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Original Article

Urinalysis as a diagnostic tool for febrile urinary tract infection in children aged 2 months - 2 years

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Abstract

Background Children aged 2 months to 2 years with febrile urinary tract infection (UTI) need special attention considering kidney complications, unspecified symptoms, and difficult urine sample collection. Urinalysis was the main supportive examination for UTI because of its immediate result and widespread availability.

Objective To estimate urine nitrite, leukocyte esterase (LE), leucocyturia, bacteriuria, and their combinations as a diagnostic tool for febrile UTI in children aged 2 months to 2 years.

Methods This is a diagnostic study held in Cipto Mangunkusumo Hospital, Tangerang General Hospital, Fatmawati Hospital, and Budhi Asih Hospital, involving 75 children aged 2 months to 2 years. Urine samples for urinalysis and urine culture were collected using urine collector in all subjects. Clinical pathologists who performed urine culture, did not know the results of urinalysis.

Results By parallel test analyses, we found that the best diagnostic value was the combination of 3 tests (LE, leucocyturia, and bacteriuria). This combination test showed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-) of 69%, 95%, 85%, 88%, 13.1, and 0.3.

Conclusion The combination test of LE, leucocyturia, and bacteriuria shows high specificity, NPV, and LR+. Therefore, the negative results of these 3 tests in combination can be used to rule out UTI. **[Paediatr Indones. 2014;54:100-8.]**

Keywords: *urinalysis, diagnostic study, febrile, urinary tract infection, children*

Urinary tract infection (UTI) is a common infection in infants and children. Moreover, UTI become the second most common cause of fever in infants and children. The prevalence of febrile UTI in children aged 2 months to 2 years in developing countries (48-64%) is almost 10 times higher than in developed countries (2-8%).[1-5]

Children aged 2 months to 2 years suffering from febrile UTI need special attention because they have the greatest risk of kidney damage (renal scarring, hypertension, and kidney failure),[6,7] they do not exert typical urinary tract clinical signs and symptoms , and it is difficult to collect the urine sample (non-toilet trained children). The most common symptom of acute pyelonephritis is acute fever without a clear focus infection. The process of collecting urine samples in infants and children is a challenge, because in practice, it is not easy and it often causes discomfort for children below 2 years of age.[8,9]

Urine culture is the gold standard in the diagnosis of UTI, but culture results are not available in the first 24 hours, so we need another faster investigation to confirm UTI. Standard urinalysis is a

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major investigation in UTI as it provides an immediate result and available in laboratories throughout the area, which is expected to be a breakthrough for the prediction of UTI. Urinalysis components that have a high diagnostic value is the biochemical analysis using test strips, such as nitrite and leukocyte esterase (LE), and microscopic examination of urine for lecocytes and bacteria.[8,9]

Based on the above studies, it appears the prevalence of febrile UTI is very high and this may contribute to the increased morbidity of UTI among children aged 2 months to 2 years. Various studies have demonstrated the role of urinalysis in detecting UTI in children, particularly for the age group of 2 months to 2 years, but those studies used a retrospective study design and there has not been a recent study about this.[8-14] To date,there has been no study examining the urinalysis diagnostic test of febrile UTI in children aged 2 months to 2 years in Indonesia. To that end, the data of the profile and urinalysis diagnostic test in febrile UTI is very necessary for early diagnosis and prompt treatment.

Methods

We performed a diagnostic study between July-September 2013 to determine the diagnostic value of urine nitrite, LE, leucocytes, bacteria tests, and their combinations on suspected UTI patients, compared to urine culture as the gold standard. Subjects were obtained by conducting consecutive sampling and include 75 children with possible UTI, aged 2 months to 2 years. Subjects were treated in Dr Cipto Mangunkusumo Hospital (RSCM), Tangerang General Hospital, Fatmawati Hospital, and Budhi Asih Hospital as inpatients or outpatients. Inclusion criteria are fever with unknown origin (more than or 39^0C), fever more than 2 days (without acute respiratory infection, acute otitis media, central nervous system infection, or measles), and no history of antimicrobial consumption in the past week. Exclusion criteria are immunocompromised state and urinary tract abnormalities. Based on UTI prevalence data, we calculated the minimum sample size required in our study to be 75 subjects.

