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The impact of childhood febrile urinary tract infection on urinary tract dilation in ultrasonography

Wpływ przebiegającego z gorączką zakażenia układu moczowego u dzieci na poszerzenie dróg moczowych w badaniu ultrasonograficznym

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Abstract

Introduction and objective: Febrile urinary tract infection in a child may be the first manifestation of congenital anomalies of the kidneys and the urinary tract. Renal and bladder ultrasonography remains the first-line imaging modality in children with urinary tract infections. Urinary tract dilation found on ultrasonography prompts further invasive diagnosis; however, when performed in the acute phase of infection, it may potentially reveal misleading findings. Our study investigated whether acute urinary tract infection is associated with urinary tract dilatation and kidney oedema on ultrasonography. **Materials and methods:** We included 62 children up to 3 years of age with the first episode of febrile urinary tract infection in this prospective cohort study. We performed three ultrasonography examinations in each child: on the first day of the treatment, as well as two and four weeks after treatment onset. We scanned 124 kidneys. **Results:** The number of kidneys with urinary tract dilation has not significantly changed in consecutive ultrasound examinations. However, both renal length and width increased in the acute phase of urinary tract infection, correlating with symptom duration and C-reactive protein levels, and then subsided within 2–4 weeks. **Conclusions:** Febrile urinary tract infection does not significantly affect the results of renal and bladder ultrasonography for congenital anomalies of the kidneys and the urinary tract in children up to 3 years old. Kidneys are often involved in children with febrile urinary tract infections. Repeated ultrasound scans before further, more invasive diagnosis are recommended.

Keywords: risk factor, diagnostic approach, vesicoureteral reflux, defect, recurrent infections

Streszczenie

Wprowadzenie i cel: Przebiegające z gorączką zakażenie dróg moczowych u dzieci może być pierwszym objawem wrodzonych wad nerek i dróg moczowych. Ultrasonografia nerek i pęcherza moczowego pozostaje badaniem pierwszego wyboru w zakażeniach układu moczowego u dzieci. Stwierdzone w badaniu ultrasonograficznym poszerzenie dróg moczowych skłania do dalszej diagnostyki inwazyjnej, ale badanie wykonywane w ostrej fazie zakażenia może dawać myląće wyniki. W niniejszej pracy zbadano, czy ostre zakażenie układu moczowego wiąże się z poszerzeniem dróg moczowych i obrzękiem nerek w badaniu ultrasonograficznym. **Materiał i metody:** W prospektywnym badaniu kohortowym wzięło udział 62 dzieci w wieku do 3 lat z pierwszym epizodem zakażenia układu moczowego przebiegającego z gorączką. U każdego dziecka wykonano 3 badania ultrasonograficzne: w 1. dobie leczenia oraz 2 i 4 tygodnie od jego rozpoczęcia. Łącznie przebadano 124 nerki. **Wyniki:** Liczba nerek z poszerzeniem dróg moczowych nie zmieniała się istotnie w kolejnych badaniach, natomiast długość i szerokość obu nerek zwiększały się w ostrej fazie zakażenia układu moczowego, korelując z czasem trwania objawów i stężeniem białka C-reaktywnego, a następnie normalizowały się w ciągu 2–4 tygodni. **Wnioski:** Przebiegające z gorączką zakażenie układu moczowego nie wpływa istotnie na wyniki badania ultrasonograficznego nerek i pęcherza moczowego w wadach wrodzonych nerek i układu moczowego dzieci w wieku do 3 lat. U dzieci z zakażeniami układu moczowego przebiegającymi z gorączką nerki często są zajęte. Zaleca się powtarzanie badań ultrasonograficznych przed dalszą, bardziej inwazyjną diagnostyką.

Słowa kluczowe: czynnik ryzyka, podejście diagnostyczne, refluks pęcherzowo-moczowodowy, wada, nawracające zakażenia

WHAT IS KNOWN – WHAT IS NEW

What is known

- Guidelines differ regarding recommended ultrasonography timing in children with urinary tract infections (UTI).
- There is concern that the acute phase of UTI-related urinary tract dilation may be due to inflammation and bacterial toxins.

What is new

- As previously suggested, we have not confirmed the influence of urinary tract infection on urinary tract dilations in ultrasonography in children.

