

Original Research Article

***Corynebacterium* species causing urinary tract infections.**

ABSTRACT

Aims: to determine the prevalence and to assess the antimicrobial susceptibility of individual *Corynebacterium* species isolated from patients with urinary tract infections.

Place and Duration of Study: Department of Medical Microbiology of the Infant Jesus Teaching Hospital, Warsaw, Poland from January 2010 to December 2016.

Methodology: This retrospective analysis included *Corynebacterium* strains derived from 211 urine samples. Microbial identification had been performed with the use of biochemical panels and matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOF MS). Antibiotic susceptibility tests were conducted according to the Polish Reference Center for Antimicrobial Susceptibility and the European Committee on Antimicrobial Susceptibility Testing guidelines.

Results: The predominant *Corynebacterium* species isolated from female urine were *C. coyleae*, *C. aurimucosum*, and *C. amycolatum*. The following species: *Arcanobacterium haemolyticum*, *C. freneyi*, *C. group G1*, *C. muciefacines*, *C. propinquum*, *C. pseudodiphtheriticum*, and *C. renale* were identified only in urine cultures from female patients.

Antimicrobial susceptibility rates were 41.9% (penicillin), 53.4% (ciprofloxacin), 83.3% (gentamycin), 77.8% (tetracycline), with all the evaluated strains susceptible to vancomycin.

27 The number of the *Corynebacteria* species isolated from urine samples consecutively raised
28 during analyzed years, from 4 in the year of 2010 up to 87 in the last analyzed year.

29
30 **Conclusion:** The observed increase in the number of *Corynebacterium* species isolated
31 from urine samples over the years suggests a more and more important role of these
32 bacteria in urinary tract infection epidemiology, especially in women. Therefore, novel
33 diagnostic procedures should be developed for the specimens from patients with urinary
34 tract infections, especially in the case of transplant recipients.

35
36 **Keywords:** *Corynebacterium*, urinary infections, antimicrobial susceptibility, MALDI-TOF MS

37 38 1. INTRODUCTION

39
40 The presence of bacteria in the urinary tract above the urethral sphincter typically indicates a
41 urinary tract infection (UTI). Customarily, the urinary tract was recognized as a sterile
42 environment, with the exception of the distal end of the urethra. However, conclusions drew
43 from recent studies on the microbial composition of healthy individuals indicate that urinary
44 tract and the bladder are inhabited by several bacterial species forming so-called urinary
45 microbiome [1]. The composition of the normal urethral microflora in females and males may
46 differ, but the microorganisms commonly isolated from both sexes are *Staphylococcus*
47 *epidermidis*, *Lactobacillus* spp., *Corynebacterium* spp., *Bacteroides* spp., *Streptococcus* spp.
48 (α -hemolytic strains).

49 In contrast, the most commonly isolated etiological factors of UTIs include: *Escherichia coli*,
50 *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, *Pseudomonas aeruginosa*,
51 and *Streptococcus agalactiae*. The prevalence of the individual species differs in males and
52 females and depends on the patient's age. UTIs can be also caused by multiple pathogens.

53 The bacteria constituting patients' physiological skin and mucosal microflora were, until
54 recently, treated merely as contaminants of analyzed urine specimens. However, these
55 microorganisms are more and more often considered to be among the etiological factors

56 behind nosocomial and community-acquired infections. These bacteria include the majority
57 of Gram-positive species of the genus *Corynebacterium*.

58 Epidemiologic data on the role of Gram-positive bacilli in UTIs are very scarce, which is most
59 likely due to the common belief that these bacteria, as part of the physiological urethral
60 microflora, are only accidental contaminants of the evaluated urine specimens. Another
61 reason for this paucity of data may be the fact that this group of bacteria has highly specific
62 growth requirements (culture media supplemented with blood, lipids). Moreover, these
63 bacteria need a longer incubation time to grow than most Gram-positive as well as Gram-
64 negative species. It is not uncommon for them to show growth only after a 72–96-hour
65 incubation. Thus, Gram-positive bacilli can be often disregarded, even in comprehensive
66 microbiological analyses, their identification being reserved only for those cases where they
67 are highly probable causative pathogens.