Urinalysis was performed in the Department of Clinical Pathology, RSCM, and the branches of Prodia Laboratory nearby Tangerang General Hospital, Fatmawati Hospital, and Budhi Asih Hospital. Urine specimens were collected using urine collector. In this study, to avoid contamination, the genital area is cleaned from cranial to caudal use *Savlon*® and rinsed with water and then allowed to dry. After urine sample is already collected in the bag, urine collector soon be released, and immediately sent to the lab. Examination of urine leucocytes and bacteria was performed by centrifugation followed by microscopic examintaion. Leucocytes were counted per high power field (HPF) and considered positive for UTI if the number of leucocyte cells was ≥ 5 cells/HPF. Bacteria were considered positive for UTI if bacteria were found in urine sediment. Dipstick urine test was used to measure the levels of nitrites and LE visually, and the results are compared to the reference colors on the box. Any color change indicated a positive result. Urine culture was performed with Mac Conkey and blood agar, with cultures incubated at 37^0C and examined after 24-48 hours. The number of bacterial colonies was counted. Positive UTI was indicated by presence of a single colony with ≥ 10^5 colony forming unit/mL (CFU/mL). Clinical pathologists who performed urine culture, did not know the results of urinalysis. This study was approved by the Medical Ethics Committee of University of Indonesia and Fatmawati Hospital.

Results

Seventy five children aged 2 months – 2 years involved in this study were admitted in 4 hospitals, as can be seen in **Figure 1**.

In this study, the prevalence of febrile UTI was 33%. The girls to boys ratio of UTI incidence was 1.3:1. No children have nutritional status of overweight nor obesity. The mean and median age of our UTI children in a row was 10.6 (SD 6.2) months and 8 months. Baseline characteristics of subjects suspected of having UTIs are shown in **Table 1.**

Clinical manifestations of UTI in children aged 2 months to 2 years were based on history and physical examination. Our UTI children mostly experienced fever <5 days (35%) accompanied by irritability (34%), decreased appetite (29%),