INTRODUCTION

Urinary tract infection (UTI) is one of the most frequent bacterial infections in infants and children <2 years of age[1]. UTI may be the first and only manifestation of an underlying congenital anomaly of the kidneys and the urinary tract (CAKUT), with vesicoureteral reflux being the most common. CAKUT, affecting 1 in 500 children, is relatively common and accounts for 40–50% of chronic kidney diseases in childhood[2]. Thus, urinary tract imaging is justified in all children with the first episode of UTI[3].

Renal and bladder ultrasonography (RBUS) is a non-invasive, relatively inexpensive, and feasible diagnostic modality. It is the first-choice imaging in children with the first episode of UTI worldwide[3]. Abnormal ultrasonography findings, namely urinary tract dilation (UTD), prompt further, more invasive diagnostic tests, such as voiding cystourethrography (VCUG) and renal scintigraphy. However, it has been found in an animal model that the urinary tract may be dilated due to *Escherichia coli* endotoxin action, leading to false-positive RBUS results if performed during the acute phase of UTI[4]. Therefore, guidelines on the approach to children with UTIs differ substantially in terms of appropriate RBUS timing in the first episode of UTI[3].

Our study aimed to investigate how acute UTIs interfere with RBUS results in children.

METHODS

We included previously healthy children up to 3 years of age with their first episode of febrile UTI in our prospective, single-centre, cohort study. All recruited children were initially treated at the Medical University Warsaw Children's Hospital between March 2017 and October 2018.Children with known CAKUT or antibiotic therapy initiated before hospital admission were excluded from the study. Urinary tract infection was diagnosed per Polish guidelines in febrile children with leukocyturia, defined as above ten white blood cells (WBC) per high power field on microscopic examination in centrifuged urine[5]. Urine was obtained from clean-catch midstream void or the bladder catheterisation accordingly to the child's age and general condition on admission to the hospital. A positive urine culture defined as above 10^3 colony-forming units (CFU)/mL in catheterised urine and above 10^4 CFU/mL in clean voided urine confirmed the UTI diagnosis[5].

We performed routine blood tests on admission in all children included in the study using standard laboratory methods. We analysed WBC count (10^3/μL), neutrophil count (10^3/μL), and C-reactive protein (CRP) levels (mg/dL).

Two independent radiologists examined children with RBUS three times. We performed the first RBUS within 24 hours after treatment initiation, the second one approximately two weeks later (median 14 days; range 11 to 20 days), and the third one four weeks after treatment initiation (median 28 days; range 23 to 37). All examinations were performed with iU22 (Philips Healthcare, Eindhoven, The Netherlands) ultrasound machine using a 5–8 MHz micro convex probe.

The variables studied in RBUS were kidney size (length and width in mm), anterior-posterior renal pelvic diameter (mm), calyceal diameter (mm), and ureteral diameter (mm). Urinary tract dilation was defined according to *Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system)* as the anterior-posterior renal pelvic diameter of ≥10 mm or any dilation of calices or ureters[6]. Further diagnostic decisions were made by paediatricians and nephrologists independently from our study protocol. We evaluated all participants by follow-up phone calls at the end of the study period.

SAMPLE SIZE

Sample size calculations were based on the primary outcome measure of UTD. Pilot data from the first 30 patients with UTI suggested that the proportion (percentage) of diagnosed kidneys with UTD in the first measurement does not differ significantly from those recognised in measurements 2 and 3, at a significance level of 5%. Therefore, increasing the sample did not change hypothesis testing. Thus assuming 90% power of a binary hypothesis test and a significance of 0.05, we decided to recruit 60–70 children with UTI.

Children who did not report to the second RBUS were excluded from the study. Children who had the first and the second RBUS performed and did not report to the third one were still included in the analysis because the usual reason for the non-reporting to the third ultrasonography was the normal result of the second one. Therefore, excluding children due to non-reporting to the third RBUS would make selection bias more significant than the bias from missing third RBUS results.