68 Another problem involves the identification of bacteria of the genus *Corynebacterium*. If the
69 specimen is believed to be contaminated, microbial identification is not even attempted. In
70 those cases where identification is conducted, it is most commonly phenotypic; i.e. based on
71 bacterial morphology; biochemical properties; and, in some species, a synergistic hemolysis
72 test – CAMP (Christie, Atkins, Munch-Petersen).

73 More advanced species identification techniques for Gram-positive bacilli include total
74 cellular fatty acid profiling, phospholipid-derived fatty acid (PLFA) profiling, cell-wall
75 composition analysis, and DNA or RNA nucleotide sequencing. However, these methods are
76 expensive, time-consuming, and require specialized equipment; which is why they are
77 mostly used in reference centers for research purposes. Mass spectrometry (MALDI-TOF
78 MS), which is one of the most modern methods of bacterial identification, is becoming more
79 and more common in routine microbial diagnostics. [2, 3]

80 The challenges associated with culture and identification of bacteria from the genus
81 *Corynebacterium* have resulted in our limited knowledge of the role these microorganisms

play in infection etiology and on their antimicrobial susceptibility. Widespread, often inappropriate, use of antibiotic therapy in nosocomial and community-acquired infections contributes to the emergence and spread of multi-drug resistant strains, including strains of the genus *Corynebacterium*.

Apart from the toxigenic strains of *C. diphtheriae*, which are strict human pathogens, the following *Corynebacterium* species were reported to be pathogenic in humans: fermenting species: *C. diphtheriae* group (including non-toxigenic strains), *C. xerosis*, *C. striatum*, *C. minutissimum*, *C. amycolatum/striatum*, *C. glucuronolyticum*, *C. argentoratense*, *C. matruchotii*; non-lipophilic, non-fermenting species: *C. afermentans*, *C. auris*, *C. pseudodiphtheriticum*, *C. propinquum*; and lipophilic species: *C. jeikeium*, *C. urealyticum*, *C. lipophilum*, *C. accolens*, *C. macginleyi*, CDC groups F-1 and G, and *C. bovis*. [4]

More recently, a number of other species, isolated from human clinical samples, were identified. Interestingly, *C. renale*, which used to be considered pathogenic in animals, has been isolated from human clinical samples. [5]

Moreover, bacterial taxonomic studies have led to some species being reclassified into other taxa. One example of this is a reclassification of *C. haemolyticum* as *Arcanobacterium haemolyticum*.

This species has been reported as an etiologic factor of pharyngeal, skin, and soft-tissue infections, as well as sepsis, [6] with, so far, only one report [7] of the involvement of this bacterial species in UTIs.

Since, for many years, this species was classified as part of the genus *Corynebacterium*, as well as due to the growing interest in this species as an important human pathogen, we decided to include it in our study.

2. MATERIALS AND METHODS

2.1 SAMPLES

108 Our study involved a retrospective analysis of isolates identified as representatives of the
109 genus *Corynebacterium* derived from 211 urine specimens collected from the Infant Jesus
110 Teaching Hospital patients of the following clinics: "General, Oncologic, and Functional
111 Urology", "General and Transplantation Surgery", "Immunology, Transplantation, and
112 Internal Medicine", "Transplantation Medicine, Nephrology, and Internal Medicine", "Internal
113 Medicine and Cardiology", "Ophthalmology", "Dermatology", "Obstetrics and Gynecology",
114 "Anesthetics and Intensive Care", "Orthopedic and Accident Surgery of the Musculoskeletal
115 System", in the period from Jan. 1, 2010, to Dec. 31, 2016.

116 The study population comprised 164 females and 47 males. The patient's age ranged from
117 20 to 92 years, median 57 years, mean 56 years).

118 All the cultures were performed in the case when urinary tract infection was recognized by
119 the clinician based on laboratory and/or clinical findings.

