DIAGNOSIS AND TREATMENT OF URINARY TRACT INFECTION IN CHILDREN: DIAGNOSIS

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Scope of Guidelines

Specialist assessment and management is required for children who are considered at high risk of serious illness (underlying structural urinary tract abnormalities or neurogenic bladder or kidney transplant recipients). These children are beyond the scope of these guidelines and it is important that they are excluded from the recommendations detailed below.

GUIDELINES

a. We recommend that the diagnosis of urinary tract infection (UTI) only be made on the basis of clinical symptoms (see below) in association with a positive urine culture. (1B)

b. We suggest that the presence of bacteriuria (by microscopy with gram stain) on an appropriately collected urine specimen can be used as the basis for a presumptive diagnosis of UTI. (2B)

c. We recommend that culture of appropriately collected urine specimen (see below) is required for definitive diagnosis of UTI (1B), and that UTI diagnosis not be made solely on the basis of:
   - Urinary dipstick testing for leucocyte esterase or nitrite (1B); or
   - The presence of white cells on microscopy, in the absence of bacteriuria. (1B)

d. We suggest that the occurrence of a positive urine culture in the absence of clinical symptoms (asymptomatic bacteriuria) does not warrant treatment or further investigation for UTI. (2B)

Urine Collection

e. Suprapubic aspirate (SPA) is the most definitive method of urine culture, but is regarded as more invasive than other methods. We recommend the use of clean catch urine (CCU), mid-stream urine (MSU) or in-out catheter specimen urine (CSU) as satisfactory alternate methods for urine collection. (1B)

f. If positive urine culture by bag urine is obtained, we recommend it is confirmed on repeat urine culture by SPA, CSU, CCU or MSU. (1B)

g. We suggest that suprapubic aspirate (SPA) collection follow a protocol that ensures a full bladder prior to the procedure. This may involve either clinical assessment of good hydration and delay after voiding by one hour or use of bladder ultrasound or both. (2B)

Urine Culture

h. We recommend the following minimum counts of colony forming units (CFU) grown on urine culture be considered as diagnostic of UTI (1B):
   - SPA: any growth
   - CSU: >10^6 CFU/L (10^6 - 10^8 CFU/L; possible UTI)
   - MSU or CCU: >10^8 CFU/l (10^7 - 10^8 CFU/l; possible UTI)
   - Bag/ Pad/ Cotton ball: not recommended for definitive culture.
i. We suggest that the following be taken as indicators of possible contamination (2C):
   - Any growth from a bag specimen
   - Growth of more than one organism from any method of urine collection
   - Growth of skin commensals
   - CFU counts less than the recommended minimum counts.

j. If contamination is possible on initial urine culture, we suggest repeat urine culture if any of the following conditions apply (2C):
   - Convincing urinary symptoms are present
   - The child has a structurally abnormal urinary tract
   - There is a history of complicated UTIs.

**UNGRADED SUGGESTIONS FOR CLINICAL CARE**

a. UTI is more likely in girls and uncircumcised boys (especially between 3-6 months), infants <12 months, and if a fever has been present for >2 days and there is an absence of another source of fever on examination. No factor can predict with 100% accuracy the absence of serious bacterial illness in febrile infants <3months (ungraded).

b. In children with culture-proven UTI, a serum procalcitonin value >0.5 ng/mL predicts reasonably well the presence of renal parenchymal injury, as evidenced by early DMSA scintigraphy (within two weeks of diagnosis) (ungraded).

**IMPLEMENTATION AND AUDIT**

Units should consider an audit of current practices of assessment and treatment of children with symptoms of UTI that includes a review of patient outcomes and alignment of current procedures with the guideline recommendations. Following audit and review, key areas for focus of an implementation strategy should be identified and a site specific plan developed.

**BACKGROUND**

Urinary tract infection in children is common, with about 6% of girls and 2% of boys experiencing an episode before their 7th birthday [1]. Having had one infection the child is at a 13 - 19% risk of having another UTI [2-4]. UTI causes pain, discomfort and irritability to the child, and anxiety, stress and inconvenience to the family. Prompt diagnosis and early treatment are central to good clinical care.

**SEARCH STRATEGY**

**Databases searched:** MeSH terms and text words for UTI, bacteriuria, bacterial infection, pyuria or pyelonephritis with MeSH terms and text words for fever, dysuria; abdominal, flank and loin pain; suprapubic aspirate, bag specimen, catheter specimen, clean catch, urinalysis, nitrites, leukocytes, esterases, procalcitonin and urine culture with MeSH terms and text words for paediatric populations. The search was carried out in Medline. The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of search/es:** 1950 to 15 August 2014.
**WHAT IS THE EVIDENCE?**

**Clinical symptoms:**

Urinary symptoms (dysuria and frequency) and general appearance of the child, particularly those assessed to be very unwell, may be the two best clinical predictors of UTI. However, no fluid intake in the previous 24 hours, fever >39°C and the presence of chronic disease are also strong predictors [5].

For infant girls, age <12 months, caucasian race, temp >39°C or higher, fever >2 days and absence of another source of fever on examination has a high sensitivity (0.95) and a PPV of 6.4% with >=2 variables; for <=2 variables the NPV is 0.8% [6]. On the basis of this decision rule with 5 risk factors, an infant girl with no more than 1 risk factor has a less than 1% probability of a UTI and <=2% probability with no more than 2 risk factors [7]. For infant boys, the individual risk factors are non-black race, temperature >39°C, fever >24 hours and absence of another source of infection. The major determinant is whether they are circumcised: the probability of UTI in infant boys exceeds 1% even with no risk factors other than being uncircumcised. For all infant boys, the probability of UTI is <=1% with no more than 2 risk factors and <=2% with no more than 3 risk factors [7]. Uncircumcised infants have 10-fold increased risk (OR 10.4, 95% CI: 4.7-31.4) with a 2-fold increased risk if the maximum temperature is >39°C (OR 2.4, 95% CI: 1.5-3.6) [8]. The highest risk for boys is between 3-6 months with circumcised boys greater than 12 months having the lowest risk [9]. No factor can predict with 100% accuracy the absence of serious bacterial infection (SBI) in febrile infants <3 months [10].

In older children UTI is more common in Caucasian girls and may be associated with abdominal pain [11]. Malodorous urine also increases the possibility of UTI (OR 2.83, 95% CI: 1.54-5.20) although it cannot be used to definitely rule in or out a diagnosis of UTI [12].

**Definition of UTI:**

The practical definition of UTI for clinical practice is the combination of symptomatic evidence of infection of the urinary tract (including one or more of: abdominal pain, dysuria, frequency, fever, loin pain and irritability in infants) in association with a urine sample containing a positive bacterial culture.

The presence of symptoms without a positive urine culture, without an alternative explanation, warrants a repeat urine culture. False negative cultures can occur due to sterilization by antiseptic preparation, technical errors in culture conditions, atypical fastidious organisms or anatomical abnormalities of the urinary tract. The more common confusion revolves around the absence of definitive symptoms, but bacterial growth on urine culture. This can result from contamination or represent asymptomatic bacteriuria. Treatment and further investigation of asymptomatic bacteriuria are not warranted as there is no evidence of any increased risk of development of clinical symptoms or long-term adverse outcomes [13, 14].

