Prevalence of urinary tract infection in febrile infants

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Received - 22 December 2019 Initial Review - 19 January 2020 Accepted - 18 February 2020

ABSTRACT

Background: Urinary tract infection (UTI) is one of the most common bacterial infections in infancy, with a high risk of recurrence, and maybe an indicator of underlying urinary tract abnormality. It is often misdiagnosed due to irregular and unrelated symptomatology in the absence of directed screening. **Objectives:** The objectives of the study were to assess the feasibility of mid-stream clean catch method in infants for collecting a urine sample, compare the reliability of urinalysis in comparison with urine culture and to determine the prevalence of UTI among febrile infants in a rural setting. **Materials and Methods:** The study was conducted in a level-2 pediatric hospital involving 320 febrile infants attending the out-patient department from January 1, 2018, to June 30, 2018. Urine specimens were collected using midstream clean-catch urine (CCU) method and tested by urinalysis and culture. **Results:** Urine sample was successfully obtained by the CCU method in 320 (88.9%) out of 360 infants, of which only 8 (2.5%) showed contamination in culture. A total of 20 (6.25%) infants were culture positive for UTI. Only 14 (70%) of these showed positive urinalysis, while 17 (85%) of the culture-positive cases had a provisional diagnosis other than UTI. Further radiological examination revealed renal abnormalities in two out of six culture-positive infants who underwent subsequent studies. **Conclusion:** CCU method is reliable method for successful collection of urine and low contamination and can be used reliably in the absence of supra pubic aspiration/catheterization. Urinalysis lacks sensitivity in comparison with urine culture, necessitating the use of urine culture to diagnose/rule out UTI in infants. Culture-positive infants need to undergo a radiological examination to screen for abnormalities of the renal tract.

Key words: *Febrile infant, Urinalysis, Urinary tract infection, Urine culture*

Urinary tract infection (UTI) is one of the most common bacterial infections in infancy, yet its diagnosis remains elusive [1]. However, fever appears to be the most consistent symptom in infants with UTI, and urinary tract related symptoms such as increased frequency, dysuria, and pyuria may be entirely absent [2-10]. UTI may also be present when the source of fever, such as upper respiratory infection (URI) or gastroenteritis, is identified, additionally contributing to missed diagnoses in many cases [8,11]. Early diagnosis is crucial in infants to minimize pyelonephritis and prevent renal scarring, in addition to identifying risk factors such as vesicoureteric reflux (VUR) and congenital abnormalities to prevent recurrence [5]. If untreated, UTI will lead to hypertension, uremia, renal scars, and end-stage renal failure [7-9].

Microscopic urine analysis for leukocytes and bacteria is often used as a diagnostic tool for UTI, sometimes as an alternative or precursor to urine culture [12]. However, the sensitivity and specificity of this test are highly questionable [8,13]. Consequently, several guidelines require a positive urine culture to diagnose UTI [12,14]. However, urinalysis may be preferred to screen for UTI due to a lack of laboratory facilities and/or time delay of culture results. To the best of our knowledge, there is no study comparing the efficacy of these diagnostic techniques in a non-medical college hospital or non-urban Indian context.

Suprapubic aspiration or urethral catheterization are the recommended methods to collect urine specimens for culture in non-continent infants [3,12,14]. However, these procedures may be viewed as too invasive and unfeasible by physicians and parents, especially in a rural setting. Alternatively, most infants are non-toxic, allowing for urine collection by void midstream clean-catch urine (CCU) method [1]. However, there are large differences in the reported diagnostic yield of urine collected using the CCU method, with regard to the success rate of urine collection and contamination of the urine specimen [15-17].

The present study was conducted to assess the feasibility of CCU method in infants for collecting urine sample, compare the reliability of urinalysis in comparison with urine culture, and to determine the prevalence of UTI among febrile infants in a rural setting.

