

A Retrospective Study of Pediatric Urinary Tract Infections of Tamatave University Hospital Center, Madagascar

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Authors' contributions

This work was carried out in collaboration among all authors. Author ABAR designed the study. Author AMA wrote the protocol, managed the literature searches. Author NMLR managed the literature searches. Authors HR, VCMA, JDLCR and NR managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Urinary tract infection (UTI) is very common in children. The future of kidney function depends on its management. Our objective was to investigate the epidemio-clinical, bacteriological and therapeutic profile of UTI in the Pediatric Department of Tamatave University Hospital Center, Madagascar for better care of children.

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Methods: This is a retrospective and descriptive study that was carried out in the Pediatrics Department of Tamatave University Hospital over a three-year period from January 1, 2017 to December 31, 2019. The parameters retained and studied were age, gender, clinical signs, pathogens identified with the results of the antibiotic susceptibility tests and the treatments received.

Results: The frequency of UTI was 7.46%. The average age was 11.21 months, with extremes of 2 to 120 months. Fever was the main symptom found (80.95%) followed by urinary signs. *Escherichia coli* was the most frequently isolated bacteria (61.90%). Almost all of the isolates found (98%) were resistant to amoxicillin, tetracycline and cotrimoxazole. Ceftriaxone alone was the most used (44.44%).

Discussion: This study suggests that gentamicin and ceftriaxone (even though ESBLs were found) should be included in the treatment protocol for UTIs in the absence of an antibiogram, which is not always available in our context.

Keywords: Urinary tract infection; paediatrics; *Escherichia coli*; gentamicin; Tamatave.

1. INTRODUCTION

Urinary tract infections are the most common bacterial infections in pediatrics. It is estimated that girls have a 3-5% risk of urinary tract infection (UTI) and boys have a 1-2% risk of UTI before puberty [1]. It is remarkable because of the different clinical varieties related to the different topographical sites of infection and the broad concept, ranging from asymptomatic infection to pyelonephritis with sepsis.

In Pediatrics, recognizing a UTI, especially a febrile one, and treating it rapidly is an imperative for quality care, as it affects the physical integrity of the child. In fact, infection of the renal parenchyma is all the more dangerous as it occurs on a growing organ with risk of renal scarring even after a single episode of acute pyelonephritis [2]. Faced with this scourge, research on UTIs in children with the aim of reducing their morbidity and mortality is unavoidable.

The aim of this study is to describe the epidemiological, clinical, bacteriological and therapeutic profile of urinary tract infections in the paediatrics department of the Tamatave University Hospital in order to improve the management of children, to update local bacteriological data and to adjust the protocol for the management of pre-existing UTIs on the basis of the results obtained.

2. METHODS

Retrospective and descriptive study that was carried out in the Pediatrics department of Tamatave University Hospital, Madagascar over a three-year period from January 1, 2017 to December 31, 2019. Recruitment of these

patients is done exhaustively in all children of both sexes, from birth to 15 years of age, who have been hospitalized in the Pediatrics Department of the UHC with a proven UTI during this period have been included. We used a pre-established collection form for this study.

These data were collected from hospitalization registers and medical observations as well as the results of the urine culture carried out. The data were entered and processed with Microsoft Excel 2016 software. The data are expressed in the form of number (n), percentage (%).

Our study includes all children of both sexes from birth to the age of 15 years, admitted to the Paediatrics Department from January 1, 2017 to December 31, 2019. for UTI or other reasons, but subsequently diagnosed at discharge as a urinary tract infection and having complete data with respect to the variables retained from the study.

Methods of collection: For newborns and infants who do not urinate voluntarily, we have used a specific sterile collector (clean-catch) which is put in place after careful disinfection of the urogenital part of the baby and cannot be left in place for more than 20 minutes to reduce the risk of contamination. In older children, the first morning urine was collected in the sterile bottle in the middle of the jet after a genitourinary toilet with soap and water from the pubis to the anus. The collected urine was sent quickly to the laboratory or stored at +4°C in a cooler if the delay was longer than one hour.

The bacteriological criteria for UTI are based on the classic criteria with monoflora bacteriuria greater than or equal to 10^4 /ml associated with leukocyturia greater than 10^4 /ml.

