Is ultrasonography mandatory in all children at their first febrile urinary tract infection?

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Abstract

Background This study investigated whether performing kidney ultrasound (KUS) only in children presenting either a pathogen other than *E. coli* at their first febrile urinary tract infection (fUTI) or experiencing fUTI recurrence would increase missed diagnoses of kidney anomalies.

Methods Patients aged 2–36 months with fUTI who underwent KUS evaluation from 2 January 2013 to 31 June 2018 were enrolled. Cystourethrography was performed after pathological KUS or recurring fUTIs. Thereafter, we retrospectively assessed the detection rate of kidney anomalies through performing KUS only in patients with atypical pathogen at first fUTI or with recurring fUTIs.

Results In 263 patients included, the isolated pathogen was *E. coli* in 223 cases (84.8%) and atypical in 40 cases (15.2%). KUS detected kidney anomalies in 14/223 (6.3%) of fUTIs caused by *E. coli* and in 11/40 (27.5%) of fUTIs caused by an atypical pathogen (OR 5.5, 95%CI 2.5–14.5). Cystourethrography was performed in 40 patients and vesicoureteral reflux (VUR) found in 20 cases. None of the high grade VUR diagnoses or other kidney anomalies would have been lost through a different diagnostic protocol that required the presence of an atypical pathogen at the first fUTI or a fUTI recurrence to perform the KUS.

Conclusions A diagnostic protocol that requires presence of an atypical pathogen at the first fUTI or a second episode of fUTI to perform the KUS would allow a reduction in the number of negative ultrasounds with a negligible risk of missed diagnoses of kidney anomalies.

Keywords Children · Febrile urinary tract infections · Recurrence · Kidney ultrasound · VCUG · CAKUT

Abbreviations

CAKUT	Congenital anomalies of the kidney and urinary tract
fUTI	Febrile urinary tract infection
KUS	Kidney ultrasound
SINEPE	Italian Society of Paediatric Nephrology
VCUG	Voiding cystourethrography
VUR	Vesicoureteral reflux

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Introduction

In recent decades, different tests have been recommended by guidelines in the management of first febrile urinary tract infection (fUTI) in children, including kidney ultrasound (KUS), cystography and renal scintigraphy [1–6]. In particular, KUS plays a pivotal role in decision-making when choosing which patients require further testing in order to exclude underlying kidney anomalies. The majority of guidelines, such as the Italian Society of Paediatric Nephrology (SINEPE) guidelines [1], American Academy of Pediatrics guidelines [2], EAU/ESPU guidelines [3] and Canadian Paediatric Society guidelines [4], continue to recommend a

routine KUS for all children at the first fUTI, likely in part given the non-invasive nature of the investigation. On the other hand, due to the fact that this approach is not based on robust evidence or a convincing cost-benefit ratio, other guidelines such as NICE [5] and KHA-CARI [6] suggest that KUS should only be performed on a number of selected patients according to specific risks.

Despite being a non-invasive and radiation-free method, KUS tests negative in 83% of cases of fUTIs and possesses low specificity for low grade vesicoureteral reflux (VUR) [7]. This lack of specificity, together with the strikingly high number of normal KUS performed on all children in adherence to the current guidelines [1–4], often results in a waste of resources and time [4–6].

Although current guidelines have led to a remarkable reduction in the number of voiding cystourethrographies (VCUGs) performed, the large number of negative ultrasounds remains an issue [1–9] and prompts investigations about the real usefulness of KUS. From this perspective, studies aimed at identifying patients at higher risk may limit the universal use of KUS in children at their first fUTI. Recent evidence regarding VUR suggests that the presence of pathogens different from *E. coli* may help to identify children who necessitate further investigations [8–12].

The aim of this study was to investigate whether performing KUS only in patients presenting either a pathogen other than *E. coli* at their first fUTI or experiencing a second fUTI episode would result in a significant number of missed kidney anomalies, challenging the Italian guidelines in a retrospective simulation. Furthermore, we determined the benefit of this approach in terms of number of KUS and VCUGs that would have been avoided and the relative cost saving.

