Cochrane Library

Cochrane Database of Systematic Reviews

Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children (Review)

Shaikh KJ, Osio VA, Leeflang MMG, Shaikh N

Shaikh KJ, Osio VA, Leeflang MMG, Shaikh N.
Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children.
Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD009185.
DOI: 10.1002/14651858.CD009185.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Diagnostic Test Accuracy Review]

Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children

Kai J Shaikh[1], Victor A Osio[2], Mariska MG Leeflang[3], Nader Shaikh[4]

[1]Department of Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA. [2]Department of General Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA. [3]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands. [4]General Academic Pediatrics, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Contact address: Nader Shaikh, Nader.Shaikh@chp.edu.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2020.

Citation: Shaikh KJ, Osio VA, Leeflang MMG, Shaikh N. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No.: CD009185. DOI: 10.1002/14651858.CD009185.pub3.

ABSTRACT

Background

In children with urinary tract infection (UTI), only those with pyelonephritis (and not cystitis) are at risk for developing long-term renal sequelae. If non-invasive biomarkers could accurately differentiate children with cystitis from children with pyelonephritis, treatment and follow-up could potentially be individualized. This is an update of a review first published in 2015.

Objectives

The objectives of this review were to 1) determine whether procalcitonin (PCT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) can replace the acute DMSA scan in the diagnostic evaluation of children with UTI; 2) assess the influence of patient and study characteristics on the diagnostic accuracy of these tests, and 3) compare the performance of the three tests to each other.

Search methods

We searched MEDLINE, EMBASE, DARE, Web of Science, and BIOSIS Previews through to 17th December 2019 for this review. The reference lists of all included articles and relevant systematic reviews were searched to identify additional studies not found through the electronic search.

Selection criteria

We only considered published studies that evaluated the results of an index test (PCT, CRP, ESR) against the results of an acute-phase ^{99}Tc-dimercaptosuccinic acid (DMSA) scan (conducted within 30 days of the UTI) in children aged 0 to 18 years with a culture-confirmed episode of UTI. The following cut-off values were used for the primary analysis: 0.5 ng/mL for procalcitonin, 20 mg/L for CRP and 30 mm/hour for ESR.

Data collection and analysis

Two authors independently applied the selection criteria to all citations and independently abstracted data. We used the bivariate model to calculate pooled random-effects pooled sensitivity and specificity values.

Main results

A total of 36 studies met our inclusion criteria. Twenty-five studies provided data for the primary analysis: 12 studies (1000 children) included data on PCT, 16 studies (1895 children) included data on CRP, and eight studies (1910 children) included data on ESR (some studies

had data on more than one test). The summary sensitivity estimates (95% CI) for the PCT, CRP, ESR tests at the aforementioned cut-offs were 0.81 (0.67 to 0.90), 0.93 (0.86 to 0.96), and 0.83 (0.71 to 0.91), respectively. The summary specificity values for PCT, CRP, and ESR tests at these cut-offs were 0.76 (0.66 to 0.84), 0.37 (0.24 to 0.53), and 0.57 (0.41 to 0.72), respectively.

Authors' conclusions

The ESR test does not appear to be sufficiently accurate to be helpful in differentiating children with cystitis from children with pyelonephritis. A low CRP value (< 20 mg/L) appears to be somewhat useful in ruling out pyelonephritis (decreasing the probability of pyelonephritis to < 20%), but unexplained heterogeneity in the data prevents us from making recommendations at this time. The procalcitonin test seems better suited for ruling in pyelonephritis, but the limited number of studies and the marked heterogeneity between studies prevents us from reaching definitive conclusions. Thus, at present, we do not find any compelling evidence to recommend the routine use of any of these tests in clinical practice.

PLAIN LANGUAGE SUMMARY

Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children

What is the issue?

In some children with urinary tract infection (UTI), the infection is localized to the bladder (lower urinary tract). In others, bacteria ascend from the bladder to the kidney (upper urinary tract). Only children with upper urinary tract involvement are at risk for developing permanent kidney damage. If non-invasive biomarkers could accurately differentiate children with lower urinary tract disease from children with upper urinary tract disease, treatment and follow-up could potentially be individualized.

What did we do?

We examined the usefulness of three widely available blood tests (procalcitonin, C-reactive protein, erythrocyte sedimentation rate) in differentiating upper from lower urinary tract disease. We found 34 relevant studies of which 24 provided data for our primary outcome. Twelve studies (1000 children) provided data for the procalcitonin test; 16 studies (1895 children) provided data for the C-reactive protein test, and 8 studies (1910 children) provided data for the erythrocyte sedimentation rate test.

What did we find?

We found all three tests to be sensitive (summary sensitivity values ranged from 81% to 93%), but not very specific (summary specificity values ranged from 37% to 76%).

Conclusions

None of the tests were accurate enough to allow clinicians to confidently differentiate upper from lower urinary tract disease.

SUMMARY OF FINDINGS

Summary of findings 1. Accuracy of procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of pyelonephritis in children

Accuracy of procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of pyelonephritis in children

Population: children with UTI

Setting: not specified

Tests: PCT, CRP, ESR

Reference test: DMSA renal scan conducted within 1 month of the diagnosis of UTI

Test (cut-off)	Studies (participants)	Summary sensitivity (95% CI)	Summary specificity (95% CI)	False negative rate in a population of 1000[1]	False positive rate in a population of 1000[1]	Post-test probability of pyelonephritis given a positive test[1]	Post-test probability of pyelonephritis given a negative test[1]	Heterogeneity between studies[2]
PCT (0.5 ng/mL)	12 (1000)	0.81 (0.67 to 0.90)	0.76 (0.66 to 0.84)	114	96	84%	27%	Very high
CRP (20 mg/L)	16 (1895)	0.93 (0.86 to 0.96)	0.37 (0.24 to 0.53)	42	252	69%	22%	High
ESR (30 mm/hour)	8 (1910)	0.83 (0.71 to 0.91)	0.57 (0.41 to 0.72)	102	172	74%	31%	Moderate

[1]Assuming a pre-test probability of 60% (see text for justification)

[2]Degree of heterogeneity assessed visually from the ROC plot

DMSA - ^{99}Tc-dimercaptosuccinic acid; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; PCT - procalcitonin; UTI - urinary tract infection

BACKGROUND

Urinary tract infection (UTI), which affects approximately 3% of young children annually, is the most common serious bacterial infection in children (Freedman 2005). In some children with UTI, infection is localized to the bladder (cystitis). In others, bacteria ascend from the bladder to the kidney causing acute pyelonephritis. Only children with pyelonephritis (and not cystitis) are at risk for developing long-term renal sequelae (e.g. renal parenchymal injury, hypertension). Accordingly, there has been interest in tests that can accurately differentiate children with cystitis from children with pyelonephritis.

However, accurate and non-invasive tests that can differentiate the conditions have not been readily available. Signs and symptoms alone, especially in preverbal children, cannot be used to reliably differentiate children with cystitis from children with pyelonephritis (Coulthard 2009; Shaikh 2008). For example, although the presence of high fever (> 39°C) is suggestive of pyelonephritis (Shaikh 2007), many children with cystitis also have fever. Although ^{99}Tc-dimercaptosuccinic acid (DMSA) scan has been shown to be accurate in identifying pyelonephritis (sensitivity, specificity of 0.86, 0.91, respectively; Craig 2000), it has not gained favour for use as a screening test because: 1) it requires an additional trip to the hospital; 2) it necessitates placement of an intravenous line; 3) it may require sedation; 4) it incurs an additional cost; 5) it requires specialized equipment and personnel, which may not be available locally; 6) its results are not available at the time of UTI diagnosis; 7) differentiation of old scars from pyelonephritis may be difficult in children with pervious UTIs or dysplasia; and 8) it requires exposure to radiation.

With the growing literature on non-invasive biomarkers, it is important to systematically review and compare the accuracy of these tests. This review examined whether readily-available blood tests (procalcitonin (PCT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)) can be used to accurately differentiate children with pyelonephritis from children with cystitis. This review was initially published in 2015; this update has added 12 new studies.

Target condition being diagnosed

Pyelonephritis (bacterial infection involving one or both kidneys) is the target condition of interest.

Index test(s)

Procalcitonin - a precursor of the hormone calcitonin released from the thyroid gland in response to systematic infection - has recently been proposed as a marker for pyelonephritis. CRP, an inflammatory factor produced in the liver in response to inflammation, has also been proposed as a marker for pyelonephritis. Finally, ESR, which measures the speed (mm/hour) at which erythrocytes fall in a sample of blood, is increased when inflammatory factors like fibrinogen are present in the serum. These tests can be obtained at the time of diagnosis and are available in most outpatient general practice clinics or hospitals.

Clinical pathway

Currently, young febrile infants with UTI are generally treated with 10 days of antimicrobials. In some countries imaging is also performed after the first UTI.

Prior test(s)

No prior tests are available.

Role of index test(s)

If index tests could accurately differentiate acute pyelonephritis from cystitis, children with cystitis could potentially be treated with shorter courses of antibiotics and without further imaging.

Alternative test(s)

Although several other tests have been proposed (e.g. urinary interleukin-6 and interleukin-8, neutrophil gelatinase-associated lipocalin), they are not reviewed here.

