

Corynebacterium urealyticum: a comprehensive review of an understated organism

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Abstract: *Corynebacterium urealyticum* is a Gram positive, slow-growing, lipophilic, multi-drug resistant, urease positive micro-organism with diphtheroid morphology. It has been reported as an opportunistic nosocomial pathogen and as the cause of a variety of diseases including but not limited to cystitis, pyelonephritis, and bacteremia among others. This review serves to describe *C. urealyticum* with respect to its history, identification, laboratory investigation, relationship to disease and treatment in order to allow increased familiarity with this organism in clinical disease.

Keywords: *Corynebacterium urealyticum*, cystitis, pyelonephritis, bacteremia, micro-organisms

Introduction

Corynebacterium urealyticum (formerly known as coryneform CDC 79 group D2) was first recognized to be involved in human infections 80 years ago. It is a Gram positive, slow-growing, asaccharolytic, lipophilic, multi-drug resistant, urease positive micro-organism with diphtheroid morphology. It was named *C. urealyticum* stressing its strong ability to split urea.¹

C. urealyticum is isolated from the groin of elderly patients receiving broad spectrum antibiotics with relative frequency, thus providing an ideal environment that may favor colonization of urinary catheters with subsequent infection of bladder mucosa particularly in the setting of co-morbidities (trauma, tumor, or inflammation).¹

C. urealyticum is an opportunistic nosocomial pathogen mainly causing acute cystitis, pyelonephritis, alkaline encrusted cystitis, and encrusted pyelitis and may also cause bacteremia preferential in patients with chronic urological diseases.²

C. urealyticum isolates are usually missed in routine urine cultures since it does not grow well after an overnight incubation.³ However *C. urealyticum* can be isolated after 48 hours of incubation at 35°C–37°C preferably in 10% CO₂ mainly on blood agar. Colonies are characteristically pinpoint, whitish, opaque, smooth, convex, circular, and non-hemolytic.⁴

The identification of *C. urealyticum* is one of the biggest challenges facing the laboratory.⁵ Phenotypic studies using home-made media or commercial systems (API Coryne) can be used for proper identification.⁶ Identification can also be confirmed by polymerase chain reaction (PCR) amplification.⁷

The majority of *C. urealyticum* strains are highly resistant to a large number of antibiotics, including aminoglycosides, B-lactams, and macrolides although teicoplanin

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and vancomycin remain universally active against these isolates.³

C. urealyticum can be considered an underestimated cause of sepsis among hospitalized patients. However, adequate identification and therapy may be lifesaving.⁸

The aim of this review is to highlight the historical context of *C. urealyticum*, its relationship to disease, differentiation from other infectious agents, and detection patterns of antibiotic sensitivity for proper management of patients.

C. urealyticum

Historical overview

C. urealyticum is one of the non diphtherial corynebacteria (coryneforms). Coryneforms were considered to be simple contaminants with little potential pathogenicity. After decades of uncertainty about their clinical significance, coryneforms have emerged as important pathogens causing many serious infections.^{6,9}

In 1972, King described a non-spore-forming, aerobic and Gram-positive bacillus with strong urease activity as coryneform CDC group D2. A case of pneumonia in a debilitated patient from whom such an organism was isolated, was described in 1979 by Jacobs and Perlino. In 1985, Ponte et al published a report where this organism was implicated for the first time in urinary tract infections (UTIs) in four patients with alkaline encrusted cystitis. In the same year, eight cases of UTI caused by this organism were reported with results subsequently confirmed in a larger case series.²

The name *C. urealyticum* was first proposed in 1986 to describe the formation of bladder stones in vivo in an animal model by urealytic bacteria of the CDC coryneform group D2 (old name of *C. urealyticum*).³

Taxonomic features

C. urealyticum belongs to the family Corynebacteriaceae and the genus *Corynebacterium* (Table 1).¹⁰ According to Funke et al,¹¹ medically relevant species in the genus *Corynebacterium* are classified into the following:

1. nonlipophilic, fermentative corynebacteria
 - *C. diphtheriae* group
 - *C. xerosis* and *C. striatum*
 - *C. minutissimum*
 - *C. amycolatum/striatum*
 - *C. glucuronolyticum*
 - *C. argenteoratense*
 - *C. matruchotii*
2. nonlipophilic, non-fermentative corynebacteria
 - *C. afermentans*

Table 1 The taxonomic classification of *C. urealyticum*

Kingdom	Bacteria
Phylum	Actinobacteria
Order	Actinomycetales
Suborder	Corynebacterineae
Family	Corynebacteriaceae
Genus	<i>Corynebacterium</i>
Species	<i>Corynebacterium urealyticum</i>

Note: Data from Lehmann & Neumann 1896.⁶²

- *C. auris*
 - *C. pseudodiphtheriticum*
 - *C. propinquum*
3. lipophilic corynebacteria
 - *C. jeikeium*
 - *C. urealyticum*
 - *C. lipophilum*
 - *C. accolens*
 - *C. macginleyi*
 - *CDC group F-1 and G*
 - *C. bovis*.

The taxonomic classification of *C. urealyticum* was originally characterized based on its biochemical properties, including failure to produce acid from carbohydrates and the ability to hydrolyze urea.^{12,13} The cell wall peptidoglycan of *C. urealyticum* contains meso-diaminopimelic acid. Arabinose and galactose are the major cell wall sugars. Tuberculostearic acid and short-chain mycolic acids are present resembling mycobacterium tuberculosis.² The degree of relatedness of *C. urealyticum* to other *Corynebacterium* species can be determined by using DNA–DNA hybridization studies^{2,14} and 16S ribosomal ribonucleic acid (rRNA) sequence analysis. A 16S rDNA sequence-based phylogenetic tree of the species belonging to the genus is shown in Figure 1.^{15,16} Studies were done using a small-subunit rRNA sequence data and observed a close phylogenetic relationship between *C. urealyticum* and *C. jeikeium*.² However, the difference between them is that *C. jeikeium* is non-urealytic and produces acid from glucose among others.^{17,18}

Genomic structure

In a study done by Tauch et al,³ the genome sequence and lifestyle of *C. urealyticum* established by pyrosequencing was determined. According to the study, the genome of *C. urealyticum* DSM7109 consists of a circular chromosome with a size of 2,369,219 bp and a mean G + C content of 64.2%.² Table 2 shows the general features of *C. urealyticum* DSM7109 genome.