Methods

We conducted a retrospective monocentric study enrolling all patients aged 2 to 36 months diagnosed with first fUTI, in accordance with SINEPE guidelines, who subsequently underwent US evaluation for study of the kidneys and urinary tract (Fig. 1) [1, 10]. Patients with fUTI were recruited from 2 January 2013 to 31 June 2018. Urine cultures were carried out in the microbiology laboratories of the Integrated University Healthcare Hospital of Trieste and the Institute for Maternal and Child Health Burlo Garofalo. Patients with a minimum follow-up of 24 months from the first episode of fUTI were included. Urine samples were collected following SINEPE recommendations according to the child's clinical condition:

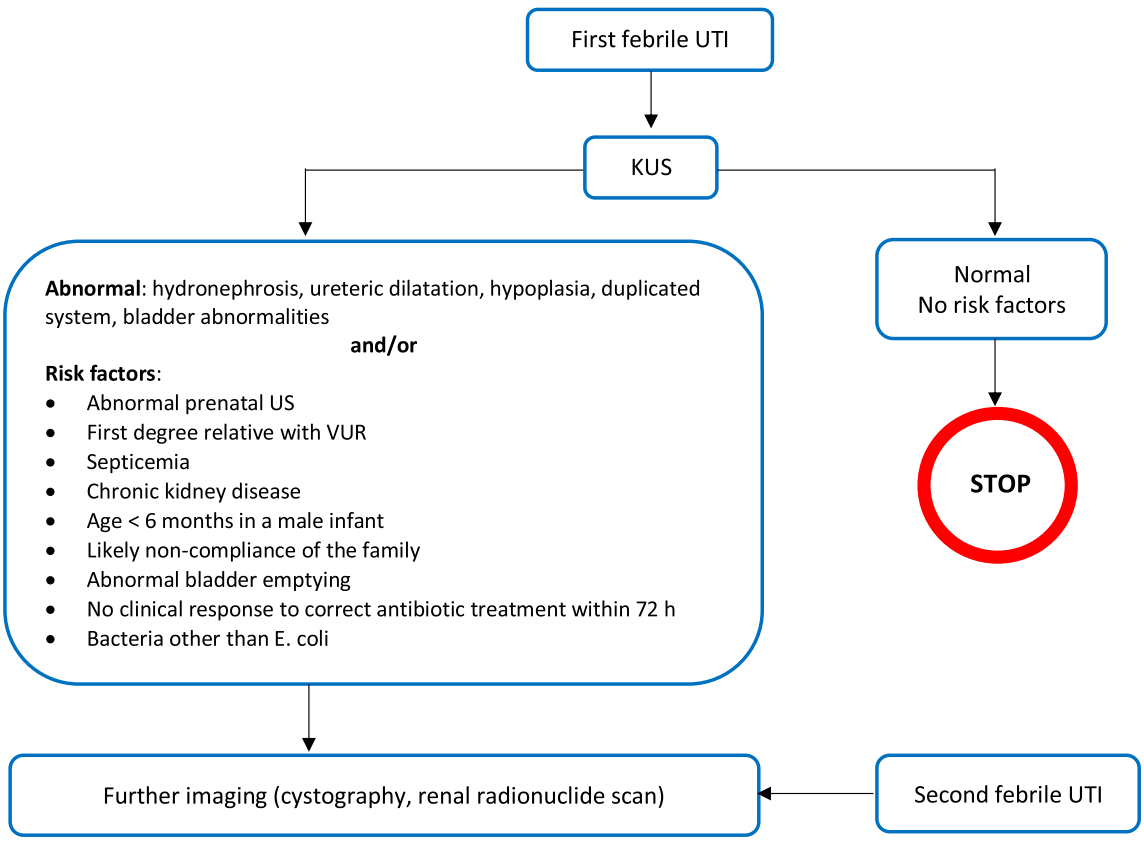

Fig. 1 Suggested imaging approach after a febrile UTI in children aged 2 months to 3 years of age (modified from SINEPE guidelines [1, 9])