120 **2.2 ISOLATION AND IDENTIFICATION OF BACTERIA FROM URINE SAMPLE**

121 Midstream urine specimens were cultured according to a standard protocol (1- μ L samples
122 plated onto the chromogenic CHROMID® CPS 3 and the MacConkey media (both
123 manufactured by bioMérieux, France). The cultures were incubated at 37°C for 24 hours in
124 aerobic conditions. In the period from January 2010 to September 2014, bacteria of the
125 genus *Corynebacterium* were identified with API Coryne bacterial identification test kits
126 (bioMérieux France), according to the manufacturer's instructions; in the period from October
127 2014 onward, identification was conducted via MALDI-TOF MS with a Vitek MS system
128 (bioMérieux, France).

129 In some cases, bacterial identification was conducted only to the genus level. Isolates were
130 analyzed only if the culture yielded significant bacterial counts - 10^5 cfu/mL.

131

132 **2.3 DETERMINATION OF ANTIMICROBIAL RESISTANCE OF THE**

133 **CORYNEBACTERIA STRAINS**

134 Antibiotic susceptibility tests to penicillin, ciprofloxacin, gentamycin, tetracycline, and
135 vancomycin were performed.

136 Briefly, according to the of the Polish Reference Center for Antimicrobial Susceptibility 2010
137 (KORLD) [8] antibiotic susceptibility was examined by MIC determination by the E-test
138 gradient diffusion method AB Biodisc, Sweeden), and since 2014, according to the European
139 Committee on Antimicrobial Susceptibility Testing 2014 (EUCAST) guidelines [9] by the
140 Kirby-Bauer disk diffusion method. For both methods Mueller Hinton agar supplemented with

141 5% defibrinated horse blood and 20 mg/L β -NAD (MH-F) (bioMérieux, France) was used.

142 For disc diffusion antibiotic-impregnated disks (OXOID Limited, UK); benzylpenicillin 1 unit,
143 ciprofloxacin 5 μ g, gentamycin 10 μ g, vancomycin 5 μ g, tetracycline 30 μ g were applied
144 onto the surface of the inoculated plates. After incubation, strains were characterized as
145 susceptible or resistant to antibiotics based on the inhibition zone size or the MIC value
146 according to interpretive criteria of the appropriate guidelines.

147

148 3. RESULTS

149

150 During the analyzed period, urine cultures yielded significant bacterial counts from a total of
151 211 strains of the genus *Corynebacterium*.

152 A total of 144 (68.2%) out of the 211 grown strains were identified to the species level,
153 whereas the remaining 67 strains (31.8%) could be identified only to the genus level
154 (*Corynebacterium*). Predominant species included: *C. coyleae*, 32 strains (15.2%); *C.*
155 *aurimucosum*, 26 strains (12.3%); *C. amycolatum*, 25 strains (11.8%); *C.*
156 *tuberculostearicum*, 15 strains (7.1%); and *C. xerosis*, 15 strains (7.1%). Other species
157 constituted less than 3% each. Table 1 presents detailed information on the identified
158 species and their number, stratified by year.

159

160

161

162 Table 1. Individual *Corynebacterium* strains grown from urine specimens in 2010–2016.

	Number of isolates (%)	Number of isolates from:	
Identification	Total (%)	Females	Males
<i>A. haemolyticum</i>	1 (0,5)	1	0
<i>C. amycolatum</i>	25 (11,8)	19	6
<i>C. aurimucosum</i>	26 (12,3)	24	2
<i>C. coyleae</i>	32 (15,2)	31	1
<i>C. freneyi</i>	1 (0,5)	1	0
<i>C. glucuronolyticum</i>	3 (1,4)	1	2
<i>C. group G 1</i>	1 (0,5)	1	0
<i>C. jeikeium</i>	3 (1,4)	0	3
<i>C. minutissimum</i>	3 (1,4)	1	2
<i>C. mucifaciens</i>	2 (0,9)	2	0
<i>C. propinquum</i>	1 (0,5)	1	0
<i>C. pseudodiphtheriticum</i>	1 (0,5)	1	0
<i>C. renale</i>	1 (0,5)	1	0
<i>C. simulans</i>	4 (1,9)	3	1
<i>C. striatum</i>	5 (2,4)	3	2
<i>C. tuberculostearicum</i>	15 (7,1)	8	7
<i>C. urealyticum</i>	6 (2,8)	4	2
<i>C. xerosis</i>	15 (7,1)	10	5
<i>C. species</i>	66 (31,3)	52	14
Sum	211 (100)	164	47