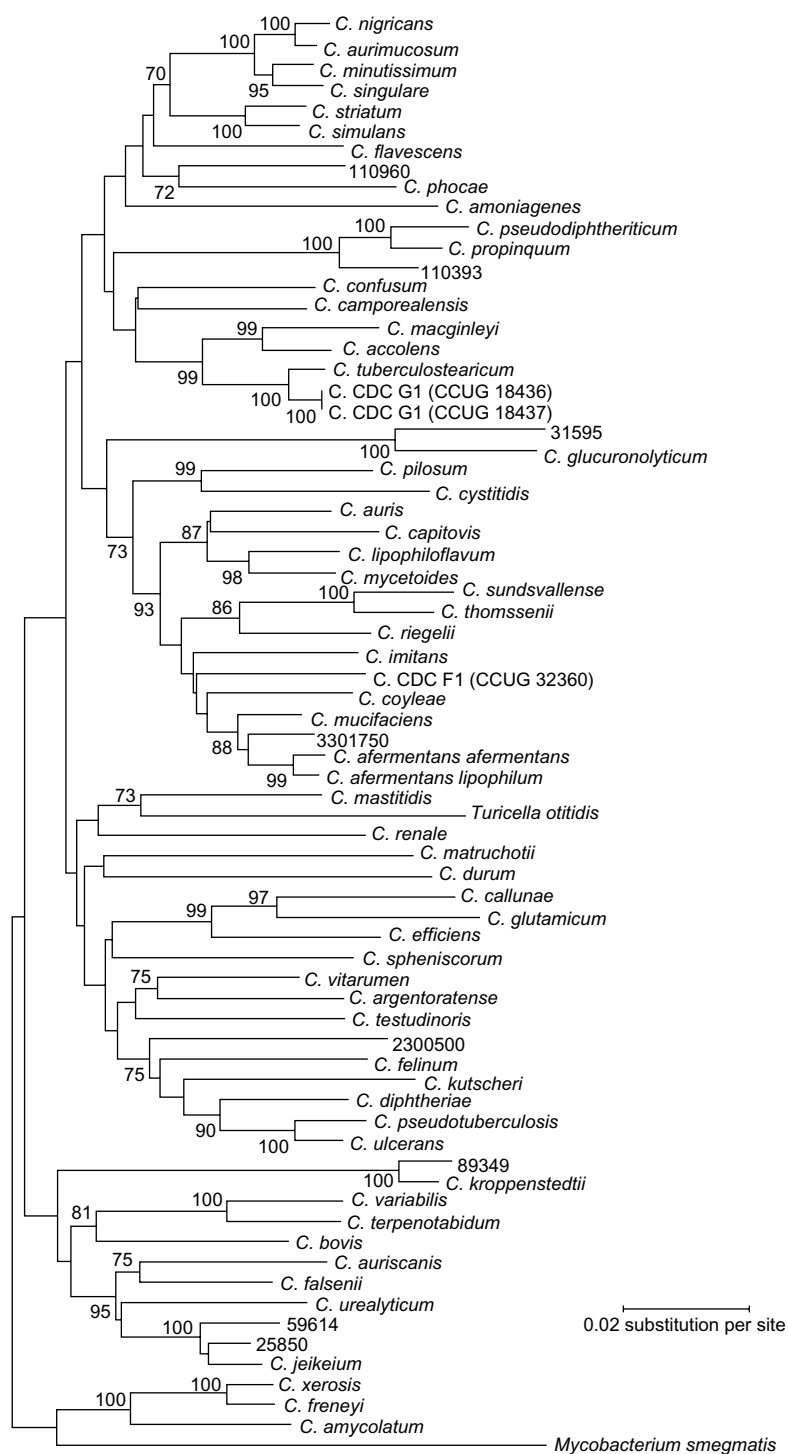


Figure 1 Dendrogram representing phylogenetic relationships of *Corynebacterium* type species and not-well-classified isolates by the neighbor-joining method.

Note: Reproduced with permission from American Society for Microbiology from Khamis A, Raoult D, La Scola B. Comparison between rpoB and 16S rRNA Gene Sequencing for Molecular Identification of 168 Clinical Isolates of *Corynebacterium*. *J Clin Microbiol*. 2005;43(4):1934–1936. doi: 10.1128/JCM.43.4.1934–1936.2005.¹⁶

The size of the *C. urealyticum* DSM7109 chromosome is smaller than that of the genomes from other pathogenic corynebacteria and is about 100 kb, suggesting that further gene reduction occurred during the evolution of the *C. urealyticum* chromosome.¹⁹ The *C. urealyticum* DSM7109 chromosome has

three rrn operons on the leading strands, one on the right and two on the left replicore. This is different from *C. jeikeium*, which contains three rrn operons on the leading strand of the right replicore, indicating the occurrence of structural rearrangements in the chromosome of *C. urealyticum* DSM7109.²⁰

Table 2 The general features of *C. urealyticum* DSM7109 genome

Feature	Data obtained after ultrafast pyrosequencing	Data deduced from the complete genome sequence
Genome size (bp)	2,294,755	2,369,219
Assembled contigs	69	1
G + C content (%)	64.4	64.2
Coding sequences	2,027	2,039/2,024
Coding density (%)	90.2	89.6
Average gene length (bp)	1,036	1,052
Ribosomal RNAs	5	3×(16S-23S-5S)
Transfer RNAs	46	51
CRISPRs	Not determined	70

Notes: Republished with permission of Elsevier from Tauch A, Trost E, Tilker A, et al. The lifestyle of *Corynebacterium urealyticum* Derived from its Complete Genome Sequence Established by Pyrosequencing. *J Biotechnol.* 2008;136(1–2):11–21. Permission conveyed through Copyright Clearance Center, Inc.³

Abbreviations: RNAs, ribonucleic acids; CRISPRs, clustered regularly interspaced short palindromic repeats.

In addition to that in their study a total of 51 transfer RNA (tRNA) genes were detected in the *C. urealyticum* DSM7109 genome as well as 2024 protein-coding sequences were identified and classified into the Clusters of Orthologous Groups of proteins.²¹ Comparison of proteins of the *C. urealyticum* DSM7109 genome with the proteins encoded by *C. jeikeium* K411 revealed 1,589 proteins from *C. urealyticum* DSM7109 (78.5%), which were considered as orthologous with proteins from the *C. jeikeium* K411 genome. This subset of orthologous proteins indicated the close phylogenetic relationship between the lipid-requiring species *C. urealyticum* and *C. jeikeium*.¹⁹ Recently a study established the genome sequence of another strain of *C. urealyticum*; DSM 7111 which contains 79 specific genes.²²

Epidemiological aspects of *C. urealyticum*

Although formerly considered as a contaminant, *C. urealyticum* is being increasingly reported as the causative organism of many infections, especially in those at risk.¹²

Incidence

C. urealyticum is the *Corynebacterium* most frequently isolated from clinical specimens, if the specimens are adequately processed. The incidence varies from 0.016% to 0.32% among all samples sent for routine culture. When specimens with diphtheroid morphology on culture are specifically chosen, the rates of detection are increased by a factor of 3–30.²

The incidence of UTI from *C. urealyticum* in the general population has been reported to be 1%–2%.²³ Rizvi

et al²⁴ identified nine *C. urealyticum* isolates out of 139 *Corynebacterium* isolates with an incidence of 6.5% which were revealed from three patients with a UTI, two patients with peritonitis, two patients with a wound infection, one with a neonatal umbilical tip infection and one with a soft tissue infection.

Geographic distribution

In five major studies done in France, United Kingdom, South Africa, the United States, and Spain, the incidence of *C. urealyticum* UTI ranged from 0.5% to 2.5% for UTIs in non-selected populations there. In the United States, infections with *C. urealyticum* are being reported more frequently, especially those associated with medical devices such as urethral catheters, artificial valves, intravascular catheters, and central nervous system (CNS) drainage devices.²³

More infections with *C. urealyticum* are being reported worldwide in studies done in Saudi Arabia,²⁵ Spain,² Poland,²⁶ and Russia.²⁷ Although *C. Urealyticum* infection has been reported in these countries, it may be more widespread yet under-reported.^{2,25–27} The actual incidence of diseases related to this organism remains unknown.

Age and sex

C. urealyticum causes UTIs including pyelonephritis and encrusted cystitis, which can occur at any age (mean age of 55–65 years). On the other hand, encrusted pyelitis usually occurs at an earlier age (with a mean age of 40–45 years).²

A sex-related affinity of *C. urealyticum* for skin colonization is supported by the fact that it has been isolated from the skin of 25%–37% of healthy elderly individuals, predominantly females.³

Infection with *C. urealyticum* is uncommon in children but must be considered. An unusual case of a 19-year-old kidney recipient with necrotizing pyelitis due to *C. urealyticum* in the absence of mucosal encrustation or calculi was reported. In such cases diagnosis must be rapid, and conservative treatment administered if possible.²³

Risk factors

According to Pagnoux et al,¹² the risk factors for *C. urealyticum* infection include the following:

1. prolonged use of a urinary catheter.
2. Hospitalization for long periods.
3. Immunocompromised patients.
4. Kidney transplantation.
5. Recent urologic procedure.
6. Chronic debilitating disease.

