ARTICLE ORIGINAL

Urinary tract infection in the neonates: what radiologic investigations should we do?

Infection urinaire chez le nouveau-né : quelles investigations radiologiques faut-il préconiser ?

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RÉSUMÉ

Introduction : L'infection urinaire est l'infection bactérienne la plus fréquente chez les nouveau-nés fébriles. Sa prévalence reste difficile à évaluer. Les investigations radiologiques restent une source de controverse.

Objectif : Etablir un algorithme d'exploration radiologique devant un premier épisode d'infection urinaire néonatale.

Méthodes : Il s'agit d'une étude rétrospective menée à l'unité de néonatologie du service de pédiatrie de l'Hôpital Mongi Slim La Marsa sur une période de 10 ans, allant de Janvier 2007 à Décembre 2016.

Résultats : Nous avons colligé 75 nouveau-nés admis pour premier épisode d'infection urinaire. L'âge médian était de 15 jours. Le sexe ratio était 2.26. L'échographie morphologique était pratiquée chez 70 parturientes (90%), 14 (20%) étaient pathologiques. E.Coli était le germe le plus fréquemment isolé chez 62 patients (83%). L'échographie rénale était pratiquée chez tous les malades, elle était pathologique chez 20 d'entre eux (27%). L'urétrocystographie rétrograde était réalisée chez 32 nouveau-nés (43%), elle était pathologique chez 11 patients (34%); elle a mis en évidence un reflux vésico-urétérale chez 8 enfants (73%). La comparaison entre les patients avec ou sans uropathie malformative, a conclu à l'absence de différence statistiquement significative concernant l'âge, le sexe, le germe isolé et la positivité de l'hémoculture. Une anomalie à l'échographie anténatale était prédictive d'uropathie malformative (p=0.001). La sensibilité de l'échographie rénale dans la détection des uropathies malformatives était de 81.8%, la spécificité était de 81%; la valeur prédictive positive était de 69.2% et la valeur prédictive négative était de 89.5%.

Conclusion : Nous avons ainsi conclu que l'échographie rénale, ainsi que la détection précoce d'une récidive de l'infection est suffisante dans l'exploration d'un premier épisode d'infection urinaire chez le nouveau-né.

Mot clés : infection urinaire, nouveau-né, échographie rénale, urétrocystographie rétrograde, uropathie malformative

SUMMARY

Abstract : Urinary tract infection (UTI) is the most common bacterial infection in febrile newborns.

Aim: The exact prevalence is difficult to determine. Our objective is to determine if renal ultrasound is sufficient in newborns diagnosed with urinary tract infection (UTI) or if they require a routine voiding cystourethrogram.

Methods: Retrospective data analysis for infants admitted in the neonatal department in Mongi Slim Hospital in Tunis between January 2007 and December 2016 and diagnosed with UTI in the first month of life.

Results: 75 newborns were diagnosed with the first episode of UTI during their hospitalization. The median age was 15 days; there were 52 (70%) males. Fetal ultrasound data were available for 70 patients (90%), of whom 14 (20%) had abnormal findings. E.coli was the most common causative pathogen founding 62 patients (83%). Renal ultrasound was performed in all patients, of which 20 (27%) were reported as abnormal. VCUG results were available for 32 infants (43%), of which 11 (34%) were interpreted as abnormal; Eight of them (73%) demonstrated vesicoureteric reflux (VUR). Comparison of the patients with and without malformative uropathy in our study, concluded that there was no significant difference in age, gender, urine culture specimen and positivity of blood culture. However antenatal ultrasound abnormalities were predictive of vesicoureteric reflux and other renal abnormalities (p = 0.001). The sensitivity of renal ultrasound for detection of vesicoureteric reflux and other renal or ureteral abnormalities was 81.8 %, specificity was 81 %. The positive predictive value (VPP) was 69.2 % and the negative predictive value was 89.5 %.

Conclusion : We concluded that in infants presenting with UTI in the first month of life, conservative follow-up with renal ultrasound examination and early detection of recurrent UTI are sufficient.

