

Urinary tract infection due to *Streptococcus pneumoniae* and its relationship with nephrourological malformations

Infección urinaria por *Streptococcus pneumoniae* y su relación con malformaciones nefrourológicas

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What do we know about the subject matter of this study?

Urinary tract infection (UTI) is a prevalent pathology in pediatrics, with *Streptococcus pneumoniae* being an exceptional etiological agent. There is no agreement on the need to investigate the urinary tract in the presence of infections by atypical germs (other than *Escherichia coli*).

What does this study contribute to what is already known?

A case of a 2-year-old patient with UTI due to *Streptococcus pneumoniae* with concomitant vesicoureteral reflux is described. The analysis of the case presented, along with that of the other published patients with UTI due to *Streptococcus pneumoniae*, revealed a high prevalence of underlying renal and urological malformations. These findings suggest the need to investigate the urinary tract of patients with UTI due to this germ.

Abstract

Urinary tract infections (UTIs) are one of the most frequent bacterial conditions in children, being enterobacteria the predominant etiologic agents. *Streptococcus pneumoniae* is an exceptional cause of UTI in the pediatric population. **Objective:** To report the case of a UTI caused by *Streptococcus pneumoniae*, and to discuss the need for urinary tract imaging studies based on a literature review. **Clinical Case:** A 2-year-old girl with megaureter and left hydronephrosis diagnosed in the context of a recurrent UTI, with poor adherence to prophylactic treatment, was hospitalized due to a new episode of febrile UTI without response to outpatient treatment with a broad-spectrum antibiotic. *Streptococcus pneumoniae* was isolated in the urine culture. She received parenteral therapy with ceftriaxone with good clinical course and, due to UTI caused by an atypical germ added to her history of renal malformation, prophylaxis was reinitiated and imaging studies were completed. Voiding cystourethrogram showed left grade V vesicoureteral reflux. Renal scintigraphy showed severe functional compromise of the left kidney, thus, surgical indication was considered. This

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case, along with 16 additional cases identified in a literature review, revealed that 12 of them (70%) showed concomitant renal-urolological conditions. **Conclusion:** UTIs caused by *Streptococcus pneumoniae* are frequently associated with renal-urolological alterations, which suggest the need to study the urinary tract in these patients.

Introduction

Urinary tract infections (UTI) are one of the most frequent bacterial conditions in the pediatric age group,¹⁻² affecting 3% of girls and 1% of boys in the prepubertal age group¹. Enterobacteriaceae are the predominant etiological agents of these infections in this population. Among them, *Escherichia coli* is the most frequent, causing 85-90 % of cases, followed in frequency by *Klebsiella spp*, *Proteus spp*, *Enterococcus spp*, and *Enterobacter spp*¹.

Urinary tract malformations or dysfunctions are predisposing factors for the development of UTI and, in patients with that kind of pathologies, atypical germs can be causative of such infections³. A long-term complication of acute pyelonephritis is the formation of renal scarring, which can increase the risk of arterial hypertension and chronic kidney disease in adult life. Timely diagnosis, as well as appropriate antibiotic treatment within 48 hours after the onset of fever and prevention of recurrences, reduce the risk of renal scarring¹.

Streptococcus pneumoniae is one of the most common causes of pneumonia, otitis media, rhinosinusitis, meningitis, and sepsis in children⁴. This germ is part of the normal flora of the nasopharynx, being acquired in the first months of life, with a higher colonization rate in kindergarten and preschool attendants. Nasopharyngeal carriage is the previous step for invasive disease by this germ; whose mortality, according to WHO, reaches 5% in children under 5 years of age⁵. Considering that pneumococcal conjugate vaccines (PCV) provide coverage of over 80% against invasive pneumococcal disease⁵, the PCV-10 began to be administered in Chile in 2011, with a primary schedule of 3 doses and 1 booster. In 2012, based on local epidemiology, the current scheme consisting of 2 doses with a booster at 12 months (2+1) was defined and as of 2017, PCV of 13 serotypes was incorporated throughout the country in 2+1 scheme (2, 4, and 12 months).⁶ In the same line, PCV-13 was incorporated into the Argentine National Calendar in January 2012 with a 2+1 scheme (2, 4, and 12 months)⁵. Despite this strategy, the impact of these vaccines on the prevention of UTIs is unknown.

