



BRIEF REPORT

Urinary tract infections due to *Globicatella* spp. in pediatric patients with complex uropathies

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KEYWORDS

Urinary tract infections;
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Abstract *Globicatella* is a genus of catalase-negative, facultative anaerobes, and non-hemolytic Gram-positive cocci, arranged in pairs or in short chains. Twenty-five positive urine cultures, mainly obtained by catheterization, and two urinary stone cultures due to *Globicatella* spp. were retrospectively recorded from patients between January 1, 2014 and October 31, 2024. Isolates were identified by mass spectrometry (Vitek MS), 16S rRNA gene sequencing and biochemical tests. Most patients had complex uropathies or congenital malformations of the urinary tract. A high percentage of the isolates showed high ceftriaxone (CRO) MICs (MIC50 and MIC90: 2–16 µg/ml) and almost half of them had low penicillin (PEN) MICs (MIC50 and MIC90: 0.25 and 2 µg/ml). The present study is the most extensive report of *Globicatella* urinary tract infections in children.

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PALABRAS CLAVE

Infecciones urinarias;
Globicatella;
Pediatría;
Uropatías

Infecciones urinarias por *Globicatella* spp. en pacientes pediátricos con uropatías complejas

Resumen *Globicatella* es un género de cocos gram positivos dispuestos en pares o en cadenas cortas, catalasa negativos, anaerobios facultativos y no hemolíticos. Se registraron retrospectivamente 25 urocultivos positivos, obtenidos principalmente por cateterismo, y dos cultivos de cálculos urinarios por *Globicatella* spp. de 26 pacientes entre el 1 de enero de 2014 y el 31 de octubre de 2024. Los aislamientos se identificaron mediante espectrometría de masas (Vitek MS), secuenciación del gen 16S ARNr y pruebas bioquímicas. La mayoría de los pacientes

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presentaban uropatías complejas o malformaciones congénitas del tracto urinario. Un alto porcentaje de los aislamientos presentó CIM más elevadas para ceftriaxona (CRO) (CIM50 y CIM90: 2 y 16 µg/ml) y casi la mitad de aquellos mostraron CIM bajas para penicilina (PEN) (CIM50 y CIM90: 0,25 y 2 µg/ml). Esta es la serie más extensa de infecciones del tracto urinario debidas a *Globicatella* en niños.

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Globicatella was described for the first time in 1992 as a new genus of catalase-negative, facultative anaerobes, and non-hemolytic gram-positive cocci, arranged in pairs or in short chains⁴. Two species belonging to this genus were described: *Globicatella sanguinis* (previously *G. sanguis*) and *Globicatella sulfidifaciens*¹⁶. The importance of the latter species in human pathology remains unclear, given that the identification methods currently used are not completely reliable for determining the species¹⁴. *Globicatella* spp. are unusual pathogens that, through the use of commercial phenotypic methods, could be identified or misdiagnosed as group viridans streptococci (GVS) due to their similarity in colonial morphology. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a reliable method for the identification of *Globicatella* spp. at the genus level, but not at the species level¹³.

Bacteria of this genus can colonize the inguinal skin and other mucosal surfaces. They have occasionally been found as causal agents of bacteremia¹², osteomyelitis⁹, meningitis¹², endocarditis¹³, and endophthalmitis² in humans, and of animal infections⁸. However, the epidemiology and clinical significance of this pathogen remain largely unknown.

Globicatella spp. have seldom been isolated from urine samples^{12,13}, but these were insufficiently studied cases of urinary tract infections (UTIs), mostly in elderly patients.

The precise identification of these microorganisms is important not only for epidemiological purposes, but also because of their pattern of low minimal inhibitory concentrations (MICs) of penicillin (PEN) and high MIC of ceftriaxone (CRO), unusual for similar bacteria, such as most GVS and other related organisms¹².

The aim of this study was to describe a series of cases of UTI due to *Globicatella* spp. in pediatric patients diagnosed in a high complexity pediatric hospital of the City of Buenos Aires, Argentina.

A retrospective and descriptive cross-sectional study was conducted between January 1, 2014 and October 31, 2024. Clinical records of patients with UTI due to *Globicatella* spp., either as unique isolate or as part of a mixed microbiota, were analyzed. A hospital computer system was used to obtain patients' clinical data. The following data were recorded: age, sex, symptoms and underlying diseases.

Catheterized urine samples were collected by specialized personnel or by patients or family members trained in the

procedure. Clean-catch or midstream urine samples were obtained using standard methods.