Keywords : Neonate ; malformative uropathy ; renal ultrasound ; urinary tract infection ; voidingcystourethrogram

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INTRODUCTION

Urinary tract Infections (UTI) occur commonly in both pediatric and neonatal populations (1). Prevalence of UTI varies from 0.1 to 1% in all neonates and 4 to 25% in preterm infants (2, 3).Further investigations of confirmed UTI in children aims to prevent renal scaring and future complications (4).In 2011, the American Academy of Pediatrics (AAP) revisedtheir practice parametersregarding the diagnosis and management of initial UTI in infants and young children aged 2 to 24 months (5). Infants less than two months of age were excluded from the AAP guidelines, hence specific diagnostic and management guidelines are lacking in the neonate's population.

Nowadays, there are no Tunisian data on neonatalUTI nor on the prevalence of urinary tract abnormalities in this population.

The objective of our study was to determine the most effective approach to the further investigation of confirmed first episode of UTI in newborns.

METHODS

Study population :

It was a retrospective data analysis from the department of neonatology in the Mongi Slim Hospital in Tunis. We included all neonates with first episode of UTI admitted between January 2007 and December 2016.

Initial inclusion criteria included newborns diagnosed with UTI during hospitalization. Those without a positive urine culture were subsequently excluded from the study.

Perineal urine bag collection was the method used in our study. A positive urinary culture was defined as any positive culture with at least one pathogenic organism (growth> 10^5/ml).

Demographic characteristics, clinical manifestations of UTI, laboratory data and imaging results were collected from medical records.

Renal ultrasound (RUS) and voiding cystourethrogram (VCUG) were read by attending radiologists. The dimercaptosuccinic acid (DMSA) scans were interpreted by nuclear medical specialists.

We conducted univariate analysis to evaluate patient's characteristics that were associated with VCUG status.

Statistic alanalysis :

Data were analyzed by SPSS version 19.0 using independent t test for comparing quantitative variable; chi-square test and Fisher test wereused for comparing qualitative variable. The statistical indices used to evaluate the properties of the diagnostic test were sensitivity, specificity and predictive values (positive and negative). The difference was considered significant for $p < 0.05$.

RESULTS

Descriptive study :

A total of 75 newborns were diagnosed with UTI during the studyperiod. Sixty-two (83%) were born in our hospital and thirteen (17%) were outborn.

Median age of first UTI diagnosis was 15 days +/- 8 days (interquartile 2-28 days). The age at diagnosis of UTI was < 7 days in 16 infants (21%) and beyond the first week of life in 59 patients (79%)

There were 52 males (70%) and 23 females (30%) (Sex ratio was 2.26).

Of the 75 infants of the study, seventy-two (96%) were full term and three (4%) were premature.

5-minute Apgar score was >= 7 in 73 patients (93%).

Fetal ultrasound data were available for 70 patients (90%), of whom 14 (20%) had abnormal findings.

In our study, clinical signs leading to urine examination were: isolated fever (75%), jaundice (7%), fever with jaundice (9%), failure to thrive (5%) and severe general illness (4%).

Escherichia coli was the most common organism identified on first positive urine culture in 62 infants (83%). The other pathogen organisms found were Klebsiella pneumonia in 8 patients (10%), enterobactercloace in 3 patients (4%), proteus mirabilis in 1 patient and pseudomonas aeruginosa in 1 infant. Four infants (5%) had a positive blood culture at the time of UTI diagnosis, and all of them grew the same organism from both sites.

Our biological data showed that the CRP level was elevated in 67 patients (89%); the median rate was 15 mg/l +/- 38.76 mg/l (Interquartile: 1 – 154 mg/l).

Renal ultrasound was performed in all patients, of which 20 (27%) were reported as abnormal and 55 (73%) were reported as normal. Abnormalities were generally minor

(dilated pelvis (n = 3), dilated ureter (n = 5) or dilated pelvis and calices (n = 9), parenchymal echogenicity (n = 3)).The median number of days between the diagnosis of UTI and renal ultrasonography was 11 days (interquartile range 10-15 days).