7. Broad spectrum antibiotic treatment.
8. Cytotoxic drug usage.
9. History of previous UTIs.

It is noteworthy that patients at highest risk are those with prior urinary tract abnormalities or who have recently undergone urologic procedures as well as elderly patients who have had prolonged surgery.²⁸

Risk factors for developing pyelonephritis include immunosuppression and kidney transplantation. Risk factors for the development of encrusted cystitis include urological diseases and previous UTIs in patients with chronic debilitating conditions as well as bladders damaged by trauma, tumor or intravesical administration of cytotoxic drugs.²³

A cohort of 163 renal transplant recipients who were screened for UTIs due to *C. urealyticum* revealed that infection was closely related to obstructive uropathy. *C. urealyticum* has been reported in 10% of kidney recipients.²⁹

Nosocomial versus community acquired infections

C. urealyticum has been isolated from the hospital environment which suggests it could be transmitted nosocomially or by air.^{2,30} Patients who were hospitalized for a prolonged period have shown infection with *C. urealyticum*. Outbreaks of nosocomial infections have been described. It can be deduced from several studies that nosocomial transmission of *C. urealyticum* infection is more common than community acquired infection.⁸

Hospitalized patients, especially ICU patients, tend to have more risk factors than non-hospitalized patients do, and have the highest infection rates. These highly resistant organisms deserve special attention in health care facilities. The availability of vulnerable patients, increased potential for transmission from larger numbers of colonized or infected patients “colonization pressure”, selective pressure exerted by antimicrobial use determine transmission and persistence of the resistant strain.⁸

Pathogenesis of *C. urealyticum*

Colonization and adherence to host tissues

C. urealyticum is known to be a natural colonizer of the human skin and urinary tract, especially in patients receiving broad-spectrum antibiotics.¹² It is characterized by adherence to uroepithelial cells, which was observed for both urinary isolates and strains from healthy skin.^{2,23} If a patient is asymptomatic but his/her urine culture was positive for *C. urealyticum*, this patient is considered to be experiencing urinary colonization with this bacteria.²⁹ Adherence to host tissues may be mediated

by adhesive pili. These pili are covalently anchored to the *Corynebacterium* cell wall by a transpeptidylation mechanism to facilitate contact between the organisms and host tissue. *C. urealyticum* expresses a proteinaceous pilus with some structural similarity to the pilus of *C. diphtheria*.³¹

Adherence may occur in the absence of a pilus shaft. *C. urealyticum* has a SpaE subunit of its SpaDEF pilus which is covalently anchored to the cell wall. This provides tight contact between the bacterial cell and the host tissue. Similarly, adherence of *C. diphtheriae* to pharyngeal epithelium is mediated by the minor pilin SpaB of the structurally related SpaABC pilus.³¹ Previous studies have shown that only few *C. urealyticum* isolates that strongly adhered to uroepithelium were pilated.³

Moreover, human skin provides a habitat for *C. urealyticum* growth via provision of appropriate fatty acid composition. The gene repertoire of *C. urealyticum* DSM7109 reflects its adaptation as a lipophilic species to those habitats. In this context some studies have found that *C. urealyticum* strains were more frequently isolated from female patients than from males.²³ Adherence of *C. urealyticum* to the skin has also been explained through studying the metabolic analysis of the genome sequence of *C. urealyticum*, which provided evidence that the lipid-requiring phenotype of *C. urealyticum* is due to the absence of a microbial type I fatty acid synthase gene provided by human skin that provide an appropriate amount of exogenous fatty acids for growth.³

Furthermore, the presence of *C. urealyticum* at a specific skin site excludes the colonization of the same body site by *C. jeikeium* and vice versa. *C. jeikeium* is also a strictly lipophilic species that is recovered from the axillary, inguinal, and perineal areas of the human body and, unlike *C. urealyticum*, it is more prevalent on the skin of male patients than on females.¹²

Consequently, one can assume that *C. urealyticum* strains commonly colonize the human skin, and after urological instrumentation gain access from the skin to the urinary tract of inpatients.²³

Adherence to medical devices

A critical factor in the initiation of nosocomial UTIs by *C. urealyticum* is its adherence to foreign body materials in the urinary tract and also efficient adherence to intravascular catheters, artificial valves, and CNS drainage devices.¹²

Adherence of *C. urealyticum* to catheter materials such as polyvinyl chloride, Teflon and Teflon-coated rubber, may depend on the hydrophobicity of the cell surface of *C. urealyticum* that promotes the development of biofilms on solid surfaces.³² Analysis of the genome sequence revealed that *C. urealyticum* DSM7109 contains genes for two putative surface proteins

(surA and surB) that display internal repeats in their amino acid sequences and may play important roles in UTIs of catheterized patients. Therefore, the surface proteins SurA and SurB may play important roles in UTIs of catheterized patients.³²

Urease activity

C. urealyticum is a micro-organism with strong urease activity, which plays a fundamental role in its pathogenicity.³ The ureABC genes encode the structural subunits of the urease, whereas the ureEFGD genes code for accessory proteins. These proteins are homologous between urease gene clusters and are required for the assembly of the nickel metallocenter within the active site of the urease enzyme.³³ When the organism adheres to the urinary tract, it grows under the stimulation of the urea present in the urine. Hydrolysis of urea leads to hyperammonuria and the alkalization of human urine, which can cause supersaturation with struvite and calcium phosphate with consequent crystallization of struvite and can also be facilitatory to urological disease.³⁴

Clinical significance of *C. urealyticum*

C. urealyticum is an opportunistic nosocomial pathogen causing mainly acute cystitis, pyelonephritis, alkaline encrusted cystitis, and encrusted pyelitis and may cause bacteremia mainly in patients with chronic urological diseases.²

UTIs

C. urealyticum was identified as a pathogen causing chronic or recurrent cystitis, bacteriuria, bladder stones, and pyelonephritis.¹² UTIs can be acute or chronic.

Acute UTIs

Acute cystitis is the more common clinical picture, although in many reported cases no differentiation between cystitis and pyelonephritis was made.⁶ Diagnosis of an acute UTI is made if symptoms of a UTI are present with leukocyturia and more than two urine samples positive for *C. urealyticum*. A UTI is considered acute if symptoms are present for less than 4 weeks. Pyelonephritis is defined as the presence of fever ($>38^{\circ}\text{C}$), flank pain, with detection of *C. urealyticum* in urine and/or blood.⁶ Pyelonephritis due to *C. urealyticum* has been diagnosed in previous studies, with isolation from urine or from urine and blood or from urine obtained through a perirenal catheter. Patients were usually immunosuppressed.²⁸

Chronic UTIs

Encrusted cystitis

Encrusted cystitis is one of the most frequent chronic infections caused by *C. urealyticum*, a condition of chronic

ulcerative bladder inflammation, with deposits of (magnesium ammonium phosphate) on the surface and on the walls of the ulcer.³⁵ *C. urealyticum* converts urea into ammonia, making urine alkaline, which precipitates struvite and calcium phosphate crystals, forming stones and encrustations on the infected mucosa. This produces a fibrotic and retractile bladder with reduced capacity, which may produce stenosis of the ureteral meatus, leading to dilatation of the upper urinary tract as shown in Figure 2. Bladder wall histology after resection of calcified encrustations shows three distinct zones: a necrotic layer containing calcified encrustations, an inflammatory layer containing bacterial colonies, lymphocytes and polymorphonuclear cells, and normal tissue (Figure 2).³⁶