STATISTICAL METHODS

Summary statistics are presented as means for continuous data and proportions for categorical data. We tested comparisons between the groups (the first, the second, and the

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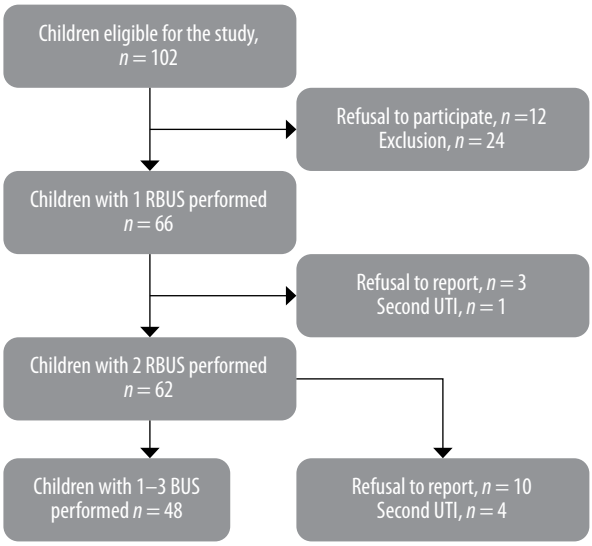

Fig. 1. The flowchart of patient selection

third RBUS results) using the ANOVA analysis if the data were normally distributed (checked using the Kolmogorov–Smirnov test, K–S). In the case of non-homogeneity variance (Levene's test, Lv), means were compared using Welch's ANOVA. Where data were not normally distributed, we used the non-parametric Mann–Whitney *U* test for independent samples. Statistical analyses were performed using SAS and EG. All tests were two-tailed, and a p-value <0.05 was taken to represent a statistically significant result.

RESULTS

One hundred and two infants and children below the age of 3 years with febrile UTIs were treated in the Medical University Warsaw Children's Hospital during the study period. Parents of 12 children refused to participate, and we excluded further 24 patients: 16 because of known CAKUT and 8 because of antibiotic treatment before recruitment. Four children did not report for the second RBUS and thus were excluded as well. Finally, we included 62 children with 124 kidneys in our analysis (Fig. 1).

Characteristic	All	Boys	Girls
Number of patients	62	35	27
Age [months], median (IQR)	7.7 (4.3–16)	4.3 (3.1–6.2)	13.8 (7.7–17.6)
C-reactive protein [mg/dL], median (IQR)	14.4 (5.2–17.8)	5.8 (4–14.8)	15.6 (7.4–19.2)
White blood cells count [$\times 10^3$/μL], median (IQR)	20.1 (16.2–22.9)	19.5 (15.9–22)	20.1 (16.7–23)
Neutrophil count [$\times 10^3$/μL], median (IQR)	10.4 (7.6–15)	8.8 (7.3–14.2)	12 (8.1–16)
Aetiology (*n*; %)	*E. coli* (58; 93.5%) *E. cloacae* (1; 1.6%) Mixed (2; 3.2%) Unknown (1; 1.6%)	*E. coli* (32; 91.4%) *E. cloacae* (1; 2.9%) Mixed (1; 2.9%) Unknown (1; 2.9%)	*E. coli* (26; 96%) Mixed (1; 4%)
Antibiotic treatment duration [days], median (min–max)	10 (6–21)	10 (7–16)	10 (6–21)
Recurrent UTI (*n*, %)	15; 24%	6; 17%	9; 33.3%

IQR – interquartile range; **UTI** – urinary tract infection.

Tab. 1. Demographic and clinical characteristics of the study group

The demographic and clinical characteristics of the study group are shown in Tab. 1. Children were admitted to the hospital from 0 to 8 (mean 2.7 ± 1.7) days after their first UTI symptoms. Before admission to the hospital, symptom duration significantly correlated with patients' age ($r = 0.41$, $p = 0.0025$). In most cases, *E. coli* was the aetiological factor (93.5%), with only one strain producing extended-spectrum beta-lactamase (ESBL+). Intravenous cefuroxime was the first line and only treatment in 42 (67.7%) children. One child received amoxicillin with clavulanic acid as a first-line treatment. In 2 children, cefuroxime was combined with gentamycin. In 3 other children, cefuroxime was followed by trimethoprim-sulfamethoxazole. Thirteen (21%) children were treated with 3rd generation cephalosporin (either ceftriaxone or cefotaxime), and in one case, ESBL+ infection, cefuroxime was switched to meropenem.