The following sections review the criteria to distinguish urine culture results compatible with infection as compared to contamination.

**Urine dipstick/microscopy and gram stain:**

Because urine culture results are not available for 24 hours, urinalysis can be used on a fresh (<1 hour after voiding at room temperature or <4 hours after voiding with refrigeration) specimen to guide presumptive therapy. Microscopy for white cells and bacteria by gram stain is the preferred method of urinalysis when possible as it has a greater sensitivity, specificity and PPV than standard urinalysis [7]. The accuracy of microscopy for bacteria with Gram stain is higher than other laboratory tests with relative diagnostic odds ratio compared to bacteria without Gram stain of 8.7 (95% CI: 1.8-41.1), white cells of 14.5 (95% CI: 4.7-44.4), and nitrite of 22.0 (95% CI: 0.7-746.3). Phase contrast microscopy is the most useful point-of-care diagnostic tool when available as it is 100% sensitive, making it very useful to rule UTI's out [15].

Sensitivity for leucocyte esterase or nitrite positive dipstick is 88% (95% CI: 82-91) and specificity 79% (95% CI: 69-87) and nitrite-only positive dipstick is sensitivity 49% (95% CI: 41-57) and specificity 98% (95% CI: 96-99) [16]. Therefore, if nitrites are positive, the test is helpful to rule in UTI because it is highly specific. The presence of nitrites are not very sensitive because the conversion of dietary nitrates
to nitrites takes approximately 4 hours and infants empty their bladders frequently [17]. A positive leucocyte esterase result should be interpreted with caution as there are many causes for pyuria: a negative result however, can be useful for ruling out UTI. The positive likelihood ratios (LR) of both nitrite and leucocyte positivity are good for children greater than 2 years compared to younger children: positive LR 38.54 (95% CI: 22.49-65.31) and negative LR for both negative 0.13 (95% CI: 0.07-0.25) for children greater than 2 years compared to positive LR 7.62 (95% CI: 0.95-51.85) and negative LR 0.34 (95% CI 0.66-0.15) for children < 2 years [18]. Similarly a more recent retrospective study of 321 children aged <2 years presenting to an ED with a febrile illness reported a positive LR 1.52 (95% CI: 1.37-1.69) and negative LR 0.11 (95% CI 0.03-0.32) [19].

The meta-analysis of 95 studies in 95,703 children reports a sensitivity and specificity for gram-stained bacteria of 91% (95%CI: 80-96) and 96% (95%CI: 92-98) and for unstained bacteria 88% (95% CI: 75-94) and 92% (95%CI 84-96) respectively. For urine white cells the sensitivity is 74% (95%CI 67-80) and specificity is 86% (95%CI 82-90) [16].

**Methods for urine collection and microbiological definition of a UTI on urine culture.**

A pure growth of a single bacterial species with a significant colony number is generally regarded as evidence of a true UTI. Mixed growths, growth of skin commensals or low colony counts are regarded as evidence of contamination. However, there may be occasions when these may represent true UTIs, especially in individuals with abnormal urinary tracts (see section on ‘Microbiological definition of a contaminated urine culture’ below). The threshold for the accepted minimum colony count on urine culture varies by collection method.

a. Suprapubic aspirate (SPA): It is assumed that any culture from an SPA sample is a true growth as this comes directly from a sterile site, whereas all other methods of collection are potentially contaminated by flora from the perineum, prepuce or vagina. However, it is important to recognize that the majority of SPA cultures are still likely to have colony counts of >10^5 CFU/l [20, 21]. Furthermore, occasional samples can be contaminated by skin commensals during the percutaneous sampling procedure [22].

SPA is no longer widely used in studies and even less so in primary practice as it is perceived as invasive, requires some technical expertise and procedural facilities. One randomised study has also suggested a higher level of pain experienced in young infants having an SPA compared with catheter-specimen urine (CSU) [23]. SPA samples are successfully obtained in 25-92% of attempts [22, 24-27]. This compares with CSU success rates of 72-100% [23, 24, 28]. Use of ultrasound to confirm sufficient urine volumes prior to SPA in two studies has led to improved success rates of 44% to 93% [29-31]. Ultrasound also improved success of catheterised urine sampling from 72% to 96% [28]. Another study found that performing SPA after ensuring good hydration and no passage of urine for 1 hour led to success in 80% of cases; addition of ultrasound improved this to 87% [32].

b. Catheter-specimen urine (CSU): The next most reliable sampling technique is urethral catheterization. While this technique is performed under sterile conditions, the passage of the catheter through the perineum still leads to an occurrence of contamination above that of SPA. This has created difficulty in setting an appropriate threshold between true infection and contamination, with various studies using levels of 10^5; 2 \times 10^7; 5 \times 10^5 and 10^6 CFU/l. The minimum growth of >10^5 CFU/l is derived from studies by Kass in 1956 [33], which showed that CSUs from 95% of women with pyelonephritis had colony counts >10^6 CFU/l, whereas colony counts below 10^6 CFU/l were found in women with asymptomatic bacteriuria. There was an overlap of asymptomatic and true UTI in the range of 10^7 - 10^8 CFU/l. CSU in well children having elective surgery yielded cultures with >10^6 CFU/l in 7.2% of samples [25]. Conversely, 3/32 CSUs from children with UTI had <10^6 CFU/l [34]. Hoberman defined a cut-off of 5 \times 10^5 CFU/l, with contamination occurring in 36/60 cases below this level, but only 7 of 109 above this level [35].

Heldrich found 80% CSUs in children with UTI had >5 \times 10^5 CFU/l, but a further 18% had between 10^6 – 5 \times 10^5 CFU/l [36, 37]. Cheng et al examined colony counts of CSUs in children with UTI defined by positive culture, symptoms and urinary leukocytes. They found 10^6 CFU/l to be the most reliable cut-off, but no absolute cut-off ruling out UTI as demonstrated by the following likelihood ratios (LRs): 10^2-10^6 CFU/l LR 0.11, 10^5-10^6 CFU/l LR 0.45, 10^6-5 \times 10^5 CFU/l LR 1.52, >5 \times 10^5 CFU/l LR 20.5 [38]. Wringer et al examined predictors of contamination in a prospective
cohort of 185 children <3 years of age. UTI was diagnosed in 18 (10%) and 140 (76%) had a clean sample. Contamination was identified in 27 (14.6%) of the samples, either on the basis of a non-pathogen or <10,000 CFU/mL or multiple pathogens. Univariate analysis of potential predictors of contamination were: age <6 months: OR 6.8 (95%CI: 2.6, 17.9); difficult catheterisation: OR 3.6 (95%CI: 1.5, 8.6); uncircumcised boys: OR 5.7 (95%CI: 1.2, 29.4) [39].

c. Clean voided urine (CVU) incorporates non-invasive urine collection by either midstream urine (MSU) in toilet-trained children or clean catch urine (CCU) in infants and non-toilet-trained children by waiting with a collection container for spontaneous voiding. CCU is regarded as a surrogate for MSU, but has the drawbacks of being time-consuming, prone to contamination of a container held for long periods near the perineum and an inability to ensure a mid-stream collection.
   i. MSU- Perineal contamination is a potential problem occurring in 8-20% of specimens [34, 40-45]. Furthermore, low colony counts of $10^5 - 10^6$ CFU/l can occur in 17-23% samples with confirmed UTI [26, 40].
   ii. CCU- In 28 confirmed UTIs by CSU, CCU samples grew $>10^6$ CFU/l in 27 cases [46]. However, contamination rates can be considerable. In well neonates with sterile SPAs, 12% of CCUs grew $>10^6$ CFU/l and an additional 44% between $10^7 - 10^8$ CFU/l [22].