Rationale

Differentiating children with cystitis from children with pyelonephritis could be useful in several ways. Children with pyelonephritis could require longer courses of antibiotics than children with cystitis. One recent study suggests that children with significant pyelonephritis may benefit from treatment with corticosteroids (Huang 2011). Furthermore, children with one or more episodes of pyelonephritis may benefit from more aggressive follow-up (e.g. antibiotic prophylaxis, imaging). Although little evidence exists that supports the need to manage children with pyelonephritis differently from children with cystitis, this evidence will likely emerge, especially if reliable biomarkers become available.

A previous systematic review has examined the accuracy of procalcitonin in differentiating cystitis from pyelonephritis children (Mantadakis 2009) and found significant heterogeneity in the accuracy estimates from the various primary studies. An individual patient data meta-analysis published in 2013 examining the accuracy of procalcitonin in predicting pyelonephritis reported a sensitivity and specificity of 71% (67% to 74%) and a specificity of 72% (67% to 76%) at the 0.5 ng/mL cut-off (Leroy 2013). To our knowledge, there have been no systematic reviews of the accuracy of CRP or ESR in the diagnosis of pyelonephritis. This systematic review aimed to provide evidence on the diagnostic performance of procalcitonin, ESR and CRP paying special attention to investigation of sources of heterogeneity.

OBJECTIVES

The objectives of this review were:

- To determine whether any of these laboratory tests (procalcitonin, CRP, ESR) can replace (Bossuyt 2006) the acute DMSA scan in the diagnostic evaluation of children with UTI
- To assess the influence of patient and study characteristics on the diagnostic accuracy of these tests
- To compare the performance of the three tests to each other.

METHODS

Criteria for considering studies for this review

Types of studies

We considered published studies that evaluated the results of an index test (procalcitonin, CRP, ESR) against the results of an acute-phase DMSA scan only. Cross-sectional, cohort and case-control designs were all acceptable.

Participants

Studies including children from birth to 18 years of age with a culture-confirmed episode of UTI were eligible for inclusion. UTI was defined as growth of one or two organisms at:

- ≥ 10^4 CFU/mL from a catheterized specimen, or
- ≥ 10^5 CFU/mL clean catch, midstream, or bag specimen, or
- any growth from a suprapubic specimen (Hoberman 1994).

Studies that did not meet these minimum, and rather permissive criteria, were excluded. Because specimens obtained using a perineal bag are often falsely positive, the effect of including studies in which some of the urine specimens were collected using a bag was explored. Because antibiotics can influence the levels of inflammatory markers, only studies in which blood (for ESR, CRP, or procalcitonin) was collected before administration of antibiotics were included.

Index tests

Studies that examined the accuracy of procalcitonin, CRP, or ESR were considered.

Target conditions

Acute pyelonephritis as evidenced by photopenia (with or without a change in contours) on an acute-phase DMSA scan was the target condition of interest.

Reference standards

The current reference standard for assessing the presence and extent of pyelonephritis is to conduct a planar DMSA renal scan. When radiolabeled DMSA is given to patients whose tubular cell function is impaired because of pyelonephritis, the scan will show a photon-deficient area(s). This test is conducted by trained nuclear medicine physicians in a hospital's radiology department. For the purpose of this analysis, any photopenia (with or without a loss of contours) was considered as pyelonephritis.

Only studies in which a planar DMSA scan was performed within the first month of the diagnosis of UTI were included. Because the accuracy of the DMSA scan decreases significantly if obtained later than two weeks after the diagnosis of UTI (Stokland 1996), we conducted meta-regression with respect to timing of the DMSA scan. Because single-photon emission computed tomography (SPECT) DMSA scans have much lower specificity (66%, Craig 2000), studies in which SPECT DMSA scans were used were not included in this review.

Search methods for identification of studies

Electronic searches

We searched MEDLINE (OvidSP), EMBASE (OvidSP), Web of Science, BIOSIS Previews (Web of Science) and the Cochrane Register of Diagnostic Test Accuracy Studies. The most recent search was undertaken on 17 December 2019 using search strategies developed in consultation with the Cochrane Kidney and Transplant Information Specialist.

DARE (Database of Reviews of Abstracts of Effects) was searched via *The Cochrane Library* for relevant systematic reviews.

Strategies for MEDLINE, EMBASE and BIOSIS Previews are presented in Appendix 1. Strategies for DARE and Web of Science were adapted from these.

Searching other resources

The reference lists of all included articles and relevant systematic reviews were reviewed to identify additional studies not found through the electronic review.

Data collection and analysis

Two authors independently applied the selection criteria to all citations (titles and abstracts).

Selection of studies

The full-text of all articles identified by either author was retrieved and reviewed.

Data extraction and management

For each study meeting the inclusion criteria, we used a standardized form to abstract the following information.

- Age range of participants
- Fever (whether measured or by touch) required (yes, no)
- Prospective (yes, no)
- Used perineal bags to collect urine specimen (yes, no)
- Excluded children with previous UTI (yes, no)
- Excluded children with genitourinary abnormalities (yes, no)
- Maximal delay in DMSA scan (≤ 7 days versus 7 to 14 days versus 14 to 30 days).

Two by two tables were constructed independently by two authors from the data in the publication. Only studies for which two by two data were available (or could be reconstructed) were included.

Assessment of methodological quality

Two authors used the QUADAS-2 questionnaire (Whiting 2011), a validated four-domain tool (patient selection, the index test, the reference standard, and flow/timing) tool specifically designed for review authors to evaluate quality of diagnostic accuracy studies, to independently assess the quality of all studies that met our inclusion criteria. Disagreements were resolved by discussion. See Appendix 2 for a description of the QUADAS-2 items. We applied QUADAS- 2 signalling questions to each study and report results in the graphical form. We evaluated the effect of excluding studies with a high or unclear risk of bias any of the domains.

Statistical analysis and data synthesis

The primary analysis was to compare each test against the reference standard and to estimate summary sensitivity and specificity values. Different studies, however, used different cut-off values (or thresholds) when reporting accuracy. Accordingly, we considered two different options for analysing these data: describing how sensitivity and specificity values varies with the changing threshold by estimating a summary receiver operating characteristic curve for each test, or estimating the average sensitivity and specificity of each test at one cut-off (per test). We chose the latter option because the majority of the studies we found reported data for the following cut-offs: 0.5 ng/mL for procalcitonin; 20 mg/L for CRP, and 30 mm/hour for ESR. Early

studies established that a cut-off of 20 mg/L for CRP was ideal for discriminating between cystitis and pyelonephritis (Hanson 1983; Pylkkanen 1981). Therefore, this was the cut-off most commonly reported and the cut-off which we used for the primary analysis. For procalcitonin, a cut-off of 0.5 ng/mL has been recommended by the manufacturer and is widely accepted. In contrast, for the ESR test, no cut-off has been established. A value of > 10 mm/hour is considered abnormal but very few studies used this cut-off. Accordingly, for the primary analysis, we used the cut-off most commonly reported in the studies meeting our inclusion criteria: 30 mm/hour. Authors of papers using other cut-offs were contacted for data relative to the cut-offs listed. Articles for which no data could be obtained for the above cut-offs were excluded from the primary analyses. Nevertheless, to give readers a sense of how much data was excluded, forest plots showing the sensitivity and specificity of the tests at other cut-offs are presented.

Data from the two-by-two tables were used to calculate sensitivity and specificity for each study and to derive sensitivity and specificity forest plots. We used the bivariate model to calculate random effects pooled sensitivity and specificity values. This model included both the logit-transformed sensitivity and specificity and thus took into account the correlation between the sensitivity and specificity across studies. We calculated the 95% confidence ellipse around the summary estimate of sensitivity and specificity. All results were transformed back to the original scale and plotted in the receiver operating characteristic (ROC) space. Proc NLMIXED in SAS 9.4 was used for the meta-analysis (SAS 2011).

In some studies more than one test was conducted on the same children. Accordingly, the accuracy of the tests can be directly compared with each other (direct comparison) (Hayen 2010). We performed direct comparisons when there were at least four studies with data comparing two tests. For the secondary analysis, we present forest plots showing the sensitivity and specificity of the tests at other cut-offs are presented.

Investigations of heterogeneity

We used meta-regression (Proc NLMIXED, SAS 2011) to investigate heterogeneity. The influence of the following factors on accuracy was investigated.

1. Fever required (yes, no)
2. Used bag-collected specimen (yes, no)
3. Timing of DMSA scan (≤ 7 days versus 7 to 14 days versus 15 to 30 days) after diagnosis of UTI.