Incomplete records or children treated as UTIs but without bacteriological evidence were excluded.

The parameters retained and studied were age, gender, clinical signs, bacteria pathogens identified with the results of the antibiotic susceptibility tests and the treatments received.

The data have been encoded, entered, used and processed using Microsoft Excel 2010 software. The data are expressed in terms of number (n), percentage (%).

3. RESULTS

During the study period, 3,422 cases were examined and 126 children were retained (7.46%) because they had a UTI confirmed by cytobacteriological urine exam.

The mean age of children with UTIs was 11.21 months, with extremes of 2 to 120 months. The median age was 8 months. There were no cases of neonatal UTIs in our study. We noted a high frequency of UTIs in the 2-24 months age group in 86 (68.25%) cases, 10 (11.62%) cases were in the first three months of life. Among these 10 infants, 70% were small boys (n=7). After the second year of life, the frequency of UTIs was 31.74% (n=40) of which 65.50% (n=27) were in girls and 32.50% (n=13) in boys with a sex ratio of 0.48.

According to the reasons for consultations, fever was found in 102 (80.95%) children, followed by urinary signs such as crying during urination in 44 (34.94%) children, pollakiuria in 34 (26.98%) children and urinary burning in 12 (9.52%) children. Digestive signs (abdominal pain, vomiting and diarrhea) were found in 12 (26.98%) children.

The antimicrobials used as first-line agents during our study were ceftriaxone alone in 56 (44.44%) children, ceftriaxone combined with gentamicin in 40 (31.74%) children, and amoxicillin combined with clavulanic acid in 17 (13.49%) children (Table 1).

Table 2 shows that all of the children included had a cytobacteriological examination of the urine.

Among the bacteria found, *E. coli* was the most frequently isolated bacterium in 78 (61.90%) children followed by *Klebsiella sp* in 16 (12.69%) children and Coagulase-negative Staphylococcus in 13 (10.31%) children (Table 2).

Table 3 show that almost all isolates (98.0%) found were resistant to amoxicillin, tetracycline and cotrimoxazole.

Table 1. Frequency of first-line antibiotic therapy prescribed

Antimicrobials	Number	%
Ceftriaxone + gentamicin	40	31.74
Ceftriaxone	56	44.44
Cefotaxime	9	7.14
Ciprofloxacin	2	1.58
Amoxicillin + Clavulanic acid	17	13.49
Amoxicillin	1	0.79
Cotrimoxazole	1	0.79
Total	126	100

Table 2. Distribution of bacteria found

Bacteria	Number	%
<i>Escherichia coli</i>	78	61.90
<i>Klebsiella sp</i>	16	12.69
Coagulase negative Staphylococcus	13	10.31
<i>Enterobacter gergoviae</i>	8	6.34
<i>Enterobacter aerogenes</i>	3	2.38
<i>Staphylococcus aureus</i>	3	2.38
<i>Streptococcus sp</i>	4	3.17
<i>Proteus mirabilis</i>	1	0.79
Total	126	100

Concerning enterobacteria isolates, we found 10 (7.94%) cases of extended spectrum beta-lactamase (ESBL). All isolates of Enterobacteriaceae were susceptible to colistin, amikacin and imipenem. Gentamicin and ciprofloxacin were susceptible in almost three quarters of the cases (Table 4).

For Gram-positive cocci isolates, vancomycin was always sensitive. No cases of methicillin-resistant *Staphylococcus aureus* (MRSA) were found. Gentamicin, ceftriaxone, pristinamycin, clindamycin and fusidic acid were susceptible in almost all cases.

4. DISCUSSION

Our study reports the findings of the cases of UTIs found in the pediatrics department of Tamatave University Hospital, Madagascar. It has allowed us to highlight the importance of cytobacteriological urine examinations for the management of children presenting a urinary infection, both diagnostic and therapeutic. It is true that the cytobacteriological urine examination is the only proof of a urinary infection. However, the other diagnostic tool, the

rapid biochemical strip test, seems to play an important role in the diagnostic management of patients. In the department, the urine test strip is performed first, and it is only in the event of a positive urine strip that the cytobacteriological urine examination is prescribed.