Fourteen children did not report to the third ultrasonography. Eleven of those had no urinary tract dilatation on the second ultrasonography. After phone-call evaluations, we found four children non-attending the third RBUS to have a second UTI, and 11 children to have recurrent UTIs afterward. Among 15 children with recurrent UTIs, 13 had VCUG performed, which revealed grade II–III vesicoureteral reflux in 3 children. VCUG was completed in 7 more children after a single UTI episode and showed no abnormalities in this group. Two children with no additional risk factors had scintigraphy performed, which revealed no abnormalities. These diagnostic decisions were made independently of our study protocol.

Thirty-six children had UTD in the first RBUS (15 right kidneys, 30 left kidneys), while 30 children in the second RBUS (9 right kidneys, 27 left kidneys). The third RBUS showed UTD in 26 children (6 right kidneys, 24 left kidneys). The differences in UTD numbers in consecutive RBUS examinations did not reach statistical significance. Moreover, in some children, UTD was found only on the second or the third RBUS examination.

The kidney length and width decreased in consecutive RBUS examinations. The difference in kidney length between the first vs. second RBUS reached the significance level only for the right kidney (3.18 mm; $p = 0.03$), whereas between the first and the third RBUS for both right and the left kidneys (4.67 mm, $p = 0.003$ and 4.75 mm, $p = 0.006$, respectively). The median increase in kidney length in the first vs. third RBUS was 4.1% (interquartile range, IQR 0–8.4%) for the right kidney and 3.7% (IQR 1.3–7.9%) for the left one. We also observed significant differences in the kidney width for the right and left kidneys (2.3 mm, $p = 0.0138$, and 1.86 mm, $p = 0.006$, respectively) between the first and the third RBUS examinations. The differences

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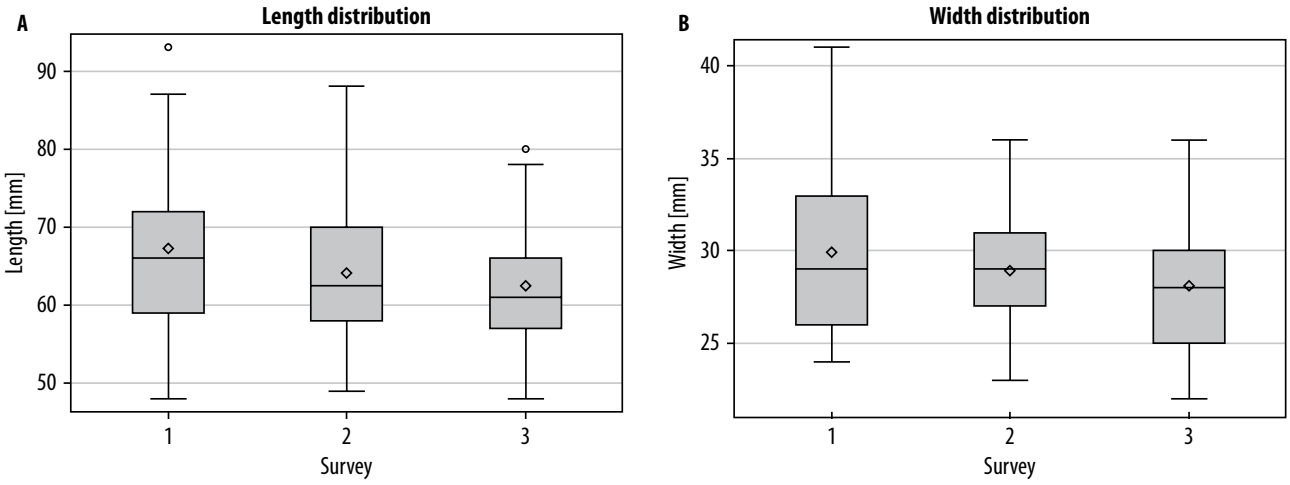

Fig. 2. A, B. Kidney length and width on consecutive ultrasound examinations

in kidney length and width on consecutive RBUS examinations are presented in Fig. 2.

The increase in kidney length for both right and left kidneys correlated significantly with the duration of symptoms ($r = 0.42$, $p = 0.003$ and $r = 0.35$, $p = 0.015$, respectively) and CRP ($r = 0.37$, $p = 0.01$ and $r = 0.44$, $p = 0.002$, respectively) (Fig. 3).

