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Letter to the Editor

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Male genitourinary infections by *Corynebacterium glucuronolyticum*. A review and clinical experience

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Sir,

Corinebacteria are often considered as part of the commensal microbiota that can be found in the genitourinary tract, however, there is growing evidence that their pathogenic role is being underestimated, even in immunocompetent individuals with no predisposing factors. The species on which this study is focused, *Corynebacterium glucuronolyticum*, is occasionally involved in human infections, so it has an opportunistic pathogen role, presenting some specificity towards the male genitourinary tract [1].

Thus, different research groups have contributed by highlighting its important role in non-gonococcal urethritis in male [1-3]; in chronic bacterial prostatitis (CBP) monomicrobial paucisymptomatic [4]; in the pathogenesis of persistent cystitis in males without predisposing factors [5] and its adverse influence on various laboratory parameters of semen, unknown until very recently [6], has also been investigated.

There are very few bibliographic references abous this species, hardly half a dozen relevant publications focusing on the genitourinary tract. As Mestrovic et al. (2018) points out, one of the main reasons for this fact is that its presence in clinical samples is not usually investigated, as its detection generally requires employing methods that are not part of the basic diagnostic protocols for genitourinary infections [1].

The pathogenic role of typical commensal microorganisms, such as corinebacteria, may come to play in the genitourinary tract has not been fully clarified yet. For this reason, identifying more accurately each species of corinebacteria is essential to move forward in this line of research. In this way, an increasingly precise determination of the pathogenicity of each species may be established, make it posible to differentiate those who behave as harmless commensal bacteria from those usually involved in infections. This precise identification will gradually become easier with the implementation of sequence-based molecular identification diagnostic methods or mass spectrophotometry (MALDI-TOF), fortunately increasingly spreading in laboratories, which are relegating biochemical methods, much less accurate, to identification second level.

Given the rarity of male genitourinary infections in which the participation of *C. glucuronolyticum* as an etiological agent has been reported, in this study we review the cases of genitourinary infectious pathology in which the involvement of this species has been proved so far and those publications in which the bacteria is described as a participant in the pathogenesis of CBP.

The genus *Corynebacterium* groups more than 60 species, many of which were recently described. Most have been isolated from animals and humans, and many of them in samples from the urogenital tract [7]. Some are only commensal species and are part of the normal microbiota, while others behave like opportunistic pathogens, so it is necessary to make an identification of the isolate until reaching the species level [8]. They may be part of the normal microbiota of the skin or upper respiratory tract, digestive or genitourinary apparatus.

A way to group corinebacteria, as it appears in a study led by Funke, et al. (1997), is based on its lipophilic or non-lipophilic character [8]. Lipophilic species, in turn, are classified as fermenters and non-sugar fermenters. The species *C. glucuronolyticum* belongs to the group of fermenting lipophilic bacteria.

It was first described by Funke et al. in 1995 [9], isolating it from samples mostly belonging to males in which there was clinical suspicion of a genitourinary infectious process. During the same year another independent research group, headed by Riegel, also isolated a new species belonging to the genus *Corynebacterium*, from semen cultures from males with a his-

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tory of prostatitis and infertility, which he named *Corynebacterium seminale* [10].

Initially, it was considered that two different species had been described, but soon after it was discovered that both had an identical biochemical profile [11]. This seemed to indicate that the two were, in fact, a single species. This was confirmed, in 1997, by Funke et al., by carrying out genetic tests of the alleged two species, which were eventually called *C. glucuronolyticum* [8]. This thesis received the final confirmation two years later, when Tanner et al. sequenced the 16S subunit of rRNA of the strains of the two alleged species, both being genetically identical, with an homology of 97% [12]. Subsequent investigations by Devriese, et al. [13] confirmed that it was definitely the same species.

