

# Case histories of five years of neonatal urinary tract infections: practical aspects of treatment and the need for agreed-upon guidelines

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## Abstract

Case series of urinary tract infection (UTI) in neonates (0 to 1 month of life) hospitalized in the neonatal care unit of Cagliari's university hospital during a five-year period. The major findings of this study are the prevalence of the infections in the male sex, the very high sensitivity of leukocyte esterase in detecting UTI, a higher C reactive Protein (CRP) sensitivity and specificity in comparison with procalcitonin (PCT) among markers of pyelonephritis. Moreover *E. coli* demonstrated an elevated ampicillin resistance. The retrospective evaluation of the data has led to an improvement in preventive strategies and medical-therapeutic choices applied in our department for the management of UTI. In view of the lack of national and international guidelines for UTI in this specific period of life, our data will contribute to establishing generally accepted treatment procedures in this age group.

## Keywords

Newborn, urinary tract infection, diagnosis, treatment.

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## Introduction

It is known that urinary tract infections (UTIs) represent one of the most common pathological conditions in children. It is estimated that even in the countries with the most advanced health care programmes, such as the United States, UTIs represent the most common serious infections in infancy and small children [1] following significant decreases in infections caused by *S. pneumoniae* and *H. influenzae* obtained through the most recent vaccination campaigns [2]. The incidence appears to be especially high in the earliest stages of life, reaching 13.6% in feverish neonates and 5% in infants [3]: in this population, UTIs represent the most common febrile illness, although the non specific clinical presentation often leads to diagnostic underestimation. One of the major issues in UTIs is the possible renal involvement due to acute pyelonephritis (APN) that if not early recognized and properly treated, it may lead to permanent renal parenchymal damage (scarring). About 15-41 % of children with APN develop scars [4, 5] which are considered one of the main causes of renal damage acquired in the paediatric age capable in some cases of evolving into arterial hypertension and chronic renal insufficiency [6]. The real incidence of these complications is not clear since in the past many children with congenital rather than acquired dysplastic renal damage were also included in this group.

Neonatal UTIs surely represent a special case among pediatric UTIs and need specific considerations and separate treatment with respect to later age: is no coincidence that the main national and international guidelines for the diagnosis and treatment of UTIs, such as the American Academy of Pediatrics (AAP) and the working group of the Italian Society of Pediatric Nephrology, exclude from their indications the newborn and the infant under two months of age, since in this group of patients a series of considerations must be taken into account and they may limit the application of evidence emerging from studies conducted on children from two to twenty-four months of age [2, 5, 7].

This article reports on case histories of five years of neonates hospitalized in the neonatal care unit of the University Hospital of Cagliari, with an evaluation of the main epidemiological, clinical and laboratory aspects as well as studies by images. The purpose is to improve and optimize present-day strategies and the medical and therapeutic options

in cases of UTIs at the departmental level. A further aim is to contribute through diffusion of our data to a better understanding of this complex pathology so as to arrive at a protocol and agreed-upon guidelines also for this specific age group.

## Methods

Retrospectively, we found and analyzed cases of UTI with neonatal onset (0-1 month of life) hospitalized in the Neonatal Care Unit of the University Hospital of Cagliari (where neonates of gestational age of  $\geq 34$  weeks who do not require respiratory support are hospitalized) in the period from January 2005 to December 2009. We defined UTI as positivity in the cultural examination (performed on a urine samples collected with plastic bags in 26 newborns and with suprapubic puncture in 3 cases) for a number  $> 100,000$  colony-forming units per ml (CFUs/ml) of a single pathogen in patients with clinical and laboratory signs suggesting UTI and without other signs of localization [2].