Sensitivity analyses

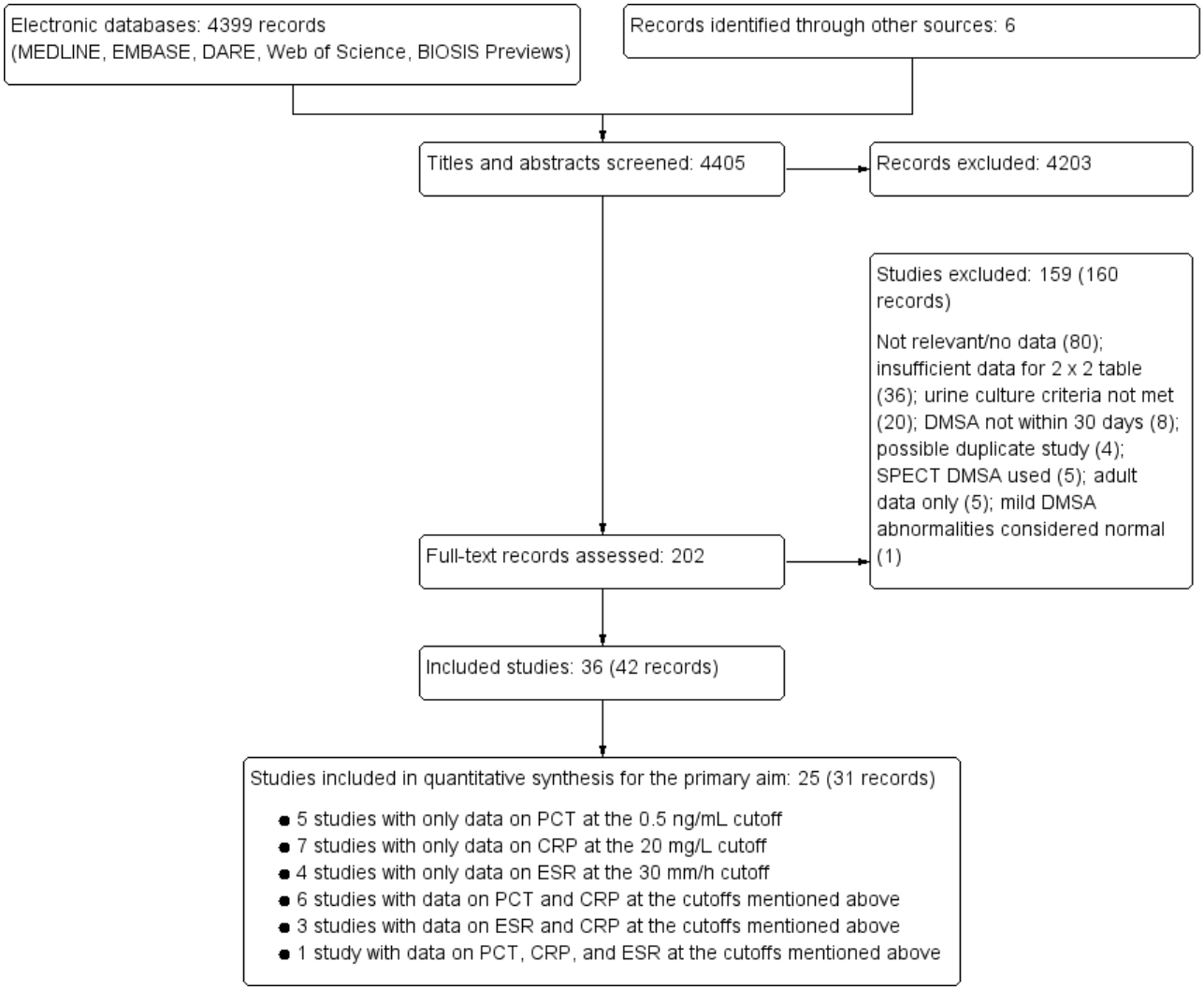
Because scars from prior UTIs or congenital scars may be confused with acute pyelonephritis on DMSA, we examined the effects of including studies that enrolled children with a history of UTI or major urologic or renal anomalies (other than vesicoureteric reflux) on the results. We also investigated the effect of excluding studies at high risk of bias.

RESULTS

Results of the search

The results of the search strategy are shown in Figure 1. Of the 4405 records were identified, 202 records were retrieved and reviewed. A total of 36 studies (42 records) met our inclusion criteria; 13 authors were successfully contacted for clarification and additional data. Twenty-five studies provided data for the primary analysis: 12 studies (1000 children) included data on procalcitonin (Barati 2016; Bigot 2005; Bouguila 2013; Bressan 2009; Chen 2013; Kim 2017; Kotoula 2009a; Mahyar 2014; Nikfar 2010; Shaikh 2019; Sheu 2011; Tuerlinckx 2005); 16 studies included data on CRP (1895 children) (Benador 1997; Bigot 2005; Bouguila 2013; Bressan 2009; Chen 2013; Hoberman 1999; Kotoula 2009a; Levtchenko 2001; Martin Aguado 2000; Montini 2007; Nikfar 2010; Printza 2012; Sheu 2007; Taskinen 2005; Tuerlinckx 2005; Xu 2014), and eight studies (1910 children) included data on ESR tests (Donoso 2004; Fretzayas 2000; Hoberman 1999; Kotoula 2009a; Mahyar 2014; Mohkam 2010; Montini 2007; Tekin 2015). Some studies had data on more than one test.

Figure 1. Study flow diagram
CRP - C-reactive protein; DMSA - ^{99}Tc-dimercaptosuccinic acid; ESR - erythrocyte sedimentation rate; PCT - procalcitonin; SPECT - single-photon emission computed tomography



A listing of the excluded studies and their characteristics is provided (Characteristics of excluded studies).

Methodological quality of included studies

An important methodological limitation was that of the 36 included studies, 12 had an unclear or high risk of bias for the *Patient Selection* domain (Figure 2). Radiologists were blinded to the test results in only 15 studies. However, because the interpretation of the DMSA scan is largely objective, it is unlikely that the lack of blinding would have biased the results. Other limitations include the use of bag specimen, late performance of the DMSA scan, and inclusion of children without fever. None of the studies included information on uninterpretable tests or on uninterpretable reference standards. Some of these aforementioned limitations are not reflected in the QUADAS-2 checklist (Figure 2). None of the included studies used a case-control design.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

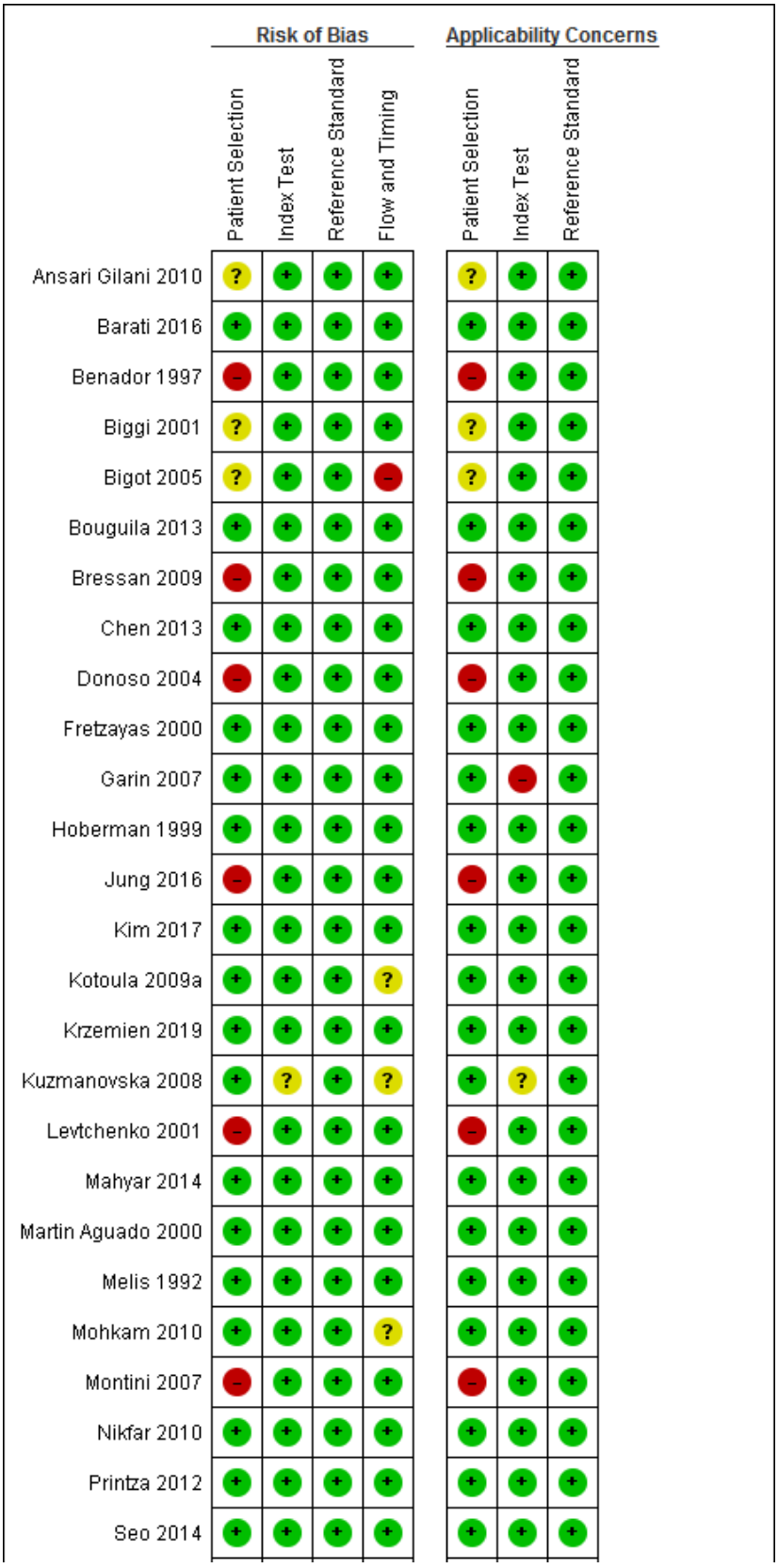
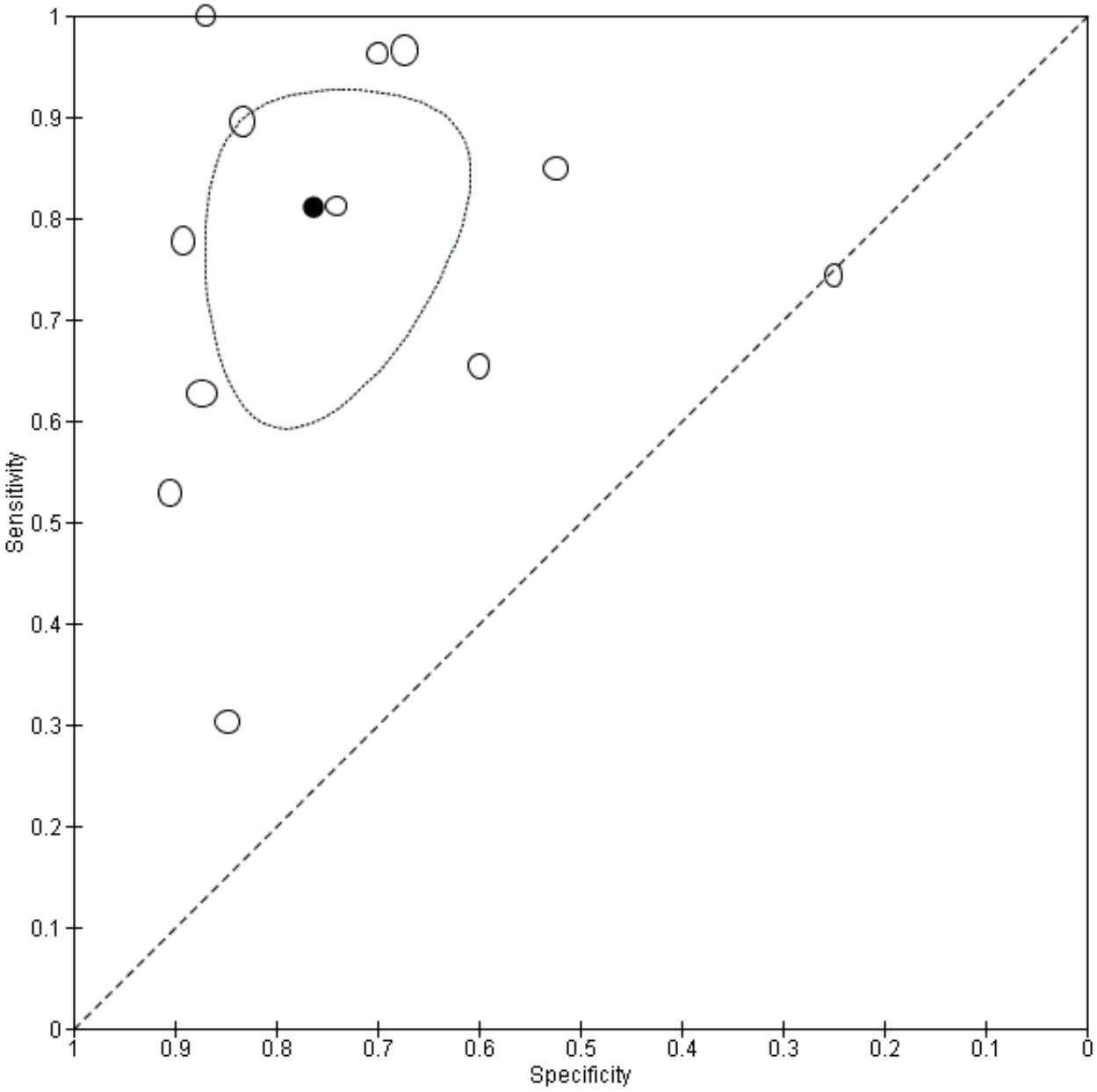