Encrusted cystitis is not a life-threatening disease, but is a very painful condition. It causes long-lasting symptoms in the lower urinary tract, with frequent relapses.^{37,38} It is also possible to demonstrate uretero-hydronephrosis by intravenous pyelography.³⁹

A case of a 61-year-old man who presented with encrusted cystitis associated with bilateral hydronephrosis 4 months after adenomectomy complicated by vesicocutaneous fistula was described.³⁸ Also a case of encrusted cystitis caused by *C. urealyticum* in a 69-year-old female who was admitted for recurrent cystitis following bladder catheterization after orthopedic surgery was reported, and despite prolonged non-specific and differentiated antibiotic therapy this patient had calcium-oxalate and struvite “stones” expelled daily in her urine with an alkaline (pH 8–9), and severe bladder incontinence.³⁶

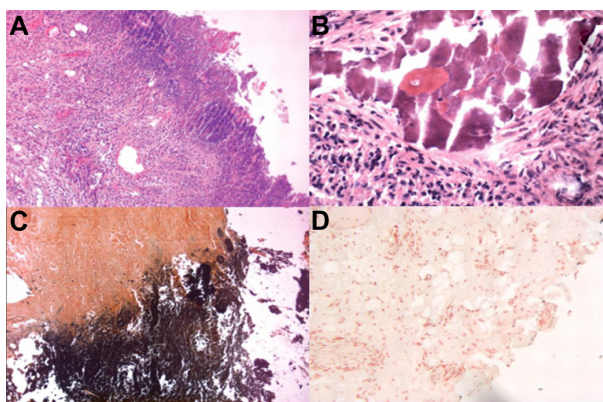


Figure 2 Bladder wall histology of *C. urealyticum*.

Notes: (A) Hematoxylin and eosin staining of bladder biopsies before treatment, showing necrotic tissue and inflammatory infiltration 100 \times and focal evidence of calcified encrustations on the wall, 400 \times (B). Von Kossa staining showing calcium deposition at the surface level, 100 \times (C); Von Kossa staining negative for calcium deposition, 100 \times (D) after treatment. Reproduced from Del Prete D, Polverino B, Ceol M, et al. Encrusted cystitis by *Corynebacterium urealyticum*: A Case Report With Novel Insights Into Bladder Lesions. *Nephrol Dial Transplant*. 2008;23(8):2685–2687, by permission of Oxford University Press.³⁶

Another case of encrusted cystitis due to *C. urealyticum* was described in a 39-year-old female with ANCA associated vasculitis. She received several immunosuppressant medications since the onset of her vasculitis, with cycles of broad-spectrum antibiotics during the acute initial phase of her disease. Treatment of encrusted cystitis in this patient was successful with Teicoplanin.¹²

Encrusted pyelitis

Encrusted pyelitis is another serious chronic infection,³⁵ which is characterized by the presence of struvite encrustations on the renal pelvis wall, identified when the pelvis is open during a urological intervention.⁴⁰ It has been mainly described in renal transplant recipients and has been reported to facilitate graft destruction.^{41,42} An unusual case of a 19-year-old kidney recipient with necrotizing pyelitis due to *C. urealyticum* in the absence of mucosal encrustations or calculi has been reported.²³

Encrusted cystitis and encrusted pyelitis are uncommon in children but must be considered. Diagnosis must be rapid, and conservative treatment administered if possible. Nevertheless, graft loss can occur in kidney transplant recipients with encrusted pyelitis.²³

Skin and soft tissue infections

C. urealyticum is a colonizer of the skin of hospitalized patients with or without UTIs. There is evidence that *C. urealyticum* may be transmitted by air so skin colonization in compromised patients could occur by that route. There are also well-documented cases of wound infections caused by *C. urealyticum*.^{2,6} A few cases of breast abscesses and other wound and soft tissue infections caused by *C. urealyticum* have also been reported.⁸

Bacteremia

C. urealyticum is probably an underestimated cause of sepsis among hospitalized patients mainly due to the difficult microbiologic identification of the organism.⁸ Prolonged hospitalization, prior antibiotic use, and the presence of intravenous lines are important factors placing patients at risk for *C. urealyticum* bacteremia. Bacteremia due to *C. urealyticum* remains with mortality rate up to 20%.⁸ Previous studies have demonstrated well-documented cases of bacteremia caused by *C. urealyticum* with mean age 52.9 years, some had urological disorders others had leukemia or AIDS.²

C. urealyticum is the cause of some cases of endocarditis that have been reported. These patients either had endocarditis on native valves or on a prosthetic valve. One of these

patients was a drug addict. Another patient had a valvular prosthesis, developed endocarditis, and died.^{2,6}

A case of sepsis by *C. urealyticum* in an 86-year-old patient acquired in the hospital was described. In this patient, admission for a *Pseudomonas aeruginosa* infection of the urinary tract was complicated by severe sepsis caused by *C. urealyticum*. Sepsis occurred through the intravenous line 17 days after *P. aeruginosa* had been successfully eradicated.⁸

Other infections caused by *C. urealyticum* have been documented, for example: osteomyelitis and pneumonia, which were documented in patients with urological disorders, neutropenic patients, patients with breast cancer, and acute leukemia.^{2,6}

Some related species to *C. urealyticum* may be clinically relevant, and thus must be identified to the species level. For example, *C. jeikeium* can cause bacteremia; endocarditis; pneumonia; prosthetic joint infection or otitis media. *C. pseudodiphtheriticum* on the other hand can cause pneumonia (occasionally with pseudomembranous formation), keratitis or conjunctivitis.⁴

Laboratory diagnosis of *C. urealyticum*

C. urealyticum is isolated frequently in laboratories but usually not properly identified. Identification is important to differentiate contamination and/or colonization from infection, which influences decisions regarding clinical intervention.¹⁷ The correct identification is important because the antimicrobial susceptibilities of different coryneform bacterial isolates are quite variable.⁴⁴

C. urealyticum should be thoroughly identified when isolated in pure cultures, when isolated from blood or sterile body fluids, when isolated repeatedly from specimens, or when isolated as the predominant organism from a mixed infection.⁹

The clinician should be notified immediately if *C. urealyticum* is present in blood culture, and the clinical significance of *C. urealyticum* must be carefully examined by cooperation between the microbiology laboratory and the clinician. Care must be taken in the interpretation of the results for those patients in whom half or more of the blood specimens taken for culture become positive, because not all blood samples taken from patients with *C. urealyticum* infection may eventually become positive.²

Sample collection and storage

C. urealyticum can be isolated from different samples including urine, blood, and pus from wounds. Samples are collected under complete aseptic conditions according to standard procedures and transported quickly (within 2 hours) keeping