Since *Streptococcus pneumoniae* is an exceptional cause of UTI in the pediatric population⁷, the objec-

tive is to report the case of a 2-year-old girl with UTI caused by this germ and to discuss the need to perform urinary tract studies based on a literature review on the subject.

Clinical Case

A 2-year-old female patient, eutrophic, in previous follow-up due to a history of recurrent UTI (3 episodes due to usual uropathogens of outpatient management) with ultrasound finding of left hydronephrosis with an anteroposterior pelvic diameter of 40 mm and left megaureter. Prophylaxis with trimethoprim-sulfamethoxazole had been indicated until completion of urinary tract studies, which was not fulfilled.

She consulted due to a 24-hour history of fever and dysuria. On physical examination, she was in good general condition and hemodynamically stable (heart rate 108/min, respiratory rate 18/min, blood pressure 90/60 mmHg). Abdominal examination within normal limits with negative lumbar fist percussion sign. No associated respiratory symptoms. An otoscopy was normal.

Given the clinical picture and her history, a urinalysis was performed which showed density 1010, pH 6, protein +, negative glucose, negative ketones, hemoglobin traces, positive nitrites, and sediment with leukocytes 15-20/hpf. Suspecting UTI, a urine culture sample was collected and empirical treatment with ceftriaxone 50 mg/kg/day via intramuscular was started on an outpatient basis.

On the fourth day of evolution, *Streptococcus pneumoniae* > 100,000 CFU/ml (sensitive to oxacillin, penicillin, aminopenicillins, levofloxacin, trimethoprim-sulfamethoxazole, and third-generation cephalosporins) was isolated in the urine culture. As the fever persisted on the fourth day of intramuscular antibiotic treatment, the patient was hospitalized for intravenous therapy. A complete schedule of 13-valent pneumococcal vaccine (2 + 1 schedule) was confirmed. It was also recorded that the child was an only child and did not attend daycare.

During hospitalization, tests were performed and revealed leukocytosis of 19600/mm³ with left deviation (neutrophils 48%), normocytic hypochromic anemia with hemoglobin 9.3 g/dL, hematocrit 31.3% (mean

corpuscular volume 74 fl and mean corpuscular hemoglobin 22 pg), platelets 361,000/mm³, normal renal function with creatinine 0.27 mg/dL, urea 15 mg/dL, and elevated C-reactive protein 131 mg/L (reference value: 0 - 5 mg/L).

Renal ultrasound showed right kidney 80 mm in longitudinal diameter, eutopic, with preserved shape and ultrastructure, with adequate corticomedullary differentiation, without urinary tract dilation or lithiasis images, and left kidney 80 mm in longitudinal diameter, eutopic, with renal pelvis dilation of 34 mm, ipsilateral dilated ureter in all its extension measuring in its distal third 13 mm and parenchymal thinning (8 mm), with corticomedullary differentiation loss, without significant changes in relation to previous ultrasound studies.

She received treatment with intravenous ceftriaxone 50 mg/kg/day with cessation of fever and clinical improvement after 24 hours, without abscesses or other complications. Blood cultures collected at the time of admission (after 4 doses of intramuscular ceftriaxone) were negative. Laboratory tests performed before discharge showed improvement of inflammation parameters (leukocytes 10,200/mm³ and C-reactive protein 23 mg/L). She was discharged after 5 days, completing 10 days of oral antibiotic therapy with amoxicillin-clavulanic acid at 40 mg/kg/day.

Subsequently, under antibiotic prophylaxis, voiding cystourethrogram (VCUG) was performed, which revealed the presence of left grade V vesicoureteral reflux (VUR) with normal urethra and bladder (Figure 1A).