MATERIALS AND METHODS

This was a prospective observational study conducted between January 1, 2018, and June 30, 2018, in the out-patient department (OPD) of a level-2, 25 bedded pediatric hospital catering mainly rural and low socioeconomic status population. Infants were recruited at the time of their first visit for fever by convenience sampling. Any febrile infant with an axillary temperature of >100°F or 37.8°C irrespective of provisional diagnosis was included in the study. Febrile infants who had received antibiotics before attending OPD and those requiring admission, intensive care therapy and/or immediate antibiotics in cases of pyogenic meningitis, severe pneumonia, shock, status epilepticus, etc., were excluded from the study.

A detailed history was obtained with special emphasis on urinary symptoms such as increased frequency, crying while voiding, and pyuria. Complete general and systemic examinations were also done with attention to urological findings such as phimosis, vulval synechiae, suprapubic mass, renal mass, dysmorphic features, and other associated congenital anomalies [14]. A provisional diagnosis was made mainly based on presenting signs and symptoms.

Mothers were trained through verbal instructions to collect urine using the CCU method in a sterile bottle. They were asked to clean the perineum with clean water, breastfeed the baby frequently, and apply mild pressure over the suprapubic area every 15 min [13]. In routine urine analysis, urine microscopy was done using uncentrifuged urine. An observation of more than 5 pus cells/high power field (HPF) was the threshold for pyuria, a positive diagnosis of UTI [18]. For urine culture, the urine specimen was inoculated for culture in MacConkey culture media using the standard loop technique. The average time from urine collection to inoculation was 30 min. UTI was diagnosed only when a single uropathogen with CFU $\geq 10^5$/mL was present, designated as significant growth [14]. Growth of uncommon organisms, such as staphylococcus, pseudomonas, and Citrobacter, and growth of multiple organisms were considered a sign of urine sample contamination [19]. The culture-positive cases were tested for sensitivity by inoculating in nutrient agar and using combined Gram-negative microbial sensitivity disks for UTI.

In culture-proven infants, further investigations such as abdominal ultrasonogram (USG), micturating cystourethrogram (MCU), and isotope scan studies were advised to know the underlying anomalies of the renal tract. These infants were treated with appropriate antibiotics for 10 days and were asked to continue with prophylactic medications until all the imaging studies were over.

Data were entered into MS-Excel and later exported to SPSS Version 23. Results are presented in terms of frequencies and percentages. Chi-square test was used to test the association between variables. The study was conducted in conformation with the Declaration of Helsinki. Informed written consent was obtained from the parents/guardian of the febrile infants at the time of recruitment.

RESULTS

A total of 748 febrile infants <1-year-old attended the OPD during the study period. Of these, 290 had received antibiotics before the visit, 26 infants had severe illnesses, and 72 parents refused to enroll the child. Of the 360 eligible infants, 320 mothers were successful in collecting the CCU specimen, 18 mothers missed (voided and not caught), and 22 stopped the procedure as they could not wait for a longer period to collect the mid-stream urine. The mean time to collect urine was approximately 75 min; few mothers tried for as long as 4 h to collect a urine sample. Of the 320 infants included further in the study, 186 (58.1%) were males and 134 (41.9%) were females with a male to female ratio of 1.39:1. A total of 184 (57.5%) infants were 0–6 months old, and 136 (42.5%) were 6–12 months old.

The maximum temperature recorded was 103°F. Provisional diagnoses of URI were made in 104 infants, bronchiolitis in 62, gastroenteritis in 44, septicemia in 16, UTI in 9, short-duration fever without focus in 8, viral fever in 31, lower respiratory infection in 8, and bacillary dysentery in 5 infants. A total of 33 infants had other different type of illnesses with a frequency of < 5. None of the patients had icterus, mass per abdomen, external congenital anomaly, or dysmorphic features.