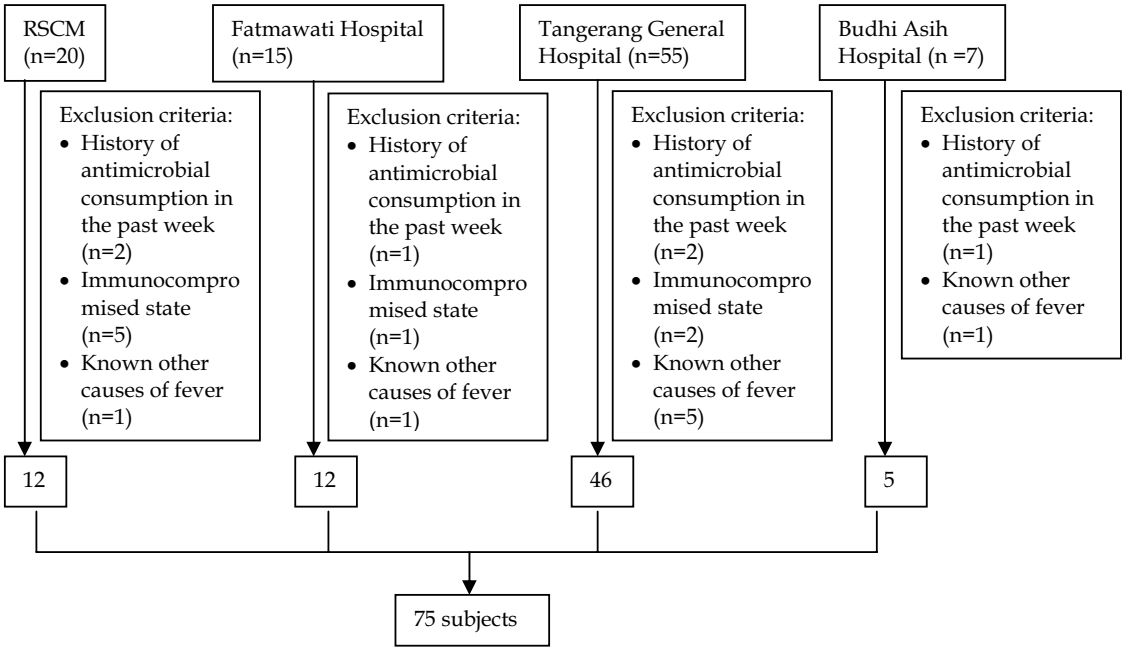

Figure 1. Flow-chart of subjects recruitment

Table 1. Baseline characteristics of study subjects

Characteristics	UTI (n=25) n	Not UTI (n=50) n,%
Gender, n		
Boys	13	31 (62)
Girls	12	19 (38)
Age, n		
≥2 months–1 years	9	25 (50)
1–2 years	16	25 (50)
Nutritional status		
Undernourished	9	11 (22)
Well-nourished	16	39 (78)
Urine culture results		
Single colony with < 10^5 CFU/mL	25	11 (22)
Multiple colonies with ≥ 10^5 CFU/mL	-	13 (26)
Sterile	-	26 (52)

diarrhea (27%), and vomiting (27%). All male subjects have not been conducted circumcision. Specific clinical manifestations on urinary tract, such as crying during urination, dribbling urination, and reddish external urethral orifice (EUO) found only in a minority of patients. Vulvar synechiae was not found on physical examination in all subjects. Clinical manifestations of UTI in our participants can be seen in **Table 2.**

There were 25 children with meaningful culture results, that is the number of a single bacteria colony with ≥10^5 CFU/mL, using urine bag as the collection method. Most bacteria found were *Escherichia coli* (17/25). Whereas contaminant culture results in this study contained 11 subjects with urine culture results only grows single bacteria with <10^5 CFU/mL and 13 subjects with multiple pathogens with the number of each ≥10^5 CFU/mL. The results of urine cultures can be found in **Table 3.** Diagnostic value of urinalysis components that include urine nitrite, LE, leucocyturia, or bacteriuria, and the combined results are presented in **Table 4**.

Table 2. Clinical manifestations of UTI

Clinical manifestations	UTI (n=25) n	Not UTI (n=50) n, (%)
History		
Fever <5 days	19	35 (70)
>5 days	6	15 (30)
Vomiting	11	30 (85.7)
Diarrhea	13	35 (70)
Decreased appetite	14	35 (70)
Irritability	19	38 (76)
Cry during urination	4	2 (4)
Dribbled urine	4	2 (4)
Failure to thrive	0	4 (8)
Foul smell urine	0	1 (2)
Other symptoms*	4	11 (22)
Physical examination#		
Temperature ≥40°C	4	37 (74)
Temperature ≥39-<40°C	21	13 (26)
Look severe illness	3	2 (4)
Look moderate illness	22	42 (84)
Look mild illness	0	6 (12)
Phymosis	5	13 (26)
Reddish *orificium urethrae externum*	8	17 (34)

* Other symptoms in history include bloating (1 subject), febrile seizure (2 subjects), and urticaria (1 subject).
# One children can have one or more signs and symptoms

Table 3. Urine culture results

Bacterial types	Single colony ≥10^5 CFU/mL (n=25)	Single colony <10^5CFU/mL (n=11)	Multiple* colonies ≥10^5CFU/mL (n=13)
Escherichia coli	17	1	5
Enterococcus sp	4	3	2
Klebsiella pneumoniae	2	1	3
Staphylococcushaemolyticus	1	1	3
Staphylococcus epidermidis	1	2	3
Candida sp	0	2	0
Enterobacter aerogenes	0	1	2

