

A follow-up urine sample has limited value after treatment for urinary tract infection in children

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ABSTRACT

INTRODUCTION: A routine follow-up urine sample (FUS) in the form of a midstream urine sample (MSU) is recommended after treatment for urinary tract infection (UTI) according to the Danish Paediatric Society (DPS) and “Lægehåndbogen” published by Danish Regions. We studied the effect of FUS with a focus on patients without symptoms at the time of FUS.

METHODS: Consecutive patients below 16.0 years treated for upper or lower UTI from 1 January 2009 to 31 December 2009 at Hvidovre Hospital in accordance with the guidelines of the department and the DPS. All patients were asked to provide a FUS within 21 days.

RESULTS: A total of 87 patients were treated for upper UTI: 59 girls and 28 boys, the median age was 1.1 year (range: 0.1-15.6 years); and 42 girls were treated for lower UTI, their median age was 8.2 years (range: 2.5-15.3 years). After treatment, the risk of a UTI was 0% (0/87) after upper UTI versus 19% (8/42) after lower UTI (Fisher's exact test (FE), $p < 0.0001$). Among those without symptoms at FUS, the risk of a UTI was 0% (0/75) (95% confidence interval (CI): 0-4.9%) after upper UTI versus 4% (1/26) (95% CI: 0.1-19.6%) after lower UTI (FE, $p = 0.2754$). The cost of requesting a FUS in patients without symptoms was 166 euro after treatment for upper UTI and 66 euro after treatment of lower UTI.

CONCLUSION: We do not recommend a FUS after treatment for UTI as the 95% CI of risk of missing UTI after treatment for upper UTI was below 5%. This strategy will save the patients/families and the health-care system. However, if a child has symptoms after treatment for UTI, it must be examined.

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TRIAL REGISTRATION: The study was approved by the Danish Data Protection Agency (J. no. 2007-58-0015).

During childhood, nearly 10% of girls and 3% of boys are treated at least once for urinary tract infection (UTI) [1]. UTI in children is divided into upper and lower UTI. Upper UTI can damage the kidneys and there is a risk of developing an elevated blood pressure, preeclampsia and end-stage renal disease [1-5]. Most data support the concept that delays in the treatment of pyelonephritis increase the risk of renal damage [1-7]. Congenital urological anomalies and other causes of incomplete bladder emptying increase the risk of UTI [1, 3-5].

The definition of UTI is based on significant bacteriuria and symptoms [1-5]. A child with upper UTI has a temperature above 38 °C and is clinically ill. Children younger than two years of age with upper UTI may have vague symptoms and no fever [1-5]. A child with cystitis has no fever and no general feeling of sickness, and is older than about two years of age [1].

Asymptomatic bacteriuria is bacteriuria without symptoms or leucocyturia, and treatment of the condition is not indicated [1-5].

After treatment for UTI, a routine follow-up urine sample (FUS) in the form of a midstream urine sample (MSU) is recommended according to the guideline for UTI in children by the Danish Paediatric Society [1] and the online guideline “Lægehåndbogen” published by Danish Regions [5].

Retrospective studies have not shown “proof of bacteriological cure” cultures to be beneficial [8, 9], and studies demonstrating that clinical response alone ensures bacteriological cure are not available [10]. The “American textbook of Pediatrics” states that a urine culture one week after treatment of a UTI is not routinely needed [4].

In Denmark, children treated for UTI are generally requested to deliver a FUS. The FUS procedure takes time for the patient/family and the health-care system, and it is costly, primarily in this sense.

In this study, we evaluated the benefits of FUS after treatment of UTI in children with a focus on patients without symptoms at the time they provided a FUS.

METHODS

Included were consecutive patients younger than 16.0 years of age who were treated for upper or lower UTI from 1 January 2009 to 31 December 2009 at the Department of Paediatrics, Hvidovre Hospital, in accordance with the guidelines of the department. These guidelines are in line with those published by the Danish Society of Paediatrics [1]. Patients were only included once, with their first possible episode.