in febrile children in good clinical condition, urine samples were collected by clean voided urine or by bladder catheterisation if clean catch was not possible. In febrile children in poor general clinical condition, urine samples were collected by transurethral bladder catheterisation or suprapubic aspiration [1, 10]. Patients with urine culture who tested negative or with the presence of polymicrobial flora, patients with positive urine culture and prenatal diagnosis of congenital anomalies of the kidney and urinary tract (CAKUT) and those who had not performed the follow-up with KUS after the first episode of fUTI were excluded. VCUG was performed after a pathological KUS or after the recurrence of fUTI even after a negative KUS, in adherence to SINEPE guidelines [1, 10]. None of our patients was on antibiotic prophylaxis.

The following data were collected: demographic patient data (date of birth, gender) and type of pathogen in urine cultures classified as "*E. coli*" and "other than *E. coli*", which was defined as "atypical". The follow-up was performed at the paediatric nephrology department of the Institute for Maternal and Child Health Burlo Garofalo. KUS and VCUG were performed, in adherence with SINEPE guidelines [1, 10], at the radiology department of the Institute for Maternal and Child Health Burlo Garofolo.

The primary outcome of the study was to assess the rate of lost kidney anomalies through a different type of follow-up consisting of performing KUS only in patients with an atypical pathogen at the first fUTI or with recurring fUTIs, regardless of the type of causal pathogen (Fig. 2), compared with the standard nephrological follow-up according to SINEPE guidelines [1, 10] (Fig. 1). The secondary outcome was to see how many KUS and VCUGs would have been avoided following this approach and the relative cost saving. Categorical variables are described as absolute frequency and percentage, while median and interquartile range were used for quantitative variables. The difference in the continuous variables between the groups of a dichotomous variable was tested by non-parametric Wilcoxon Mann-Whitney test. Association between categorical variables was evaluated by Chi-square test. To evaluate the probability of obtaining a positive KUS, a logistic regression model was constructed. Type of bacterium at the first urine culture was the independent variable, and the model was adjusted for age class and sex. A p value < 0.05 was considered as statistically significant. All statistical analysis was conducted using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Institutional Review Board of the Institute for Maternal and Child Health Burlo Garofalo (ID 2018-120).

Results

Four hundred and five patients with fUTI and positive urine cultures aged 2–36 months were enrolled. Of these, 38 patients with a prenatal diagnosis of urinary tract malformations and 104 patients in which the KUS was either not performed or unavailable after a first diagnosis of fUTI were excluded.