d. Alternative methods for non-invasive urine collection in incontinent children have proved difficult. Methods include bag / pad/ cotton ball urine collections. All of these have high sensitivity rates, but unacceptably high contamination levels ranging between 27-100% [27, 41, 47-57]. There is some evidence that obtaining repeat urine cultures with these techniques can reduce the contamination rates considerably (from 36.8% on initial culture to 2.6% after obtaining a second culture [54]). While these data are limited and numerous studies report high rates of contamination, these alternative methods remain inappropriate methods for culture-based diagnosis, such that any diagnostic evidence of UTI should be confirmed by one of the accepted methods listed above. However, these alternative collection methods may be used to exclude UTI if negative results are obtained by culture or by screening with non-culture-based diagnostic methods, such as urinalysis and microscopy (see section on non-culture based techniques for diagnosis of UTI).

Studies examining techniques head-to-head are difficult to compare as reference standards used vary and the most reliable, SPA, is used infrequently. In addition, some studies are designed to determine contamination rates, using asymptomatic individuals, whereas other studies target sensitivity, using individuals with risk factors for UTI. The following provides a summary of the performance of urine collection methods head-to-head, with the second method the reference standard:

a. CSU vs SPA- in well children: specificity 92.8% with first 5ml collected; 97.5% with second 5ml collected [25].

b. CVU vs CSU- in well children: specificity 96.5% if $>10^6$ CFU/l [40]. In children with presumed UTI using a threshold of $>10^7$ CFU/l: 78-96% sensitivity; specificity 92% [26, 34, 46].

c. CVU vs SPA- in well neonates: $>10^6$ CFU/l detected in 20% by CVU vs 8% by SPA [22]. In children with suspected UTI, using a cut-off of $>10^6$ CFU/l: Sensitivity 81-89%, specificity 95% [30, 58].

The only systematic review of head to head comparisons, included 5 studies and was found to have good agreement with pooled positive likelihood ratio (LR) 7.7 (95% CI 2.5-23.5) and negative LR 0.23 (95% CI 0.18-0.30), (although specific colony counts for confirming definite UTI and ruling out contamination were not detailed) [59, 60]. However, the heterogeneity in these studies and the test performance were demonstrated by the wide ranges of sensitivity, 75-100% and specificity, 57-100%.

**Microbiological definition of a contaminated urine culture.**

There is no universal definition of a contaminated positive culture compared with a “true” UTI. Generally accepted criteria for contamination include the following:

a. Growth of 2 or more organisms
b. Low colony count below the accepted threshold (see below)
c. Growth of atypical organisms, such as skin commensals and other gram-positive bacteria
None of the above criteria for contamination are sufficient to exclude the possibility that the culture result does indeed reflect a true UTI. This is particularly so for certain patient groups: low colony counts may occur in infants with frequent voiding of dilute urine or in children after skin preparation with antiseptics; mixed growth, skin organisms and atypical organisms can represent true UTIs in children with structural abnormalities of the urinary tract, a history of instrumentation of the urinary tract and immunosuppressed children [61]. Culture results should therefore be interpreted in the context of the individual child. There is some evidence that repeat urine cultures can facilitate the discrimination between true and contaminated urine cultures [62].

**Procalcitonin.**

Serum pro-calcitonin (PCT) is a more reliable biologic marker than the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or leukocyte count for the early prediction of renal parenchymal injury in children with a first episode of urinary tract infection. The greater the elevation of PCT at admission, the more positive the correlation for subsequent permanent renal damage [63, 64]. The sensitivity and specificity of PCT were 77% and 89%, respectively, in prediction of renal involvement, whereas CRP had a sensitivity of 80% and a specificity of 65%. In children with culture-proven UTI, a PCTT value >0.5 ng/mL predicts reasonably well the presence renal parenchymal injury, as evidenced by DMSA scintigraphy. Pro-calcitonin may aid in the identification of children with UTI, necessitating more intense evaluation and management [65].

The systematic review of 12 studies (526 children) Leroy et al reported a sensitivity and specificity for diagnosis of VUR on a PCT ≥0.5 ng/L of 83% (95% CI: 71.91) and 43% (95% CI 38, 47) [66]. A subsequent prospective single centre study reported the following sensitivities and specificities for the diagnosis in 18 children of 72.2% (95%CI: 46.5, 90.2) and 70.8% (95%CI: 55.9, 83) respectively for a PCT >0.50 ng/mL; and 66.7% (95%CI: 41, 86.6) and 77.1% (95%CI: 62.7, 88) for a PCT >0.56 ng/mL [67]. Secondary analysis of prospective studies of 494 children with high grade VUR identified a decision rule for cystography in children with a first febrile UTI in with ureteral dilatation and serum PCT ≥0.17 ng/mL to have a sensitivity and specificity of 86% (95%CI: 74, 93) and 47% (95% CI: 42, 51) respectively [68].

**Topics not covered in this review**

a. Laboratory techniques for urine handling and culture.
b. Urine preservation: time, temperature, preservative, transport.
c. Combination of urinalysis and bag urine culture (as bag urine cultures have an excessive false positive rate, such that delay in diagnosis and treatment awaiting the results is likely to outweigh the benefits of avoiding a small number of alternative methods of urine collection).

**SUMMARY OF THE EVIDENCE**

In summary, initial treatment of urinary tract infection is guided by clinical presentation, however reliance on clinical symptoms may result in under treatment. The practical definition of UTI for clinical practice is the combination of symptomatic evidence of infection of the urinary tract (including one or more of: abdominal pain, dysuria, frequency, fever, loin pain and irritability in infants) in association with a urine sample containing a positive bacterial culture.

A pure growth of a single bacterial species with a significant colony number is generally regarded as evidence of a true UTI. Mixed growths, growth of skin commensals or low colony counts are regarded as evidence of contamination. However, there may be occasions when these may represent true UTIs, especially in individuals with abnormal urinary tracts.

There is no universal definition of a contaminated positive culture compared with a “true” UTI and none of the criteria for contamination are sufficient to exclude the possibility that the culture result does indeed reflect a true UTI. Culture results should therefore be interpreted in the context of the individual child. Pro-calcitonin may aid in the identification of children with UTI, warranting more intense evaluation and management.
WHAT DO THE OTHER GUIDELINES SAY?

The National Institute for Health and Clinical Excellence (NICE), UK. Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children (August 2007, last updated 30 March 2010).[69]

a. Infants and children with unexplained fever >38°C should have a urine sample tested within 24 hours.

b. Urine collection: clean catch urine is the preferred method, but if not possible other non-invasive methods such as urine collection pads should be used. If collection by non-invasive methods is not possible, catheter sample or suprapubic aspiration (SPA) should be used.

c. Before SPA is attempted, ultrasound guidance should be used to demonstrate the presence of urine in the bladder.

d. For children under 3 years obtain urine sample for microscopy and culture prior to commencing antibiotics. For children 3 years and older use urine dipstick to diagnose UTI: treat as UTI if both leukocyte and nitrite positive; don’t treat as UTI if both leukocyte and nitrite negative. Send urine for culture if leukocyte or nitrite positive alone, with intermediate-high risk of serious illness, diagnosis of pyelonephritis/ upper urinary tract infection or recurrent UTI.