Figure 2. (Continued)

Findings

For the procalcitonin test, 12 studies reported data for the 0.5 ng/mL cut-off. The summary sensitivity and specificity estimates were 0.81 (0.67 to 0.90) and 0.76 (0.66 to 0.84), respectively (Figure 3). However, substantial heterogeneity between studies limits our confidence in these summary measures (Data table 1). One study (Bigot 2005) reported paired sensitivity/specificity values that were both 90% or higher (i.e. comparable to the DMSA), but the remainder of the studies reported much lower accuracy values. Sensitivity analysis was limited because of the small number of studies (Table 1). Meta-regression did not show statistical significance evidence ($P < 0.05$) of an association between any of the covariates (fever, use of bags to collect urine samples, delay in performance of the DMSA) and test accuracy. Pooled sensitivity and specificity values were similar when we excluded studies with high risk of bias: 0.80 (0.65 to 0.89) and 0.77 (0.65 to 0.85), respectively. Nine studies reported data using cut-offs other than 0.5 ng/mL; a forest plot of the sensitivity and specificity at these cut-offs is shown in Figure 4. As expected, the test appeared to be more specific at cut-off values higher than 0.5 ng/mL.

Figure 3. Summary ROC plot of procalcitonin > 0.5 ng/mL (solid point = pooled accuracy; dotted oval = 95% confidence region)



Test 1. PCT > 0.5 ng/mL

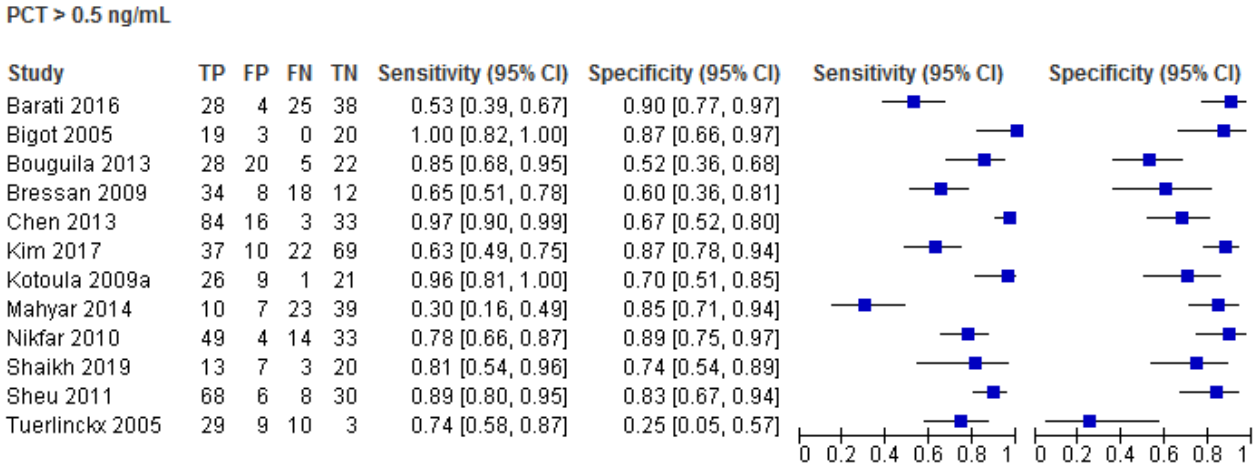
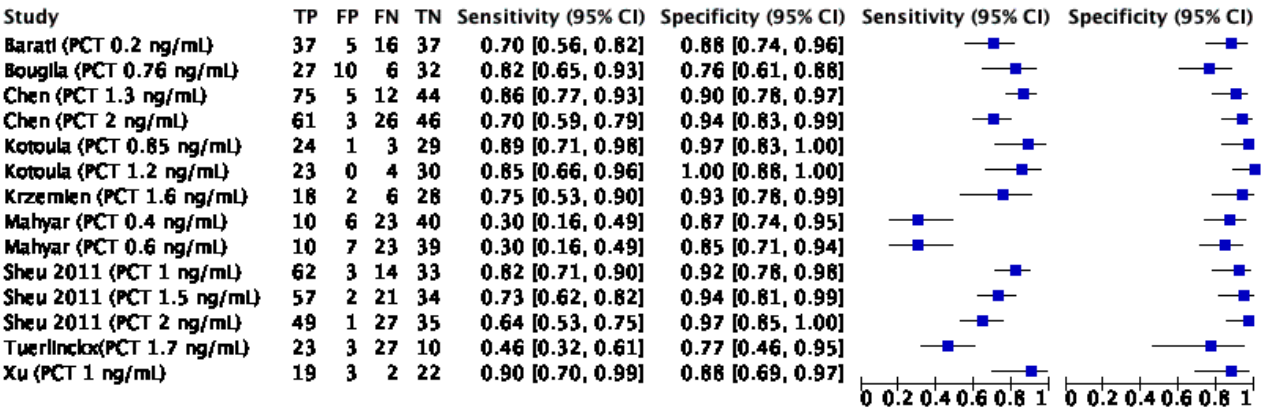
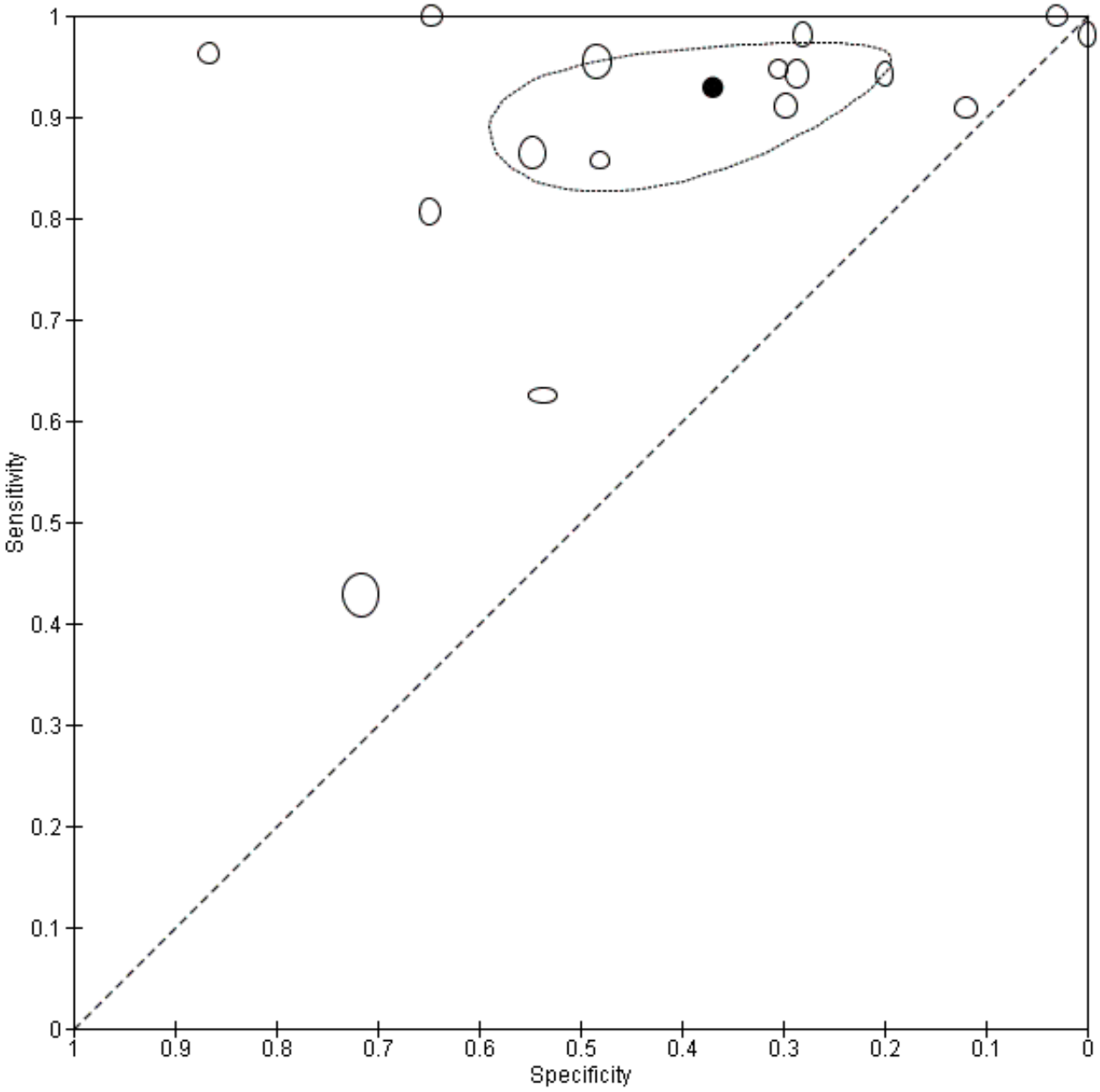