Table 3 Biochemical characteristics of lipophilic *Corynebacterium* species

Organism	Fermentation (F)/oxidation (O)	Lipophilism	Nitrate reduction	Urea hydrolysis	Esculin hydrolysis	Pyrazinase activity	Alkaline phosphatase activity	Acid production from			CAMP reaction	Other characteristics
								Glucose	Maltose	Sucrose		
<i>C. accolens</i>	F	+	+	-	-	V	-	+	-	V	-	-
<i>C. afermentans</i> subsp. <i>afermentans</i>	O	-	-	-	-	+	+	-	-	-	V	-
<i>C. afermentans</i> subsp. <i>lipophilum</i>	O	+	-	-	-	+	+	-	-	-	V	-
<i>C. amycolatium</i>	F	-	V	V	-	+	+	+	V	V	-	Mostly O/129 resistant
<i>C. argentoratense</i>	F	-	-	-	-	+	V	+	-	-	-	-
<i>C. aureus</i>	O	-	-	-	-	+	+	-	-	-	+	Dry, slight adherence
<i>C. bovis</i>	O	-	-	-	-	V	+	+	-	-	-	β -Galactosidase positive Yellowish
<i>C. cystitidis</i>	F	-	-	+	-	+	+	+	-	-	-	-
<i>C. diphtheriae gravis</i>	F	-	+	-	-	-	-	+	+	-	-	-
<i>C. diphtheriae intermedius</i>	F	+	+	-	-	-	-	+	+	-	-	-
<i>C. diphtheriae mitis</i>	F	-	+/-	-	-	-	-	+	+	-	-	Fructose negative, no growth anaerobically
<i>C. jeikeium</i>	O	+	-	-	-	+	+	+	V	-	-	-
<i>C. kutscheri</i>	F	-	V	+	+	V	-	+	+	+	-	-
<i>C. Macginleyi</i>	F	+	+	-	-	-	+	+	-	+	-	-
<i>C. matruchotii</i>	F	-	+	V	+	+	-	+	V	V	-	"whip handle"
<i>C. minutissimum</i>	F	-	-	-	-	+	+	+	+	-/(+)	-	Fructose positive Yellow pigment
<i>C. Pilosum</i>	F	-	+	+	-	+	+	+	-	-	-	Tyrosine positive
<i>C. Propinquum</i>	O	-	+	-	-	V	V	-	-	-	-	-
<i>C. pseudodiphtheriticum</i>	O	-	+	+	-	+	V	-	-	-	REV	-
<i>C. pseudotuberculosis</i>	F	-	V	+	-	-	V	+	+	V	-	+
<i>C. renale</i>	F	-	-	+	-	+	-	+	-	-	+	Tyrosine positive
<i>C. striatum</i>	F	-	+	-	-	+	+	+	-	V	V	Glycogen positive
<i>C. ulcerans</i>	F	-	-	+	-	-	+	+	+	-	REV	-
<i>C. urealyticum</i>	O	+	-	+	-	+	V	-	-	-	-	O/129 susceptible
<i>C. xerosis</i>	F	-	V	-	-	+	+	+	+	+	-	-
CDC group F-I	F	+	V	+	-	+	+	+	+	+	-	-
CDC group G	F	+	V	-	-	+	+	+	V	V	-	Fructose positive, growth anaerobically

Notes: Reproduced with permission from American Society for Microbiology from Funke G, von Graevenitz A, Clarridge JE 3rd, Bernard KA. Clinical Microbiology of Corynebacterium Bacteria. Clin Microbiol Rev. 1997;10(1): 125–159.¹¹

Abbreviation: CDC, Centers for Disease Control; REV, reverse CAMP reaction; -, negative reaction; +, positive reaction; V, variable reaction.

in mind that *C. urealyticum* is a fastidious organism. No specific transport media are required.⁴

Urine samples must be collected according to standard procedures. Likewise, culture swabs are carefully taken from the site of infection without touching adjoining areas to avoid commensal contamination from indigenous flora. The correct anatomic site that represents a location of active disease should be selected because even careful collection methods will produce a specimen of low clinical value if it is not obtained from a site where the infection is active.¹⁷

Processing, isolation, and identification

Microscopic identification

Gram staining of *C. urealyticum* shows slightly curved Gram positive rods with sides not parallel to each other and slightly wider ends giving it an atypical club shape. It is non motile, non spore forming and non acid fast.²

Isolation on culture media

According to Pagnoux et al,¹² *C. urealyticum* can be isolated after culture by streak method on selective or non selective media including:

- a. non selective media:
 - i. sheep blood agar;
 - ii. chocolate agar.
- b. Selective media:
 - i. CBU agar medium: CBU agar is a lipid-enriched peptone-based agar. Addition of antibiotics (β -lactam antibiotics or clindamycin plus nalidixic acid) to CBU agar medium can be done to inhibit or reduce other organisms present in the sample.
 - ii. Loeffler's serum medium. Constituents: three parts of sheep or horse serum plus one part of glucose broth.

Selective media for isolating *C. urealyticum* have great epidemiological value, but are not useful for management of patients, as most strains isolated only from selective media have no clinical relevance. That is why the use of selective media is not recommended for isolation of *C. urealyticum* for routine purposes, and sheep blood agar is the recommended medium for isolation.¹²

Incubation temperature and duration

Most *C. urealyticum* isolates are missed in routine cultures because the organism does not grow after "overnight" incubation. Therefore, incubation should last longer than 24 hours. *C. urealyticum* can be easily overlooked because it grows slowly requiring 48 to 72 hours incubation at

35°C–37°C for colonies to grow on agar plates and thus would be missed if the culture plates are examined after overnight incubation and discarded as negative before full 48 to 72 hours incubation. This is why clinical suspicion should be communicated to the microbiologist when samples are sent for culture.³⁴

Identification from culture

Diphtheroid morphology of *C. urealyticum* could be interpreted falsely as representing contamination from skin or mucous membrane flora.²⁹

- a. Appearance on sheep blood agar and chocolate agar: the organism grows on blood agar as pinpoint, whitish, opaque, smooth, convex, circular, entire, and non-hemolytic colonies.¹⁷
- b. Appearance on CBU agar: *C. urealyticum* forms typical colonies surrounded by a red halo on CBU agar. Because of its strong urease activity, when >10 colonies grow on this medium, the whole plate is usually pink and only the colonial morphology of *C. urealyticum* allows its recognition. Other urease-producing bacteria isolated on the medium grow faster or are glucose fermenting and no clear red halo is usually seen.¹²
- c. Appearance on Loeffler's medium: the color of *C. urealyticum* isolates tends to be yellowish white on Loeffler's medium.¹²

Biochemical identification

Conventional biochemical tests

C. urealyticum is the only known *Corynebacterium* that is lipophilic, asaccharolytic, and strongly urease positive. Other urease positive *Corynebacterium* species can be differentiated from *C. urealyticum* because they produce acid from glucose, except *C. pseudodiphtheriticum* which is weakly urease positive and asaccharolytic, yet unlike *C. urealyticum* it is nonlipophilic and nitrate positive,¹⁷ Table 3 shows the biochemical characteristics of different *Corynebacterium* species. A closely related species, *C. jeikeium* can be easily differentiated from *C. urealyticum* because it is non-urealytic and produces acid from glucose.¹⁷

API Coryne (bioMérieux, Marcy l'Etoile, France)

Biochemical identification can be easily performed by phenotypic studies, using home-made media or commercial systems.¹⁷ The API Coryne version 2.0 (bioMérieux, Marcy l'Etoile, France) is one of these systems and it is useful in identifying the majority of the non-diphtherial *Corynebacterium* species with clinical relevance.⁵

The principal disadvantage of these systems is that large inocula are required, much time as well as expensive strips can be wasted working with insignificant isolates. That is why a minitube was developed to enable a rapid biochemical test for urease production to be carried out expediently and with minimal inocula, providing a presumptive identification of *C. urealyticum* in much less time.⁴⁵

The diagnostic performance of the API Coryne system, version 2.0, was evaluated and was able to identify 90.5% of *Corynebacterium* species.¹¹ In several reports on new species of *Corynebacterium*, the API Coryne was used to phenotypically characterize the new isolates and biocodes were generated from the patterns of positive and negative reactions.⁵

A comparative study was done to compare the ability of the API Coryne system to identify *Corynebacterium* isolates with respect to conventional biochemical tests which were considered as reference methods.