On admission, the neonates underwent an accurate medical history and clinical evaluation and the number of white blood cells was determined (normal values  $\leq 11.000/\text{mm}^3$ ) with the leukocyte differential formula C reactive protein (CRP) (normal values  $< 1$  mg/dl), procalcitonin (PCT) (normal values  $\leq 0.5$  ng/ml) and, prior to beginning any antibiotic therapy, a urine analysis with sediment and a urine and blood culture was begun. During their hospitalization all neonates underwent a reno-vesical sonograph.

UTI was defined as low UTI when neonates had low grade fever ( $\leq 38^\circ\text{C}$ ) and normal white blood cells as well as negative CRP and PCT. Neonates were defined as affected by high UTI (APN) when a positive urine culture was documented, fever of  $> 38^\circ\text{C}$ , abnormally increased white blood cells, and had positivity the infection indices evaluated.

At the time of the diagnosis all APN patients were treated according to our therapeutic protocol using a double empirical antibiotic regiment (ampicillin-sulbactam 50 mg/Kg/twice daily and gentamicin 5 mg/Kg/once daily) intravenously. Depending on the clinical state and on the basis of the antibiogram, a subsequent switch to orally treatment was performed. Neonates further received antibiotic prophylaxis until completion of diagnostic work-up.

On hospital discharge, the patients were assigned two different follow-up regimes (F.U.) depending on the diagnosis of low or high UTI:

- all cases of low UTI were followed exclusively by means of a periodic clinical evaluation, laboratory analyses (monthly urine analysis with sediment) and a renal sonograph for a period of approximately one year;
- all cases of APN entered a follow-up regime implemented together with the paediatric urology unit of the Brotzu Hospital of Cagliari and underwent a voiding cystourethrogram (VCUG) and renal scintigraphy with Mercaptoacetyltriglycine (MAG3).

## Results

This study takes into consideration a total of 29 patients with UTI, 24 males and 5 females, aged from 5 to 30 days of life, with an average of 15.4 days at the time of hospitalization. The gestational age (GA) of the patients at birth was between 37 and 41 weeks, all with a body weight appropriate for their age. Hospitalization lasted from a minimum of 3 days to a maximum of 26, with an average of 8.87 days.

Of the neonates studied, 21 had APN and 8 low UTI. Concerning the APN, CRP was positive in all cases (100%), while PCT became positive only in 6 neonates (28.5%). However, the latter parameters were negative in all neonates with low UTIs. While in the APNs we invariably found a significant increase in leukocytes with neutrophilia (100%), in the low UTIs this finding was never observed. Clinically, the presence of fever ( $\geq 38^{\circ}\text{C}$ ) was found in all cases of APN (by definition), while only 2 patients with low UTI had a low fever (B.T.  $\approx 37\text{-}38^{\circ}\text{C}$ ). The laboratory examination of the urine performed with the multistick was positive for leukocyte esterase in all cases of UTI (100%); in 10 cases, all with APN, there was positivity for nitrites (34.4%) at the same time. The study of the urine sediment (observed under the 800 X optical microscope) in all cases revealed the presence of a significant number of leukocytes ( $\geq 10$  leukocytes per field). in 3 cases of APN (14.2%) a concomitant positive blood culture (*E. coli*) was found. In 1 of these 3 cases which was complicated by osteoarthritis, urine, blood and synovial fluid cultures were positive for *E. coli*. Analysis of the urine culture was positive for *E. coli* in 25 out of 29 cases (86.3%), for *Kl. pneumoniae* in 3 out of 29 cases (10.3%) and in 1 case for *Ps. aeruginosa* (3.4%) We observed 21 pyelonephritis and 8 Low UTIs. In Low UTIs *E. coli* was the unique agent. The microbiological identification was followed

by antibiogram, which documented a resistance to ampicillin in 14 out of 25 cases associated with *E. coli* (56%), as in all the remaining 4 cases caused by other germs (*Kl. pneumoniae* and *Ps. aeruginosa*).

On the average, the antibiotic treatment continued for 12 days (in all cases between 7 and 14 days, in accordance with the AAP guidelines), with a switch from intravenous to oral administration, which never took place before the fifth day of treatment.