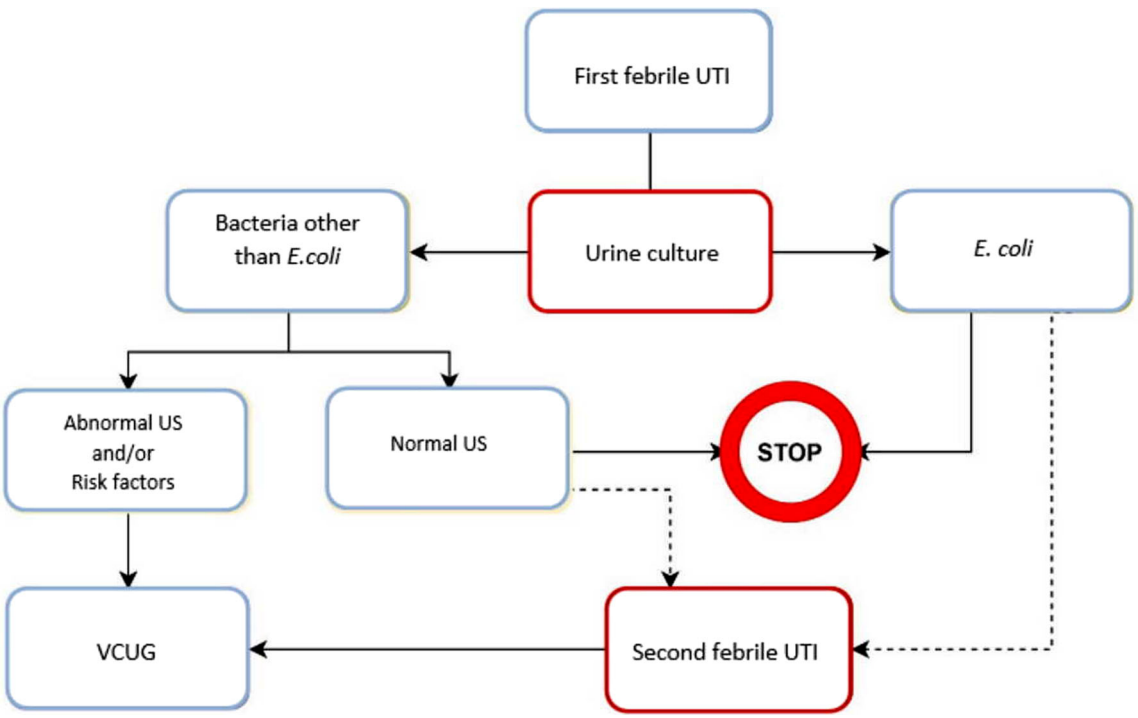

Fig. 2 The study diagnostic protocol

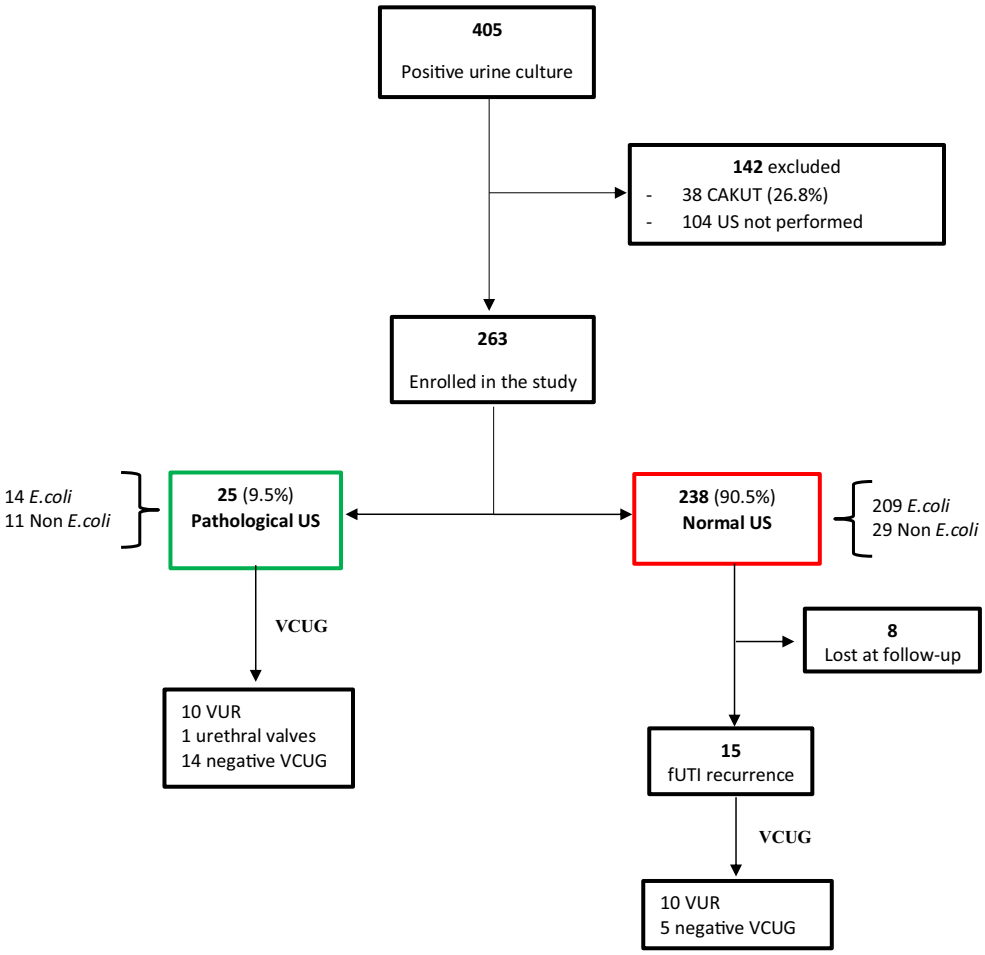

Fig. 3 Study flowchart with the "standard" protocol, according to SINEPE guidelines