The study showed that the API Coryne was able to identify 91% of *Corynebacterium* species correctly without need for further testing and it identified all strains of *C. urealyticum* correctly. It was considered “proper identification” when the system biocodes obtained indicated that it was excellent identification, “low discrimination” when additional tests were needed for proper identification suggested by the manufacturer and “misidentification” when the biocodes corresponded to a species different from that identified by conventional biochemical methods.⁵ In a study done by Adderson et al,⁴⁴ comparing the API Coryne system and sequence analysis of 16S rRNA and rpo genes in identification of *C. urealyticum* isolates, the most sensitive tests for identification were found to be the API Coryne system and amplification and sequencing of the 16S rRNA gene using primers optimized for corynebacteria. Phenotypic combined with genotypic systems correctly identified up to 75.0% of control isolates to the species level.

Previously published studies found that the efficacy of biochemical identification systems is limited by the need to perform additional tests to definitively identify strains to the species level. The accuracies of phenotypic identification systems may be limited by the entries present in their respective databases. Additional difficulties when depending upon biochemical results from organisms that were particularly slow growing and relatively biochemically inert may have arisen. Such characteristics may make it hard to achieve sufficient inocula for testing and may result in weak biochemical reactions that are difficult to discriminate. The latter may affect the reproducibility and accuracy of test results.⁴⁴

Roux et al⁴⁶ found that 16S rRNA gene sequencing identified 90.3% of *Corynebacterium* species correctly whereas the API Coryne system led to the correct identification of only 75.8% of the strains.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing is a phenotypic method where isolates can be differentiated by generating antimicrobial resistance profiles. By understanding antimicrobial use patterns in certain environments, geographic locations, and health care settings, the occurrence of resistance to certain antimicrobials could provide a means to differentiate among isolates of different origins. Various testing methods, such as disc diffusion on Muller Hinton blood agar, broth microdilution, and E-test exist and can be performed to verify the susceptibility of *C. urealyticum* to antimicrobial agents.³⁴ Table 4 shows possible antibiotic sensitivity of *C. urealyticum* isolates using microdilution.

The Clinical and Laboratory Standards Institute guidelines do not provide breakpoints for disc diffusion. CLSI (Clinical and Laboratory Standards Institute)⁴⁷ recommends penicillin, vancomycin, erythromycin, and gentamicin for primary testing. The European Committee on antimicrobial Susceptibility testing (EUCAST) provides breakpoints for corynebacteria antibiotic susceptibility testing. It recommends the usage of benzylpenicillin, ciprofloxacin, moxifloxacin, gentamicin, vancomycin, clindamycin, tetracycline, linezolid, and rifampicin.⁴⁷

Molecular identification

Molecular identification systems for *Corynebacterium* species have been outlined. Progress in molecular taxonomy (DNA–DNA hybridization and 16S rRNA sequencing) and in chemotaxonomy has profoundly modified the classification of *Corynebacterium* species. The improvements in taxonomy and means of detection, together with an increased interest in *Corynebacterium* as an opportunistic infectious agent in humans, have resulted in the delineation of a plethora of new *Corynebacterium* species from human sources. Amplified rDNA analysis, and amplification of the 16S–23S gene spacer regions can differentiate between species that are difficult to be differentiated by biochemical reactions. With the application of molecular methods the number of species in the genus *Corynebacterium* has expanded.¹⁶

PCR

PCR is primarily used for rapid diagnosis of *C. urealyticum*. PCR is closely patterned after the natural DNA replication

Table 4 Antibiotic sensitivity of *C. urealyticum* isolates

Antibiotic	MIC, µg/mL			Percentage of resistant isolates (n=38)	Cut-off value for resistance, µg/mL
	50	90	Range		
Vancomycin	0.5	1	<0.06 to 2	0	>32
Teicoplanin	0.25	0.5	<0.06 to 1	0	>32
Rifampicin	0.06	2	<0.06 to 4	5.3	>4
Penicillin G	>512	>512	<0.06 to 512	76.3	>4
Cefotaxime	>512	>512	<0.06 to 512	71.1	>64
Norfloxacin	216	>512	2 to >512	84.2	>16
Ciprofloxacin	16	64	0.25 to >512	79	>4
Erythromycin	256	>512	<0.06 to >512	68.4	>8
Azithromycin	256	>512	<0.06 to >512	65.8	>8
Clarithromycin	2	>512	<0.06 to >512	44.7	>8
Clindamycin	>512	>512	<0.06 to >512	86.4	>4
Chloramphenicol	64	128	1 to 128	76.3	>32
Tetracycline	2	32	0.5 to 32	39.5	>16
Gentamicin	>512	>512	<0.06 to 512	57.9	>8

Notes: Reproduced from López-Medrano F, García-Bravo M, Morales JM, et al. Urinary Tract Infection due to *Corynebacterium urealyticum* in Kidney Transplant Recipients: An Underdiagnosed Etiology for Obstructive Uropathy and Graft Dysfunction-Results of a Prospective Cohort Study. *Clin Infect Dis*. 2008;46(6):825–830, by permission of Oxford University Press.²⁹

Abbreviation: MIC, minimum inhibitory concentration.

process. Each round of PCR synthesis involves three steps: denaturation, annealing, and extension.

This three-step PCR cycle is repeated several times. The number of target DNA copies approximately doubles every cycle (Roche Diagnostics, Germany). *C. urealyticum* was identified by PCR using mycobacterial primers in a case of suspected tuberculosis. Sequencing was further done for confirmation.⁷

Types of PCR

Conventional PCR: Molecular detection techniques, like PCR, can be used for identification of *C. urealyticum*, when other tests remain negative and suspicion is strong.¹²

Real time PCR (RT-PCR): RT-PCR is also used for detecting *C. urealyticum* where fluorescent dyes or fluorophore-containing DNA probes are used to measure the amount of the amplified product as the amplification progresses (Roche Diagnostics).

Many studies have been using RT-PCR recently for rapid identification of different *Corynebacterium* species including *C. urealyticum*.⁴⁸

Gene sequencing techniques

16S rRNA gene sequencing: Another molecular technique useful for difficult-to-identify organisms, as *Corynebacterium* species, is rRNA gene sequencing, because conventional PCR is used for identifying *Corynebacterium* species. The purpose of conventional PCR is amplification of normal

DNA templates using Taq DNA polymerase enzyme (Roche Diagnostics). Of the universal distribution of species-specific variable regions in the genes, the 16S rRNA gene sequence analysis plays an important role in the unambiguous species level identification of corynebacteria in the clinical laboratory. Even more importantly, sequence analysis may provide a degree of resolution that allows discrimination of different *Corynebacterium* species isolated from the same patient, which may help in determining the clinical significance of these multiple isolates.⁴⁹

Another genotypic identification system, the MicroSeq 500 16S bacterial sequencing kit, is designed to sequence the first 527 bp of the 16S rRNA gene for bacterial identification. This system is a simplified version of the original MicroSeq system, which uses only two sequencing primers to analyze a single PCR product, thereby significantly reducing the cost and labor required for identification.⁴⁹

Due to the difficulty in identifying *Corynebacterium* species with standard phenotypic methods, the MicroSeq system's ability was compared with that of standard phenotypic identification methods. *Corynebacterium* identification using the MicroSeq was faster than conventional methods.