Figure 4. Forest plot of PCT at cut-offs other than 0.5 ng/mL



For the CRP test, we found 16 studies that reported data for the 20 mg/L cut-off. The summary sensitivity and specificity estimates were 0.93 (0.86 to 0.96) and 0.37 (0.24 to 0.53), respectively (Figure 5). There was considerable heterogeneity among accuracy values from the various studies (Data table 2). Meta-regression did not show statistical evidence (P < 0.05) of an association between covariates (fever, use of bags to collect urine samples, delay in performance of the DMSA) and test accuracy. However, because of the small number of studies, we had limited power to detect differences. Pooled sensitivity and specificity values were similar when we excluded studies with high risk of bias: 0.93 (0.87 to 0.96) and 0.42 (0.24 to 0.61), respectively. Although sensitivity analysis was limited, the specificity of the test was somewhat improved when we limited the analysis to studies in which bag collection was not used (Table 1). Twenty-three studies reported data using cut-offs other than 20 mg/L; a forest plot showing the sensitivity and specificity at these cut-offs is shown in Figure 6. None of the studies reported paired sensitivity and specificity values that were both close to 90%.

Figure 5. Summary ROC plot of C-reactive protein > 20 mg/L (solid point = pooled accuracy; dotted oval = 95% confidence region)



Test 2. CRP > 20 mg/L

CRP > 20 mg/L

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Benador 1997	108	33	17	40	0.86 [0.79, 0.92]	0.55 [0.43, 0.66]
Bigot 2005	18	16	1	7	0.95 [0.74, 1.00]	0.30 [0.13, 0.53]
Bouguila 2013	30	37	3	5	0.91 [0.76, 0.98]	0.12 [0.04, 0.26]
Bressan 2009	49	16	3	4	0.94 [0.84, 0.99]	0.20 [0.06, 0.44]
Chen 2013	82	35	5	14	0.94 [0.87, 0.98]	0.29 [0.17, 0.43]
Hoberman 1999	145	48	7	45	0.95 [0.91, 0.98]	0.48 [0.38, 0.59]
Kotoula 2009a	26	4	1	26	0.96 [0.81, 1.00]	0.87 [0.69, 0.96]
Levtchenko 2001	53	18	1	7	0.98 [0.90, 1.00]	0.28 [0.12, 0.49]
Martin Aguado 2000	51	33	5	14	0.91 [0.80, 0.97]	0.30 [0.17, 0.45]
Montini 2007	116	48	155	121	0.43 [0.37, 0.49]	0.72 [0.64, 0.78]
Nikfar 2010	50	13	12	24	0.81 [0.69, 0.90]	0.65 [0.47, 0.80]
Printza 2012	10	38	6	44	0.63 [0.35, 0.85]	0.54 [0.42, 0.65]
Sheu 2007	41	12	0	22	1.00 [0.91, 1.00]	0.65 [0.46, 0.80]
Taskinen 2005	29	32	0	1	1.00 [0.88, 1.00]	0.03 [0.00, 0.16]
Tuerlinckx 2005	53	14	1	0	0.98 [0.90, 1.00]	0.00 [0.00, 0.23]
Xu 2014	18	13	3	12	0.86 [0.64, 0.97]	0.48 [0.28, 0.69]

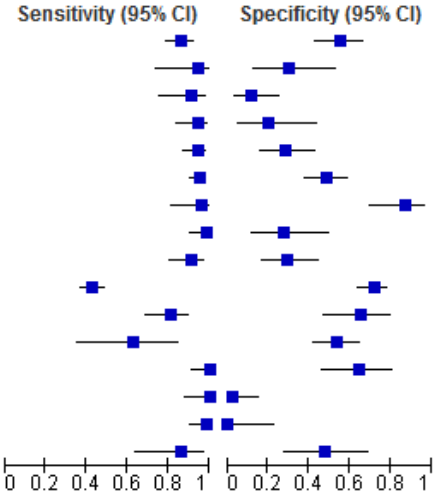
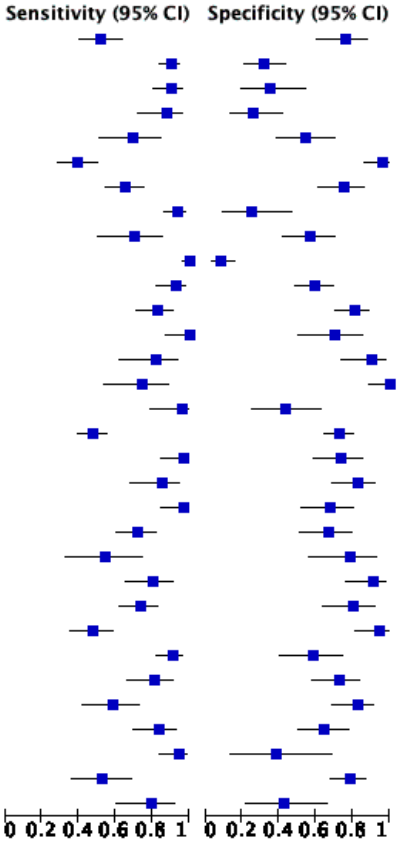