American Academy of Pediatrics, Pediatrics, 2011; 128; 595-610.

a. If a clinician decides that a febrile infant with no apparent source for the fever requires antimicrobial therapy to be administered because of ill appearance or another pressing reason, the clinician should ensure that a urine specimen is obtained for both culture and urinalysis before an antimicrobial agent is administered; the specimen needs to be obtained through catheterization or SPA, because the diagnosis of UTI cannot be established reliably through culture of urine collected in a bag.

b. If the clinician determines that the febrile infant is not in a low-risk group, then there are 2 choices. Option 1 is to obtain a urine specimen through catheterization or SPA for culture and urinalysis. Option 2 is to obtain a urine specimen through the most convenient means and to perform a urinalysis. If the urinalysis results suggest a UTI (positive leukocyte esterase test results or nitrite test or microscopic analysis results positive for leukocytes or bacteria), then a urine specimen should be obtained through catheterization or SPA and cultured; if urinalysis of fresh (<1 hour since void) urine yields negative leukocyte esterase and nitrite test results, then it is reasonable to monitor the clinical course without initiating antimicrobial therapy, recognizing that negative urinalysis results do not rule out a UTI with certainty.

c. To establish the diagnosis of UTI, clinicians should require both urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of at least 50 000 colony-forming units (CFUs) per mL of a uropathogen cultured from a urine specimen obtained through catheterization or SPA.


a. Urinalysis is helpful in providing immediate information to suspect UTI and enable initiation of treatment. Confirmation of the diagnosis on urine culture is necessary.

b. Cultures of urine specimens collected from a bag applied to the perineum have unacceptably high false positive rates, and are not recommended. Bag specimens are, however, a useful indicator of the absence of infection if no growth or a very scanty growth of usual urinary pathogens is found.

c. Probability of UTI varies by method of collection and colony count on culture:

a. Suprapubic aspiration- any growth- 99%

b. Urethral catheterization- at least 50,000 CFU/ml- 95%

c. Midstream clean catch- >10^5 CFU/ ml- 90-95%
Very young children can present with gastrointestinal and non-specific symptoms and signs, but more severe UTI is associated with high fever and dehydration. Bag specimens are helpful to exclude infection, but positive results should be confirmed with SPA, CSU or MSU samples. Definitive diagnosis depends on positive urine culture with >100,000 cfu/ml of one pathogen, although lower counts are acceptable according to technique:

- SPA: >10 cfu/mL
- CSU: >1,000-50,000 cfu/mL
- MSU: >10,000 cfu/mL with symptoms; >100,000 cfu/mL without symptoms

Urine dipstick analyses have limitations for all tests with gram stain and pyuria being most predictive of UTI in infants, whereas pyuria and positive nitrite are most predictive in older children. CRP>20 µg/mL distinguishes between acute pyelonephritis and other causes of bacteriuria.

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**Italian Society of Pediatric Nephrology (2012):** [73] In young children suspect UTI with limited symptoms in very young children, it may present with fever alone. Identify likely UTI with urine dipstick or microscopy and confirm UTI by urine culture. Clean voided urine (CVU) is method of choice due to invasive nature of collecting urine by catheter or suprapubic aspiration. Bag urine is considered an acceptable second option, but a severely unwell child should have urine collected by bladder catheterisation. In general, blood tests are not helpful, but serum procalcitonin is the best test to diagnose renal parenchymal involvement. Significant levels of growth on culture depend on collection technique:

- CSU: >10,000 CFU/mL
- CVU: >100,000 CFU/mL
- Urine bag: >100,000 CFU/mL

**SUGGESTIONS FOR FUTURE RESEARCH**

None made

**CONFLICT OF INTEREST**

Drs Kausman and Danchin have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