Phenotypic identification of *Corynebacterium* species routinely requires 3 to 4 days while identification based on the MicroSeq can be completed within 48 hours.⁴⁹

rpoB gene sequencing: Among the universal genes that can be used for taxonomic analysis and gene sequence-based identification, the RNA polymerase beta subunit-encoding gene

(rpoB) can also be used for identification of *Corynebacterium* species.¹⁸ rpoB is a single-copy gene, it belongs to the common set of genes and it is long enough to contain phylogenetically useful information. It might be less prone than the 16S rRNA gene to lateral gene transfer due to its housekeeping function and it has already been used for bacterial species delineation in selected cases as well as to estimate the DNA G + C content of whole bacterial genomes. Among some alternative protein-coding genes, the rpoB gene showed the highest correlation to average amino-acid identity, which reflects whole genome-level relatedness.¹⁴

Restriction fragment length polymorphism (RFLP)

RFLP is a genotypic method where bacterial isolates are differentiated based on the profile generated following restriction enzyme digestion of bacterial chromosomal DNA or plasmids. This method has the advantage of being rapid and easy to perform.¹⁶

RFLP analysis, allowed the identification of *Corynebacterium* species, three different restriction enzymes are used, it has been demonstrated to be of use for the identification of species within the genus *Corynebacterium*.¹⁸

The abilities of 16S rRNA and rpoB gene sequencing to identify *Corynebacterium* isolates from clinical specimens were directly compared by Khamis et al,¹⁶ who found rpoB sequencing to be the most sensitive assay, positively identifying 91% of isolates, compared to 81% by 16S rRNA gene sequencing.

Matrix-assisted laser desorption/ionization coupled to time of flight (MALDI-TOF) MS

Recently, detection of *C. urealyticum* has been accomplished by automated methodology including MALDI-TOF, and BD-Phoenix among others. Additional studies have shown that all isolates identified as *C. urealyticum* by API Coryne were also identified by MALDI-TOF MS.^{50,51}

Antimicrobial resistance to *C. urealyticum*

The majority of *C. urealyticum* strains obtained from clinical samples display multiple resistance to antibiotics¹⁷ which suggests the organism may be acquired from the hospital environment and, therefore, the use of antibiotics in the hospital setting could favor the appearance of multi-resistant strains.⁵²

A case report of *C. urealyticum* infection acquired in the hospital demonstrated the potential to achieve a complete recovery even among those patients whose disease is

caused by *C. urealyticum* strains resistant to a wide range of antibiotics (β -lactams and aminoglycosides), if the appropriate treatment with teicoplanin, vancomycin, linezolid or quinupristin-dalfopristin, the only antibiotics to which this organism is universally susceptible, is given and started in time.^{8,18,30}

Antibiotic resistance determinants of the *C. urealyticum* DSM7109 genome

The presence of an ErmX determinant encoding a 23S rRNA adenine N-6-methyltransferase in the genome of *C. urealyticum* has been demonstrated. Variants of the erm(X) gene were detected previously in other pathogenic corynebacteria, including *C. jeikeium*, *C. diphtheriae*, and *C. striatum*, as well as in cutaneous propionibacteria and *Arcanobacterium*.²⁰ The erm(X) gene can be organized as an integral part of transposons that are active in corynebacterial species.⁵³

Antimicrobial groups and mechanism of resistance of each

Macrolides

In a recent study, the frequency of macrolide resistance mechanisms in clinical isolates of *Corynebacterium* species was described. The study showed high resistance of the different strains to macrolides. Erythromycin, clindamycin as well as other macrolides showed poor activity against *C. urealyticum*, *C. jeikeium*, and *C. amycolatum*. Telithromycin is more active in vitro than erythromycin, but only against erythromycin-susceptible and erythromycin-intermediate isolates, while cethromycin is only poorly active against *C. urealyticum*.³³

In a previous study, antibiotic susceptibility assays with *C. urealyticum* DSM7109 revealed high minimum inhibitory concentrations (MICs) for the macrolide erythromycin (>128 μ g/mL) and the lincosamide lincomycin (>256 μ g/mL).³

The erm(X) resistance gene conferred resistance in corynebacteria to telithromycin and to a spectrum of macrolides and lincosamide antibiotics, such as erythromycin, azithromycin, josamycin, midecamycin, roxithromycin, spiramycin, tylosin, clindamycin, and lincomycin. That study concluded that erm(X) confers the high resistance levels for macrolides, lincosamides, and the ketolide telithromycin.⁵⁴

Quinolones

C. urealyticum isolates were previously found to be susceptible to ofloxacin, norfloxacin, and ciprofloxacin, but more

recent studies revealed an increased level of resistance to fluoroquinolones. Another study indicated that only 20.3% of the tested *C. urealyticum* isolates were susceptible to ciprofloxacin. Newer fluoroquinolones are more effective in vitro than ciprofloxacin and norfloxacin, but may remain ineffective against high-level ciprofloxacin-resistant isolates.⁵⁵

Aminoglycosides

C. urealyticum is mostly resistant to aminoglycosides. According to a previous study, annotation of the genome sequence of *C. urealyticum* DSM7109 revealed the presence of the aph(3')-Ia gene encoding a member of the aminoglycoside 3'-phosphotransferase protein family. (Figure 3). The aph(3')-Ia gene is part of a larger chromosomal region that is almost identical to a DNA segment of the multi-drug resistance plasmid pTP10 from *C. striatum* M82B.³ This DNA region also contains the strA-strB tandem pair of resistance genes that encode aminoglycoside-3"-phosphotransferase and aminoglycoside-6-phosphotransferase, which confer high levels of streptomycin resistance. The strA-strB genes are widespread among bacteria and can be associated with transposons, such as Tn5393-related elements.

The strA-strB coding regions of *C. urealyticum* DSM7109 are located downstream of the tnpR gene from a Tn5393-like transposon that is disrupted by the Tn5715 element containing the aph(3')-Ia gene (Figure 3).⁵⁶

Consequently, the presence of the aph(3')-Ia gene may be related to the resistance of *C. urealyticum* strains to a wide range of aminoglycosides, whereas the strA-strB genes may specifically confer the observed resistance to the aminoglycoside streptomycin.⁵⁵

The MIC of *C. urealyticum* DSM7109 for the aminoglycosides, kanamycin, and streptomycin are >256 µg/mL and >128 µg/mL, respectively.⁵⁶

Chloramphenicol

The genome of *C. urealyticum* DSM7109 contains two identical genes (cmx1 and cmx2) that encode a chloramphenicol exporter of the major facilitator superfamily.³ Like the orthologous counterparts from *C. glutamicum* and *C. striatum*, the cmx1 gene of *C. urealyticum* DSM7109 is part of a structurally unusual transposable element, in conjunction with the transposase gene tnp7109-14. The cmx2 gene is located in the chloramphenicol and aminoglycoside resistance gene region of *C. urealyticum* DSM7109 (Figure 3).⁵⁶

The MIC of *C. urealyticum* DSM7109 for chloramphenicol is >32 µg/mL. Chloramphenicol resistance was detected also in the majority of *C. urealyticum* isolates during earlier antimicrobial susceptibility assays, revealing MICs in the range from 16 to >128 µg/mL. The mobile cmx gene is thus a likely candidate to mediate chloramphenicol resistance in *C. urealyticum* strains.³

Tetracyclines

It was found that the genome sequence of *C. urealyticum* DSM7109 contains a gene region that comprises the tetA-tetB gene pair (Figure 3). The tetAB proteins represent a specific group of tetracycline resistance determinants that use ATP rather than the proton gradient as energy source.⁵⁷ Antibiotic susceptibility assays reveal that *C. urealyticum* DSM7109 is resistant to tetracycline (MIC >32 µg/mL) and susceptible to doxycycline (MIC <1 µg/mL). The tetAB genes may contribute to the tetracycline resistance of clinical *C. urealyticum* isolates, but may not confer resistance against doxycycline that was recognized in some *C. urealyticum* strains. The tetAB genes are flanked at the 5' junction by an IS1249, indicating that a Tn3598-related element integrated into the genome of *C. urealyticum* DSM7109 (Figure 3).⁵⁸

Multi-drug resistance

As with many organisms, antibiotic use could favor the appearance of multiresistant strains obtained via the transfer of resistance genes,⁸ which confer multi-drug resistance in corynebacteria.