Intraoperative urine samples and stones were collected in the operating room by the surgeons. Urinalysis involved microscopic observation of the sediment, estimation of the number of leukocytes and red blood cells per 400X field, determination of pH and other parameters that were not considered in this study.

Urine samples were cultured using the calibrated loop method on CHROMagar™ Orientation (CHROMagar, Paris, France) and chocolate agar. Plates were incubated in an atmosphere of 5% CO₂ for 72 h. A colony count >10⁴ CFU/ml was considered a positive result.

Stone culture was performed according to the classic method of Nemoy and Stamey¹⁰, i.e., the collected stones were washed four times with sterile physiological saline. Each washing solution was cultured using the calibrated loop method on CHROMagar™ Orientation and chocolate agar. After washing, the stones were crushed and suspended in the same volumen of sterile saline used in the previous washes, then shaken to obtain a homogeneous suspension. This solution was cultured immediately after crushing. Bacteria were considered to be within the stone if the colony count of the crushed stone was more than 1 log higher than that of the fourth wash.

Gram-positive organisms growing in chocolate agar were identified by mass spectrometry and conventional tests. Identification by mass spectrometry was performed with the bioMérieux (MALDI-TOF MS Legacy, Marcy l'Etoile, France) spectrometer using the Acquisition Station software and VITEK® FLEXPREP™ software. A colony of each isolate was spotted onto an analytical slide and extracted with 0.5 µl of 70% formic acid (spot technique) and, subsequently allowed to dry at room temperature. Samples were then covered with 1 µl of α-cyano-4-hydroxycinnamic acid (HCCA) matrix until crystallized at room temperature. Mass spectra were analyzed within the range of 2000–20 000 m/z. The isolates were identified using VITEK MS software version V3.0.

For result interpretation, cutoff points were applied according to the manufacturer's recommendations: a score of ≥60% (i.e., indicating a confidence level of 60% or more) is considered reliable, resulting in a "single-choice identification" at the genus level. A score of ≥60% is also indicative of a "good species identification." Furthermore, internal studies of the system indicate that values of ≥95% represent high confidence at the species level. The VITEK system con-

siders $\geq 60\%$ a reliable level, given its population database and advanced algorithm.

Conventional biochemical tests were also used. The catalase test and hemolysis on sheep blood agar were the initial screening tests. For catalase-negative non-hemolytic gram-positive cocci, other biochemical tests, including bile esculin, NaCl 6.5%, H_2S production in triple sugar iron (TSI), pyrronidonyl arilamidase (PYR) and leucine aminopeptidase (LAP), were used. PYR and LAP kits were provided by Laboratorios Britania (Buenos Aires, Argentina).

Molecular methods

The near-full-length 16S rRNA gene was PCR-amplified and sequenced using specific primers 63f and 1387r, as previously described by Marchesi et al.⁷.

Phylogenetic analysis was conducted using the maximum likelihood method implemented in the PhyML web server⁵. Reference sequences were selected from GenBank (<https://www.ncbi.nlm.nih.gov/genbank/>) and SILVA ribosomal RNA gene databases (<https://www.arb-silva.de/>)¹¹.

Antimicrobial susceptibility tests to penicillin and ceftriaxone were performed for 19 and 17 isolates respectively, using Etest (bioMérieux, Marcy l'Etoile, France) on Mueller Hinton agar supplemented with 5% sheep blood. The breakpoints for susceptibility and resistance to PEN and CRO used were those recommended by the CLSI for viridans group streptococci: $S \leq 0.125 \mu\text{g/ml}$; $R \geq 4 \mu\text{g/ml}$, and $S \leq 1 \mu\text{g/ml}$; $R \geq 4 \mu\text{g/ml}$, respectively³. Antimicrobial susceptibility to other antibiotics (trimethoprim-sulfamethoxazole, levofloxacin) was tested by the disk diffusion method only when clinically necessary. These results were not included in this study.

Twenty-four positive urine cultures (excluding repeated positive cultures), mainly obtained by catheterization ($n = 19$), along with one intraoperative culture plus urinary stones, and an additional urinary stone culture from 26 patients were positive for *Globicatella* spp. The median age of the patients was 12 years (IQR: 1–18), with an equal distribution for males and females. All but one patient had severe underlying conditions, including myelomeningocele, ureterohydronephrosis, posterior urethral valve, urethral duplication, epispadias, renal hypoplasia, cystic kidney disease, bladder exstrophy, anorectal malformation, prune belly syndrome, or were kidney transplant recipients (Table 1).