VCUG results were available for 32 infants (43%), of which 11 (34%) were interpreted as abnormal. Eight of them (73%) demonstrated vesicoureteric reflux (VUR).(Table I).

Table 1. Abnormalities in voiding cystourethrogram

Type of abnormality	number	Frequency / Total of abnormalities
Unilateral vesicoureteric reflux grade I	2	18 %
Unilateral vesicoureteric reflux grade II	2	18 %
Unilateral vesicoureteric reflux grade III	2	18 %
Unilateral vesicoureteric reflux grade IV	2	18 %
Pelviureteric junction obstruction	2	18 %
Posterior urethral valve	1	9 %

Among the 20 patients with a pathologic renal ultrasound, thirteen had a VCUG, which was abnormal in nine infants. The other seven patients (with no VCUG practiced) all had a minor anomaly on ultrasound (discrete unilateral ureteral dilation in 4 patients and dilated pelvis in the 3 others). Five of them had a normal follow-up renal ultrasound; the others two were lost to follow-up.

Among the 55 patients with normal renal ultrasound, 19 had a VCUG, of which only 2 was abnormal, showing unilateral vesicoureteric reflux grade I. there was no high-grade vesicoureteric reflux in VCUG in patients with normal renal ultrasound (Table II).

Table 2. The distribution of the patients who had VCUG and ultrasound results

	abnormal VCUG	Normal VCUG	total
Abnormal renal ultrasound	9 (69.2%)	4 (30.8%)	13
Normal renal ultrasound	2 (10.5%)	17 (89.5%)	19

VCUG: voiding cystourethrogram

DMSA renal scan was performed in five patients. The median age of this investigation was 8 months (5 – 12 months).It was normal in two patients who had unilateral vesicoureteric reflux grade II. It showed kidney size and function asymmetry in two patients (one with Unilateral vesicoureteric reflux grade III and the other had Unilateral vesicoureteric reflux grade IV). Renal scared was identified in one patient who had unilateral vesicoureteric reflux grade IV and recurrent UTI.

Univariate analysis :

Comparison of the patients with and without malformative uropathy in our study, concluded that there was no significant difference in age (p = 0.371), gender (p = 0.185). In urine culture specimen, it was no higher incidence of malformative uropathy found among neonates with non-E. coli induced UTI (p = 0.304). The positivity of blood culture (p = 1.00) and the rate of CRP (p = 0.311) were not a predictor of malformative uropathy either.

However antenatal ultrasound abnormalities were predictive of vesicoureteric reflux and other renal abnormalities (p = 0.001). The comparison of antenatal ultrasound results with VCUG data is summarized in table III.

Table 3. Number and frequency of Malformative uropathy in terms of antenatal ultrasound

	Normal antenatal ultrasound	Abnormal antenatal ultrasound	P value	Odds ratio (IC 95%)
No malformative uropathy in VCUG(21)	18 (86%)	3 (14%)	0.001	24
Malformative uropathy In VCUG (11)	2 (18%)	9 (87%)		

VCUG: voiding cystourethrogram
$p < 0.05$

The sensitivity of renal ultrasound for detection of vesicoureteric reflux and other renal or ureteral abnormalities was 81.8 %, specificity was 81 %. The positive predictive value (VPP) was 69.2 % and the negative predictive value was 89.5 %.

DISCUSSION

The major strength of this study was the choice of the population (neonate patients); to our knowledge, there are few publications focused on this population; moreover, no Tunisian study has published results on diagnosis and management of UTI in newborns.

This study has several limitations, namely inherent biases related to the retrospective design and the relatively small sample size. The VCUG rate of the study population was low (43 %); as a result, the prevalence of malformative uropathy may have been underestimated. Moreover, the urine culture collected in our study was bag sampling, and even if rigorous asepsis has been observed, perineal urine bag collection has a high rate of contamination.