Setting

Patients suspected of having upper UTI were treated intravenously with gentamicin and ampicillin for at least three days. Subsequently, oral antibiotics were given for

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! ABBREVIATIONS

CI = confidence interval
 cfu = colony-forming units
 FE = Fisher's exact test
 FUS = follow-up urine sample
 MAG3-renography = ^{99m}technetium-mercaptoacetyltriglycine scienti- and renography
 MSU = midstream urine samples
 MW = Mann-Whitney test
 SPA = suprapubic bladder aspiration
 UTI = urinary tract infection
 UPB = uropatogenic bacteria

at least 10 days in accordance with the resistance profile of the proven uropatogenic bacteria (UPB). The patients underwent ultrasonic examination of the kidneys and urinary tract and ^{99m}technetium-mercaptoacetyltriglycine scienti- and renography (MAG3-renography) to evaluate for urological anomalies.

Patients treated for lower UTI were given oral antibiotics for 3-10 days. The treatment was adjusted according to the resistance profile of the proven UPB. Urological examination included an ultrasonic examination of the kidneys and urinary tract; and in some cases of recurrent UTI, a MAG3-renography was also performed.

If further urological evaluation or treatment was indicated, the patients were referred to the Department of Paediatric Surgery, Rigshospitalet.

Excluded were patients who were not treated with antibiotics for UTI according to the described procedures and patients who had a catheterisation performed.

Microbiological analyses

All included patients had significant urine cultures described by the Department of Clinical Microbiology, Hvidovre Hospital. A significant urine culture was growth of at least 1,000 colony-forming units per ml (cfu/ml) of UPB in monoculture from a suprapubic bladder aspiration (SPA), or at least 10,000 cfu/ml of UPB in monoculture from 2 MSU taken within 24 hours.

All urine samples were collected before the patients received antibiotics. UPB included: *Escherichia coli*, *Klebsiella species*, other *Enterobacteriaceae*, *Enterococcus species*, *Staphylococcus saprophyticus*, haemolytic *Streptococci*, *Aerococcus species*, and *Pseudomonas aeruginosa*. The findings were reported according to the European guideline for urine analysis [11].

Follow-up urine samples

All patients were asked to return to the department with a FUS within 1-10 days, a maximum of 21 days, after finishing antibiotic treatment. At the time the FUS was provided, a nurse asked if the patient had symptoms that could be caused by a UTI or had any unspecific symptoms. A dipstick analysis of the FUS was done with Bayer Multistix 7; and the FUS underwent microbiological analysis if the dipstick was compatible with UTI, or "just to be sure".

As a FUS was only 1 MSU, significant growth was 100,000 cfu/ml of a UPB in monoculture. Furthermore, a doctor contacted the family if 10,000 cfu/ml of a UPB was exhibited to decide if antibiotic treatment or a new sample of urine was indicated or if no further procedures were necessary. For children younger than one year of age, the lower limit for contact was 1,000 cfu/ml. Contamination was polybacteria, i.e. more than 1 UPB, skin and genital flora, mixed flora or less than 10,000 cfu/ml of a UPB [12].

For patients who did not provide a FUS, we noted if they were being treated for UTI at the Department of Paediatrics or had a significant urine culture the Department of Clinical Microbiology during the following two months. If no new UTI was proven, the patients were categorised as being without symptoms at the time of providing the FUS.

Consequences of follow-up urine sample

At the time of the FUS, the patients were divided into those without symptoms and those with unspecific symptoms.

At the time of the microbiological result of the FUS and after contact to the patients if indicated, the pa-

TABLE 1

Data of 129 children treated for upper or lower urinary tract infection.

	Upper UTI	Lower UTI
Patients, total (girls/boys), n	87 (59/28)	42 (42/0)
Temperature, median (range), °C	38.7 (36.7-40.8)	36.9 (36.1-37.9)
Leucocyte concentration, median (range), × 10 ⁹ /l	16.7 (6.4-34.2) ^a	–
C-reactive protein concentration, median (range), mg/l	62 (6-248) ^a	–
Normal creatinine and urea level	All ^a	–
<i>Escherichia coli</i> , n		
2 MSU with ≥ 10.000 cfu/ml	77	37
In SPA	3	0
<i>Other uropatogenic bacteria</i> , n		
2 MSU with ≥ 10.000 cfu/ml	5	5
In SPA	2	0
Urological anomalies, including residual urine, phimosis and labia adhesions, % (n/N)	25 (22/87) ^b	43 (18/42) ^c