**REFERENCES**


## APPENDICES

### Table 1. Summary of included studies

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| Craig et al (2010)[5] | 15,781  | Prospective cohort. Single centre (Australia) | Children <5 years presenting to emergency department with a febrile illness. Febrile illness defined as one or more:  
- ≥38°C (measured or parental report.  
- Felt hot - parental report  
- Presenting problem related to fever. Exclude if transferred from another hospital. Intervention: Mandatory evaluation of 40 clinical features. Outcome: diagnosis of serious bacterial infection (UTI, pneumonia and bacteraemia) and accuracy of clinical model and clinician judgement. Until case definition of serious bacterial infection or fever resolved for ≥24 hr. | High follow up (93%). UTI confirmed in 3.4% (95%CI 3.2, 3.7%). Selected 26 clinical items for the final multinomial logistic model. Receiver operating characteristics (ROC):  
- Diagnostic model for UTI AUC 0.80 (95%CI 0.78, 0.80)  
- Early physician estimation corresponds to:  
  - Low sensitivity (0.1 to 0.5)  
  - High specificity (0.9 to 1.0)  
- Clinician judgment after initial assessment was less accurate.  
- Clinical features widely considered to be indicative of UTI were found to be highly discriminatory. For example urinary symptoms, general appearance (very unwell) associated with diagnostic ratios >1 while non UTI related symptoms were associated with diagnostic ratios <1.  
- Limitations:  
  - Microbiological confirmation not available for all children.  
  - Uncertain validity of physician estimates of disease. |
| Gorelick et al (2000) [6] | 1,469 (girls only) | Prospective cohort. Single centre (US). | Girls <2 years and boys <1 year presenting to emergency department with temperature ≥38°C. Excluded children who did not have a catheterised urine sample collected. Outcome: Prediction of culture confirmed UTI by demographic and physical examination factors. | Not stated | Overall rate of UTI 4.3%. Positive predictors of UTI in girls in univariate model:  
- Age <12 months OR:2.82 (95%CI: 1.6-5.1)  
- Race white vs nonwhite OR 6.0 (95%CI: 3.7-9.5)  
- Any urinary symptoms OR 3 (95%CI: 1.5-8.1)  
- Ill general appearance OR 2.3 (95%CI: 1.4-3.8)  
- Any tenderness OR 3.4 (95%CI: 1.2-10.1)  
- Absence of alternate source of fever OR 1.9 (95%CI: 1.1-3.2)  
- Presence of 2 or more of <12 months, white race, temperature >39°C, fever for more than 2 days and absence of another source on examination predicted UTI with:  
  - Sensitivity 0.95 (95%CI: 0.85, 0.99)  
  - Specificity 0.31 (95%CI: 0.28-0.34) |
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| Zorc et al       | 1025    | Prospective cohort. Multi-centre (US)                                                     | Infants ≤60 days presenting to emergency departments with temperature ≥38°C. Clinical appearance assessed using the Yale Observation Scale. | Not stated     | Overall rate of UTI 9%. Multivariable predictive factors associated with UTI:  
  - Uncircumcised (vs circumcised) 10.4 (95%CI: 4.71-31.4) [Rate of uncircumcised boys 52%]  
  - Maximum temperature reached 2.4 (95%CI: 1.5-3.6)  
  - Female (vs circumcised male) 2.2 (95%CI: 0.9-6.6)  
  - Age <28d (vs >28) 1.6 (95%CI: 0.96-2.6)  
  - Ill appearance (vs YOS<10) 0.68 (95%CI: 0.14-1.6)  
  - White (vs other race) 0.79 (95%CI: 0.35-1.5)  
**Limitations:**  
  - High non enrolment rate (30% of eligible infants) who had significantly lower UTI rate and it is not possible to characterise further.  
  - Limited presentation of data.                                                                                                                                                                                                                                                                                                                  |
| Gajdos et al     | 315     | Retrospective analysis of medical files. Single centre (France)                           | Consecutive consultations of febrile infants (<3 months) in emergency department.                                                               | NA             | Overall rate of SBI was 25.1% with UTI 22.5%. Factors significantly associated with SBI were:  
  - Male  
  - Temperature >38°C and lasting >24 hours.  
  - Absence of ear nose and throat symptoms.  
  - High white blood cell count >50% neutrophils  
  - High serum CRP >20mg/L Only high blood cell count and CRP significant predictor in multi-variate analysis:  
  - Sensitivity 90.9% (95%CI 87.6, 94.2)  
  - Specificity 44.6% (95%CI 38.9, 50.3).  
**Limitations:**  
  - Retrospective review of records.  
  - Single centre.                                                                                                                                                                                                                                                                                                                         |
| Williams et al   | 95 studies, 95,703 children.                | Systematic review and meta-analysis of non randomised diagnostic test studies.                                                                | Studies of children (≤18 years) comparing urine culture (reference) with one or more rapid tests (index) for the diagnosis of UTI. | NA             | White cell count (urine microscopy, unpaired data) – 49 studies:  
  - Sensitivity 0.74 (95%CI 0.67, 0.80); Specificity 0.86 (95%CI 0.82-0.90).  
  - DOR 18 (95%CI 12.1, 26.8)  
Gram stain (urine microscopy, unpaired data) – 17 studies:  
  - Sensitivity 0.91 (95%CI 0.80, 0.96); Specificity 0.96 (95%CI 0.92, 0.98).  
  - DOR 253.9 (95%CI 115.1, 560.4)  
**Limitations:**  
  - Urine dipstick/microscopy and gram stain  
  - Diagnostic odds ratio (DOR) used
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| Mori et al (2010) [18] | 6 studies (2,714 children) | Systematic review of diagnostic test studies (search up to May 2009). | Studies of diagnosis of UTI in children including both leucocyte esterase and nitrite and comparing microscopy and urine dip stick analysis to test for UTI. Positive and negative likelihood ratios. | NA | Urine dip stick testing by age:  
- Pooled LR+ (for positive nitrite plus positive leucocyte esterase): 34.61 (95%CI: 17.8, 63.3)  
- Pooled LR-(for negative nitrite plus negative leucocyte esterase): 0.15 (95%CI: 0.08, 0.29)  
- Only 2 studies compared infants under 1 and 2 years with older children. Testing for interaction showed significant difference in ability to rule out bacteriuria between the two age groups (P=0.01).  
Microscopy versus dipstick children <1 year:  
- WBC cut off of 5: LR+ for dipstick 6.24 (95%CI: 1.14, 34.22), LR+ for microscopy 1.63 (95%CI: 1.24, 2.31)  
- WBC cut off of 10: LR+ for dipstick 15.6 (95%CI: 4.16, 58.44), LR+ for microscopy 6.24 (95%CI: 1.14, 34.22)  
- WBC cut off of 5: LR- for dipstick 0.27 (95%CI: 0.07, 0.99), LR- for microscopy 0.31 (95%CI: 0.13, 0.71)  
- WBC cut off of 10: LR- for dipstick 0.31 (95%CI: 0.13, 0.71), LR- for microscopy 0.66 (95%CI: 0.44, 0.97)  
Microscopy versus dipstick children ≥1 year:  
- WBC cut off of 5: LR+ for dipstick 27.10 (95%CI: 11.44, 64.21), LR+ for microscopy 1.69 (95%CI: 1.52, 1.87)  
|
## Study ID | N  | Study design and setting | Participants and Interventions | Follow up | Comments and results
---|---|---|---|---|---
Coulthard et al (2010) [15] | 203 | Comparative study (paired urine samples). Single centre (UK) | Children with suspected UTI able to provide a second urine sample. Collection of sequential urine samples using sterile pad for infants, clean potties for toddlers and CCU samples for older children. Comparison of phase contrast microscopy with urine culture. Excluded apparently positive UTI on basis of contradictory results between first and second sample. | NA | Phase contrast microscopy for bacteria had a sensitivity of 1 as did a single urine culture using a cut off of $10^5$ CFU/ml and a specificity of 0.860 compared to 0.925 for the single urine culture sample. Specificity is low in girls older than 9 years (0.61) due to contamination but increased (0.81) when urethral stream samples are collected. Nitrite positivity has high specificity (0.985) but low sensitivity (0.61). Limitations: Single centre with small numbers of UTI. No gold standard for comparison with UTI reliant on comparison of the sequential samples only.
Ramlakhan et al (2011) [19] | 321 | Retrospective study. Single centre (UK) | Children <2 years presenting to ED with a febrile illness. Urine samples collected at the discretion of the examining doctor. | NA | Clean catch samples were taken in 97% of the cases and 78 samples (24.3%) were culture positive. A test positive for nitrite, leucocyte esterase and blood in the urine sample: Sensitivity 96.2%[19] (95%CI: 89.3, 98.7) Specificity 36.6% (95%CI: 30.8, 42.3) +LR 1.52 (95%CI: 1.37, 1.69) -LR 0.11 (95%CI: 0.03, 0.32) Limitations: Retrospective analysis of hospital records. High rate of urine results (37%) were unavailable for analysis. Limited to children less than 2 years old. Single centre study.

- WBC cut off of 10: LR+ for dipstick 27.10 (95%CI: 11.44, 64.21), LR+ for microscopy 10.87 (95%CI: 5.95, 19.75)
- WBC cut off of 5: LR- for dipstick 0.04 (95%CI: 0.00, 0.59), LR- for microscopy 0.17 (95%CI: 0.07, 0.41)
- WBC cut off of 10: LR- for dipstick 0.17 (95%CI: 0.07, 0.41), LR- for microscopy 0.51 (95%CI: 0.35, 0.73)

Authors conclude that dipstick urine testing can be recommended in children over 2 years but not for younger children.