After 6 months free of UTI, renal scintigraphy with dimercaptosuccinic acid was performed, showing the left kidney with severe functional compromise (relative renal function 7%) and the right kidney with normal uptake (Figure 1B), after which she awaits urological resolution (left nephroureterectomy), maintaining antibiotic prophylaxis until surgery. In addition, nephrological follow-up continues due to a single functional kidney.

Discussion

UTI due to *Streptococcus pneumoniae* in pediatrics is exceptional and its association with the presence of urinary tract malformations has not yet been well defined. A literature search was performed in PubMed using the key terms "urinary tract infection", "*Streptococcus pneumoniae*", and "pneumococcosuria". Articles involving patients under 18 years of age were included, without restriction by language or year of publication. Subsequently, the references of the evaluated articles were manually reviewed for ad-

ditional citations. Table 1 summarizes the clinical data of the cases identified along with the one presented here⁷⁻¹³. Two of the selected articles lacked sufficiently detailed information to be included in the table. On the one hand, Miller et al.¹⁴ retrospectively analyzed 53,499 urine cultures from pediatric patients, in which *Streptococcus pneumoniae* was detected in 43 samples (0.08%). However, the authors were only able to relate the urinary findings of 31 samples belonging to 28 patients. Of these, only 7 had symptoms compatible with UTI and 6 other foci of probable pneumococcal origin (pneumonia, otitis, sinusitis). In addition, 93% of these cases had low bacterial counts¹⁴, making the diagnosis of UTI due to *Streptococcus pneumoniae* even more difficult and making it impossible to estimate its true incidence. On the other hand, Burckhardt et al.¹⁵, in a sample of 100,000 urine cultures, identified *Streptococcus pneumoniae* in 26 samples belonging to 18 patients, 10 of whom were children. Although most of the patients in this series had underlying renal and urological pathology, the authors did not specify which ones corresponded to pediatric cases. In addition, they did not detail the presenting symptoms or urinary sediment results, so it was not possible to discriminate between UTI and asymptomatic bacteriuria¹⁵.

Taken together, these observations highlight the challenge of differentiating between UTI, asymptomatic bacteriuria, and *Streptococcus pneumoniae* urine culture findings in the context of patients presenting with pneumonia or other concomitant *Streptococcus pneumoniae* infections. Beyond this, the main conclusion that emerges from Table 1 is that 70% of the patients presenting UTI due to *Streptococcus pneumoniae* had associated renal and/or urological pathology.

The need to perform a VCUG is a subject under continuous review; in fact, in recent years, the performance of this type of study has been increasingly restricted. Within its indications, there is disagreement about the conduct to be followed in patients with UTI due to atypical germs (other than *Escherichia coli*). While some guidelines recommend performing the VCUG in all children under 6 months with atypical UTI and only in the presence of abnormal ultrasound, family history of VUR, or recurrent UTI for patients between 6 months and 3 years, others advise individualized evaluation of the performance of VCUG in patients with UTI due to atypical germs¹⁻³. However, considering that usually 30% of patients with UTI have urinary tract malformations¹⁻², the very high percentage (70%) associated with *Streptococcus pneumoniae* infection, suggests the need to study the urinary tract of these patients. Although it should be recognized that probably most of the reported patients also met the criteria for pathologic ultrasound to proceed with imaging studies, it should be kept in mind that ultra-