Out of 320 infants, urine culture showed significant growth of a single uropathogen in 20 infants, while 292 infants had no growth and 8 showed contaminations (growth of multiple/unusual organisms). Urinalysis was positive for pyuria (>5 pus cells/HPF) in 14 infants and six had below threshold pus cells (<5 pus cells/HPF). Notably, six infants with <5 pus cells/HPF tested positive on urine culture and none of the culture-negative patients had >5 pus cells/HPF. The prevalence of UTI was 6.25% among febrile infants. The mean age of culture-positive infants was 0.8±0.1 months. Of the culture-positive infants, 13 (6.98%) were males and 7 (5.22%) were females. There was no association between the age and sex of the febrile infants in causing UTI.

Using the CCU method, urine specimen was collected in 320 (88.9%) out of a total of 360 infants in which the method was attempted for urine sampling. Contamination was observed in only 8 (2.5%), out of 320 urine specimens collected. Table 1 shows various diagnoses in urine culture-positive febrile infants. Gastroenteritis was the most common illness, observed in six infants. *Escherichia coli* was the most common isolated organism in 18 (90%), followed by *Klebsiella* in 1 (5%) and Proteus in 1 (5%) patient.

Aminoglycosides, amikacin in 19 (95%) and gentamycin in 8 (40%), and fluoroquinolones, ofloxacin in 15 (75%) and norfloxacin in 12 (60%), showed the highest sensitivity in culture. All 20 organisms (100%) showed resistance to cefotaxime and co-trimoxazole, while only 2 (10%) were sensitive to ceftriaxone and cefixime each (Table 2). One patient with growth of amikacin resistant *E. coli* presented with recurrent fever, failure to thrive, and Grade III protein-energy malnutrition. Only six patients underwent abdominal USG. One had left-sided hydronephrosis with pelviureteric junction (PUJ) obstruction; DTPA scintigraphy showed a 30% reduction in the

Table 1: Various diagnosis in urine culture-positive febrile infants

Provisional diagnosis	Number	Percentage
Gastroenteritis	6	30
Fever without focus	5	25
Upper respiratory infection	3	15
Urinary tract infections	3	15
Septicemia	2	10
Bronchiolitis	1	5

Table 2: Antibiotic sensitivity of organisms growing urine culture samples

Antibiotic	Number	Percentage
Amikacin	19	95
Ofloxacin	15	75
Norfloxacin	12	60
Gentamycin	08	40
Nitrofurantoin	03	15
Nalidixic acid	03	15
Ceftriaxone	02	10
Cefixime	02	10
Cefotaxime	0	0
Co-trimoxazole	0	0

function of his left renal cortex. Another infant had Grade-2 VUR. Nobody underwent MCU.

DISCUSSION

In the present study, the prevalence of UTI was 6.25%, based on urine culture. These results compare favorably to the wide prevalence range, 2.48%–10.78%, observed in the other studies [6,8,9,16]. Only 14 of the 20 culture-positive patients were positive on urinalysis, even though sub-threshold (5 pus cells/HPF) pus cells were observed in the remaining six patients. The prevalence was not significantly different across gender or age (0–6 months and 6–12 months). While urinalysis had a high negative predictive value relative to urine culture (98% for pyuria, and 100% when <5 pus cells/HPF were included), its positive predictive value (70%) was unreliable. A negative urine culture is required to rule out UTI, since urinalysis is unreliable [3,13,20,21].

The culture-positive infants had a myriad of provisional diagnoses, with 17 (85%) having a provisional diagnosis other than UTI. Gastroenteritis and fever were the most common provisional diagnoses. Notably, 5 (60%) out of 8 cases of fever without focus were culture positive, warranting increased suspicion for UTI as a cause of fever without focus. These results were in accordance with the study by Indian Society of Pediatric Nephrology *et al*. (ISPN) [14]. Similarly, diarrhea has been shown to be a significant risk factor for UTI, even though the infections may be unrelated, as reported by Fallahzadeh and Ghane [21].