* Urine culture results can have two or more colonies
CFU = *colony forming unit*

Table 4. Diagnostic value of urinalysis components and their combinations

Urinalysis components	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	NPV (95% CI) (%)	LR+ (95% CI)	LR- (95% CI)
Nitrite	24 (12-43)	94 (84-98)	66 (35-88)	71 (59-80)	4 (1.1-14.6)	0.8 (0.6-1)
LE	68 (48-83)	80 (67-89)	63 (44-78)	83 (70-91)	3.4 (1.8-6.3)	0.4 (0.2-0.7)
Leucocyturia	56 (37-73)	86 (73-93)	66 (45-83)	79 (67-88)	4 (1.8-8.6)	0.5 (0.3-0.8)
Bacteriuria	52 (34-70)	90 (79-96)	72 (49-88)	79 (67-88)	5.2 (2.1-12.9)	0.5 (0.3-0.8)
Nitrite and LE	43 (21-67)	95 (84-99)	75 (40-93)	83 (70-91)	8.8 (2-38.6)	0.6 (0.38-0.9)
Leucocyturia and bacteriuria	55 (34-74)	93 (82-98)	78 (52-92)	82 (69-90)	8 (2.5-25.7)	0.4 (0.3-0.8)
Nitrite and leucocyturia	33 (16-56)	94 (83-98)	67 (35-88)	78 (66-87)	5.2 (1.5-18.6)	0.7 (0.5-1)
Nitrite and bacteriuria	39 (20-61)	94 (82-98)	70 (40-89)	80 (67-88)	5.9 (1.7-20.5)	0.6 (0.4-0.9)
LE and leucocyturia	70 (47-87)	90 (78-96)	75 (50-90)	88 (76-95)	7.6 (2.8-20.3)	0.3 (0.1-0.7)
LE and bacteriuria	75 (50-90)	92 (80-97)	80 (55-93)	90 (77-96)	9.8 (3.2-30)	0.3 (0.1-6.3)
Nitrite, LE, and leucocyturia	46 (23-70)	95 (84-98)	75 (40-93)	85 (72-92)	9.5 (2.2-41.3)	0.6 (0.3-0.9)
Nitrite, LE, and bacteriuria	50 (25-75)	95 (83-98)	75 (41-93)	86 (72-93)	9.5 (2.2-41)	0.5 (0.3-0.9)
Nitrite, leucocyturia, and bacteriuria	40 (20-64)	93 (82-98)	67 (35-88)	82 (69-90)	5.8 (1.7-20.6)	0.6 (0.4-1)
LE, leucocyturia, and bacteriuria	69 (44-86)	95 (83-98)	85 (58-96)	88 (75-95)	13.1 (3.3-52.4)	0.3 (0.2-0.7)
Nitrite, LE, leucocyturia, and bacteriuria	54 (28-78)	95 (83-99)	75 (41-93)	88 (75-95)	10.3 (2.4-44.3)	0.5 (0.3-0.9)

Discussion

Prevalence of UTI in this study was 33%. The prevalence of febrile UTI in infants aged 2 months to 2 years have been reported in previous studies, with varying results because of differences in urine sampling methods. Several studies using a urinary catheter and clean-catch urine as a sampling method shows a smaller prevalence of UTI (5-15%)[9,10,13] compared to our study, as the methods pose a smaller risk of contamination when compared to the urine collector used in our study. The girls to boys ratio of UTI in our study was 1.3:1, which was similar to previous study in RSCM (1:1).[2]