Of the 263 patients included in the study (Fig. 3), 96 were males (36.5%) and 167 were females (63.5%). The median age at the first episode of fUTI was 8.5 months (IQR 3.9; 12.9); the median age was 5.2 months (IQR 2.5; 9.5) in males and 10.4 months (IQR 6.2; 16.0) in females. The median follow-up was 3.6 years (IQR 2.0; 5.1). KUS was normal in 238 cases (90.5%) and pathological in 25 cases (9.5%) (Table 1). The isolated pathogen was "*E. coli*" in 223 cases (84.8%) and "non-*E. coli*" in 40 cases (15.2%) (Table 2). The KUS detected kidney anomalies in 14 out of 223 cases (6.3%) in UTIs caused by *E. coli* and in 11 out of 40 cases (27.5%) in fUTIs caused by an atypical pathogen (OR 5.5, 95%CI: 2.5–14.5, $p < 0.001$).

Table 1 Anomalies found on pathological ultrasounds

Pathological KUS	Number	Percentage
Hydronephrosis	14	56
Hydroureteronephrosis	7	28
Renal hypoplasia	1	4
Duplicated collecting system	1	4
Ureterocele	1	4
Bladder diverticula	1	4
Total	25	100%

Table 2 Isolated pathogens in patients with positive urine culture

Germ detected in the urine culture	Number	Percentage
E. coli	223	84.8
Atypical pathogen	40	15.4
Klebsiella spp.	12	4.5
Proteus	11	4.1
Enterococcus faecalis	7	2.6
Enterobacter spp.	2	0.7
Citrobacter	2	0.7
Pseudomonas	2	0.7
Serratia species	1	0.4
Sphingomonas paucimobilis	1	0.4
Staphylococcus warneri	1	0.4
Streptococcus agalactiae	1	0.4
Total	263	100%

Therefore, in the "new" protocol that requires the presence of an atypical pathogen to perform the KUS, 40 out of 263 patients would have undergone the KUS, and of those, 11 (27.5%) would have had a pathological KUS. Of the 223 patients presenting *E. coli* at the first fUTI, KUS would have been performed on 30 (13.5%) of them due to a second episode of fUTI. Of these 30 ultrasounds, 10 (33.3%) would have tested positive (Fig. 4). Bacteria isolated in the 30 patients with a fUTI recurrence are shown in Table 3.

VCUG was performed on a total of 40 patients, due to pathological KUS in 25 cases and fUTI recurrence in the remaining 15. VUR was found in 20 out of 40 patients (50%), and anterior urethral valves were found in one case (2.5%). In 19 out of 40 cases (47.5%), VCUG tested negative (Table 4). None of the VUR diagnoses found with the "standard" protocol according to SINEPE guidelines [1, 10] would have been missed with this "new" protocol (Fig. 4). Furthermore, following the "new" protocol would have resulted in a 47.5% decrease in VCUGs performed. Of the 20 patients with normal KUS after a fUTI recurrence in the retrospective simulation (Fig. 4), in reality (Fig. 3), 19 had normal VCUGs (no VUR missed), while 1 patient was lost at follow-up and did not undergo VCUG.