Limitations: Data does not address performance of tests when only one parameter was positive. Small number of studies. Studies likely to have included children with asymptomatic bacteriuria.
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<tr>
<td><strong>Methods for Urine Collection – Suprapubic aspirate (SPA)</strong></td>
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| Hansson et al (1998) [20] | 366 | Retrospective analysis of medical records. Single centre (Sweden) | Infants <1 year with symptomatic UTI in whom urine sample for culture and diagnosis collected by SPA. | NA | • 19.9% of infants had <10^5 CFU/ml.  
• No culture had more than one organism. |
| Nelson and Peters (1965) [22] | 25 | Prospective cohort. Single centre. | Uncircumcised, premature male infants. SPA sample collected 1 hour prior to clean voided sample. Outcome: urine culture | NA | • No growth recorded in 76% of SPA compared to 8% of clean voided sample.  
• 3 infants contained one of two colonies of coagulase-negative staphylococci. |
| Kozer et al (2006) [23] | 58 | Randomised controlled study (single blind). Single centre (Israel) | Infants 0-2 presenting to ED with fever (rectal temperature >38°C) needing a urine culture. SPA vs. Urethral catheterisation. Outcome: Primary observation of videotaped upper body and assigning DAN neonatal pain point score. Secondary outcomes VAS for ranking of pain by nurse and parent (independently). Duration of cry | NA | Mean difference between SPA and Urethral catheterisation:  
• DAN scores 2.5 (95% CI: 1.4, 3.7).  
• VAS by parent 16.8mm (95% CI: 1.8, 31.8).  
• VAS by nurses 19.6mm (95%CI: 7.4, 31.8)  
• Duration of cry 13.2 seconds (95% CI: 4.3, 30.7).  

Limitations: Clinically meaningful differences for all outcomes is unknown. Reliance on subjective outcomes. No inclusion of clinical outcomes/complications of procedure to allow benefit harm assessment, rather relies on literature review of relative success rates. Small single centre study. |
| Munir et al (2002) [29] | Phase 1: 38, Phase 2: 43 | Prospective cohort (2 phase). Single centre (Australia) | Children <2 years presenting to ED requiring urine culture. Phase 1: volume cut off for SPA as determined by ultrasound. SPA attempted when volume >2ml. Phase 2: Randomised to ultrasound and SPA on full bladder (10ml) or following hydration) vs. no ultrasound ‘full’ bladder assessed on basis of dry nappy. | NA | Phase 1 SPA success rate:  
• Volume >2 mL: 29 (88%)  
• Volume >10 mL 28 (90%)  
• Volume >20 mL 24 (100%)  

Phase 2 SPA success rate:  
• Ultrasound 31 from 39 (79%), no ultrasound 16 from 36 (44%), RR 1.79 (95%CI: 1.20, 2.66).  

Limitations: Small single centre study. No statistical basis for defining cut-off value in Phase 1, which is essentially an arbitrary value. No details of randomisation provided. No baseline data for either Phase 1 or Phase 2 provided. |
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<tr>
<td>Ramage et al (1999) [30]</td>
<td>49 (58 paired specimens)</td>
<td>Prospective cohort. Single centre (UK)</td>
<td>Children &lt;24 months in whom urine culture was indicated.  Composed clean catch urine (CCU) with SPA and SPA with and without ultrasound to estimate bladder volume.  Outcome: Positive urine culture defined as ( &gt;10^5 ) CFU/ml for CCU and growth of any organism by SPA and first time success rate for collection.</td>
<td>NA</td>
<td>First time success of SPA at first attempt using ultrasound compared to no ultrasound:  • 26 of 28 with ultrasound (93%) compared to 13 of 21 without ultrasound (62%) ( P=0.008 ).  Limitations: Small single centre study. No detail provided on individual patients that might explain differences in success rates.</td>
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<tr>
<td>Chu et al (2002) [32]</td>
<td>60</td>
<td>Randomised controlled trial. Single centre (Hong Kong).</td>
<td>Children &lt;12 months in whom urine culture was indicated.  Ultrasound assisted SPA (sample attempt with estimated bladder volume ( &gt;3)ml) vs. pre-hydration conventional “blind” SPA.  Outcomes: Success rate with no more than 3 attempts being allowed.</td>
<td>NA</td>
<td>Success rates for ultrasound assisted compared to no ultrasound:  • All attempts: 26 of 30 (87%) vs 24 of 30 (80%) RR 1.08 (95%CI: 0.86, 1.36).  Successful compared to unsuccessful ultrasound attempts were associated with greater:  • Bladder depth MD 7.00 mm (95% CI: 2.68, 11.32)  • Calculated bladder volume MD 9.00 ml (95%CI: 3.88, 14.12)  • Bladder length: MD 9.00 ml (95%CI: 3.63, 14.37)  Limitations: Small single centre study. Unblinded study. Unable to determine cut off values for bladder measurements to guide success using ultrasound.</td>
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<tr>
<td>Pryles et al (1959) [25]</td>
<td>42</td>
<td>Prospective comparative study. Single centre (US).</td>
<td>Children aged from 3 months to 10 years admitted for elective surgery with no clinical evidence of UTI. Samples collected after surgery while still under anaesthetic.  SPA compared to CSU obtained from the same child compared to first few mLs - CSU = 25 (59.5%). Seven (16.7%) samples had ( &gt;10^7 ) organisms per mL. UTI specificity 92.8%</td>
<td>2 months</td>
<td>The success rate for SPA was 25% with 168 patients being subjected to SPA in order to obtain the 42 SPA samples.  All children confirmed at follow-up to show no clinical evidence of UTI.  Specimens showing no growth:  • SPA – 40 (95.2%). Positive samples &lt; 1,000 organisms pre mL  • First few mLs - CSU – 25 (59.5%). Seven (16.7%) samples had ( &gt;10^7 ) organisms per mL. UTI specificity 92.8%</td>
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### Methods for Urine Collection – Catheter Specimen urine (CSU) and Clean Voided Urine (CVU)

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<th>Method</th>
<th>Success Rate</th>
<th>Limitations</th>
<th>Additional Details</th>
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<tr>
<td>CSU</td>
<td>59.5%</td>
<td>Small single centre study. Unblinded study.</td>
<td>Unable to determine cut off values for bladder measurements to guide success using ultrasound.</td>
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<tr>
<td>SPA compared to CSU</td>
<td>59.5%</td>
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</tr>
<tr>
<td>First few mLs - CSU</td>
<td>25 (59.5%)</td>
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<td>Unable to determine cut off values for bladder measurements to guide success using ultrasound.</td>
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</table>

### Notes
- SPA = Suprapubic aspiration
- CSU = Clean Specimen Urine
- UTI = Urinary Tract Infection
- CFU = Colony Forming Units
- CI = Confidence Interval
- RR = Risk Ratio
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| Braude et al (1967) [34] | 68 | Comparative study. Single centre (UK). | Children with suspected UTI based on clinical presentation aged >1 month to 11 years. Paired samples: Non catheter (mid stream and bag) and catheter. | NA | • Second few mLs - CSU –33 (80.5%). UTI specificity 97.5%  
• Tip of catheter – CSU – 39 (93%)  
• CVU (n=16) – 5 (31.2%)  

Limitations: Predominantly male (83%). Non febrile patients. Trial designed to assess hypothesis that CSU causes UTI. Small single centre study. |
| Hoberman et al (1994) [35] | 2181 | Retrospective cohort. Single centre (US) | Children <24 months in ED from whom a urine specimen had been obtained by catheter. | NA | No growth on culture:  
• Catheter 39 (57%).  
• Mid stream 3 (4%)  
• Urine bag 0 (0%).  

Correspondence between catheter and non catheter specimens:  
• 54 of 68 cases (80%).  
• 7 (10%) of non catheter samples gave false negative.  