Neonates seem to be especially susceptible to develop urinary tract infection with a reported prevalence of 1%-2% (6, 7). This finding might be explained by the compound effect of immaturity of the local defense mechanisms (decreased uroepithelial bactericidal activity, low levels of local immunoglobulin A, decreased urinary acidification) and heavy periurethral colonization occurring in healthy neonates and gradually resolving after the first 6 months of life (6, 7).

The exact prevalence is difficult to determine, but studies that included infants younger than 2 months reported a prevalence of 4.6% to 7.5% (8, 9). Additionally, most of these studies were performed in febrile infants, which could potentially under-estimate the true prevalence of UTI in newborns because a large proportion of them do not present with fever (10)

The heavy colonization of the preputial area in male neonates is probably the cause of the much higher rate of UTI in this group (11). The 2.26 higher incidence of UTI among our male patients is similar to other reported series (7, 12).

Cleper et al (6) showed that the rate of diagnosis of VUR was 50% of the patients seen in the first week of life, 26.9 % of those seen in the second week of life and 13 % of those seen in the second half of the first month (6). In our study, we did not found a correlation between the age group and the prevalence of VUR.

This same study showed that E.coli was the most common causative pathogen found in 73.4% of patients; however, VUR was diagnosed in only 11% of these patients compared to 43% of those in whom Klebsielle pneumonia was found to be the causative agent; this difference was statistically significant ($p < 0.005$) by the pearson chi-square test (6). Our results were not similar, and in comparison of the patients with and without malformative uropathy, there was no significant difference in the urine culture specimen in the two groups.

The role of pre-natal ultrasound is unclear (13, 14). In our study, we concluded that antenatal ultrasound abnormalities were predictive of malformative uropathy. While others authors found that fetal ultrasound results are not predictive of VUR or other renal anomalies in neonates with UTI (6, 12)

There is uncertainty about the most appropriate and effective way to manage urinary tract infection (UTI) in children, and whether or not investigations and follow-up are justified. The American Academy of Pediatrics (AAP) revised its guidelines in 2016 and state that a VCUG is required in children aged 2-24 months only after a febrile urinary tract with abnormal renal ultrasound findings, recurrent febrile UTI, or atypical circumstances (15). Guidelines from the National Institute of Health and Care Excellence (NICE) recommended that most infants and children with febrile UTI should have a renal ultrasound performed, but suggest restricting VCUG for only certain circumstances (16).

In other side, a study conducted by E.J.Kass on 468 patients do not support the concept of eliminating VCUG from the protocol for patients with normal renal ultrasound; Indeed, this study showed that 23 % of patients with both normal DMSA scan and renal ultrasonography had VUR on VCUG, giving a negative predictive value of 77% for determining the absence of VUR for these patients (17).

S.Mahant et al, in a retrospective study of the renal ultrasound and VCUG results, in 162 children under 5 years old of age admitted with their first episode of UTI, concluded that renal ultrasound findings are neither sensitive nor specific for vesicoureteric reflux in children with a first UTI, and that clinicians should not use renal ultrasound results to influence the decision on whether or not to proceed with a VCUG in the investigation in this group (18).

Another Italian study conducted in 2009, by Montini et al, demonstrated the lack of usefulness of routinely performing ultrasonography, scintigraphy and VCUG after a first febrile UTI for small children with normal prenatal ultrasound results; however, in the absence of prenatal

ultrasounds evaluations, it would be reasonable to perform ultrasonography to exclude the possibility of congenital genitourinary malformations (19).

However, all these studies above-mentioned excluded newborns and infants less than two months. Indeed,radiological evaluation needed after the first episode of UTI is less defined in the neonatal population.

A study sample published in 2000, included term infants with a diagnosis of UTI during their first month of life, showed that VCUG is imperative for male infants with a diagnosis of non-E.coli UTI in the first 2 weeks of life, and that severely abnormal renal ultrasound findings at diagnosis are an additional red flag; however for female and male infants presenting with E.coli UTI in the first month of life (especially the later half) conservative follow-up with ultrasound examination and early detection of recurrent UTI are sufficient.In this study, younger age at presentation with UTI and causative pathogen other than E.coli were considered as risk factors of VUR (6).