Corinebacteria contain catalase and grow better in the presence of oxygen, so they can be considered aerobic or facultative anaerobic. They grow in conventional culture media used in the laboratory, albeit in a variable way depending on the species. They multiply well at the standard incubation temperature (37ºC) [14] and are not overly demanding species in terms of environmental conditions, although they do grow faster in atmospheres with an enriched concentration of CO_2 to 5%. One factor that needs to be taken into account is incubation time. After 24 hours, the colonies generated by *C. glucuronolyticum* are not yet very evident, so it is advisable to wait until a minimum of 48 (figure 1). Regarding their phenotypical characteristics, the colonies are mucous and white-yellow. Its shape is convex and its diameter, small, about 1 mm in length. In addition, they exhibit a characteristic smell that has been called "English caramel"[10].

Microscopic observation of colonies of *C. glucuronolyticum* after undergoing a Gram's stain yields similar results to those of other species of corinebacteria. They are described as elongated grampositive bacilli, between 1 and 3 µm in length [8], which can be grouped, either forming pairs, angular shapes, etc.; or even rather isolated [10].

Concerning the results of biochemical tests, variability between different strains is often found. Many of them are able to hydrolyze sculin, making of *C. glucuronolyticum* one of the few species causing human infections with this capacity. Some strains have marked urease activity and others show little or none urease activity. They all ferment glucose and sucrose, and none of them mannitol. Fermentation of maltose, xylose and ribose, as well as nitrate reduction is variable. As a result of glucose metabolization, they produce propionic acid. Other of the metabolites they release are lactate and succinate. *C. glucuronolyticum* shows a powerful ß-glucuronidase and leucine arilamidase activity. Its colonies are non-hemolytic in blood agar, but an intense CAMP effect does occur when they come into contact with the ß-hemolisin produced by *Staphylococcus aureus* [8, 10, 15].

To identify at the species level those strains of corinebacteria that were detected in the laboratory methods such as API Coryne (BioMerieux, France), based on biochemical tests, used to be employed. However, due to the variability of results provided by different strains of the same species, the results of these techniques were not always reliable. Therefore, it is preferable to use methods based on mass spectrometry in order to get the most accurate identification at the species level. Thus, currently, *C. glucuronolyticum* is correctly identified through

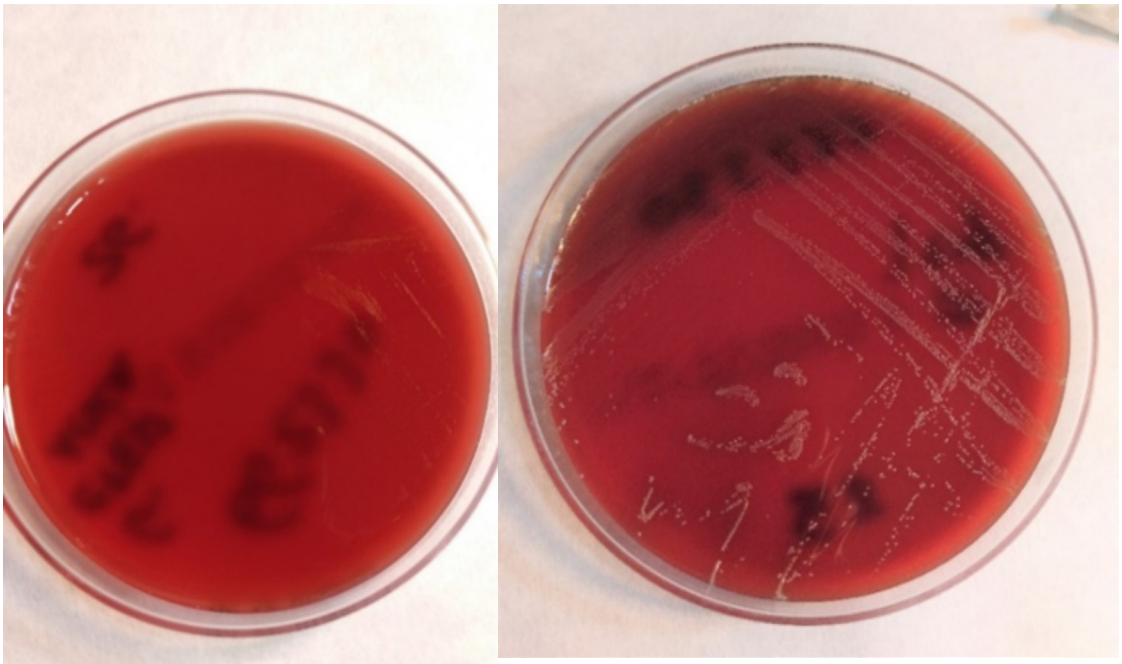

Figure 1 | **Images of the growth of colonies of *C. glucuronolyticum* in lamb blood agar medium at 24 h (left) and 48 h (right), in the presence of CO_2**