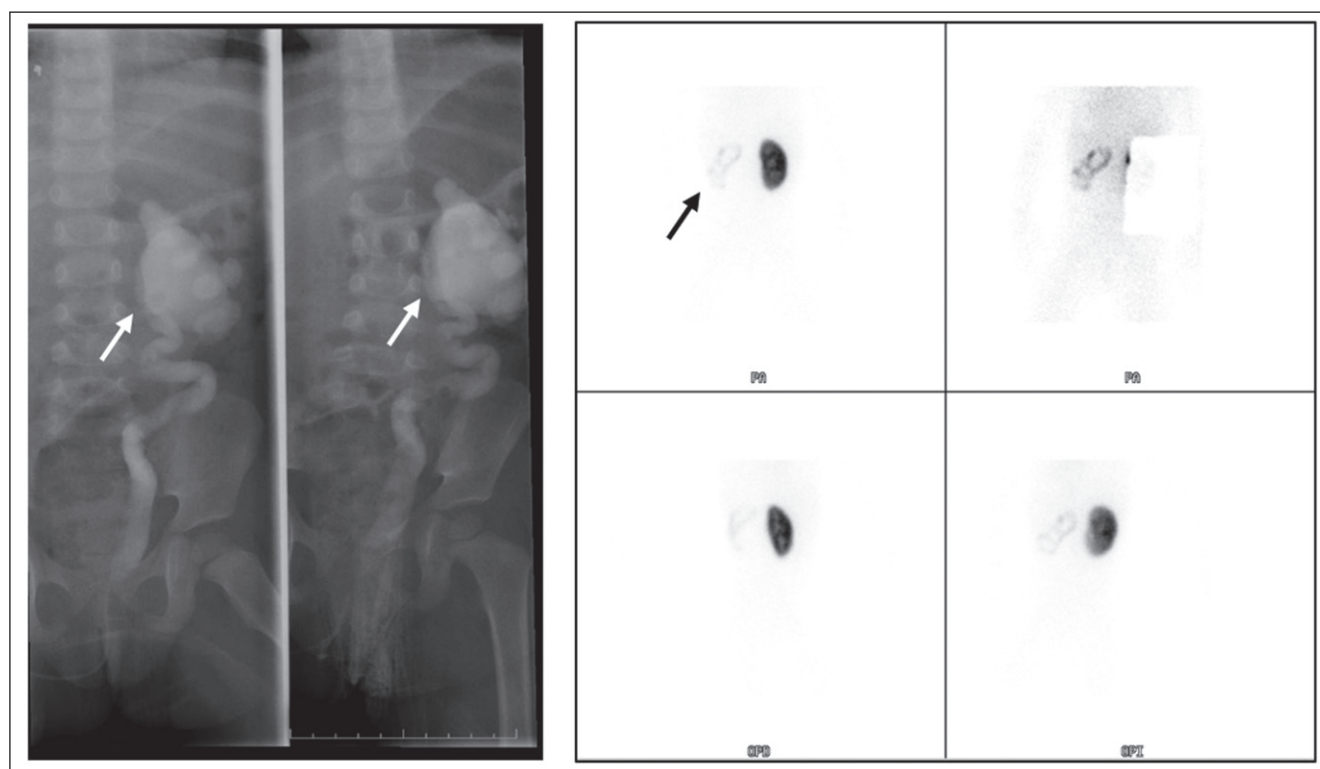


Figure 1. Complementary studies of the presented patient. **A.** Voiding cystourethrogram. **B.** Renal scintigraphy with dimercaptosuccinic acid.

Table 1. Reported cases of urinary tract infection by *Streptococcus pneumoniae*.

Reference	Year	Case	Age (years)	Sex	Fever	Urinary Symptoms	Germ Count	Serotype	Concomitant Nephrourological Pathology
This report	2023	1	2	F	Si	Si	$> 10^5$	NE	Left grade 5 VUR
(8)	2022	2-6 ^a	3 (media)	3 F 2 M	Si (Todos)	Si (Todos)	3/7 10^4 4/7 $> 10^5$	NE	Present in 3 of 5: (1) Horseshoe kidney (2) Polycystic kidney + Right UPJ obstruction (3) Bilateral VUR + Megaureter + Neurogenic bladder
(9)	2017	7	4	F	Si	No	10^4	NE	Pelvic kidney
(10)	2013	8	4	F	No	Si	10^4	NE	None
(11)	2013	9	0,58	F	No	No	$> 10^5$	23F	Bilateral double collecting system
(11)	2013	10	2,3	M	No	Si	$> 10^5$	6B	Bilateral grade 4 VUR
(11)	2013	11	9	F	Si	No	$> 10^5$	11A	Bilateral renal dysplasia - Kidney transplant
(12)	2012	12	1,5	M	Si	NE	$> 10^5$	NE	PUV
(7)	2011	13	1,9	M	Si	Si	$> 10^5$	15B	PUV - Bilateral cystic renal dysplasia
(7)	2011	14	12	M	No	No	$> 10^5$	34	PUV - Kidney transplant
(7)	2011	15	7	F	Si	No	10^4	19F	Cystinuria - Kidney stones
(13)	1981	16	2	F	Si	No	10^4	6	None ^b
(13)	1981	17	1,4	F	Si	No	$> 10^5$	19	No ^c