Limitations: No gold standard comparison. Reliance on clinical signs of UTI for identification of false positives. Small single centre with large age range. |
| Heldrich (2000) [36] | 254 | Retrospective cohort. Single centre (US) | Children aged < 2 months to >120 months presenting to ED with symptomatic UTI. Urine specimen collected by catheter (91%) or clean catch/bag (9%). Cut off for further investigation: ≥1000 CFU/mL. | NA | Contamination in <5x10⁷ CFU/L compared to ≥5x10⁷ samples:  
• 36 of 60 (60%) samples contaminated vs. 7 of 109 (6.4%): RR 9.34 (95% CI: 4.43, 19.7)  

Limitations: Study aims were not to define CFU cut off. No comparison with gold standard method. Retrospective analysis. |
| Cheng et al (2005) [38] | 952 | Retrospective cohort. Single centre (China) | Children aged 1 to 18 months who had catheter urine cultures performed. | NA | Of the 435 (46% of total) samples that were culture positive:  
• 352 (81%) were a single organism  
• 83 (19%) were mixed organisms.  

CFU cut of values in diagnosing UTI in uncircumcised males and females:  
• >10⁵ CFU  
  o Male: sen 98%, spec 68%, PPV 53%, NPV 99%.  
  o Female: sen 91%, spec 91%, PPV 67%, NPV 98%.  
• >10⁶ CFU  
  o Male: sen 88%, spec 90%, PPV 76%, NPV 96%.  

Limitations: No comparison with gold standard collection method. Study not designed to evaluate a CFU cut-off with value chosen essentially being arbitrary for identification of those warranting further investigation. |
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| Pryles et al (1959) [40]       | 170 | Prospective comparative study. Single centre (US) | Girls (2 to 12 years) admitted to the hospital and requiring collection of a urine sample. Three groups: Clean voided, non-clean voided, catheter. | NA        | Female: sen 81%, spec 95%, PPV 77%, NPV 96%.  
  >10⁵ CFU  
  Male: sen 81%, spec 96%, PPV 88%, NPV 93%.  
  Female: sen 69%, spec 96%, PPV 79%, NPV 94%.  
  Limitations: Only includes uncircumcised boys. No comparison with gold standard.  

| Aronson et al (1973) [42]      | 120 | Prospective comparative study Single centre (Sweden) | Infants (0-18 months) and children (3-12 years) submitted for SPA following diagnosis of bacteriuria or leucocyturia of doubtful significance from urine samples collected by clean bag (infants) or clean-voided mid-stream specimens (children). | NA        | Misleading information about bladder bacteriuria was obtained from clean-voided samples in 39 of the 120 (33%) patients (31 being false positives and 8 being false negatives).  
  Limitations: Single centre.  

| Saccharow and Pyles (1969) [26] | 154 | Prospective comparative study. Single centre (US) | Outpatients of a paediatric renal clinic aged 6 months to 12 years. SPA compared to clean void sample collected immediately following SPA. | NA        | In 45 (29%) children the SPA sample was sterile and clean-voided contained up to 1,000 CFU/ml.  
  In 13 children with UTI identified by SPA, 10 had CFU values greater than 10⁷ per ml, while 3 (23%) had relatively low CFU values between 10⁴ and 10⁷ per ml.  
  Limitations: Small single centre study.  

| Pryles (1961) [46]             | 27  | Prospective comparative study. Single centre (US). | Infants (2 weeks to 23 months) with UTI. Clean-voided sample compared to catheter. | NA        | In 9 (33%) infants with UTI, the CFU in clean-voided sample was between 10⁷ and 10⁸ per ml.  
  Limitation: Small single centre. No gold standard comparison. UTI diagnosed on basis of clinical evidence.  

| Li et al (2002) [54]           | 100 | Prospective cohort. Single centre (Hong Kong) | Infants (1-24 months) followed up for previous UTI. Urine sample collected by parents using sterile bag. Second bag | NA        | Positive results in first bag sample was obtained for 40 (40%) children.  
  Positive result in second bag after further instruction was 23 (23%) with the remaining 17 being considered as false positives in the first bag.  
  Of the second bag samples 14 were negative for nitrite and WBC but yielded significant growth on culture. Of these 12 were identified as false positives.  