Table 1 **Review of reported cases of genitourinary infection caused by *C. glucuronolyticum*.**

Patient number (reference/publication year)	Age/sex	Predisposing factors	Clinical manifestations	Clinical sample	Treatment	Microbiological diagnostic method
1 (13/ 2000)	UNK /M	UNK	Infertility	Semen	UNK	16S rRNA sequencing
2 (13/ 2000)	UNK /M	UNK	Infertility	Semen	UNK	16S rRNA sequencing
3 (13/ 2000)	UNK /M	UNK	Infertility	Semen	UNK	16S rRNA sequencing
4 (13/ 2000)	UNK /M	UNK	Infertility	Semen	UNK	16S rRNA sequencing
5 (13/ 2000)	UNK /M	UNK	Infertility	Semen	UNK	16S rRNA sequencing
6 (13/ 2000)	UNK /M	UNK	Urethritis	Urethral exudate	UNK	16S rRNA sequencing
7 (13/ 2000)	UNK /M	UNK	Urethritis	Urethral exudate	UNK	16S rRNA sequencing
8 (11/ 2002)	46 /M	None	Urethritis	Semen	Trimethoprim-sulfamethoxazole 3 weeks PO	RapID CB Plus system
9 (2/ 2011)	18 /M	Sexual intercourse with multiple partners	Urethritis	Urethral exudate	Ciprofloxacin PO	API Coryne
10 (22/ 2014)	24 /M	None	Urethritis	Urethral exudate and semen	Doxycycline 1 week PO	API Coryne
11 (3/ 2015)	37 /M	None	Urethritis	Urethral exudate, semen and urine	Ciprofloxacin 10 days PO	MALDI-TOF 16S rRNA sequencing
12 (11/ 2015)	57 /M	None	Cystitis	Urine	Vancomycin IV	16S rRNA sequencing
13 (1/ 2018)	28/ M	*Chlamydia trachomatis* urethritis treated with doxycycline (1 week, PO)	Persistent urethritis	Urethral exudate	UNK	API Coryne MALDI-TOF
14 (1/ 2018)	36/ M	*Chlamydia trachomatis* urethritis treated with doxycycline (1 week, PO)	Persistent urethritis	Urethral exudate	UNK	API Coryne MALDI-TOF
15 (1/ 2018)	21/ M	*Chlamydia trachomatis* urethritis treated with doxycycline (1 week, PO)	Persistent urethritis	Urethral exudate	UNK	API Coryne MALDI-TOF
16 (OP/ 2019)	36/ M	None	Chronic prostatitis	Semen	Doxycycline + amoxicillin-clavulanic PO	MALDI-TOF
17 (OP/ 2019)	52/ M	None	Chronic prostatitis	Semen	Levofloxacin 2 weeks PO	MALDI-TOF

UNK: unknown, OP: our patient.

the MALDI-TOF technique with relative ease, providing usually scores above 2 [16].

In order to study the published clinical processes related to this bacteria, an open search of articles in MEDLINE database, with the keywords "*Corynebacterium glucuronolyticum*" was carried out in February 2019. This research made it posible to obtain a total of 15 publications. Subsequently, only published studies showing the pathogenic action of this bacterium at the genitourinary tract were selected by manual reviewing. This led to the final selection of 7 scientific papers (table 1).