Some limitations should be discussed from our study, such as the case of negative urine strips in infants under 3 months of age or in children infected with microbes that do not secrete nitrite and do not systematically lead to the prescription of cytobacteriological urine examination. All this may mask some cases of proven UTIs. On the other hand, the precariousness of the financial resources of the family of hospitalized children

was an obstacle to the bacteriological confirmation of the clinically suspected UTI in children with a positive urine test strip. This will undermine estimation of the actual frequency UTI in the paediatrics department of Tamatave University Hospital.

In our study, we found 7.46% of UTIs. A Togolese study found an identical frequency in 7.84% of cases [3]. We found that in the first three months of life, the majority of our population were boys (70%), which was similar to a study carried out by Bensman [1]. The predominance of UTI in boys in this age group in our study was due to the presence of the foreskin, which retains a certain amount of urine,

Table 3. Sensitivity profile of *Escherichia coli* isolates

Antimicrobials	Sensitive	Intermediates	Resistant
Amoxicillin	0	0	27
Amoxicillin + clavulanic acid	4	0	23
Ciprofloxacin	20	0	7
Nitrofurane	8	0	19
Cotrimoxazole	1	0	26
Colistin	27	0	0
Ticarcilline	18	0	9
Ticarcillin + clavulanic acid	20	0	7
Amikacin	27	0	0
Gentamicin	20	4	7
Tétracycline	0	0	27
C1G	8	0	19
C2G	9	0	18
C3G	21	0	6
Imipenem	27	0	0
Colistin	27	0	0

Table 4. Sensitivity profile of the other isolates of Enterobacteriaceae isolated to antibiotics

Antimicrobials	Sensitive	Intermediates	Resistant
Amoxicillin	0	0	27
Amoxicillin + clavulanic acid	4	0	23
Ciprofloxacin	20	0	7
Nitrofurane	8	0	19
Cotrimoxazole	1	0	26
Colistin	27	0	0
Ticarcillin	18	0	9
Ticarcillin + clavulanic Acid	20	0	7
Amikacin	27	0	0
Gentamicin	20	4	7
Tétracycline	0	0	27
C1G	8	0	19
C2G	9	0	18
C3G	21	0	6
Imipenem	27	0	0
Colistin	27	0	0

thus promoting bacterial proliferation. However, this figure is overestimated because of frequent contamination of the urine sample in uncircumcised boys whose foreskin cannot be retracted [4]. To remedy this, some authors propose bladder catheterisation or suprapubic bladder puncture to minimise contamination [5,6].

The high frequency of UTI in the 2-24 month age group (68.25%) is also reported by other authors such as Dunand and al. and Alexander et al. [6,7]. It is in this age group that vesico-ureteral reflux and obstructive uropathies should be systematically suspected and investigated [1]. After the second year of life, the frequency of UTI was 31.74% with a female predominance of 65.50%. This situation was mentioned by some authors, including Ganesh et al. in a study in Nepal, who also found a female predominance of 63.30% in this age group [8]. This predominance of women is in fact partly explained by poor perineal hygiene, which overlaps with the age of toilet training [7].

Unexplained fever remains the main symptom revealing UTI in children, especially before the age of 2 years [9,10]. In our study, it was present in 80.95% of cases, which is similar to that observed by Mendez's team in 2017 [11]. This fever is most often isolated [7]. A metanalytical study highlighted that girls with fever have a much higher prevalence of UTI during the first year of life than other children [12]. This high prevalence of UTI was also observed in children with a temperature $\geq 39^{\circ}\text{C}$ as well as in children with a temperature $< 39^{\circ}\text{C}$ regardless of age [13].

After fever, urinary signs are the most frequent reasons for consultations, such as crying during urination (34.94%), urinary frequency (26.98%) and urinary burning (9.52%). This proportion was close to the findings of Mendez et al. which is 35%, 27.5%, and 10% respectively [11].

The proportion of digestive signs (abdominal pain, vomiting, diarrhoea) found in 26.98% of cases was also reported by other authors [11]. The absence of specific clinical signs of UTI makes the diagnosis difficult and delays treatment.