		Benzylpenicillin n=179	%	Ciprofloxacin n=103	%	Gentamicin n=54	%	Tetracycline n=54	%	Vancomycin n=179	%
Identification	Number of	S		S		S		S		S	

	iso										
	lat										
	es										
A.	1	1	1	* nt	nt	nt	nt	nt	nt	1	1
haemolyti			0								0
cum			0,								0
			0								
C.	25	11	4	5	3	5	1	2	6	25	1
amycolat			4,		5,		0		6,		0
um			0		7		0,		7		0
							0				
C.	26	10	3	13	7	9	8	7	8	26	1
aurimuco			8,		2,		1,		7,		0
sum			5		2		8		5		0
C.	32	12	3	15	7	13	1	11	7	32	1
coyleae			7,		1,		0		8,		0
			5		4		0,		6		0
							0				
C.	3	0	0,	1	3	nt	nt	0	0,	3	1
glucuron			0		3,				0		0
olyticum					3						0
C. group	1	1	1	1	1	nt	nt	nt	nt	1	1
G 1			0		0						0
			0,		0,						0
			0		0						
C.	3	1	3	0	0,	0	0,	1	1	3	1

<i>jeikeium</i>			3, 3		0		0		0 0, 0		0 0
<i>C. minutissimum</i>	3	2	6 6, 7		nt	nt	nt	nt	nt	3	1 0 0
<i>C. mucifaciens</i>	2	0	0, 0	2	1 0 0, 0	nt	nt	nt	nt	2	1 0 0
<i>C. propinquum</i>	1	1	1 0 0, 0	nt	nt	nt	nt	nt	nt	1	1 0 0
<i>C. pseudodiphtheriticum</i>	1	1	1 0 0, 0	nt	nt	nt	nt	nt	nt	1	1 0 0
<i>C. renale</i>	1	1	1 0 0, 0	nt	nt	nt	nt	nt	nt	1	1 0 0
<i>C. simulans</i>	4	2	5 0, 0	1	5 0, 0	2	1 0 0, 0	2	1 0 0, 0	4	1 0 0

C. striatum	5	3	6 0, 0	nt	nt	nt	nt	nt	nt	5	1 0 0
C. tuberculo steaticum	15	5	3 3, 3	2	2 2, 2	3	6 0, 0	4	5 7, 1	15	1 0 0
C. urealyticu m	5	2	4 0, 0	nt	nt	nt	nt	nt	nt	5	1 0 0
C. xerosis	14	1	7, 1	4	3 3, 3	6	6 6, 7	9	9 0, 0	14	1 0 0
C. species	37	21	5 6, 8	11	5 5, 0	7	8 7, 5	6	7 5, 0	37	1 0 0
Sum witout C. species	14 2	54	3 8, 0	44	5 3, 0	38	8 2, 6	36	7 8, 3	142	1 0 0
Sum of all isolates	17 9	75	4 1, 9	55	5 3, 4	45	8 3, 3	42	7 7, 8	179	1 0 0

* not tested

182

183 The number of strains tested for susceptibility to each individual antibiotic was considered to
 184 constitute 100%. Susceptibility to penicillin and vancomycin was tested in all 179 strains,
 185 ciprofloxacin susceptibility was tested in 103 strains, and gentamycin and tetracycline
 186 susceptibility were tested in 54 strains.

187 The proportion of penicillin-susceptible strains (out of all strains tested (n=179), including
188 *Corynebacterium* spp. (n=37)) was 41.9%.

189 The proportion of ciprofloxacin-susceptible strains (out of all strains tested (n=103), including
190 *Corynebacterium* spp. (n=20)) was 53.4%.

191 Very few strains exhibited intermediate antimicrobial susceptibility, with 1 *C. amycolatum*
192 strain and 1 *C. species* strain intermediately susceptible to penicillin and 1 *C. species* strain
193 intermediately susceptible to ciprofloxacin. These strains constituted 1.1% and 1% of the
194 analyzed isolates, respectively.