In general, CBPs are common infections in males, representing the main cause of prostatic disease in patients under 50 years old and the third cause in patients over 50 years old (only overcome by prostate hyperplasia and prostate cancer) [17]. Although they may be asymptomatic, they usually present with dysuria, tenesm, polaquiuria, nicturia, urinary retention, perineal pain, discomfort during ejaculation, etc. [11]. The most common clinical manifestations in patients with significant microbiological study are perineo-testicular pain, ejaculatory discomfort and hemospermia [17]. Typical urinary pathogens, such as gramnegative bacilli and some enterococci, are the most common cause of bacterial prostatitis. The main etiological agents described in our environment are *Escherichia coli* and *Enterococcus faecalis* [17, 18]. Generally, protocols applied in laboratories are aimed at detecting these etiological agents, making them ineffective in diagnosing other less common agents, such as corinebacteria [11].

To reach the etiological diagnosis of CBP, both urine and semen culture are used in the microbiology laboratory.

The classic method, designed by Meares and Stamey in 1968, which remains the Gold-standard despite its limitations, consists of the conduction of quantitative cultures of pre-ejaculation urine, semen and post-ejaculation urine [19]. Diagnosis of CBP requires a significant count of bacteria in semen and/or post-ejaculation urine, compared to the count obtained in pre-ejaculation urine, although, as suggested by the study conducted by Heras-Cañas et al., the fractional culture for microbiological diagnosis of CBP could be simplified by growing pre-semen urine and semen, without the need to culture samples of post-ejaculation urine. In this series of cases, 96.7% of CBP patients had positive semen cultures, while only 22.95% had positive post-ejaculation urine cultures [17].

However, interpreting the results obtained in segmented cultures is not always an easy task, since, as Nickel concludes, the absence of growth of the microorganism in the culture does not exclude its participation in the pathological process [20]. This, based on the results provided by biopsies of CBP patients, maintains the hypothesis that, through the influence of immune defense and in response to antibiotics, the bacteria can be cantoned in the ducts and prostate acinos forming tiny colonies or biofilms surrounded by a layer of polymers, which protect the bacteria and allow it to persist, even if antibiotics are used to eradicate it.

During the month of June 2018, in the Microbiology Laboratory of the Hospital Virgen de las Nieves in Granada, the species *C. glucuronolyticum* was selectively isolated in counts greater than 10,000 CFU/mL, in two samples of semen from males who were being studied in suspicion of CBP by urologists of the same hospital.

The established protocol for the study of CBP proposed by Heras-Cañas et al., in 2016 [17] was followed. Culture mediums of 5% blood agar and chocolate agar revealed the presence of tiny whitish-yellow colonies convex and circular, with regular edges. Both media were incubated at 37ºC in a CO_2-enriched atmosphere. Bacterial growth could only be clearly detected after 48 hours of incubation, remaining almost undetectable for the first 24 hours. In the two cases described, a CFU number greater than 10,000/mL were obtained; reaching therefore clinically significant values in both cases. The correct identification of the bacteria was carried out through the MALDI-TOF technique.

The first strain isolated corresponded to a 36-year-old patient whose medical history did not report anything relevant except for an alleged allergy to sulfamides. His main complaint when he visited the doctor was a feeling of perineal discomfort that had been present during the previous two weeks; it irradiated to the groin area and was accompanied by a feeling of polaquiuria. In the last 5 days, febricula of up to 37.5ºC, of evening predominance, had appeared. The pre- and post-ejaculation urocultures provided negative results, but *C. glucuronolyticum* could be isolated in semen samples. The isolated strain showed the following MIC values, which were interpreted as susceptible according to the criteria of CLSI 2015 for corinebacteria: trimethoprim/sulfamethoxazole (0.75 mg/L), linezolid (0.064 mg/L), penicillin (0.094 mg/L) and tetracycline (0.0125 mg/L). In addition, the values of MIC were interpreted as resistant following the criteria mentioned above against ciprofloxacin (>32 mg/L), phosphomycin (>256 mg/L) and gentamicin (8 mg/L).