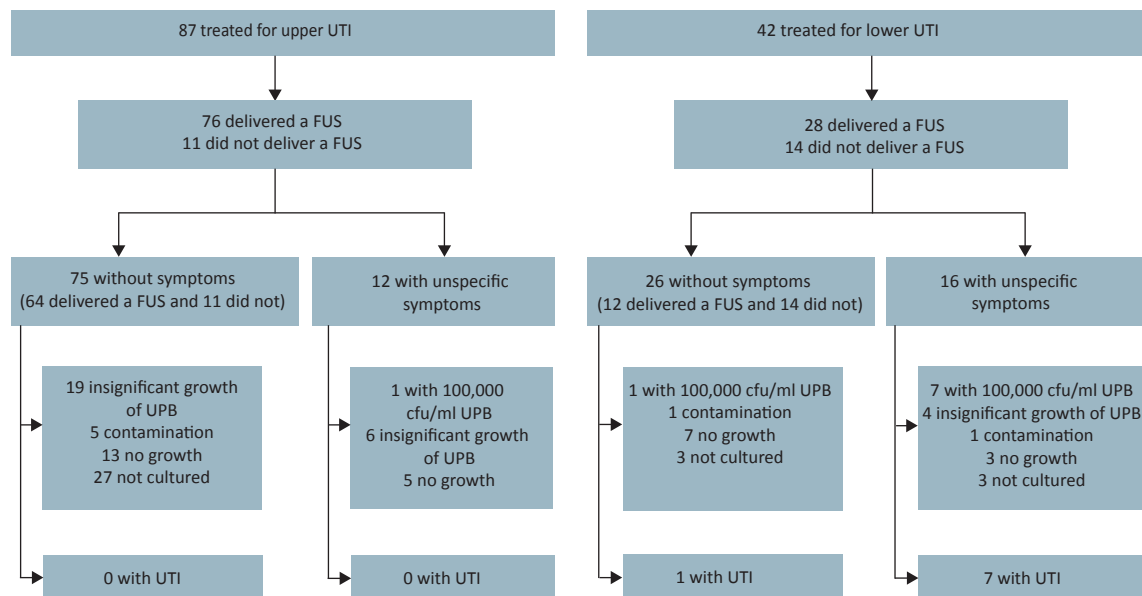
cfu = colony-forming units; MAG3-renography = ^{99m}technetium-mercaptoacetyltriglycine scienti- and renography; MSU = midstream urine samples; SPA = suprapubic bladder aspiration; UTI = urinary tract infection.

a) n = 82 patients.

b) n = 86 patients with renal and bladder ultrasound examination and 83 patients with MAG3-renography.

c) n = 38 patients with renal and bladder ultrasound examination and 30 patients with MAG3-renography.

FIGURE 1



The benefits of a follow-up urine sample among 129 patients treated for urinary tract infection at a department of paediatrics.

FUS = follow-up urine sample; UPB = uropatogenic bacteria; UTI = urinary tract infection.

tients were classified into those with no growth, bacteriuria or a new UTI.

In patients without symptoms at the time of the FUS, we studied the number of contacts between the patient/family and the department, and estimated the cost of the procedures. The diagnosis-related-group cost for an outpatient contact, including a microbiological analysis of a urine sample, was 172 euro for a child who was 0-6 years old and 109 euro for any patient who was at least seven years old. The cost of a telephone contact was 21 euro [13]. One euro is 7.5 DKK.

Statistics

Fisher's exact (FE) test and the Mann-Whitney (MW) test were used, two-sided and with a significance level of 0.05. Furthermore, 95% confidence intervals (CI) were given. IBM SPSS Statistics 19 was used for the analyses.

Trial registration: The study was approved by the Danish Data Protection Agency (J. no. 2007-58-0015).

RESULTS

We included 129 patients: 87 patients treated for upper UTI and 42 treated for lower UTI, **Table 1**. The median age of the patients treated for upper UTI was 1.1 years (range: 0.1-15.6 years). In 82 cases, it was their first upper UTI. The median age of the patients treated for lower UTI was 8.2 years (range: 2.5-15.3 years). In eight cases it was their first lower UTI.