195 The proportion of gentamycin-susceptible strains (out of 54 strains tested, including
196 *Corynebacterium* spp. (n=8)) was 83.3%.

197 The proportion of tetracycline-susceptible strains (out of 54 strains tested, including
198 *Corynebacterium* spp. (n=8)) was 77.8%.

199 All the analyzed strains identified only to the genus level (n=37), as well as those identified
200 to the species level (n=142), exhibited susceptibility to vancomycin.

201 The individual *Corynebacterium* species tested showed no significant differences in their
202 antimicrobial susceptibility. However, in some cases, the number of isolates was insufficient
203 to observe such differences.

204

205 4. DISCUSSION

206 For a long time, only obtaining a single species of primary (eg. *Enterobacteriaceae*) or
207 secondary uropathogens (eg. *Enterococcus* spp.), with a significant bacterial count in a urine
208 culture from patients with bacterial UTIs was believed to warrant further microbiological
209 testing, which involved identifying the strain and determining its susceptibility. Currently,
210 microbiological analyses are continued, especially in case of immunocompromised or
211 transplantation patients, even when the urine culture yields two or even three bacterial
212 species. [12].

213 Classifying bacteria from the genus *Corynebacterium* as uropathogenic species is
214 controversial and is mostly a result of the established belief that their growth in urine culture
215 implies that the urine specimen had been contaminated with skin microflora.

216 Our analysis showed that 33% of the analyzed specimens yielded pure cultures of
217 *Corynebacterium* spp. These findings are fairly consistent with those by Reddy et al. [10],
218 whose study on the prevalence of *Corynebacterium* species in various clinical specimens
219 yielded pure cultures only in the case of non-urine specimens. Reddy also reported that only
220 11 (25.6%) out of 43 analyzed urine specimens yielded pure *Corynebacterium* cultures. The
221 slight discrepancy may be due to the different numbers of evaluated specimens.

222 Discounting bacteria of the genus *Corynebacterium* as possible etiological factors of UTIs
223 may result in incorrectly interpreting the clinical presentation and omitting to introduce
224 antibiotic therapy, which may lead to dangerous consequences for the patient, especially in
225 the case of multidrug-resistant strains.

226 This way of thinking may lead to therapeutic failure, especially in renal transplant recipients.
227 According to literature reports, *C. urealyticum* is an established pathogen of the urinary tract.
228 Reddy et al. [10] reported to culture *C. urealyticum* only from samples where this species
229 constituted 6.1% of all pathogens isolated. Prospective studies by López-Medrano et al. [11]
230 on the occurrence of UTIs caused by *C. urealyticum* in renal transplant recipients showed
231 this species to be present (regardless of the bacterial count) in 9.8% of the evaluated
232 patients. Even when only the cultures with a significant bacterial count of 10^5 cfu/mL were
233 considered, *C. urealyticum* was still reported in 3% of the evaluated patients. This is a much
234 higher proportion than that in other patient populations. Therefore, the cited authors
235 concluded that renal transplant recipients should be considered a population at a high risk of
236 infections caused by this pathogen. They suggested that this group of patients should
237 receive antibiotic therapy when suffering from a UTI, even with microbiologically-confirmed
238 non-significant bacteriuria.

239 Our analysis, which encompassed a 7-year period, found only six strains of *C. urealyticum*.
 240 However, the specimens we analyzed derived from various patients, not only transplant
 241 recipients, and the urine culture conditions were not targeted towards this particular species.
 242 The resulting underestimation of the rates of UTIs caused by *C. urealyticum* may be due to
 243 the slow growth of this species, 48–72 hours, whereas the growth of other, more common
 244 UTI-causing pathogens is typically observed already after 24 hours. [12] Moreover, this
 245 species grows 5 times less often on standard urine-culture media than on selective media for
 246 *Corynebacterium* because, besides the longer time these bacteria need to grow (up to 72
 247 and even 96 hours), they also require supplementary growth factors and prefer a 5% carbon
 248 dioxide atmosphere. [11]