Regarding the urinalysis, all samples (100%) had a pH between 6.6 and 7.4; 78% of the urinary pellets exhibited significant leukocyturia and/or hematuria (i.e., more than 5 leukocytes or red blood cells per 400X field) and 60% of the cultures were monomicrobial, with colony counts between 10 000 and 100 000 CFU/ml on chocolate agar. Based on MALDI-TOF MS results and conventional biochemical tests (bile esculin and NaCl 6.5% positive; H_2S production in TSI; PYR and LAP negative), the isolates were identified as *Globicatella* spp. Confidence values obtained by Vitek MS for each tested strain of 99.9% for *G. sanguinis*, except for two (50% *G. sanguinis*–50% *G. sulfidifaciens*), indicated a reliable identification, at least to the genus level.

For 19 isolates, the MIC₅₀, MIC₉₀ and range of PEN were 0.25, 2.0, and 0.03 to $>32 \mu\text{g/ml}$, respectively, and those for CRO (for 16 isolates) were 2.0, 16.0, and 0.5 to $>32 \mu\text{g/ml}$.

Twenty-two patients were treated on a case-by-case basis, taking into account the susceptibility of accompanying pathogens in mixed infections. Of the 21 patients whose evolution was known, all had good clinical outcomes (Table 1).

Only six isolates were available for 16S rRNA gene sequencing. The sequence analysis of the 16S rRNA gene revealed over 99.76% similarity among them. Two sequences, G_7464 and G_9278 of bacteria isolated in the years 2024 and 2023 respectively, were identical. These six sequences also shared more than 99% similarity to sequences of the genus *Globicatella*, particularly *G. sanguinis*. Sequences were submitted to GenBank under the following accession numbers: G_7464 PV702875, G_9278 PV702876, G_1310 PV702877, G_8437 PV702878, G_G8 PV702879 and G_0699 PV702880.

Phylogenetic analysis confirmed that all six isolates belonged to the genus *Globicatella* (Fig. 1); however, species-level identification could not be determined, although the absence of H_2S in TSI medium, a characteristic of *G. sanguinis*, was observed for these isolates.

Only a few well-documented cases of UTI involving *Globicatella* spp. were published, and all of them were from adult patients. In one case, a UTI complicated by endocarditis in an 87-year-old woman with severe underlying neurological condition¹³. *G. sanguinis* was isolated both from blood and urine and identified by Rapid ID32 Strep and 16S rRNA sequencing. Urosepsis due to *G. sanguinis* was also described in an 82-year-old female by Abdul-Redha et al. in Denmark¹. In another UTI report, *G. sanguinis* was isolated from a polymicrobial urethral catheter biofilm, and in this case, proteins with potential roles in crosstalk with the host environment were studied¹⁵. Both studies involved adult patients.

At least to our knowledge, the present study is the most extensive study describing urinary tract infections of pediatric patients due to *Globicatella* spp. identified by mass spectrometry (Vitek MS), 16S rRNA gene sequencing and biochemical tests. Children with urinary infections due to *Globicatella* spp. had a median age of 12 years with a predominance of males and, notably, all of them but one had complex uropathies or congenital malformation of the urinary tract. *Globicatella* was not detected in previously healthy patients or in those with other pathologies. Most of urines were alkaline, and the majority exhibited pathological sediment. Cultures were mostly monomicrobial with high counts on chocolate agar (Table 1).

Previous studies have shown that the low divergence in 16S rRNA gene sequences between *G. sanguinis* and *G. sulfidifaciens* hinders species-level identification^{6,8,9}. Our findings align with these observations, highlighting that, although 16S rRNA analysis is undoubtedly valuable for the preliminary identification of the genus *Globicatella*, it remains inadequate for the species-level classification.

As previously described in the literature, it was observed that a high percentage of the isolates showed high CRO MICs, while almost half showed low PEN MICs^{12,13}. PEN MICs were currently lower than those of CRO. The clinical impact

Table 1 Patients, samples, and susceptibility data of *Globicatella* isolates.