In children three years of age and older, urinary symptoms such as dysuria, urgency, hematuria, or new daytime incontinence with or without gastrointestinal symptoms such as abdominal

pain, lower back pain may be used as criteria to justify a urine test strip and urine culture [4].

In our study, ceftriaxone was widely used either as monotherapy (44.44%) or as dual therapy with gentamicin (31.74%) followed by amoxicillin combined with clavulanic acid in 13.49% of cases (Table 1). Ceftriaxone alone was used as first-line therapy for febrile children or infants, and when the child presented with signs of sepsis or was known to be suffering from malformative uropathy, the combination with aminoglycoside was useful.

The frequency of fever during our series of UTIs would explain the frequent use of ceftriaxone, and in addition, this drug was readily available. The generic was available to the parents as opposed to cefotaxime which is more expensive, less available and less convenient because of its administration three times while our service has an under-staffed caregiver. Amoxicillin with clavulanic acid was used as a first-line treatment for non-febrile older children whose initial diagnosis was cystitis.

The Paediatric Infectious Pathology Group of the French Paediatric Society and the French Infectious Pathology Society recommended the use of ceftriaxone or cefotaxime combined with amikacin in cases of pyelonephritis or febrile urinary tract infections in infants and young children requiring hospitalization because of signs of sepsis or children under 3 months of age or known severe underlying uropathy. For children over 3 months of age who do not require hospitalization, this learned society recommends amikacin or ceftriaxone. In our context, the choice of gentamicin instead of amikacin was mainly due to its availability and low cost. According to the French Paediatric Society and the French Infectious Pathology Society, oral antibiotic therapy is possible with cefixime in children whose fever was recently installed, general condition preserved and without a history of urinary tract infection, uropathy, or recent antibiotic use. This working group recommends the use of 3 oral antibiotics such as cotrimoxazole or cefixime or amoxicillin with clavulanic acid [14].

We noted a clear predominance of *E. coli* in our series, with a frequency of 61.90%, followed by *Klebsiella sp* (12.69%) in second position (Table 2). There is a similarity in the etiological profile of UTIs in our study and those of Kosovo, Morocco, and Nepal [15,16,17]. This can be explained by

the reliability of the studies that established the most frequent mode of infection of the urinary tract by the digestive microbial flora. Thus a study in Kosovo by Lidvana Spahiu and *al.* had results closer than ours with a proportion of 63.88% for *E.coli* and 23.08% for *Klebsiella sp.* [15]. While a Moroccan study had a frequency of 44.7% for *E.coli* and 20.42% for *Klebsiella sp.* [16]. In Nepal, *E. coli* and *Klebsiella sp* were still at the top of the list as responsible for UTI, but with a high proportion for *E. coli* (64.66%) and 12.78% for *Klebsiella sp.* [17].

It is important to note that *E.coli* is known to be more contagious in the urinary tract according to the literature. This is related to the pathophysiology of the UTI. UTI is generally ascending, and there is a strong colonization of the perineum by enterobacteria of digestive origin, and in particular *E. coli*. In addition, there are specific factors of uropathogenicity. *Escherichia coli* has adhesins (P1S adhesin, Afa M adhesin), which are capable of binding the bacteria to the urinary epithelium and preventing its elimination through bladder emptying. Bacterial virulence is also an important factor because some isolates of *E. coli* possess specific virulence factors, giving them in particular urothelial adhesion capacity. *Escherichia coli* also has several serotypes. This serotyping plays an important role in the pathogenicity of this bacterium with regard to UTI.

Almost all isolates found (98%) were resistant to amoxicillin, tetracycline and cotrimoxazole. The increase in *E. coli* resistance to these antibiotics has been reported for a long time and has been documented in old publications [18,19,20]. This resistance concerns both developed and low-income countries. In Bujumbura Burundi, a study conducted in 2017 showed that *E. coli* was resistant to cotrimoxazole in 98.2% of cases and resistant to amoxicillin +clavulanic acid in 70.5%, while *Klebsiella* showed high resistance to 100% cotrimoxazole and 80% amoxicillin + clavulanic acid [21]. These results join those found by Raghubanshi et al. in 2010 who found a resistance rate to these antibiotics in 73.5% of cases [17]. The high resistance with these groups of antibiotics could be explained by the very old use and resistance is acquired after a prescription in an inadequate way, i.e. at an insufficient dose and for an insufficient period of time (i.e. misuse and abuse), and also because of the over-the-counter sales of these drugs, even to grocery stores or the street-sellers.