249 The rate of infections by *C. glucuronolyticum*, which was detected only 3 times during our
 250 study, may be similarly underestimated. Like in the case of *C. urealyticum*, the main problem
 251 with isolating this species is its slow growth (colonies are visible after a minimum of 24-hour
 252 incubation). Bacteria of this species have been reported to cause urogenital infections in
 253 men, in whom they may be part of physiological flora. The prevalence of these bacteria in
 254 women is unknown. [13]

255 Surprisingly, the bacterial species most commonly isolated in our study was *C. coyleae*. This
 256 is a relatively new species. It was first described in 1997 [14] and has since been only rarely
 257 reported as a causative agent of infections. There have been only a handful of reports on *C.*
 258 *coyleae* isolation from such specimens as: blood, urine, abscess aspirate, prostatic
 259 secretion, or pleural fluid. [15] *C. coyleae* may have occurred earlier, however, it had either
 260 not been identified to the species level or had been identified incorrectly. [14]

261 Fernandez-Natal et al. [15] reported a strain, which was genetically identified as *C. coyleae*
 262 but had been incorrectly identified as *C. jeikeium* based on its biochemical characteristics. In
 263 our study, the first instance of *C. coyleae* identification was in 2014 (1 strain). In subsequent
 264 years, this species was identified in 14 (2015) and 17 (2016) cultures. At this stage, we
 265 should emphasize that bacterial identification with mass spectrometry (MALDI-TOF) was first

266 introduced at our laboratory in October 2014; earlier bacterial identification had been based
267 on biochemical tests alone, which may explain the significant increase in *C. coyleae*
268 identification in 2015–2016. What is noteworthy is the fact that, in our study, *C. coyleae* was
269 grown from urine specimens collected almost exclusively from females (97%).

270 The second most commonly isolated species was *C. aurimucosum*. This species was
271 isolated 26 times over the period of 7 years. According to literature reports, these bacteria
272 have been isolated from patients with acute and chronic arthritis and osteitis, from soft
273 tissues of the foot in patients with diabetic foot, and from biopsy samples (synovial
274 membrane) collected from a patient with arthritis. This bacterial species has been also
275 reported to be part of genitourinary tract microflora in healthy women. [16, 17]

276 To date, there has been only one reported case of UTI caused by *C. aurimucosum*, in a
277 patient who underwent urethroplasty due to urethral stricture. The isolated strain was
278 resistant to penicillin and trimethoprim/sulfamethoxazole and susceptible to vancomycin,
279 tetracycline, ciprofloxacin, and imipenem. The patient received a 10-day treatment with
280 imipenem, which was therapeutically successful. [18]

281 The third species most commonly isolated in our study was *C. amycolatum*, which
282 constituted 11.8% of urine culture isolates, 72% of which were collected from women. Like in
283 the case of other species, there is no available literature reporting the involvement of this
284 species in UTIs. These bacteria have been reported to occur in wound infections, where they
285 constituted 29.2% of the isolated Gram-positive bacilli, [19] and in local surgical site
286 infections. In general, bacteria of the genus *Corynebacterium* were responsible for 24.7% of
287 infections, with *C. amycolatum* the predominant species in this group (constituting 37.1%).
288 [20].

289

290 In summary, our findings indicate that an increase in the number of strains of the genus
291 *Corynebacterium* isolated from urine specimens from one year to the next, with culture

292 methods remaining the same, may indicate the growing role of this genus in UTI
293 epidemiology, especially in women. These findings suggest that novel diagnostic algorithms
294 should be developed for dealing with clinical specimens collected from patients with UTIs,
295 especially transplant recipients. Correct identification of the isolated strains is necessary for
296 accurate UTI diagnoses.

297

298 **4. CONCLUSION**

299

300 **In summary,** our findings indicate that an increase in the number of strains of the genus
301 *Corynebacterium* isolated from urine specimens from one year to the next, with culture
302 methods remaining the same, may indicate the growing role of this genus in the UTI
303 epidemiology, especially in women. These findings suggest that novel diagnostic algorithms
304 should be developed for dealing with clinical specimens collected from patients with UTIs,
305 especially transplant recipients. Correct identification of the isolated strains is necessary for
306 accurate UTI diagnoses.

307

308 **ETHICAL APPROVAL**

309

310 Not required

311

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