Table 3 Isolated bacteria in the 30 patients with a second episode of fUTI

Isolated bacteria in recurring fUTIs	Number
E. coli	*18*
Atypical pathogen	*12*
Proteus	5
Klebsiella spp.	3
Enterococcus faecalis	2
Pseudomonas	1
Enterobacter spp.	1
Total	30

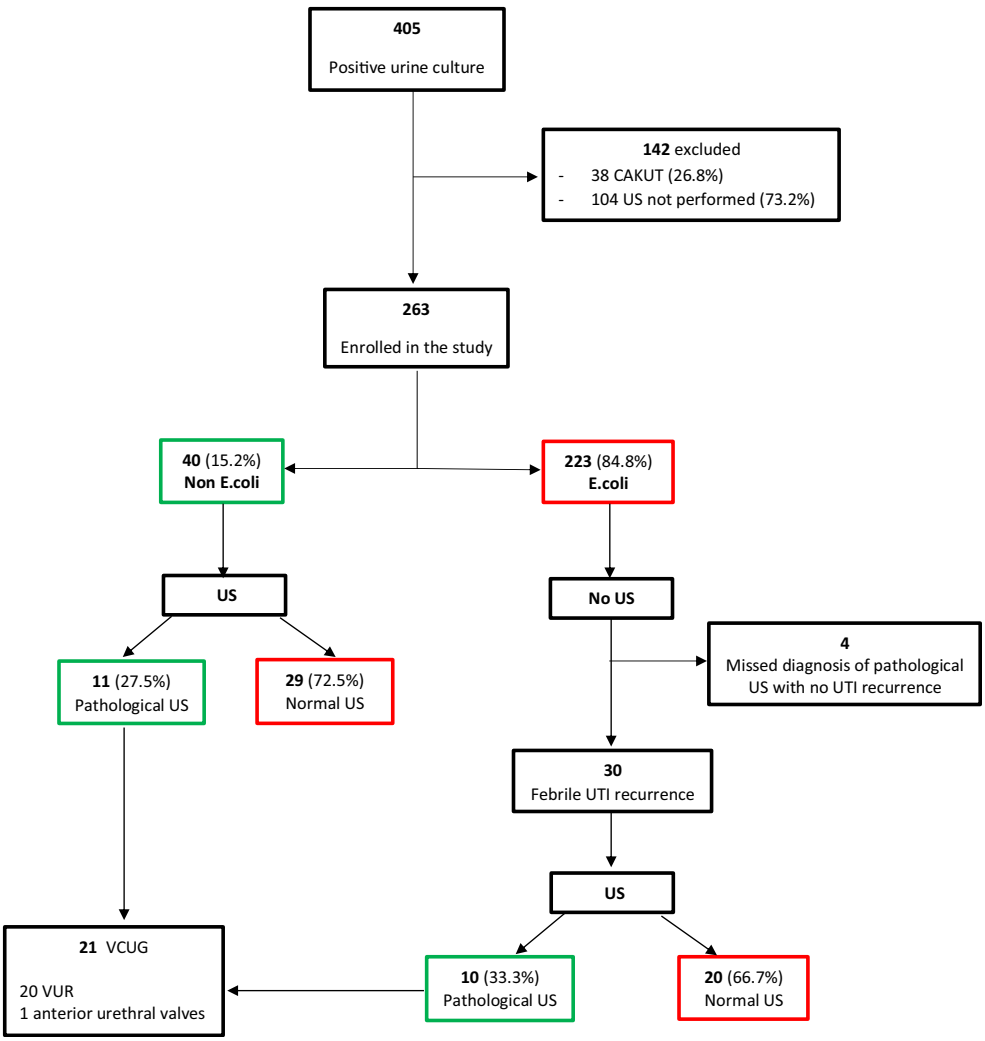

Fig. 4 Study flowchart with the "new" protocol

Table 4 Voiding cystourethrography

VCUG	Number	Percentage
Pathological	21	52.5%
VUR	20	
Grade I	2	
Grade II	2	
Grade III	10	
Grade IV	6	
Grade V	0	
Anterior urethral valve	1	
Negative	19	47.5%

Therefore, when compared with the "standard" protocol, the "new" protocol would have failed to detect four kidney anomalies, all grade 1 hydronephrosis (Table 5), with non-evolutive disease at long-term follow-up. Considering a population of 1,628,739 children between 2 and 36 months in Italy [13] and considering that about 5% of these children will experience a fUTI [14], 81,436 KUS would be performed according to the majority of current guidelines [1–4]. According to our data, 73% fewer KUS would be performed with the new protocol requiring the presence of an atypical pathogen or a fUTI recurrence, with no lost diagnoses of severe kidney anomalies and a total of 59,448 KUS avoided. Assuming an average cost across the various Italian regions of € 82 per KUS [9], the total yearly savings for the National Healthcare System would amount to € 4,874,736, plus € 304,942 considering a reduction of 47.5% VCUGs assuming an average cost of € 83 per VCUG [9].