The most common etiology of UTI in our study was *Escherichia coli*. Other causative bacterias were *Enterococcus sp., Klebsiella pneumoniae, Staphylococcus haemolyticus,* and *Staphylococcus epidermidis.* Several other studies have concluded that *Escherichia coli* is the most common cause of the first febrile UTI, up to 60-80%.[15,16] *Escherichia coli* are found in the stools, especially the stools in diapers.[17] Stools in diapers are attached in perineum and cause UTI by ascending infection.[17] Therefore, genital hygiene is an important factor that must be considered for the prevention of UTI in children. Distributions of types of germs that are meaningful and not meaningful in this study are similar with several previousstudies.[4,10] *Candida sp.* found in the urine culture results was not significant in this study. *Candida sp.* often found in patients with immunocompromise, which has received prior antibiotic therapy, critically ill, or even in patients who use urinary catheters for a long period. *Klebsiella sp.* and *Enterobacter sp.* are gram-negative bacteria that cause UTIs. Those bacterias are very rare and usually associated with abnormalities of the urinary tract or urinary catheter usage. Urinary tract infections caused by *Staphylococcus sp.* often becomes secondary to systemic infection in children.[18]

Urinary tract infections in infants aged 2 months to 2 years often occur without obvious clinical manifestations, and fever may be the only symptom.[8,19] In addition to fever, four clinical symptoms commonly found in our study are irritable, decreased appetite, diarrhea, and vomiting. Several previous studies also showed the same result with our study, that urinary tract complains were rarely found, such as crying when urinating, dribbling urination, and foul smelly urine.[2,20-29] Clinicians should consider the possibility of a diagnosis of UTI in children under 2 years who have symptoms of fever of unknown origin.[8,19] Some literatures state that in addition to fever above 39^0c, physical examination in children aged 2 months to 2 years with UTI is often not accompanied by other abnormalities.[20-28] Abnormalities that may be found is pain in costovertebral angle, kidney enlargement, palpable bladder, palpable skibala, vulvitis, foreign body irritation, balanitis, urethral stricture, phimosis and adhesions of the labia. Our study also showed no significant specific abnormalities on physical and genital examination in our subjects.

This study suggests nitrite test had the highest specificity (94%) and the lowest sensitivity (24%) compared to other components of urinalysis. These results are consistent with the previous studies using urinary catheters and clean voided urine (CVU) on sample collection methods. Nitrite test showed the highest specificity of 98% [25] and 83.4% [14] but the lowest sensitivity of 53% [25] and 42.5%.[14]

The following are some of the circumstances that can lead to false-negative nitrite test: as urine is in the bladder less than 4 hours, because the subject is dehydrated, or urine samples had higher levels of ascorbic acid.[45] The possibility of urine samples had high levels of ascorbic acid not rated, but the urine is in the bladder less than 4 hours and the possibility of subjects dehydrated very likely to occur in this study. In accordance with the literature that children often empty their bladder, so that the conversion of nitrate to nitrite by bacteria does not happened.[11,12] Clinical dehydration on our subject is likely to occur due to high fever resulting in decreased food intake, as well as evidenced by the specific gravity (SG) urine on urinalysis research subjects (> 1.030).

This study shows the leucocyter esterase (LE) test has the highest sensitivity of 68% and the lowest specificity of 80% when compared to other components of urinalysis. These results are consistent with previous studies using urinary catheters and CVU at the sample collection method, that is the value of EL test achieves the highest sensitivity of 83% [25] and 87.18% [14] and the lowest value of specificity of 78% [25] and 61.32%.[14] The use of the preservative formaldehyde and the contamination due to vaginal discharges may cause the false-positive findings on LE test.[45] In this study, urine samples do not use preservatives, but the possibility of

contamination can still occur even when the anogenital area has already been cleaned previously with *Savlon®*. False negative findings of LE test can occur when high urine glucose levels are more than 500 mg /dL, high urinary protein of more than 300 mg /dL, high urine specific gravity, high levels of oxalic acid, and urine containing antibiotics, such as cephaloxin, cephalotin, and tetracycline. In this study, dehydrated subjects were very likely to occur, although other factors, namely glucose levels and urine protein in urine samples of this study are negative / normal. Oxalic acid levels in the urine were not assessed in this study. Subjects who had previous antibiotic therapy had been excluded in this study.

