susceptibility testing results for the isolated *Corynebacterium* spp.

Surgical treatment was debridement (in the presence of an implant with retention of the implant) in five cases, definitive removal of the implant in five cases, amputation in four cases, and an exchange of the implant in two cases. Since all cases with a PJI presented with a sinus tract as a sign of chronic infection, an aggressive surgical treatment was chosen from the beginning with either a two-stage exchange in two patients, definitive removal of the prosthesis (girdlestone procedure) in one patient, and amputation in one patient.

The *Corynebacterium* species spectrum in 97 orthopedic cases was different from the spectrum in 70 cases, from whom 86 blood samples positive by culture were collected from patients with suspected bloodstream infections. The diversity of the corynebacteria in blood cultures seemed broader, with a predominance of *Corynebacterium jeikeium*, which was not detected in the orthopedic samples, and with significantly fewer *C. striatum* and *C. tuberculostearicum* bacteria from blood cultures than from orthopedic cases (Table 1).

AST. Susceptibility testing was done with 62 out of 128 (48.4%) orthopedic *Corynebacterium* isolates and 64 out of 70 (91.4%) blood culture isolates (Table 2). The percentages of susceptible orthopedic *Corynebacterium* isolates were 72% for gentamicin, 28% for penicillin, 81% for tetracycline, 100% for vancomycin, 44% for ciprofloxacin, 6% for clindamycin, 100% for linezolid, and 82% for rifampin using EUCAST breakpoints (2011 to 2015). The rates of susceptibility of the corynebacteria isolated from orthopedic samples and of isolates from blood cultures were comparable (Table 2; data for the rates are not shown). Table S2 shows the susceptibility testing results for the four *Corynebacterium* spp. most commonly isolated from orthopedic patients. All isolates were susceptible to vancomycin and linezolid. In contrast, penicillin resistance was observed in 78% of *C. tuberculostearicum* isolates, in 80% of *C. amycolatum* isolates, in 100% of *C. striatum* isolates, and in 62% of *C. afermentans* isolates. The different species showed variable frequencies of resistance to tetracycline, ciprofloxacin, clindamycin, rifampin, and gentamicin. Susceptibility testing of corynebacteria isolated between 2006 and 2010 was done according to CLSI recommendations. The rates of susceptibility of the isolates to gentamicin and vancomycin were similar when the results for the years 2006 to 2010 (CLSI criteria) and those for the years 2011 to 2015 (EUCAST criteria) were compared. For penicillin and tetracycline, a significantly lower rate of susceptibility was observed when EUCAST interpretive criteria (2011 to 2015) than when CLSI interpretive criteria were used ($P = 0.005$ and $P = 0.04$, respectively) (Table 2).

DISCUSSION

Our study identified a proven orthopedic infection due to a *Corynebacterium* sp. in only 24.2% of the cases from whom a *Corynebacterium* sp. had been isolated over a period of 10 years. We found that implant-associated infections and ulcers with or without osteomyelitis were the most common diagnosis in orthopedic patients, as previously described (21).

The *Corynebacterium* spp. isolated from orthopedic samples differed from the species spectrum isolated from cultured blood samples in nonorthopedic patients. We found 26 orthopedic cases with *C. tuberculostearicum*. This typical inhabitant of the skin is often described in association with intravascular catheter-associated infections (12) but rarely with orthopedic infections (11). *C. striatum* was found more frequently in orthopedic samples than in cultured blood samples (13.4% versus 2.9%) and accounted for three monomicrobial infections (two implant-associated infections and one case of septic arthritis). In the literature, *C. striatum* is described to be associated with foreign body-associated infections, infective endocarditis, pulmonary infections, septic arthritis, and ventilator tubes in hospital settings (12, 22, 23). *C. jeikeium* was recovered from 20% of our *Corynebacterium*-positive blood cultures but not from any of the orthopedic samples. *C. jeikeium* has been described to be the cause of endocarditis, bacteremia, cerebrospinal fluid shunt infections, peritoneal dialysis peritonitis, and, rarely, PJI (11, 24, 25). Biochemical characteristics and cell envelope structure are key factors for the adaptation to a certain habitat or for a predilection for a certain body site. Lipophilic corynebacteria are part of the human skin flora but can invade deep tissue, after surgery, for example. In contrast, we also described invasive infections with nonlipophilic corynebacteria (*C. aurimucosum*, *C. simulans*, and *C. striatum*). The pathogenesis of these infections is not yet explained.