Figure 6. Forest plot of CRP at cut-offs other than 20 mg/L

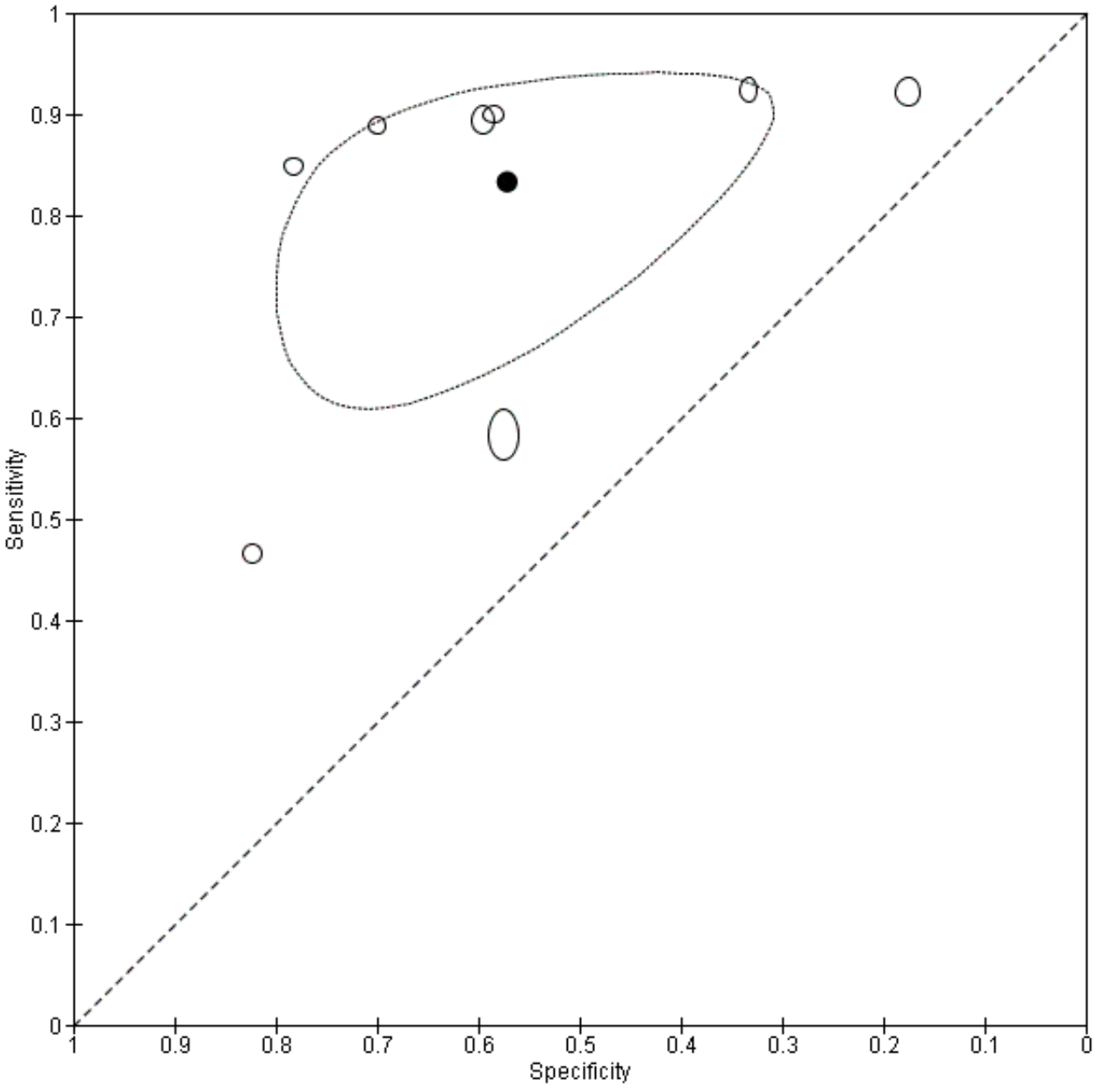
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ansari Gilani (CRP 30 mg/L)	40	10	37	32	0.52 [0.40, 0.63]	0.76 [0.61, 0.88]
Benador (CRP 10 mg/L)	113	50	12	23	0.90 [0.84, 0.95]	0.32 [0.21, 0.43]
Biggi (CRP 400 mg/L)	63	20	7	11	0.90 [0.80, 0.96]	0.35 [0.19, 0.55]
Bouglia (CRP 40 mg/L)	29	31	4	11	0.88 [0.72, 0.97]	0.26 [0.14, 0.42]
Bouglia (CRP 70 mg/L)	23	19	10	23	0.70 [0.51, 0.84]	0.55 [0.39, 0.70]
Chen (CRP 100 mg/L)	34	2	53	47	0.39 [0.29, 0.50]	0.96 [0.86, 1.00]
Chen (CRP 50 mg/L)	57	12	30	37	0.66 [0.55, 0.75]	0.76 [0.61, 0.87]
Donoso (CRP 200 mg/L)	86	18	6	6	0.93 [0.86, 0.98]	0.25 [0.10, 0.47]
Fretzayas (CRP 200 mg/L)	21	23	9	30	0.70 [0.51, 0.85]	0.57 [0.42, 0.70]
Garin (CRP 0.5 mg/L)	91	86	0	8	1.00 [0.96, 1.00]	0.09 [0.04, 0.16]
Jung (CRP 30 mg/L)	50	39	4	57	0.93 [0.82, 0.98]	0.59 [0.49, 0.69]
Kim (CRP 27.8 mg/L)	49	15	10	64	0.83 [0.71, 0.92]	0.81 [0.71, 0.89]
Kotoula (CRP 18.5 mg/L)	27	9	0	21	1.00 [0.87, 1.00]	0.70 [0.51, 0.85]
Kotoula (CRP 35 mg/L)	22	3	5	27	0.81 [0.62, 0.94]	0.90 [0.73, 0.98]
Kotoula (CRP 66 mg/L)	20	0	7	30	0.74 [0.54, 0.89]	1.00 [0.88, 1.00]
Krzemien (CRP 43 mg/L)	23	17	1	13	0.96 [0.79, 1.00]	0.43 [0.25, 0.63]
Kuzmanovska(CRP 860 mg/L)	78	32	85	87	0.48 [0.40, 0.56]	0.73 [0.64, 0.81]
Mahyar (CRP 100 mg/L)	32	12	1	34	0.97 [0.84, 1.00]	0.74 [0.59, 0.86]
Mahyar (CRP 200 mg/L)	28	8	5	38	0.85 [0.68, 0.95]	0.83 [0.69, 0.92]
Mahyar (CRP 60 mg/L)	32	15	1	31	0.97 [0.84, 1.00]	0.67 [0.52, 0.80]
Mells (CRP 10 mg/L)	52	15	20	30	0.72 [0.60, 0.82]	0.67 [0.51, 0.80]
Seo (CRP 51 mg/L)	13	5	11	18	0.54 [0.33, 0.74]	0.78 [0.56, 0.93]
Sheu 2007 (CRP 40 mg/L)	33	3	8	31	0.80 [0.65, 0.91]	0.91 [0.76, 0.98]
Sheu 2011 (CRP 60 mg/L)	56	7	20	29	0.74 [0.62, 0.83]	0.81 [0.64, 0.92]
Sheu 2011(CRP 100 mg/L)	36	2	40	34	0.47 [0.36, 0.59]	0.94 [0.81, 0.99]
Sheu 2011(CRP 35 mg/L)	69	15	7	21	0.91 [0.82, 0.96]	0.58 [0.41, 0.74]
Tekin (CRP 100 mg/L)	35	14	8	37	0.81 [0.67, 0.92]	0.73 [0.58, 0.84]
Tekin (CRP 200 mg/L)	25	9	18	42	0.58 [0.42, 0.73]	0.82 [0.69, 0.92]
Tekin (CRP 60 mg/L)	36	18	7	33	0.84 [0.69, 0.93]	0.65 [0.50, 0.78]
Tuerlinckx (CRP 34 mg/L)	47	8	3	5	0.94 [0.83, 0.99]	0.38 [0.14, 0.68]
Wu (CRP 50 mg/L)	21	16	19	60	0.53 [0.36, 0.68]	0.79 [0.68, 0.87]
Zaki (CRP 8 mg/L)	23	12	6	9	0.79 [0.60, 0.92]	0.43 [0.22, 0.66]



For the ESR test, we found eight studies that reported data for the 30 mm/hour cut-off. The summary sensitivity and specificity estimates were 0.83 (0.71 to 0.91) and 0.57 (0.41 to 0.72), respectively (Figure 7). There was moderate heterogeneity present (Data table 3). However, much of the heterogeneity was due to one large study (Mohkam 2010). The use of perineal bags, inclusion of afebrile children, and inclusion of children with previous UTIs may explain why accuracy estimates from this study differed from the accuracy

estimates from the other studies. Exclusion of Mohkam 2010, however, did not alter the pooled accuracy estimates considerably. Sensitivity analysis and meta-regression were limited because of the small number of studies. Pooled sensitivity and specificity values were similar when we excluded studies with high risk of bias: 0.79 (0.63 to 0.90) and 0.67 (0.58 to 0.75), respectively (Table 1). Eight studies reported data using cut-offs other than 30 mm/hour; a forest plot showing the sensitivity and specificity at these cut-offs is shown in Figure 8. None of the studies reported paired sensitivity and specificity values that were both close to 90%.