This study shows leucocyturia test has sensitivity and specificity that similar to a previous study using a urinary catheter for urine sample collection methods. Leucocyturia test alone showed bad sensitivity and specificity values.[25] False positive findings on leucocyturia test may occur in fever, dehydration, stress, and leukemia.[45] Lecocytes in the urine can also be a contaminant of urogenital tract, such as infections of the vagina and cervix, or the external urethral meatus in boys.[45] False-negative findings on leucocyturia test can be found in some of the following circumstances: contaminated urine specimen, insensitive criteria of leucocyturia, and asymptomatic bacteriuria.[12] In this study, all study subjects had a fever. Contamination of the urogenital tract is likely to occur because the urine sampling method is using a urine collector, although previously the urogenital area was cleaned. Meaningful leucocyturia criteria used in this study is similar to the commonly used criteria by other studies (lecocytes >5/HPF).[15] There is no criteria for asymptomatic bacteriuria in this study.

This study shows a bacteriuria test has sensitivity and specificity similar to a previous study using a urinary catheter for urine sample collection methods. Bacteriuria test alone showed bad sensitivity and specificity values.[25] False-positive findings on microscopic bacterial urine test may occur due to contaminants in the container, fecal contamination, and the urine which is left stale. Therefore urine collection should be done in proper way.[45] This study uses urine collector as urine sampling method, after the genital area is cleaned with *Savlon®*, it can reduce fecal contamination. Contaminants from the container (the tube of urine culture) cannot be avoided even if it is assumed that the tube urine culture is sterile. Urine samples in this study were not left long (stale), because it is immediately sent to the laboratory. The state of immunocompromised such as leukemia has been excluded in this study.

When compared with other studies that subject criteria include older children, it shows the opposite result. The combined results of three tests, which is the combination of LE, leucocyturia, and bacteriuria in this study resulted in sensitivity of 46% and specificity of 95%. While the results of other study[48] on the combined results of the test in children aged 2 months through 18 years had a 95% sensitivity and 59% specificity. This is because the older children have typical symptoms in the urinary tract and urine sampling is easier to do (toilet-trained children). Therefore, negative urinalysis results in children with younger age can rule out the possibility of UTI.

In this study, the combined test of urinalysis components that has the best diagnostic value is a combination of the results of LE, leucocyturia, and bacteriuria. Those tests have high specificity but low sensitivity for the diagnosis of UTI. Therefore, a negative result in all three tests can be used to rule out the possibility of UTI. The combined results of urinalysis components can be used as a diagnostic tool for febrile UTI better than one component urinalysis test in children aged 2 months through 2 years because it has the highest specificity, NPV, and LR+ of more than 10. Sensitivity and specificity, when compared with PPV and NPV, is referred to as a stable value of a diagnostic tool, because these values do not change with the prevalence of a disease. Another study using the clean void urine and urinary catheter as a method of sampling also get a high specificity for the combined results of urinalysis components, namely 92%[10] and 97 %.[9]

Urine collector is used as a method of collecting urine samples in this study, because of practical, easy to use, and relatively inexpensive, but there is the potential for bacterial contamination. In this study, to avoid contamination, the genital area is cleaned from cranial to caudal use *Savlon®* and rinsed with water and then allowed to dry. After urine sample is already collected in the bag, urine collector soon be released, and immediately sent to the lab. Other research suggests that contamination in the urine can be avoided if the urine sample was collected in a sterile and interpreted carefully.[30]

Another research needs to be done using suprapubic aspiration for the sampling method to reduce the false positive values due to bacterial contamination. Our study suggests to check a urinalysis in order to rule out UTI in children aged 2 months through 2 years with fever as the main symptom, so that the urine culture and UTI's therapy is not necessary in children with normal urinalysis.

We conclude that the combination test of LE, leucocyturia, and bacteriuria has high specificity, NPV, and LR+. Therefore, the negative results of these 3 tests in combination can be used to rule out febrile UTI in children aged 2 months through 2 years.

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