A higher frequency of patients treated for an upper

than for a lower UTI provided a FUS, 87% (76/87) versus 67% (28/42), (FE, $p = 0.0127$), **Figure 1**. The patients treated for upper UTI with a FUS were a median 0.8 years (range: 0.1-15.4 years) younger than those without, median 2.0 years (range: 0.2-15.6 years) (MW, $p = 0.022$). In contrast, the patients with FUS did not differ from those without FUS in respect of sex, *E. coli* infection, first case of UTI, urological anomalies, temperature, leucocyte count and level of C-reactive protein.

At the time of the FUS, one patient treated for upper UTI and eight patients treated for lower UTI had been prescribed prophylactic antibiotics. The frequency of patients who had been prescribed antibiotics at the time of the FUS was the same for the patients with a FUS as for those without a FUS (FE, $p \geq 0.6969$).

Upper urinary tract infection

At the time of the FUS, 75 patients 86% (75/87) had no symptoms, and 12 patients had unspecific symptoms, **Figure 1**. No patient had specific symptoms of UTI, and therefore none underwent treatment for UTI at FUS.

The FUS from both groups were provided a median of 7 days (range: 1-21 days) after concluding their antibiotics (MW, $p = 0.4179$).

No new UTI was diagnosed, either among patients without symptoms 0% (0/75) or among patients with unspecific symptoms 0% (0/12), **Figure 1**. However, in the latter group, two patients had significant bacteriuria, but at the result of the FUS or the SPA taken after FUS, respectively, they had no symptoms and therefore did

 TABLE 2

Data on 101 patients without symptoms after treatment of a urinary tract infection.

	Upper UTI	Lower UTI
Patients, total (girls/boys), n	75 (51/24)	26 (26/0)
Patients who provided a FUS, contacts	64	12
Patients < 7.0 years of age who provided a FUS, n	53	6
FUS which underwent microbiological analysis, n	37	9
100,000 cfu/ml of UPB proven, and antibiotics were ordered once more, n (additional contacts)	–	1 (1)
No growth proven, no contact to the patient, n	13	7
Contamination proven, no contact to the patient, n	10	1
UPB proven, telephone contact to the patient, no further procedures, n (additional contacts)	7 (7)	0
UPB proven, subsequently MSU without growth, which was told to the family, n (additional contacts)	2 (6)	0
UPB proven, subsequently MSU with growth, telephone contact and subsequently SPA without growth, which was told to the family, n (additional contacts)	3 (15)	0
UPB proven, subsequently analysis of a SPA without growth, which was told to the family, n (additional contacts)	2 (6)	0
Contacts between the patients/families and the department even though the patient was healthy at time of FUS, total, n (contacts/patient)	98 (1.3)	13 (0.5)
Cost per patient who was healthy at time of FUS, euro	166	66

FUS = follow-up urine sample; MSU = midstream urine sample; SPA = suprapubic bladder aspiration; UPB = uropatogenic bacteria; UTI = urinary tract infection.

not fulfil the definition of UTI. The frequency of urological anomalies was 25% (19/75) among patients without symptoms after treatment for upper UTI; similarly, it was 25% (3/12) among patients with unspecific symptoms (FE, $p = 1$).

Lower urinary tract infection

At the time of the FUS, 26 patients 62% (26/42) had no symptoms, whereas 16 patients had unspecific symptoms, Figure 1. At this time, no patient had specific symptoms of UTI, and therefore none underwent treatment. There was a tendency that FUS from patients without symptoms were provided a little earlier than FUS from patients with unspecific symptoms, a median five days (range: 1-21 days) versus a median nine days (range: 2-19 days) after concluding antibiotics (MW, $p = 0.0891$).

Among patients without symptoms at FUS, one UTI 4% (1/26) was identified which was caused by another UPB than initially. At the time of the result of the FUS, she had developed symptoms of UTI. Among the patients with unspecific symptoms, seven cases of UTI were diagnosed, four cases with the same UPB, and three cases with another UPB. The risk of a new UTI was lower in patients without symptoms than in patients with symptoms, 4% (1/26) versus 44% (7/16) (FE, $p = 0.0053$).

All eight patients with a new UTI had a positive dip-

stick for leucocytes from the FUS and symptoms at time of the result. All eight patients had had recurrent UTI, five had incomplete bladder emptying, four had constipation, two had a low daily fluid intake and one girl had horseshoe kidney. The risk of urological anomalies was 63% (5/8) among patients with a new UTI, which was not different from 38% (13/34) in the other patients treated for lower UTI (FE, $p = 0.2562$).