^aAnalysis of 46332 urine cultures: 7 UTI events were identified in 5 patients. ^bIsolation of *S. pneumoniae* in urine culture in the context of pneumonia. ^cIsolation of *S. pneumoniae* in urine culture in the context of fever, upper respiratory tract infection, and febrile seizure
F/M female/male, VUR vesicoureteral reflux, PUV posterior urethral valve, UPJ ureteropelvic junction obstruction, NE not specified

sound is only considered a reliable study if performed by an experienced operator and that the sensitivity and specificity of this study to detect VUR is low²⁻³.

The mechanism by which UTI due to *Streptococcus pneumoniae* occurs is not clear. Some authors suggest that in children it is due to perineal or urogenital colonization, probably by touching hands contaminated with nasopharyngeal secretions¹⁴. Also, it was postulated that patients with urological alterations present greater exposure to the urothelium, favoring the adherence of the germ⁹. Available studies showed that gene polymorphisms associated with susceptibility to *Streptococcus pneumoniae* infections (Toll-like receptor 4, CD14, and CD32) may favor UTI by this germ in patients with urinary tract abnormalities^{9,11}. In addition, the presence of alkaline urinary pH may contribute to the development of this type of infection, since it has been demonstrated that *Streptococcus pneumoniae* is particularly labile at acid pH (< 5.15) in which it survives for approximately 1 hour, while at higher pH its survival is several hours¹⁶. The loss of this protective mechanism is consistent with what occurred in our patient, who had a pH of 6, which could have favored the viability of the microorganism with the consequent development of the infection.

In addition, it is worth mentioning that it is not known whether certain serotypes of *Streptococcus pneumoniae* present greater virulence to generate UTI⁷⁻⁸. This is due to the very low prevalence of UTI due to this germ and to the fact that serotype identification is not routinely performed; in fact, as shown in Table 1, the serotype was investigated in less than half of the cases. Finally, the impact of the vaccine on the prevention of UTI due to this germ is also unclear⁸. It is interesting to note that of the 8 published cases in which the serotype was studied, three (11A, 15B, and 34) would not have been covered by the 13-valent pneumococcal conjugate vaccine, and only serotype 34 would not have been covered in a combined scheme with 23-valent polysaccharide vaccine; however, the authors did not specify the immunization status of their patients in order to evaluate to what extent immunization would have prevented infection^{7,11}. Although our patient had a complete schedule of 13-valent pneumococcal conjugate vaccine, as the germ was not typed, we could not analyze the effect of such immunization.

Finally, we must recognize that the patient received antibiotics throughout treatment for this episode of UTI due to *Streptococcus pneumoniae* with a broader

spectrum than necessary, with the potential risk of increased antimicrobial resistance, a fact that should be rectified in the event of further episodes¹⁷.

Conclusion

The analysis of the case presented, together with that of the other published patients with UTI due to *Streptococcus pneumoniae*, allowed us to observe a high prevalence of underlying renal and urological malformations. These findings suggest the need to investigate the urinary tract of patients with UTI due to this germ, although it should be noted that our patient already met additional criteria to advance with the study of the urinary tract, such as presenting pathological renal ultrasound and recurrent infections. It is necessary to study a larger number of cases to be able to provide a definitive recommendation.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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