DISCUSSION

Key results

Our study revealed that the prevalence of urinary tract dilation does not decrease significantly in consecutive ultrasound examinations in the acute and convalescent phases of UTI. We found that UTI affects kidney size on ultrasound, and this effect subsides within 2–4 weeks after UTI treatment onset. Renal enlargement during UTI is correlated with symptom duration before treatment implementation and CRP value at the time of admission to hospital.

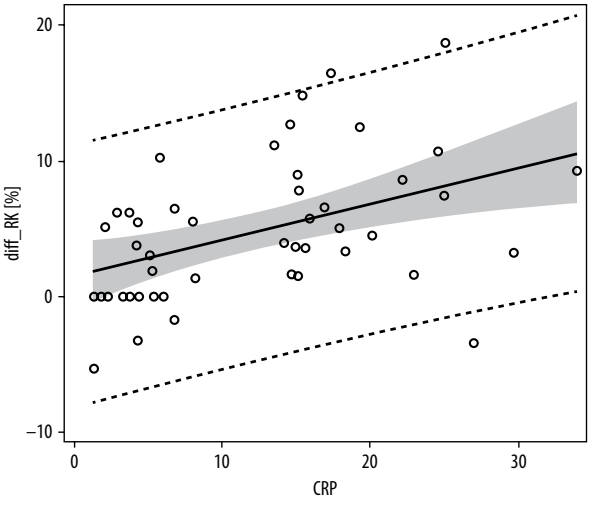

Fig. 3. Linear regression model for the increase in right kidney length with 95% confidence interval for C-reactive protein (CRP)

Limitations

The major limitation of our study is the loss of follow-up of children non-reporting to the third RBUS. Most children lost to follow-up were those with no abnormalities in the second RBUS (decreased probability of CAKUT). This resulted in a non-random selection of children who reported to the third RBUS. Another limitation of the study is that we did not measure children's height and weight at the time of the second and the third RBUS, resulting in the kidneys' size not being expressed as *Z*-scores and interpreted according to the limits of the norm.

Interpretation

We hypothesised that the number of dilated pyelocalyceal systems would decrease significantly in consecutive measurements during acute UTIs. Still, we have not found a significant difference between the first, second, and third RBUS findings on UTD. However, we have noticed limited reproducibility of consecutive RBUS findings regarding the presence of UTD, constituting an argument for repeated assessment before further, more invasive tests.

Since oedema is one of the cardinal signs of inflammation, enlargement of kidney size found in RBUS during UTI correlated significantly with CRP, probably reflecting the inflammatory process within renal tissue. Similar findings were presented by Simrén et al., who found RBUS to effectively assess renal parenchymal involvement during UTI in infants[7]. Another study by the same group revealed that initial kidney length predicted permanent renal damage diagnosed by renal scintigraphy one year after treatment completion[8]. We found that renal oedema correlated with symptom duration before treatment initiation, concluding that prompt UTI diagnosis and treatment

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may prevent permanent renal damage. Interestingly, in our study, the older the child, the longer it took to receive treatment, which may be explained by decreased parental watchfulness in older febrile children. Moreover, there is growing evidence that RBUS has limited sensitivity in predicting VUR in children with UTIs[9–11].

Furthermore, a recent publication by Gaither et al. has shown that screening RBUS after the first episode of UTIs in children <24 months of age does not meet cost-effectiveness guidelines. Instead, the authors suggest deferred screening until the second UTI[12]. In our study, it is remarkable that among 20 children who underwent VCUG, all three with VUR had a history of recurrent UTI.

GENERALISABILITY

Our study shows that postponing an ultrasound examination does not decrease the prevalence of urinary tract dilation in children up to 3 years old after the first episode of UTI. However, early ultrasound examination in the course of UTI reveals inflammatory oedema of the kidneys, which subsides within 2–4 weeks after treatment onset. Taken together with the limited reproducibility of renal and bladder ultrasonography results, this finding argues for repeated ultrasound examination before further, more invasive diagnosis.

Conflict of interest

The authors declare no conflict of interest.

Funding/Support and role of the sponsor

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Ethical approval

The study was approved by the Bioethical Committee of the Medical University of Warsaw.

Informed consent

Informed consent was obtained from all caregivers of children in the study.

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