Treatment, prevention, and control

Treatment

C. urealyticum, being a known multi-drug resistant organism (MDRO), must be treated with the right antibiotics, as failure in therapy leads to persistent infections.⁵⁹ Vancomycin

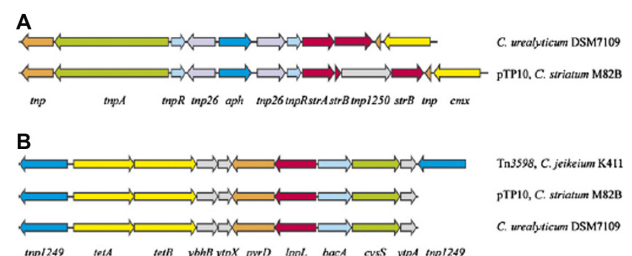


Figure 3 Comparative analysis of antibiotic resistance gene regions detected in corynebacteria.

Notes: (A) The chloramphenicol and aminoglycoside resistance gene region of *C. urealyticum* DSM7109. (B) The tetracycline resistance gene region of *C. urealyticum* DSM7109. Republished with permission of Elsevier from Tauch A, Trost E, Tilker A, et al. The lifestyle of *Corynebacterium urealyticum* Derived from its Complete Genome Sequence Established by Pyrosequencing. *J Biotechnol*. 2008;136(1–2): 11–21. Permission conveyed through Copyright Clearance Center, Inc.³

and teicoplanin have been used with great success in many patients with UTIs due to *C. urealyticum*. In some acute UTIs, acetohydroxamic acid has been concurrently administered as well as with adjuvant therapy.^{2,60}

A case of *C. urealyticum* in a 57-year-old man affected by systemic erythematosus lupus with a long history of dysuria and suprapubic pain was reported, he underwent percutaneous nephrostomy drainage with urethral stenting for lupoid obstructive uropathy. Eventually the infection was definitively cured after a course of intramuscular teicoplanin.³⁷

Studies show that bacteremic patients were usually treated with an antibiotic active against *C. urealyticum*, mainly vancomycin. A case of a neutropenic patient with acute myeloblastic leukemia and catheter related bacteremia was reported. This patient was cured after a course of vancomycin in conjunction with catheter removal.²

Development of resistance during treatment has been observed with beta-lactam antibiotics, fluoroquinolones, macrolides, rifampin, tetracycline, and gentamicin.² Teicoplanin, vancomycin, and linezolid may be useful alternatives in the treatment of *C. urealyticum* infections caused by multi-drug resistant strains.⁵²

Prevention and control

According to the CDC⁶¹ *C. urealyticum* is considered an MDRO. Interventions for prevention and control may be grouped into the following categories: education, judicious use of antimicrobials, surveillance (routine and enhanced), standard and contact precautions, environmental measures, education, and decolonization. Other measures that have been associated with a positive impact on prevention efforts are appropriate placement of hand washing sinks and alcohol-containing hand-rub dispensers in the facility and enforcing adherence to recommended infection control practices (eg, hand hygiene, standard and contact precautions) for MDROs.

Education

Educational interventions were included in several successful studies. The focus of the interventions was to encourage a behavior change through improved understanding of the problem (MDRO) that the facility was trying to control through hand hygiene, antimicrobial prescribing patterns, or other outcomes. These factors were viewed as essential to the success of the intervention.⁶¹ Educational campaigns to enhance adherence to hand hygiene practices in conjunction with other control measures have been associated temporally with decreases in MDRO transmission in various health care settings.⁶¹

Judicious use of antimicrobial agents

Limiting antimicrobial use alone may fail to control resistance due to a combination of factors; including 1) the relative effect of antimicrobials on providing initial selective pressure, compared to perpetuating resistance once it has emerged; 2) inadequate limits on usage; or 3) insufficient time to observe the impact of this intervention. Efforts should be focused on effective antimicrobial treatment of infections, use of narrow spectrum agents, avoiding excessive duration of therapy, and restricting use of broad-spectrum or more potent antimicrobials for treatment of serious infections. Achieving these objectives would likely diminish the selective pressure that favors proliferation of multi-drug resistant strains.³⁴

Surveillance

Surveillance is a critically important component of any control program, allowing detection of newly emerging pathogens, monitoring epidemiologic trends, and measuring the effectiveness of interventions. Multiple surveillance strategies have been employed, such as monitoring of clinical microbiology isolates resulting from tests ordered as part of routine clinical care. This method is particularly useful to detect emergence of new MDROs not previously detected. In addition, this information can be used to prepare facility- or unit-specific summary antimicrobial susceptibility reports that describe pathogen-specific prevalence of resistance among clinical isolates. Such reports may be useful to monitor for changes in known resistance patterns that might signal emergence or transmission of MDROs, and also to provide clinicians with information to guide antimicrobial prescribing practices.²⁷

Standard precautions

Colonization with multi-drug resistant strains is frequently undetected; even surveillance cultures may fail to identify colonized persons due to lack of sensitivity, laboratory deficiencies, or intermittent colonization due to antimicrobial therapy. Therefore, standard precautions must be used in order to prevent transmission from potentially colonized patients. Hand hygiene is an important component of standard precautions.²⁶

Contact precautions

Contact precautions are intended to prevent transmission of *C. urealyticum* which can be transmitted by direct or indirect contact with the patient or the patient's environment. A single-patient room is preferred for patients who require contact precautions. For personnel caring for patients on contact precautions, donning gown and gloves

upon room entry and discarding before exiting the patient room is done to contain pathogens, especially those that have been implicated in transmission through environmental contamination.²⁶

Conclusion

C. urealyticum belongs to the genus *Corynebacterium*, it is a Gram positive, lipophilic, asaccharolytic, non-hemolytic, urease positive micro-organism with diphtheroid morphology.

It is an underestimated cause of infections especially: acute cystitis, pyelonephritis, alkaline encrusted cystitis, encrusted pyelitis, and wound infection and it may cause bacteremia.

It is usually acquired nosocomially especially in immunocompromised patients, patients with prolonged hospitalization or catheterization, patients with underlying urological disorders or previous UTIs.

It is usually missed in routine culture because of its diphtheroid morphology (so considered a contaminant) and it requires 48 hours of incubation to grow.

It can be diagnosed using phenotypic (Urease test, API Coryne) and molecular methods (RT-PCR using mycobacterial primers). Recently MALDI-TOF MS has also been used for identification.

It is an MDRO but still sensitive to teicoplanin and vancomycin.

Recommendations

In the case of symptoms of a UTI, high urine pH, bladder stones, recent urologic manipulation, negative routine urine culture or a UTI not responding to treatment; suspect a *C. urealyticum* infection.

Standard precautions must be used in order to prevent transmission from potentially colonized patients with *C. urealyticum*. Hand hygiene is an important component. For personnel caring for such patients, gloves upon room entry and discarding before exiting the patient room is important to contain this pathogen.

Avoid unnecessary catheterization of inpatients especially those with an underlying urological disorder.

In the laboratory, do not disregard colonies with a diphtheroid morphology specially if in a pure culture, in the elderly or in immunocompromised patients.

Incubate suspected colonies of *C. urealyticum* for 48 hours instead of 24 hours. If detected in a patient do not forget to assess the bacteremia status of this patient. Deal with this pathogen as an MDRO yet teicoplanin and vancomycin can be used for treatment.

Further studies on a larger scale are needed to:

- detect the prevalence of *C. urealyticum* among hospitalized and non-hospitalized patients;
- evaluate the ability of the API Coryne system to correctly identify *C. urealyticum* isolates compared with molecular methods;
- evaluate the sensitivity of RT-PCR using mycobacterial primers in identification of *C. urealyticum* compared with the use of other primers.

Disclosure

The authors report no conflicts of interest in this work.

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