The duration of antibiotic treatment was a median 7 days (range: 3-10 days) for the eight patients who received antibiotics again and for the rest of the patients (MW, $p = 0.9681$).

Risk of a new urinary tract infection

The risk of a new UVI was 0% (0/87) (95% CI: 0-4.2%) after treatment for upper UTI, which was lower than the risk after treatment for lower UTI 192% (8/42) (95% CI: 8.6-34.1%) (FE, $p < 0.0001$).

Similarly, the risk of unspecific symptoms after treatment for upper UTI was lower: 14% (12/87) versus 38% (16/42) (FE, $p = 0.0379$).

Cost of a follow-up urine sample in patients without symptoms

The number of contacts between the hospital and the patients/families and the cost are presented in Table 2.

DISCUSSION

The study shows that absence of symptoms after treatment for upper UTI was equivalent to bacteriological cure as no patient had a significant number of bacteria in the urine, and the 95% CI was below 5%. It has not previously been demonstrated that clinical response alone ensures bacteriological cure [10]. Now it is evidence-based to omit a FUS in children without symptoms after treatment for upper UTI. This will save time for the patients, their families and the health-care system; and consequently save money; about 166 euro per patient.

The study also found that after antibiotic treatment in accordance with the present guidelines, no patient fulfilled the diagnostic criteria of a new UTI (95% CI below 5%), and the risk of asymptomatic bacteriuria was 2.2% (95% CI below 8.1%). This is in accordance with previous studies [1, 8, 9], but it has been reported that after intravenous antibiotic treatment for upper UTI the risk for symptomatic UTI was 4.7% within the next month [14]. Recently, oral antibiotics have been suggested for upper UTI, unless the child has sepsis [2, 3, 14-16], is younger than 2 [3] or 3 months [2] or has abnormalities known to be associated with recurrent UTI [2, 3, 14-16]. After oral antibiotic treatment, close clinical follow-up monitoring is indicated [3]; and a urine-analysis should be performed in case of fever or relapse



A four-month-old boy who is under treatment for upper urinary tract infection. A follow-up urine sample is not indicated, but if he has symptoms after treatment he must be examined. The parents have accepted that the picture is presented. Photo: *Susanne Østergaard*, Hvidovre Hospital.

so that failure of treatment or recurrent UTI can be diagnosed and treated promptly [3]. If we also start treating upper UTI with oral antibiotics in Denmark, it is valuable to know Danish figures for recurrent UTI and asymptomatic bacteriuria after intravenous antibiotics for upper UTI. After treatment for lower UTI, we found a 34% risk of a new UTI among girls where 80% had had recurrent lower UTI. All the patients with a new UTI had had recurrent UTI. Previously, it was reported that after treatment for lower UTI, 1% had persisting bacteriuria, and 2% had recurrence of UTI within 30 days [17]. However, it is not dangerous for the child to have lower UTI [1, 4, 5]. Logically, it makes no sense to ask for FUS after treatment for lower UTI as FUS with significant bacteriuria and a patient without symptoms is a patient with asymptomatic bacteriuria. In these cases, antimicrobial treatment may do more harm than good [1, 3, 4, 18]. Even in infants, one study reported asymptomatic bacteriuria verified by SPA in 0.9% of the girls and in 2.5% of the boys [19]. Only two out of these 50 infants developed upper UTI within two weeks; the others remained free of symptoms [19]. Based on our study, we have stopped asking for FUS. This is in accordance with recent guidelines from the UK [2] and the US [3]. It is also in line with a Danish study, which reported that home routine urine sampling from healthy children with a high risk of UTI did not prevent the development of pyelonephritis [20].

CONCLUSION

We do not recommend FUS after treatment for UTI because if the child had no symptoms after treatment for upper UTI, there was also bacteriological cure. This changed strategy will save time for the patients/families and the health-care system. However, if a child has symptoms, including unspecific symptoms, after treatment for UTI, it is mandatory to examine for UTI. The importance of the latter recommendation may increase as the treatment of upper UTI is in some cases now undergoing a change from intravenous antibiotics and in-hospital care to oral antibiotics and outpatient care.

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