Figure 7. Summary ROC plot of erythrocyte sedimentation rate ≥ 30 mm/hr (solid point = pooled accuracy; dotted oval = 95% confidence region)



Test 3. ESR ≥ 30 mm/hour

ESR ≥ 30 mm/hour

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Donoso 2004	85	16	7	8	0.92 [0.85, 0.97]	0.33 [0.16, 0.55]
Fretzayas 2000	27	22	3	31	0.90 [0.73, 0.98]	0.58 [0.44, 0.72]
Hoberman 1999	127	36	15	53	0.89 [0.83, 0.94]	0.60 [0.49, 0.70]
Kotoula 2009a	24	9	3	21	0.89 [0.71, 0.98]	0.70 [0.51, 0.85]
Mahyar 2014	28	10	5	36	0.85 [0.68, 0.95]	0.78 [0.64, 0.89]
Mohkam 2010	455	80	326	108	0.58 [0.55, 0.62]	0.57 [0.50, 0.65]
Montini 2007	154	94	13	20	0.92 [0.87, 0.96]	0.18 [0.11, 0.26]
Tekin 2015	20	9	23	42	0.47 [0.31, 0.62]	0.82 [0.69, 0.92]

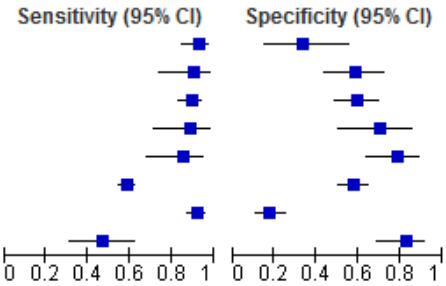
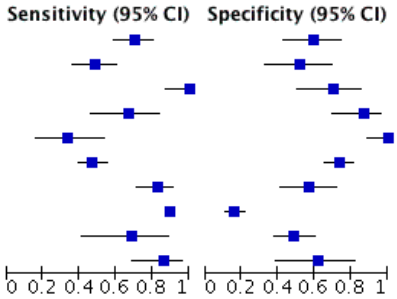


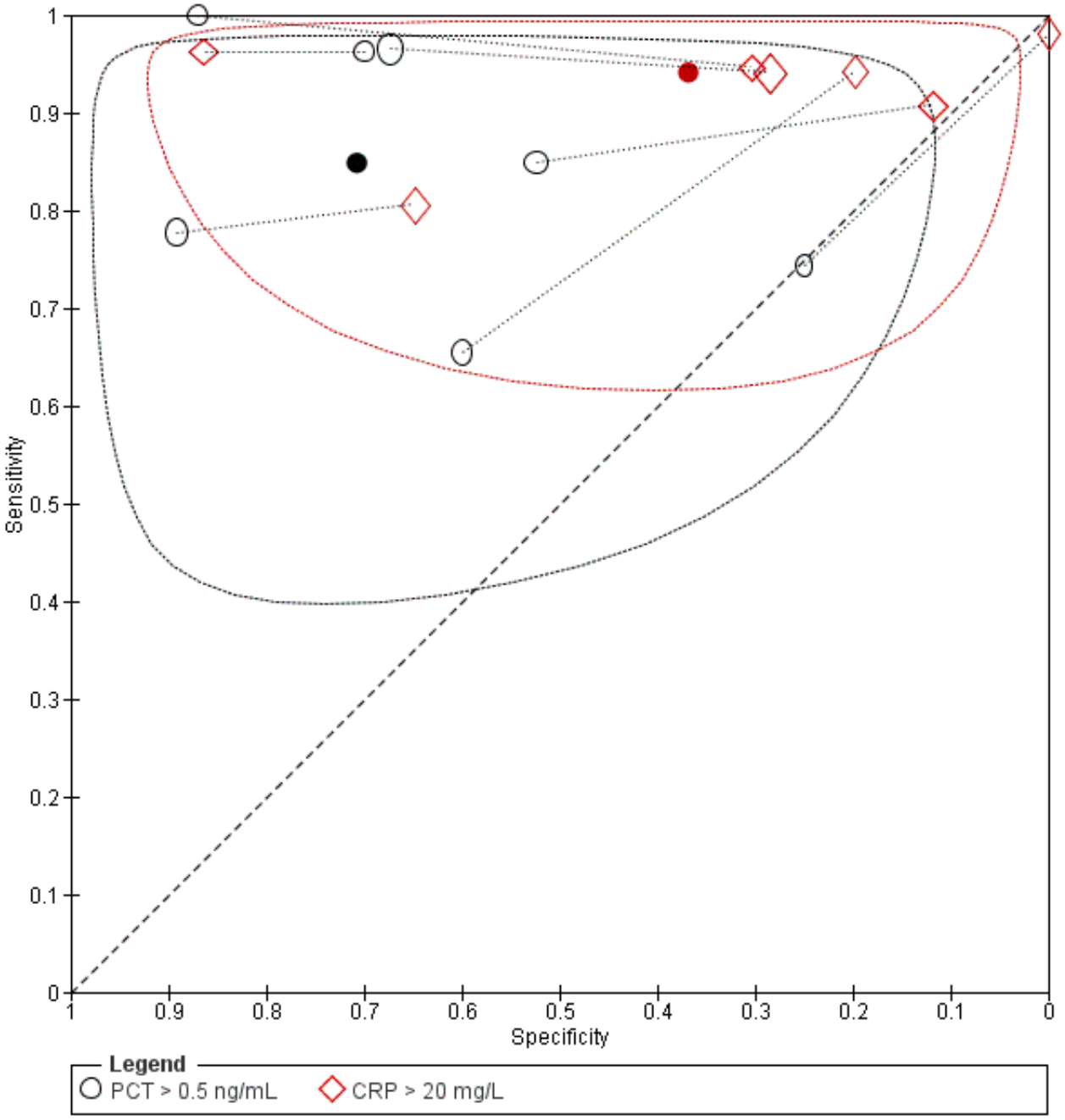
Figure 8. Forest plot of erythrocyte sedimentation rate at cut-offs other than 30 mm/hr

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ansari Gilani (ESR 40 mm/h)	54	17	23	25	0.70 [0.59, 0.80]	0.60 [0.43, 0.74]
Biggi (ESR 68 mm/h)	34	15	36	16	0.49 [0.36, 0.61]	0.52 [0.33, 0.70]
Kotoula (ESR 25 mm/h)	27	9	0	21	1.00 [0.87, 1.00]	0.70 [0.51, 0.85]
Kotoula (ESR 35 mm/h)	18	4	9	26	0.67 [0.46, 0.83]	0.87 [0.69, 0.96]
Kotoula (ESR 75 mm/h)	9	0	18	30	0.33 [0.17, 0.54]	1.00 [0.88, 1.00]
Kuzmanovska (ESR 51 mm/h)	77	31	86	88	0.47 [0.39, 0.55]	0.74 [0.65, 0.82]
Melis (ESR 20 mm/h)	52	18	11	24	0.83 [0.71, 0.91]	0.57 [0.41, 0.72]
Mohkam (ESR 20 mm/h)	701	158	80	30	0.90 [0.87, 0.92]	0.16 [0.11, 0.22]
Printza (ESR 20 mm/h)	11	42	5	40	0.69 [0.41, 0.89]	0.49 [0.38, 0.60]
Zaki (ESR 40 mm/h)	25	8	4	13	0.86 [0.68, 0.96]	0.62 [0.38, 0.82]



Direct comparison was only possible for the procalcitonin versus CRP (seven studies). Compared to CRP, the procalcitonin test had lower sensitivity (P = 0.0012) and higher specificity (P < 0.001; Figure 9, mean sensitivity/specificity in this analysis was 0.87 (0.77 to 0.92)/0.68 (0.47 to 0.83) for procalcitonin and 093 (0.88 to 0.97)/0.32 (0.16 to 0.53) for CRP).

Figure 9. Direct comparison of C-reactive protein > 20 mg/L and procalcitonin > 0.5 ng/mL



DISCUSSION

Summary of main results

In this updated review we examined the accuracy of procalcitonin, CRP, and ESR, in predicting pyelonephritis; five of 10 new studies found in this update focused on the procalcitonin test.

We found all three tests to be sensitive (summary sensitivity values ranged from 0.81 to 0.93), but not very specific (summary specificity values ranged from 0.37 to 0.76). There was limited data to allow for a direct comparison between the three tests. Furthermore, the number of studies, particularly for the ESR test, was small. Heterogeneity, particularly among the studies with data on the accuracy of procalcitonin was too great to allow for any meaningful statements regarding the accuracy of this test. This was compounded by methodological shortcomings in a large proportion of studies (use of bag specimen, issues with patient selection, late performance of the DMSA scan, inclusion of children without fever).

Nonetheless, some conclusions are possible given the data available. None of the tests appear accurate enough at the cut-offs examined to replace the DMSA scan; none had a summary accuracy estimate that approached the accuracy of a DMSA (which has a sensitivity and specificity of 86% and 91%, respectively). However, because of unexplained heterogeneity, it may be more instructive to examine the distribution of accuracy values rather than the pooled estimates. Examination the scatter plots in ROC space for the three tests reveals that only a small minority of studies had accuracy estimates (2/12 studies for procalcitonin, 1/16 studies for CRP, and 0/8 studies for ESR) had accuracy values that were close to the top left hand corner of the ROC space (corresponding to the accuracy of the DMSA). Thus, we can conclude that, at the cut-offs examined, none of the tests can replace the DMSA scan.

Nevertheless, these tests may still be useful in some clinical situations. First, let us examine the utility of these tests in infants (i.e. a high risk population). Clinicians would require a post-test probability of at least 85% to confidently rule in pyelonephritis; the post-test probability of a patient with a positive procalcitonin test comes close to this value (Summary of findings 1), and given the heterogeneity between studies, it is possible that this test could be useful in ruling in pyelonephritis if future studies support its use in certain populations (Implications for research). Clinicians would require a post-test probability of < 20% to confidently rule our pyelonephritis; the post-test probability of a patient with a negative CRP test was close to this (Summary of findings 1). Accordingly, it is possible that with continued investigation (Implications for research), a case could be made for using a CRP level < 20 mg/L to rule out pyelonephritis. In a lower risk population (with a 30% probability of pyelonephritis instead of 60% assumed above), such as one would encounter in older febrile children with urinary symptoms, none of the tests would be useful in ruling in pyelonephritis in this population. The CRP test, could be useful in ruling out pyelonephritis in this population if future research supports this.