Discussion

This study showed that a fUTI caused by an atypical pathogen and recurring fUTIs appear to be targetable risk factors to detect kidney anomalies and could both be used to identify patients for whom a KUS would likely be positive and useful.

Over the past few years, the improvement in prenatal ultrasound technique has clarified how the anomalies of the kidney and urinary tract, especially dysplastic kidney, often highlighted in association with VUR, are mainly congenital rather than caused by episodes of fUTI as was previously believed [10–16]. This is further supported by the analysis of data obtained from the dialysis and transplant registries, which confirms that aggressive protocols and surgical correction management or antibiotic prophylaxis of VUR, performed on the grounds of the assumption that kidney damage was acquired rather than congenital, did not reduce the number of paediatric patients requiring dialysis or transplant [17–20].

Table 5 Patients with positive ultrasound who would be missed with the new protocol

Patient *N*	Age (months)	Sex	RUS	VCUG
1	2.9	Male	Grade 1 hydronephrosis	Negative
2	1.6	Female	Grade 1 hydronephrosis	Negative
3	3.5	Male	Grade 1 hydronephrosis	Negative
4	23.4	Female	Grade 1 hydronephrosis	Negative

Numerous prospective randomised controlled trials assessing the efficacy of prophylaxis versus the treatment of single fUTI relapses have been conducted on these findings over the past 10 years. These studies have shown little or no benefit in the prevention of fUTIs [21–28]. These findings have led to a re-evaluation of the imaging protocols following a first fUTI, and today, all major international guidelines [1–4] recommend, albeit with some differences, the execution of KUS to select those children who will need to undergo more invasive investigations such as VCUG and renal scintigraphy. This new approach has led to an important reduction in the number of VCUGs performed (up to 88% less) but the price to be paid remains the high number of KUS which test negative (around 80%) [10, 29]. The top-down approach showed the highest sensitivity in detecting kidney damage but also the highest economic and radiation costs. There is no ideal diagnostic protocol following a first fUTI. An aggressive protocol has a high sensitivity for detecting VUR and scarring but carries high financial and radiation costs with questionable benefit [9].

The goal of this study was to create novel selection criteria in order to reduce the number of negative ultrasounds and, if possible, also that of VCUGs, and to investigate the impact this novel protocol would have on the number of missed diagnoses of kidney anomalies other than VUR. These data confirm the high percentage of negative KUS in patients with fUTI, with only 25 out of 263 (9.5%) ultrasounds performed showing some anomaly (Fig. 3). If we had performed the KUS only in patients with fUTIs caused by a pathogen other than *E. coli* (40) or with fUTIs recurrence (30), a total of 70 KUS would have been performed (Fig. 4), of which 20/70 positive (28.6%), compared with the 25/263 (9.5%) obtained following the "standard" protocol, therefore resulting in a significant reduction in KUS performed (73% less, 70 instead of 263). As a matter of fact, the probability of having a positive KUS was five times higher for those infected by an atypical agent rather than *E. coli*. This correlation could be explained on the basis that pathogens lacking the adhesive capacity to the urothelium, such as those which we classified as "other than *E. coli*", can cause infection more frequently in children with urinary tract anomalies, due to lacking of the protective mechanism provided by a normal urinary stream [15]. Alberici et al. assessed the effectiveness of the risk factors proposed by the Italian guidelines, highlighting that the only factor with a statistically significant correlation with the presence of a high-

grade VUR was the presence of a pathogen other than *E. coli* [10, 11]. Pauchard et al. found the same correlation with pathogens other than *E. coli* in 0–3-month-old babies, with the 26% chance of having a high-grade VUR rising to 55% if associated with an abnormal US [8, 12].