Patient	Date	Age/sex	Sample	Underlying disease and symptoms	Other isolates	MIC of PEN ($\mu\text{g/ml}$)	MIC of CRO ($\mu\text{g/ml}$)	Treatment and evolution
1	12/09/16	12 y/F	Catheterized urine	Kidney transplant, neurogenic bladder, bladder enlargement, Mitrofanoff	–	1.0	1.5	MEM + VAN (72 h) ^a CIP Good evolution
2	18/10/17	17 y/M	Catheterized urine	Kidney transplant, bladder enlargement, posterior urethral valve	<i>Morganella morganii</i>	0.023	1.5	CEF ^a SXT Good evolution
3	01/12/17	14 y/M	Catheterized urine	Kidney transplant, bladder enlargement, posterior urethral valve, Mitrofanoff	–	ND	ND	CRO Good evolution
4	12/12/17	9 y/M	Catheterized urine	Right ureterohydronephrosis, urinary incontinence	–	0.5	2.0	CEF ND
5	06/06/18	11 y/F	Catheterized urine	Kidney transplant	–	1.5	12.0	AMP Good evolution
6	04/07/18	1 y/F	Clean-catch urine	Single kidney, anorectal malformation	–	0.125	ND	SXT Good evolution
7	02/12/18	4 y/F	Catheterized urine	Visceral myopathy, gastrostomy, cecostomy, vesicostomy	–	ND	ND	LEV Good evolution
8	05/02/19	10 y/M	Catheterized urine (three samples)	Chronic kidney disease, anorectal malformation, surgery, single kidney (functional), neurogenic bladder, anchored marrow	<i>Proteus vulgaris</i> (in only one sample)	0.023	1.5	CIP ^a CRO Good evolution
9	11/05/19	12 y/F	Intraoperative urine	Anchored marrow, myelomeningocele	<i>Providencia rettgeri</i> <i>Escherichia coli</i>	ND	ND	CRO Good evolution
10	08/06/19	8 y/M	Catheterized urine	Prune belly syndrome, Mitrofanoff	–	0.75	8.0	ND ND
11	05/11/19	17 y/M	Catheterized urine	Myelomeningocele, bladder enlargement, Mitrofanoff	<i>Bordetella trematum</i>	ND	ND	CEF Good evolution
12	23/07/20	7 y/F	Catheterized urine (two samples)	Single kidney, double J catheter, dysuria, hematuria, kidney stones	–	1.5	1.5	PEN
13	19/10/21	12 y/M	Catheterized urine	Obstructive uropathy, kidney transplant	–	ND	ND	ND ND
14	25/10/21	15 y/M	Catheterized urine	Myelomeningocele, bladder enlargement, intestinal anastomotic dehiscence with colostomy	–	0.023	0.5	SXT ^a AMS Good evolution

Table 1 (Continued)

Patient	Date	Age/sex	Sample	Underlying disease and symptoms	Other isolates	MIC of PEN (µg/ml)	MIC of CRO (µg/ml)	Treatment and evolution
15	16/11/21	13 y/F	Bladder stone	Neonatal spinal cord injury, neurogenic bladder, bladder enlargement	<i>Oligella urethralis</i> , <i>Brevibacterium luteolum</i>	ND	ND	AMS Good evolution
16	09/12/21	18 y/M	Catheterized urine	TXR, bladder enlargement, Mitrofanoff. Recurrent UTIs	<i>Morganella morganii</i>	0.094	ND	ND ND
17	09/03/22	10 y/M	Catheterized urine	Chronic renal failure, neurogenic bladder, bladder enlargement, Mitrofanoff, hydrosyringomyelia	<i>Acinetobacter baumannii</i> , <i>Haemophilus haemolyticus</i>	ND	ND	AMC Good evolution
18	24/05/22	11 y/F	Intraoperative urine	Bladder exstrophy, bladder stones, Mitrofanoff, stenosis	–	0.75	1.5	PTZ Good evolution
19	14/03/23	5 y/M	Intraoperative urine	Ureteral duplication	–	1.0	16.0	CRO (72 h) ^a AMX Good evolution
20	03/04/23	2 y/F	Midstream urine	Recurrent UTIs, hematuria, dysuria, fever	–	>32	>32	ND ND
21	16/05/23	17 y/M	Catheterized urine	Chronic renal failure, posterior urethral valve, single kidney	<i>Escherichia coli</i>	0.125	ND	PTZ Good evolution
22	13/06/23	12 y/M	Intraoperative urine, bladder stone	Epispadia, permanent urinary incontinence, multiple surgical interventions of the urinary tract	<i>Granulicatella</i> sp.	0.25	2.0	AMS SXT Good evolution
23	12/10/23	12 y/F	Catheterized urine	Chronic renal failure, neurogenic bladder, bladder reservoir and continent stoma, single kidney	<i>Pseudomonas aeruginosa</i>	0.064	0.5	CRO ^a PTZ MEM Good evolution
24	22/03/24	17 y/F	Catheterized urine	Chronic kidney disease, anorectal malformation cloaca-type, bladder enlargement, Mitrofanoff	<i>Klebsiella pneumoniae</i>	0.125	0.38	CRO ^a PTZ FOS/PEN Good evolution
25	21/09/24	13 y/F	Catheterized urine	Chronic kidney disease, anorectal malformation	<i>Pseudomonas aeruginosa</i>	0.125	4.0	CRO ^a PTZ CIP Good evolution
26	31/10/24	18 y/F	Catheterized urine	Kidney transplant, bilateral renal hypoplasia	–	0.38	1.5	AMP Good evolution