The biochemical analysis and blood count that were requested yielded results within the normal range, without elevation of the acute phase reactants. In terms of treatment, empirical therapy with ciprofloxacin was first dispensed at doses of 750 mg every 12 hours. After verifying that the infecting strain was resistant to quinolones, the administration of trimethoprim/sulfamethoxazole was evaluated and the department of Allergology studied the patient's hypersensitivity to sulfamides. No clinical contraindications were detected and cotrimoxazole was administered at doses of 160/800 mg every 12 hours. A week later, treatment was discontinued because a delayed phase reaction was suspected when a skin rush appeared. Finally, the treatment was changed to a combination of doxycycline (100 mg every 12 hours) and amoxicillin-clavulanic (875/125 mg every 8 hours), for 6 weeks. Within 3 days of starting treatment, febricula subsided and, in the following weeks, the rest of the clinical symptoms disappeared.

The second isolation of *C. glucuronolyticum* was performed in a semen sample from a 52-year-old male, without a medical history of high-interest, who requested a consultation with a specialist of the department of Urology in February 2018. During his visit, he referred symptomatology of a month of evolution consisting of discomfort at the area of the penis, itchy feeling in the urethra, both accompanied by intermittent discomfort in the perineum and during ejaculation. The patient did not describe any febrile syndrome or voiding disfunction.

This second strain isolated showed the following MIC values, which were interpreted as susceptible according to the criteria for corinebacteria in CLSI 2015: trimethoprim/sulfamethoxazole (0.19 mg/L), linezolid (0.094 mg/L), tetracycline (0.094 mg/L), ciprofloxacin (0.047 mg/L) and rifampicin (<0.016 mg/L). In addition, the MIC values were interpreted as resistant according to the criteria mentioned above against clindamycin (>256 mg/L) and erythromycin (>256 mg/L).

Previously, the patient had gone to the emergency room where he was prescribed phosphomycin and tamsulosin. Despite some improvement with this treatment, no total remission of the symptoms had occurred. The examination of the penis and testicles was normal, with no herniary points. The appearance of the urethral meate was also normal. His family doctor, who referred him to the urologist, had requested blood count, biochemistry and urine sediment, which were all normal. PSA (<4) was within the normal range and the uroculture result was also negative. Upon suspicion of CBP, the urologist requested an abdominal and pelvic ultrasound, in which no pathological findings were detected, and the measurement of post-mictional residue that was also normal. In addition, urethral exudate, post-ejaculated urine and semen cultures were requested. The treatment was modified, adding Permixon (1 tab/12h for 1 month) and provisionally suspending tamsulosin.

After receiving the report from the Microbiology laboratory, with culture of semen positive to *C. glucuronolyticum* levofloxacin (1 tab/24h for 6 weeks) was prescribed, with disappearance of the clinical symptomatology of the patient.

In both cases, other etiological agents such as *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Ureaplasma parvum* and *Ureaplasma urealyticum*, which are common causes of genitourinary infections were excluded by using molecular PCR techniques (Becton Dickinson, Sparks, USA).

The study of antibiotic susceptibility is usually carried out by performing E-tests on isolates in lamb blood agar and in HTM in the case of trimethoprim-sulfamethoxazole. The plates are incubated according to the standard procedure, without the need for CO_2-enriched atmosphere, for a period of 24-48 hours; and the MICs are interpreted according to the updated criteria of the CLSI or the EUCAST.

Quinolones are one of the antibiotics that belong to the first line treatment in case of genitourinary tract infections. Recent studies support the success of ciprofloxacin, when it is indicated according to the antibiogram, in the treatment of genitourinary infections caused by *C. glucuronolyticum*, reaching its eradication and a total remission of symptoms [2, 3].

However, in recent years, there has been an increase in in-vitro resistances manifested by this species to different antibiotics, including ciprofloxacin [1, 6, 11, 22, 23]. Proof of this is that one of the isolated strains in the laboratory gave a MIC interpretable as resistant to ciprofloxacin (>32 mg/L). The mechanism used by *C. glucuronolyticum* to acquire such resistance could consist of a mutation in the *gyrA* gene. This can be drawn from the fact that it has been confirmed that other species of corinebacteria have acquire resistance to ciprofloxacin by using a similar mechanism [14].