Of the patients with *E. coli* infection who would not have undergone the KUS after the first episode of fUTI with no recurring fUTIs, we would have had 4 missed diagnoses of pathological KUS, all first grade hydronephrosis with non-evolutive disease at long-term follow-up. The role of prenatal US for mass screening for CAKUT in this setting appears crucial, considering the low number of urinary anomalies found in the post-natal evaluation of the cohort of our study [14–16]. We tested the Italian guidelines considering the high level of prenatal ultrasound screening in Italy where most cases of significant CAKUT are detected. Prenatal US is routinely performed in the 20° and 30° week in all pregnancies as a screening guaranteed by our National Health Care System. According to our data, 73% fewer KUS and 47.5% fewer VCUGs would be performed with the new protocol, with no lost diagnoses of severe kidney anomalies and a cost-benefit analysis predicting an almost 5 million Euro yearly saving for the Italian National Health Care System.

Furthermore, considering that a minimum of 1-h time of engagement per family is required to perform a KUS, the savings in terms of hours of work and transportation costs would be relevant as well.

Limitations of this study include the retrospective nature of the data employed. A further limitation is found in the fact that we did not perform VCUGs in all the patients with atypical pathogens and negative KUS, potentially losing some diagnoses of VUR. However, according to the data collected, almost none of those patients had a recurrence of fUTIs, making it unlikely for them to have an underlying kidney abnormality. On the other hand, our goal was not to identify low grade VUR, which is generally not indirectly detectable via KUS, which is not associated with significant kidney damage and does not require any treatment [24]. However, it is also noticed that KUS could have up to 79% sensitivity to detect high grade VUR. On the contrary, we were interested in understanding what kind of kidney diseases other than VUR would have gone undiagnosed by not performing a KUS. This choice is supported by the fact that VUR does not appear to be an important and modifiable risk factor for recurrent fUTIs, new kidney scarring or CKD stage 5. Since new kidney scarring develops only after recurrent fUTIs, the focus should be on the prompt diagnosis and treatment of fUTIs [29]. Lastly, as the study was conducted in a third level-centre which provides excellent prenatal screening, the low number of kidney anomalies detected during our post-natal evaluation could be due to this factor.

Conclusions

In conclusion, this study showed that a fUTI caused by an atypical pathogen appears to be a specific and targetable risk factor to detect kidney anomalies that could be used as a selection criterion to identify patients at the first episode of fUTI for whom a KUS would be useful. In children with *E. coli* infection, the execution of an US after a fUTI recurrence could identify a further minority of patients at risk of malformations. This approach would allow a significant reduction in the number of negative tests, saving time and reducing costs, with a negligible risk of missed diagnoses of kidney anomalies. Since children with abnormal prenatal KUS were excluded, these conclusions apply to children with normal prenatal KUS.

Further prospective multicentre randomised controlled trials will be needed to confirm our data, together with a better analysis of recurrence of fUTIs, as a tool for recognising non-previously intercepted patients to better evaluate a more specific target in the follow-up protocol of patients with fUTIs.

What is known on this subject

The kidney ultrasound is currently recommended in children at their first febrile urinary tract infection by the majority of current guidelines, but the large number of negative tests remains an issue.

Despite being a non-invasive and radiation-free method, kidney ultrasound possesses low specificity for vesicoureteral reflux.

What this study adds

A diagnostic protocol that required the presence of an atypical pathogen at the first febrile urinary tract infection or a second febrile urinary tract infection to perform the kidney ultrasound would reduce negative tests with a negligible risk of missed kidney anomaly diagnoses.

Authors' contributions Dr Amoroso, Drs Conversano, and Drs Busetti conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Giangreco, Dr Pesce, Pennesi G., and Drs Cattaruzzi designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr Pennesi M. and Prof Barbi conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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