Moreover, some studies believed that early diagnosis of and treatment of UTI are considered to be of utmost importance to reduce the risk of resultant renal scar formation, while the importance of early diagnosis of VUR remains to be further defined (6, 7)

The results of our series showed that sensitivity of renal ultrasound for detection of malformativeuropathy was 81.8% and the specificity was 81 %. The positive predictive value of renal ultrasound was low (69.2 %), while the negative predictive value was high (89.5 %). Moreover, abnormalities found in the VCUG when the renal ultrasound was normal, were all mildly abnormal (grade I). Through these results, we believe that renal ultrasound examination was sufficient in the assessment of the first episode of UTI in newborns. VCUG must be reserved for patients with abnormalities in the renal ultrasound.

The current gold standard for diagnosing renal scarring is a technetium-99m-labeled dimercaptosuccinic acid (DMSA) renal scan, which should be performed a few months after acute infection, only if clinically indicated. Routine DMSA renal scans have no role in the acute management of UTI in neonates (10). In our study, DMSA renal scanning were performed in only 5 patients.It was normal in two patients with VUR grade II; it showed kidney size and function asymmetry in two patients (VUR grade III and VUR grade IV), a kidney scarring was demonstrated in one patient with VUR grade IV and recurrent UTI. The rate of scarring in our study was 20%; even these results was similar to some others reporters (19), this low rate may be according to the fact of that DMSA renal scan was performed in only 5 patients. However, we believe that DMSA renal scan is unnecessary in patients with normal renal ultrasound or with low grade of VUR.

CONCLUSION

Based on the results found on our study, VCUG after a first UTI in neonate may be reserved for infants with abnormalities on renal ultrasound. Given these results, we proposed an imaging protocol for neonates with the first UTI (Fig 1). However, more studies, with a larger sample, are needed to evaluate the utility of a routine VCUG in neonate population and to establish guidelines appropriate to them.

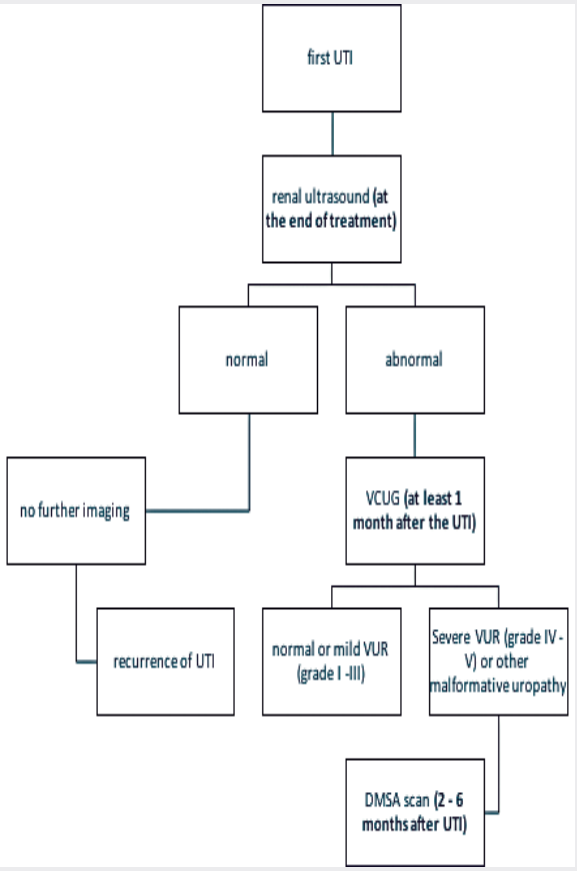

Figure 1. proposed radiologic evaluation after a first episode of UTI in neonates

UTI : urinary tract infection, VCUG : voiding cystourethrogram, VUR: vesicoureteric reflux, DMSA: dimercaptosuccinic acid

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