MIC: minimal inhibitory concentration; y: years; F: female; M: male; ND: not determined; MEM: meropenem; VAN: vancomycin; CIP: ciprofloxacin; CEF: cephalixin; SXT: trimethoprim-sulfamethoxazole; CRO: ceftriaxone; AMP: ampicillin; LEV: levofloxacin; AMC: amoxicillin-clavulanic acid; PTZ: piperacillin-tazobactam; AMX: amoxicillin; AMS: ampicillin-sulbactam; FOS: fosfomicin; PEN: penicillin V.

^a Empirical treatment.

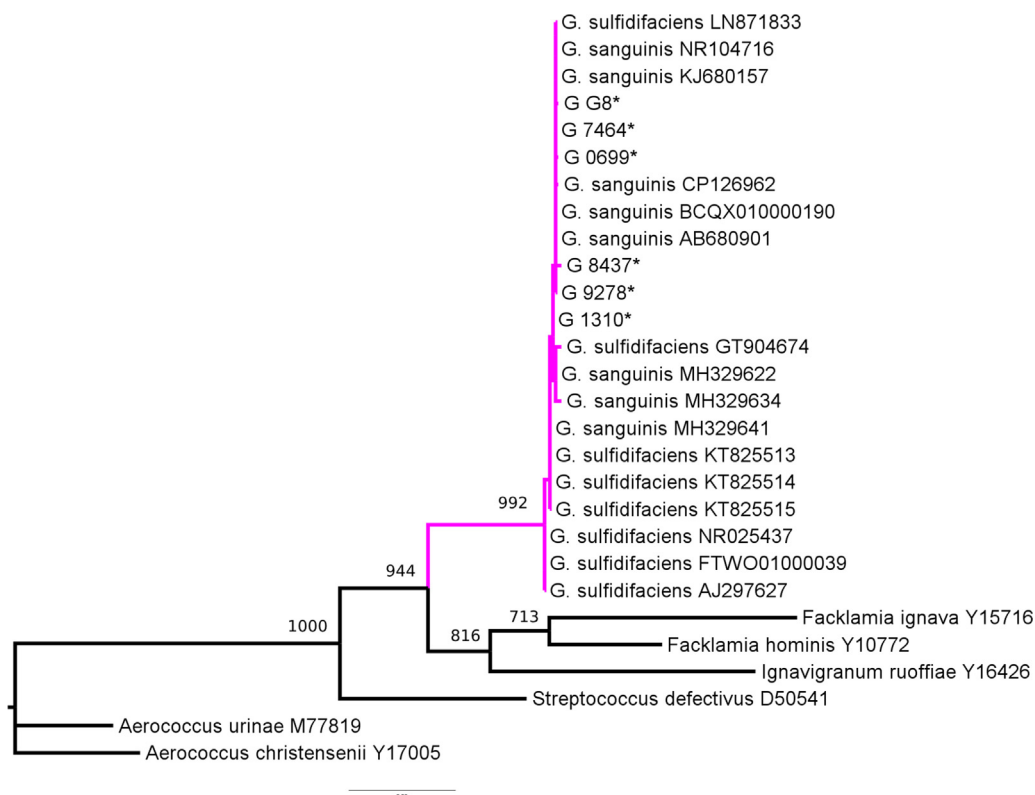


Figure 1 Maximum likelihood phylogenetic tree for the genus *Globicatella*. Magenta-colored branches indicate the clade corresponding to the genus *Globicatella*. Taxon names include both the bacterial species name and the accession number. Taxon names marked with an asterisk (*) indicate the six isolates analyzed in this study. Bootstrap values, calculated from 1000 pseudoreplicates, are shown above the tree branches.

of these ceftriaxone MIC values on the treatment of UTIs remains unclear, as urinary concentrations of this antibiotic can greatly exceed its MIC value.

A limitation of this study is that only six isolates were available for sequencing, but all of them confirmed the previous results of identification by other methods.

At least to our knowledge this is the most extensive study of *Globicatella* spp. UTI in pediatric patients, identified by molecular methods, mass spectrometry and conventional tests. Although the available evidence suggests that these are isolates of *G. sanguinis*, including the absence of H₂S production, we cannot rule out that some of them may belong to the species *G. sulfidifaciens*.

Almost all patients had complex uropathies or congenital urinary tract malformations. Accurate identification of *Globicatella* spp. is important, as these bacteria are frequently more susceptible to PEN than to CRO.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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