Identification of corynebacteria to the species level is challenging and often requires 16S rRNA and *rpoB* gene sequencing and/or, nowadays, MALDI-TOF MS analysis, in addition to morphological and biochemical characterization (15–17, 26). Before 2012, the identification of corynebacteria to the species level by biochemical identification followed by 16S rRNA gene sequencing was restricted in the laboratory of the Institute of Medical Microbiology of the University of Zurich to relevant Gram-positive rod isolates. In 2012, our laboratory introduced MALDI-TOF MS for the identification of bacteria; rapid and reliable identification became available for most Gram-positive rods. However, we do not exclude the possibility that we missed infections before the application of MALDI-TOF MS.

There are no clinical data available on how to best treat *Corynebacterium* sp. implant-associated infections. AST has to be performed on all *Corynebacterium* isolates causing orthopedic infections if antibiotics other than vancomycin are given (27–29). We found that only 20% to 38% of the *C. tuberculostearicum*, *C. amycolatum*, and *C. afermentans* isolates and none of the *C. striatum* isolates recovered were susceptible to penicillin. Clindamycin, ciprofloxacin, gentamicin, rifampin, and tetracycline were not regularly effective against these corynebacteria, making vancomycin the only valid empirical treatment until susceptibility tests are performed. Variable resistances were observed in different *Corynebacterium* spp., as already shown in the study by Reddy et al., who observed a high frequency of penicillin-resistant strains (>50%), as well as erythromycin-, clindamycin-, and gentamicin-resistant strains (30). Further studies are needed to investigate combination antibiotic treatment for the treatment of implant-associated infections, e.g., a quinolone plus rifampin, which is currently routinely used for the treatment of other Gram-positive bacterial infections, such as those caused by staphylococci (1).

Guidelines on how to perform and interpret the results of AST of corynebacteria are sparse. CLSI has provided clinical breakpoints (CBP) for broth microdilution testing of corynebacteria since 2006; EUCAST published CBPs for microdilution and disk diffusion methods in 2014. Both CLSI and EUCAST defined CBPs for all *Corynebacterium* spp. (for the MIC and/or zone diameter) based on small numbers of each *Corynebacterium* sp. or

even inferred breakpoints from staphylococcal CBP (i.e., CLSI criteria for gentamicin, vancomycin, and tetracycline); in particular, EUCAST defined clinical breakpoints without defining epidemiological cutoffs (ECOFFs) separating the wild-type population from strains with resistance to a given antibiotic (http://www.eucast.org/clinical_breakpoints/, March 2017 update). The breakpoints of CLSI and EUCAST and, as a consequence, the rates of susceptible and resistant isolates may therefore differ significantly. From 2006 to 2010, we used CLSI staphylococcal breakpoints for zone diameters due to the lack of breakpoints specific for corynebacteria. Penicillin susceptibility was observed in 65% of the isolates. In contrast, applying the EUCAST breakpoints for corynebacteria resulted in only 28% susceptible isolates. This shift was mainly caused by a change of the antibiotic discs used, with the discs with 10 units of penicillin (CLSI) used previously being switched to discs with 1 unit of penicillin at present (EUCAST). It will be necessary to collect more data on corynebacteria so that breakpoints can be defined for each species individually on the basis of the distribution of the zone diameters and MICs of strains without acquired resistance.

Our observation that a *Corynebacterium* sp. is rarely responsible for an infection when isolated on an orthopedic ward is representative of the findings for only a single hospital and may not represent experiences at other sites. However, it is also mentioned in the report of Cazanave et al. that *Corynebacterium* spp. are only occasional causes of PJI as a typical orthopedic infection (11). The strength of our retrospective analysis is the long observation period of 10 years in a large orthopedic center. We might have missed some infections due to our strict definition of at least two positive diagnostic samples. In patients with foot ulcers, often only one bone biopsy specimen was taken for microbiology and histopathology, and thus, the numbers that we present are probably an underestimation. Nevertheless, our study highlights the fact that the isolation of *Corynebacterium* spp. from orthopedic patients rarely indicates an infection even when they are isolated from more than one sample. However, when diagnosed, *Corynebacterium* sp. infections are often polymicrobial. It is crucial to test the antimicrobial susceptibility of clinically relevant *Corynebacterium* spp. since resistance varies between different species. It remains to be investigated under which conditions corynebacteria change from a commensal to an invasive pathogen.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/JCM.01200-18>.

SUPPLEMENTAL FILE 1, PDF file, 0.03 MB.

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