Tetracyclines are one of the groups of antibiotics most commonly used in the treatment of non-gonococcal urethritis. However, there have been numerous cases in which isolates of the species *C. glucuronolyticum* have turned out to be resistant to tetracyclines [1, 3, 11, 22]. Despite this fact, the two isolated strains in the laboratory of this hospital gave MIC values corresponding to the susceptible category (0.094 – 0.125 mg/L). In addition, doxycycline (at 100 mg doses for 7 days) has proven to be effective in treating urethritis caused by *C. glucuronolyticum* [23].

Azithromycin is used, associated with ceftriaxone, in the empirical treatment of urethritis. But, resistance to both azithromycin and erythromycin [2, 3, 11] is common. This is usually due to the presence of the methylase *ermX* gene, which is associated with the macrolide-resistant phenotype – lincosamide – streptogramine B (MLSb). The expression of erythromycin resistance seems to be linked to clindamycin resistance [22]. The isolate in which erythromycin was tested in this laboratory proved to be resistant, with a MIC of >256 mg/L. It was also resistant to clindamycin, obtaining MIC >256 mg/L.

Phosphomycin, indicated in the treatment of uncomplicated low-tract urinary tract infections, was tested in one of the isolated strains in this laboratory, showing it resistance to this antibiotic (MIC >256 mg/L). Conversely, the two isolated strains of *C. glucuronolyticum* turned out to be susceptible to trimethoprim-sulfamethoxazole, obtaining MICs of 0.19 and 0.75 mg/L. In addition, this antibiotic has an excellent penetration capacity in prostatic tissue.

In general, *C. glucuronolyticum* is susceptible to beta-lactamic antibiotics providing relatively low MIC values [11, 22]. Penicillins are, within this group, the most useful antibiotics to provide outpatient treatment to patients with urinary tract infections caused by grampositive bacilli, but they lack clinical efficacy, due to the difficulty they find to penetrate the prostate. Previous studies show that *C. glucuronolyticum* is susceptible to penicillin [1-3, 11, 22, 23], amoxicillin-clavulanic [22, 23] and piperacillin-tazobactam [23]. Penicillin was tested in one of the isolated strains in the laboratory and a MIC value of 0.094 mg/L was obtained, corresponding to the range of susceptible.

The use of gentamicin, despite being restricted by its toxicity and difficulty in entering the prostatic tissue, may be indicated in the treatment of other genital infections in male, since *C. glucuronolyticum* is usually susceptible to it [1, 11, 22, 23]. However, genemicin-resistant strains [3] have been detected, as sustains one of the results obtained in our hospital (MIC 8 mg/L).

To date, no resistance to linezolid has been reported [3, 22]. This is a useful antibiotic versus grampositive bacteria, representing an effective alternative for the treatment of CBPs. The two isolated strains in this laboratory were susceptible to it (MIC 0.047-0.094 mg/L). Rifampicin was also very active against this species [1-3, 11, 22], as corroborates the MIC values obtained by this laboratory, which was <0.016 mg/L in the two strains.

More recently [24] we have reviewed the antibiotic susceptibility reported by all the strains of *C. glucuronolyticum* that were isolated in the genitourinary samples that our center received during the years 2017 and 2018. In this research, a series of 7 microbiologically significant isolates of *C. glucuronolyticum*, all from males (1 urine, semen 4 and 2 of urethral exudates) were reviewed retrospectively. Linezolid, rifampicin, trimethoprim-sulfamethoxazole and vancomycin were active in all strains tested; but 83% of the strains were susceptible to tetracycline, 50% to penicillin, 43% to ciprofloxacin, 25% to gentamicin and erythromycin, and 20% to clindamycin.

Although *C. glucuronolyticum* is not frequently isolated in clinical genitourinary samples, its potential pathogenicity has been demonstrated and, therefore, the necessary procedures to detect this species should be included in the diagnostic algorithm of these infections.

To identify some of the less common ethological agents causing prostatitis, such as *C. glucuronolyticum*, some methods differing from the traditional growing in culture media need to be employed. These methods are neccessary but they are not included in the standard protocols of the laboratories.

This fact suggests that there might be an unacceptable number of false negatives. Lack of awareness means that many cases of chronic prostatitis fall directly into the category of non-infectious by providing the culture of samples with a falsely negative result.

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None to declare

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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