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| Pylkkanen et al (1979) [58]                  | 477 | Unclear whether this is a retrospective cohort or a prospective study. Single centre (Finland) | Infants and children seen at outpatient clinic all of whom had urine sample collected by SPA. Clean-voided sample compared to SPA. | NA        | Sensitivity and specificity for clean-voided sample  
  - CSU ≥10⁶ CSU/ml:  
    o Asymptomatic 89% and 73%  
    o Symptomatic 91% and 95%  
  - CSU ≥10⁴ CSU/ml:  
    o Asymptomatic 93% and 70%  
    o Symptomatic 90% and 89%  
  Limitations: Small single centre trial. First bag results compared to second bag results rather than gold standard. Likely higher rate of UTI in this population. All boys (73% of sample) were uncircumcised. |
  Index tests: microscopy or dipstick tests used to diagnose UTI or an evaluation of urine sampling methods | NA        | Diagnostic test accuracy of CVU using SPA as the reference standard:  
  - Pooled positive LR 8.8 (95% CI: 2.6, 29.6) – significant heterogeneity  
  - Pooled negative LR 0.23 (95% CI: 0.18, 0.30) – non significant heterogeneity.  
  Limitations: Insufficient studies to investigate heterogeneity. |
| Wingerter et al (2011) [39]                  | 185 | Prospective cohort. Single centre (UK) | Convenience sample of children (<3 years) from whom urine sample was collected by bladder catheterisation.  
  Questionnaire administered to physician/nurse who collected sample.  
  Outcome: contamination of urine sample. | NA        | UTI was diagnosed in 18 (10%) and 140 (76%) had a clean sample. Contamination was identified in 27 (14.6%) of the samples, either on the basis of a non-pathogen or <10,000 CFU/mL or multiple pathogens.  
  Univariate analysis of potential predictors of contamination:  
  - Age <6 months: OR 6.8 (95%CI: 2.6, 17.9)  
  - Difficult catheterisation: OR 3.6 (95%CI: 1.5, 8.6)  
  - Uncircumcised boys: OR 5.7 (95%CI: 1.2, 29.4).  
  Limitations: Small size, single centre. Catheterisation performed by multiple clinicians of varying experience. Subjective assessment of ease of catheterisation. No confirmation that low colony count represented UTI or contamination. |
| Kraracan et al (2010) [57]                   | 1067 | Retrospective review of laboratory | Children aged 2 months to 16 years with suspected UTI. | NA        | Sterile urine bag used in 517 (49%), clean catch in 532 (50%), SPA in 11 (1%) and catheter in 7 (0.7%). |
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|          |   |                          | Urine samples for culture collected by sterile bag, midstream clean catch, catheter or SPA. |           | Contamination rates:  
- Sterile bag: 43.9% (P<0.001)  
- Clean catch: 14.3%  
- SPA: 9.1%  
- Catheter: 14.3%.  
Limitations: Single centre. Definition of contamination not defined with reliance on laboratory report. Not a paired analysis. |
| Slosky and Todd (1977) [61] | 787 | Retrospective review. Single centre (US) | Children who had SPA after presentation to hospital clinic. Indications for SPA were: severe illness with equivocal culture results from alternate sampling method, urinary tract abnormality or newborn with suspected sepsicaemia. Documented UTI defined by second positive SPA sample with the same organism or a CVU or CSU with >10^5 CFU/ml. Non-infected defined as those with second CVU or CSU or SPA that did not grow the same culture or was sterile. | NA | Of the 787 consecutive SPA samples:  
- 659 (84%) were sterile and 65 (8%) were documented as infected.  
- 55 (85%) children with UTI had CFU counts per ml <10^6  
- 12 SPA samples had CFU/ml counts <10^4 of these 6 were false positives (i.e. not infected).  
- All SPA samples with CFU/ml counts >10^4 were documented as infected.  
- 2 (3%) boys had infection caused by *S. epidermis*  
- 7 (11%) children had mixed culture infection, 5 of whom had significant urinary tract abnormalities.  
Limitations: Retrospective study, single centre. Small number with confirmed UTI. |
| Coulthard et al (2010) [62] | 203 | Comparative study (paired urine samples). Single centre (UK) | Children with suspected UTI able to provide a second urine sample. Collection of sequential samples using sterile pad for infants, clean potties for toddlers and CCU samples for older children. Excluded apparently positive UTI on basis of contradictory results between first and second sample. | NA | Of the 203 children:  
- 90 (40.3%) of the first samples were sterile.  
- 35 (17.2%) of the first samples grew organisms unlikely to be uropathogens.  
- 78 (38.4%) of the first sample grew likely uropathogens of whom 57 had CFU counts per ml ≥10^5.  
The combination of 2 samples identified the following:  
- 84 uninfected children (2 sterile samples)  
- 41 case subjects likely to have UTI  
- 78 with bacterial contamination.  
Sensitivity and specificity based on differing organism cut off:  
- 10^4: First sample: 1.00, 0.869. Both samples: 1.00, 0.904  
- 10^5: First sample: 1.00, 0.928. Both samples: 1.00, 0.964  
- 10^6: First sample: 1.00, 0.952. Both samples: 1.00, 0.994  
- 10^7: First sample: 0.81, 0.976. Both samples: 0.75, 1.00 |
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| Kotoula et al  | 57      | Prospective cohort. Single centre (Greece) | Children (aged 2 months to 9 years) with a first episode of proven UTI. Urine samples collected by SPA, CSU, CVU or sterile bag. DMSA performed within 7 days of confirmed UTI to diagnose UTI with RPI. Leucocyte count, ESR, serum CRP and PCT in blood samples collected prior to antibiotic treatment. | NA        | • 27 (47%) diagnosed as having UTI with RPI. The median PCT levels increased significantly (P=0.004) with the extent of RPI as determined by DMSA.  
• Sensitivity, specificity, PPV and NPV for UTI with RPI for varying PCT cut-off values:  
  - ≥0.50 ng/ml: 100% (95%CI: 87-100), 83% (95%CI: 65-94), 84%, 100%  
  - ≥0.85 ng/ml: 89% (95%CI: 70-97), 97% (95%CI: 81-100), 96%, 91%  
  - ≥1.20 ng/ml: 85% (95%CI: 65-95), 100% (95%CI: 88-100), 100%, 88%  
Limitations: Single centre study with small number of UTI. No gold standard for comparison with UTI reliant on comparison of the sequential samples only. |
| (2009) [63]    |         |                                  |                                                                                                 |           | **Nikfar et al (2010) [64]**                                                                                                                                                                                              |
|                | 100     | Prospective case series. Single centre (Iran). | Children (aged 1 month to 14 years) admitted to clinic with fever and confirmed UTI on basis of positive urine culture. DMSA performed within 5 days of admission. Leucocyte count, ESR, serum CRP and PCT in blood samples collected prior to antibiotic treatment. | Na        | • 63 (63%) diagnosed with upper UTI on basis of DMSA  
• Sensitivity, specificity, PPV and NPV for upper UTI using a PCT cut-off value of ≥0.50 ng/ml:  
  - 77% (95%CI: 65-87), 89% (95%CI: 75-97), 92% (95% CI: 81-98), 71% (95% CI: 56-83)  
Limitations: Single centre study with small number of upper UTI. No description of basis for patient selection (e.g. consecutive over a set period). |
| Mantadakis et  | 10 studies (627 children) | Systematic review of prospective studies. (Search up to February 2009). | Prospective studies of children of any age diagnosed as having UTI with baseline PCT and DMSA performed within 14 days of presentation. | NA        | • All studies described as prospective cohorts.  
• Pooled DOR for RPI using a PCT cut-off between 0.5 and 0.6 ng/mL:  
  - 14.25 (95%CI: 4.70, 43.23)  
Limitations: Significant unaccounted heterogeneity. Half of the studies did not exclude children with a prior UTI. Majority of studies excluded non-febrile children. Some studies reported almost exclusively on girls. Variable age groups between studies with some studies reporting mainly on infants. |
<p>| al (2009) [65] |         |                                  |                                                                                                 |           |                                                                                                                                                                                                                      |</p>
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| Ipek et al (2012) [67] | 66 | Prospective analysis. Single centre (Turkey) | Children (1 month to 14 years) admitted with first UTI. Serum concentrations of CRP, OPCT and complete blood count determined in blood sample taken at admission for all children. VUR diagnosis by VCUG within 3 months of UTI treatment. | NA | VUR diagnosed in 18 children (27%).  
  - PCT >0.50 ng/mL:  
    - Sensitivity 72.2% (95%CI: 46.5, 90.2)  
    - Specificity 70.8% (95%CI: 55.9, 83).  
  - PCT >0.56 ng/mL:  
    - Sensitivity 66.7% (95%CI: 41, 86.6)  
    - Specificity 77.1% (95%CI: 62.7, 88).  
  Limitations: Single centre study. Small number with VUR. |
| Leroy et al (2011) [66] | 12 studies (526 children) | Systematic review of prospective studies (Search up to May 2008) | Studies of consecutively included children (1 month to 4 years) with a first febrile UTI, PCT measurement, and an early renal DMSA within 7 days of UTI diagnosis. | NA | Diagnosis of VUR based on a PCT ≥0.5 ng/L:  
  - Sensitivity: 83% (95%CI: 71.91)  
  - Specificity: 43% (95%CI 38, 47)  
Across the studies, 10% of children had high grade VUR≥3 which was associated with PCT ≥0.5ng/mL.  
  - Adjusted odds ratio: 4.8 (95%CI 1.3, 17.6)  
Limitations: Small number of children with VUR. Heterogeneity between studies not assessed, pooled data from different centres and analysed data as hierarchical. |
| Leroy et al (2012) [68] | 494 | Secondary analysis of prospective studies from 8 centres (Israel and Europe). | Consecutive children (1 month to 4 years) hospitalised with first febrile UTI. | NA | High grade VUR≥3, in 11% of children. The sensitivity and specificity associated with the following decision rule:  
  - Cystography should be performed on children with a first febrile UTI in cases with ureteral dilatation and serum PCT ≥0.17 ng/mL.  
    - Sensitivity 86% (95%CI: 74, 93)  
    - Specificity 47% (95% CI: 42, 51)  
Limitations: Focus is only on high grade VUR. Centres used differing urine collection techniques and differing losses to follow-up. |