The reno-vesicle sonograph was normal in all cases of low UTIs (100%). In 9 of the 21 cases of APN (42.8%) an important malformational uropathy was found, and more precisely a total of 16 malformations (considering the single kidneys): 2 hydronephroses, 11 ureterohydronephroses of which 2 associated with 1 case of posterior urethra valve (PUV) and 2 associated with 2 double renal districts. (Classification of the Society for Fetal Urology) [8].

All 21 cases of APN underwent instrumental nephro-urological examinations with VCUG and Scinti MAG3. In particular, the VCUG revealed a total of 10 VURs between the third and fifth (23.8%) (including the single kidneys). Of these, 4 were not associated with malformational uropathies visible with the sonograph or scintigraph International Classification of VUR [9] (Table 1).

**Table 1.** Results of renal ultrasound (n = 29) and VCUG (n = 21).

	Total
<b>Renal ultrasound study results</b>	<b>29</b>
Hydronephrosis	
Hydronephrosis grade II	1
Hydronephrosis grade III	1
Uretero-hydronephrosis	
Uretero-hydronephrosis grade II	3
Uretero-hydronephrosis grade III	4
Uretero-hydronephrosis grade IV	4
Other findings	
Duplication	2
PUV	1
Total malformations	no. 16 (27.5%)
<b>VCUG * study results</b>	<b>21</b>
Reflux	
VUR grade III	5
VUR grade IV	4
VUR grade V	1
Total malformations	no. 10 (23.8%)

\* voiding cystourethrogram

The scintigraph study performed after 6 months in all cases of APN revealed the formation of scars only in two kidneys. In the case of PUVs, the scintigraph showed the total loss of function in one kidney.

Finally, to be pointed out are the 8 out of 21 cases of APN (38%) in which no urological malformation was found (either with the sonograph or the scintigraph or following the VCU + Scinti. In all these 8/21 APN cases the aetiological agent isolated in the urine culture was *E. coli*.

## Discussion

A first finding that emerges from the results of our work is of an epidemiological nature: the population affected by UTI was mostly represented by male neonates. None of them was circumcised. This appears to be in line with what is found in the literature in which in the first six months of life there is a higher incidence of UTIs in uncircumcised males [7]. It must be underlined that all of our patients with UTIs were at term newborns. We didn't observe UTIs in preterm infants, but our Department of Neonatology comprises: 1) NICU; 2) Puericulture Institute; 3) Neonatal Section. All the preterm newborns of the population study described were admitted in the Puericulture Institute, object of this study, and they are preterm newborns of gestational age  $\geq 34$  weeks who do not require respiratory support or other intensive care procedures: this can explain the absence of UTIs in this series, differently from VLBW and ELBW admitted in NICU, who present a series of risk factors capable of explaining an increased incidence of UTI also in relation to the multiple invasive procedures they undergo [10, 11].

From a diagnostic standpoint, it is important to emphasize the practical value of the chemical and physical examination of the urine performed with the multistick: 100% positivity for leukocyte esterase and 60% positivity for nitrites. Concerning the nitrites, it is to be pointed out that because of the frequent bladder emptying that takes place in the neonate, its positivity does not always have a way of taking place. These data, confirmed by examining urine sediment under the optical microscope and the cultural examination, make the multistick test a simple and quick analysis and an extremely reliable indicator of infection [12]. In our opinion, a negativity for

leukocyte esterase and nitrites with the multistick can reasonably lead to excluding the presence of a UTI and make further diagnostic investigations superfluous. For this reason, parents of children at risk of UTI in a follow-up regime in our unit are advised to perform a first screening examination with a urine stick at home, whether followed or not by a clinical paediatric checkup.