The emergence of third-generation cephalosporin-resistant isolates of bacteria which constrain the treatment of the infection is now a scourge known by several countries including Madagascar [22]. Ten cases of ESBL-producing enterobacteria have been found. This ever-increasing resistance to cephalosporins should attract the attention of all treating physicians because if it is poorly controlled it could lead to several complications: irreversible renal damage, severe septicaemia and could even lead to the death of the patient [23]. This resistance, more commonly known by ESBL, is a very large and heterogeneous family of bacterial enzymes that inactivate most β -lactam antibiotics with the exception of cephamycins and carbapenems. They are inhibited by clavulanic acid *in vitro* and are mostly of plasmid origin, which explains their rapid diffusion and evolution [24]. The fact that these ESBLs are essentially found in the family of enterobacteria, mainly *E. coli* and *Klebsiella*, then justifies our results. These ESBL infections constitute a public health problem since a large number of them are of community origin, and the approach must therefore be multidimensional and integrate two components such as improving standard precautions and rationalizing antibiotic consumption and prescriptions by following the protocols established in Madagascar, since first-line treatment can vary according to the realities of each country [25,26]. Gentamicin and ciprofloxacin were resistant in a quarter of the cases. All isolates of Enterobacteriaceae, even those secreting ESBL, were susceptible to colistin, amikacin and imipenem. The study by Sekhsokh and *al.* study states that ESBL-producing bacteria are resistant to the majority antibiotics and retain a high sensitivity to imipenem and amikacin, which is consistent with our study [16].

Regarding the Gram-positive cocci isolates found, including staphylococci and streptococci, gentamicin, pristinamycin, clindamycin and fusidic acid were sensitive in almost all cases.

This present study suggests that gentamicin and ceftriaxone (even though ESBLs-producers were found) should be included in the treatment protocol for UTIs in the absence of an antibiogram, which is not always available in our context. The hygieno-dietetic measures are inseparable with antibiotic therapy and very capital for developing countries like ours. Among these measures the water intake by increasing the water intake in addition to the usual fluids

consumed at reason of 100 mL/kg for the first 10 kg of weight, 50 mL/kg for the next 10 kg and 15 mL/kg for the remaining kilograms of weight is very encouraging but a more extensive and detailed study including acceptability an increase in long-term water intake is necessary before to making proper recommendations for clinical practice [27]. Education based on TPB (the Theory of Planned Behavior (TPB) with active and interventional monitoring could improve the behavior of urinary tract infection prevention in mothers with a daughter under the age of two [28]. The Malagasy medical scientific community should develop probabilistic antibiotic therapy protocols as those currently applied are not always in line with the reality of antibiotic resistance profiles.

However, studies on a larger population should be undertaken to statistically support these results as the samples are not representative of all cases of childhood UTI that might be encountered throughout Madagascar.

5. CONCLUSION

UTIs are mainly found in children under 2 years of age, predominantly female, with no cases in newborns.

Fever with or without urinary signs was the reason for the children's consultations, and the UTI was confirmed after cytobacteriological examinations of the urine. Concerning the bacteria responsible for UTIs, *E. coli* was the most frequently encountered bacterium, followed by *Klebsilla sp.* Gentamicin combined with ceftriaxone was the most frequently prescribed treatment, despite the presence of the ESBL-secreting isolates of Enterobacteriaceae found after the antibiotic susceptibility test.

Clinical examinations combined with paraclinical examinations are an indispensable tool in the diagnostic and therapeutic management of children with UTIs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was carried out after authorization from the Head of the Pediatric Department and the Head of the Hospital, who gave their

agreement and authorization for this research to be carried out. The current study has guaranteed the confidentiality of our data by expressly omitting names from the survey questionnaires. The current study has collected and processed the data in absolute anonymity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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