As shown in the present study, UTI is most likely to go unnoticed in the absence of directed testing for UTI, and a missed diagnosis rate of 30% even when the only urinalysis is used. Therefore, urine culture is ideally necessary to diagnose/rule out UTI. A cost-effective measure in resource-constricted contexts for centers and parents would be to follow the presence of pus cells in urinalysis, especially below the diagnostic threshold, with urine culture, as endorsed by AAP in 2016 [12].

Due to the laboratory cost, lack of skilled personnel, and/or high patient burden in Indian health care facilities, urethral catheterization or suprapubic aspiration is not widely used in non-tertiary care centers for being too invasive and unfeasible, especially for a disease for which clinical symptoms have low predictive value [1,19]. However, CCU specimens do not require professional skills and can be collected by the parent. Out of 360 attempts for CCU collection, successful samples were acquired from 320 (88.9%) infants and 8 (2.5%) yielded mixed/contaminated growth. Tosif *et al*. observed a markedly high contamination rate of 52% in females and 33% in males looking at children <3 years, while Ho *et al*. observed a low rate of 4.5% contamination [15,16]. Ho *et al*. disinfected the perineum before the CCU specimen collection [15]. The high success rate and low contamination observed here may be dedicated to effective parent counseling, with specific attention to the handling of the specimen and the containing jar, indicating the importance of parental engagement to aid clinical efforts.

Almost all, 19 (95%) of the organisms were sensitive to amikacin and majority to ofloxacin and norfloxacin. Only 10% sensitivity to cefixime and ceftriaxone and 100% resistance to cotrimoxazole and cefotaxime were observed. This could be a result of widespread antibiotic usage, leading to recent surge in extended-spectrum beta-lactamase microorganisms. Amikacin was the most effective against Gram-negative micro-organisms, and this was also reported in earlier studies by Hernández *et al*. and Madhi *et al*. [22,23]. Amikacin has low nephrotoxicity and extended interval dosing is essential in infants with UTI [24]. ISPN guidelines recommend initiating antibiotic therapy on diagnosis, with the choice of antibiotic based on regional sensitivity patterns, and altering the antibiotic if necessary when the sensitivity data are available [14].

Complete radiological evaluation was advised in all the infants with UTI. Out of six infants who underwent abdominal USG, two (33%) showed underlying renal/upper urinary tract abnormality, one had hydronephrosis with PUJ obstruction and reduced function of the left renal cortex, and another infant had Grade-2 VUR. Most of the parents were unwilling to undergo the procedure due to financial incapacity and an intertwined lack of concern for the potential long-term consequences of UTI, underlining the necessity of counseling and advocacy, financial, and informational, in such situations. ISPN guidelines recommend radiological screening for renal abnormalities on the first episode of UTI in infants <1 year of age. Following these guidelines, Sinha *et al*. found significant abnormalities in 63% of children, where the sample was composed of infants <1-year-old with first episode UTI and <5 years with recurrent UTI [25]. Further research is needed to confirm the true incidence of scarring,

with a focus on follow-up of up to 2 years as recommended by Ditchfield *et al*. [26].

The present study had a few limitations. Infants with very severe illnesses were excluded from the study as they required immediate intensive care treatment rather than wasting time in the collection of urine by midstream method. Urine culture was not done in blood agar to reduce the cost of urine culture. We could not gather data to analyze renal damage in the culture-positive infants, due to lack of follow-up.

CONCLUSION

Urinalysis is unreliable due to its low positive predictive value, making urine culture a necessary step in UTI screening and diagnosis. CCU method is sufficiently reliable to collect urine specimen in non-continent infants when suprapubic aspiration or urethral catheterization is not feasible. Amikacin is the most effective antibiotic. Renal damage is notably coprevalent with UTI, making radiological screening imperative in culture-positive infants.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Marol R, Marol R, Marol R. Prevalence of urinary tract infection in febrile infants. Indian J Child Health. 2020; 7(2):85-88.

Doi: 10.32677/IJCH.2020.v07.i02.012