In our neonatal cases CRP showed greater sensitivity and specificity than did PCT in the course of APN ( $p < 0.0001$ ), although serum PCT is considered a better marker for bacterial APNs. Its value is correlated with the severity of the disease (APN and sepsis) and used as a prognostic marker of clinical evolution [13]; it is also considered predictive of the onset of renal scars [14] and the presence of vesicoureteral reflux (VUR) [15]. These data appear to confirm the usefulness of studies that compare the two parameters of infection in this specific period of life. On the contrary, hyperpyrexia is the clinical finding that appears to correlate better with a localization of the infection at the parenchymal level [2], it being present in all cases of serious urinary infection. In our findings, evaluation of the association of three data (hyperpyrexia, leukocytosis with neutrophilia and PCR), all constantly with a positive sign in the course of APN and negative in the course of low UTIs, is confirmed as a valid method for differentiating these two distinct forms of UTI.

The finding of *E. coli* as the bacterial agent mostly responsible for UTI is an expected datum, while the strong resistance to antibiotics of this germ as concerns ampicillin appears to be of special interest. For this reason, already indicated in the international literature [16, 17], in our unit we prefer the use of a protected ampicillin (ampicillin-sulbactam or amoxicillin-clavulanic acid) both in the treatment of the acute phase of UTI and for prophylaxis. Another protocol followed is that of the single daily administration of gentamicin, which increases the peaks of concentration of the drug without raising basic levels, thus ensuring optimal therapeutic effects and reducing side effects (nephrotoxicity and ototoxicity) [18].

In the literature we find different works that demonstrate that results of an oral versus parenteral antibiotic treatment do not present differences in relation to the duration of fever, the recurrence of UTI and the incidence of scars at a distance of 6 to 9 months from the infection [7, 19, 20]. On the



basis of these observations, it appears possible to reduce the timing of *switch therapy* applied up to now at the departmental level.

Three cases of APN were complicated by sepsis. Between APN and sepsis there is a two-way correlation: an APN may represent a secondary localization of an infection and an infection may be a generalization of a primitive UTI. The overall incidence of this complication could reach 45.5% [21, 22]. To be noted instead is the much rarer osteoarticular localization secondary to APN and with haematic diffusion in one of the cases described. To confirm the extreme rarity of this complication we point out that up to now only two cases of septic neonatal osteoarthritis following APN are found in the literature [23, 24]. In these particular cases the antibiotic treatment duration was 2 weeks for sepsis and 34 days for osteoarthritis.

The only study by images performed during APN was ultrasonography. Although the Scinti with Tc99m DMSA represents the gold standard among the methods of study by images, it is not recommended (especially in this period of life) since it rarely affects acute clinical management and its use is to be reserved exclusively to subsequent studies during follow-up [2, 25].

The role of the echography appears to be especially important in revealing malformational pathologies associated with APN. In 9 out of 21 patients, a major malformative uropathy was documented, for a total of 16 malformations (considering the single kidneys).

VCU is confirmed as essential in the diagnosis of VUR: 3 of the patients with malformative uropathies and 4 patients with no sonographic evidence showed VUR. Considering the single kidneys, a total of 10 VURs were diagnosed.

A final consideration concerns the 8 of 21 cases of APN in which no major malformational uropathy was found (either with echography or later with VCU + Scinti) to foresee the onset of an infective pathology. In all cases we found as infective aetiology with *E. coli*, a confirmation of the virulence of this germ which is capable of adhering to and rising along the urinary tract to the renal level and causing an APN in absence of other favouring factors.

## Conclusions

Evaluation of the data that emerge from our study has made it possible to provide a series of practical considerations for the improvement of

medical and therapeutic choices in cases of UTI followed up to the present in our neonatal care unit. However we must underline some limits of our experience (retrospective study, lack of controls). A larger number of studies and wider diffusion of data on neonatal UTIs are necessary so as to indicate and make as homogeneous as possible treatment protocols to follow in this specific period of life.

## Declaration of interest

No conflicts of interest exist.

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