In summary, the ESR test does not appear to be useful in differentiating cystitis from pyelonephritis at the cut-off investigated (Summary of findings 1). A low CRP value appears to be somewhat useful in ruling out pyelonephritis (decreasing the probability of pyelonephritis to < 20%), but the heterogeneity of the results prevents us from making firm recommendations at this time. The procalcitonin test seems better suited to ruling in pyelonephritis, but the limited number of studies and the marked heterogeneity between studies prevents us from reaching definitive conclusions. Thus, at present, we do not find any compelling evidence to recommend the routine use of any of these tests in clinical practice.

Strengths and weaknesses of the review

Our success in contacting many study authors for additional data was a strength of this review.

The small number of studies, especially relating to ESR and the procalcitonin tests was a major limitation. This was reflected in the wide confidence intervals of the pooled estimates. Most of the included studies had relatively small sample sizes. Unexplained heterogeneity among studies was a second major limitation that reduced our confidence in the final pooled estimates. A third limitation was that we focused on one cut-off per test. We did so because our main objective was to estimate average summary values for the sensitivity and specificity of each test (not to describe how sensitivity and specificity varies with changes in the threshold, which although important, is less directly applicable clinically). However, this limited the data we could use for our main analysis and direct comparisons. To address this limitation, we presented data from the studies using different cut-offs as a secondary analysis.

Finally, because of poor reporting in the original studies, we are unable to ascertain whether the laboratory procedures used for determination of CRP levels were truly identical across the different studies (the procedures for the measurement of procalcitonin and ESR are relatively uniform). Indeed, from the wide range of cut-offs used for the CRP test (ranging from 0.5 to 860 mg/L), it seems possible that different assays were used in the different studies; errors were made in reporting the units for CRP test (we attempted to contact all authors when such an error was suspected); or authors selected to report data for the threshold that optimised test accuracy.

Applicability of findings to the review question

We did not find any compelling evidence to recommend the routine use of any of these tests in clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the available data, procalcitonin, CRP, or ESR do not appear to be sufficiently accurate to be helpful in differentiating children with cystitis from children with pyelonephritis.

Implications for research

Future studies should enrol consecutive or random samples of children with suspected UTI (see Appendix 2, QUADAS-2, Domain 1: Patient selection), avoid the use of bag samples, and present results stratified by age and at various cut-offs. Since accuracy is best studied in populations suspected of having the target condition, studies should be limited to febrile children. Children with known major genitourinary abnormalities should be excluded so as to not complicate the interpretation of the DMSA scan. Performance of the acute-phase DMSA scan within one week of diagnosis is also likely to enhance the validity of results. Future studies of the procalcitonin test should also report data for cut-offs higher 0.5 ng/mL.

ACKNOWLEDGEMENTS

The authors would like to thank the editorial team for their comments and feedback during the preparation of this review. In addition, we would like to thank Drs Benador, Biggi, Bressan, Da Dalt, Donoso, Fretzayas, Gardikis, Garin, Hoberman, Kotoula, Kuzmanovska, Levtchenko, Mohkam, Montini, Piepsz, Sheu, Taskinen, Vaos, and Zaki for providing us with data and/or clarifications regarding their studies. We would like to thank Jessica Borrell, and Josh Evron for contributions to a previous version of this review.

The authors are grateful to the following peer reviewers for their time and comments: Raymond Quigley (UTSW Medical Center, Dallas, Texas, USA), Nicholas Larkins (Paediatric Nephrologist, Department of Nephrology, Perth Children's Hospital, Western

Australia, Australia), Lindsay Nicolle (Rady Faculty of Health Sciences, University of Manitoba, Canada).

REFERENCES

References to studies included in this review

Ansari Gilani 2010 *{published data only}*

Ansari Gilani K, Modaresi Esfeh J, Gholamrezanezhad A, Gholami A, Mamishi S, Eftekhari M, et al. Predictors of abnormal renal cortical scintigraphy in children with first urinary tract infection: the importance of time factor. *International Urology & Nephrology* 2010;**42**(4):1041-7. [MEDLINE: 19798584] [2819452]

Barati 2016 *{published data only}*

Barati L, Safaeian B, Mehrjerdian, Vakili MA. Early prediction of renal parenchymal injury with serum procalcitonin. *Journal of Renal Injury Prevention* 2016;**5**(3):108-11. [MEDLINE: 27689104]

Benador 1997 *{published and unpublished data}*

* Benador D, Benador N, Slosman D, Mermillod B, Girardin E. Are younger children at highest risk of renal sequelae after pyelonephritis? *Lancet* 1997;**349**(9044):17-9. [MEDLINE: 8988117]

Girardin E, Benador N, Gendrel D, Greder C, Benador D, Bohuon C, et al. Procalcitonin is a marker of severity of renal lesions in pyelonephritis [abstract]. *Journal of the American Society of Nephrology* 1997;**9**(Program & Abstracts Issue):125A. [BIOSIS Previews: PREV199800022706]

Biggi 2001 *{published data only}*

Biggi A, Dardanelli L, Pomero G, Cussino P, Noello C, Sernia O, et al. Acute renal cortical scintigraphy in children with a first urinary tract infection. *Pediatric Nephrology* 2001;**16**(9):733-8. [MEDLINE: 11511988]

Bigot 2005 *{published data only}*

Bigot S, Leblond P, Foucher C, Hue V, D'Herbomez M, Foulard M. Usefulness of procalcitonin for the diagnosis of acute pyelonephritis in children [Apport du dosage de la procalcitonine pour le diagnostic de pyélonéphrite aiguë de l'enfant]. *Archives de Pédiatrie* 2005;**12**(7):1075-80. [MEDLINE: 15893462]

Bouguila 2013 *{published data only}*

Bouguila J, Khalef I, Charfeddine B, Ben Rejeb M, Chatti K, Limam K et al. Comparative study of C-reactive protein and procalcitonin in the severity diagnosis of pyelonephritis in children [Etude comparative de la proteine C-reactive et de la procalcitonine dans lediagnostic de severite des pyelonephrites aigues de l'enfant]. *Pathologie Biologie* 2013;**61**(3):93-98. [MEDLINE: 23481452]

Bressan 2009 *{published and unpublished data}*

Bressan S, Andreola B, Zucchetta P, Montini G, Burei M, Perilongo G, et al. Procalcitonin as a predictor of renal scarring in infants and young children. *Pediatric Nephrology* 2009;**24**(6):1199-204. [MEDLINE: 19205751]

Chen 2013 *{published data only}*

Chen SM, Chang HM, Hung TW, Chao YH, Tsai JD, Lue KH, et al. Diagnostic performance of procalcitonin for hospitalised children with acute pyelonephritis presenting to the paediatric emergency department. *Emergency Medicine Journal* 2013;**30**(5):406-410. [MEDLINE: 22645218]

Donoso 2004 *{published and unpublished data}*

Donoso G, Lobo G, Arnello F, Arteaga MP, Hevia P, Rosati P, et al. Tc 99M DMSA scintigraphy in children with a first episode of acute pyelonephritis: correlation with laboratory tests, echography and the presence of vesico-ureteral reflux [Cintigrama renal DMSA en ninos con primera pielonefritis aguda: correlacion con examenes de laboratorio, ecografia y la presencia de reflujo vesico ureteral]. *Revista Medica de Chile* 2004;**132**(1):58-64. [MEDLINE: 15379054]

Fretzayas 2000 *{published and unpublished data}*

Fretzayas A, Moustaki M, Gourgiotis D, Bossios A, Koukoutsakis P, Stavrinadis C. Polymorphonuclear elastase as a diagnostic marker of acute pyelonephritis in children. *Pediatrics* 2000;**105**(2):E28. [MEDLINE: 10654988]

Garin 2007 *{published data only}*

Garin EH, Olavarria F, Araya C, Broussain M, Barrera C, Young L. Diagnostic significance of clinical and laboratory findings to localize site of urinary infection. *Pediatric Nephrology* 2007;**22**(7):1002-6. [MEDLINE: 17375337]

Hoberman 1999 *{published and unpublished data}*

Hoberman A, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics* 1999;**104**(1 Pt 1):79-86. [MEDLINE: 10390264]

Jung 2016 *{published data only}*

Jung SJ, Lee JH. Prediction of cortical defect using C-reactive protein and urine sodium to potassium ratio in infants with febrile urinary tract infection. *Yonsei Medical Journal* 2016;**57**(1):103-10. [MEDLINE: 26632389]

Kim 2017 *{published data only}*

Kim BK, Yim HE, Yoo KH. Plasma neutrophil gelatinase-associated lipocalin: a marker of acute pyelonephritis in children. *Pediatric Nephrology* 2017;**32**(3):477-84. [MEDLINE: 27744618]

Kotoula 2009a *{published and unpublished data}*

Kotoula A, Gardikis S, Tsalkidis A, Mantadakis E, Zisimopoulos A, Deftereos S, et al. Comparison of serum procalcitonin and commonly used inflammatory markers for the early prediction of acute pyelonephritis in children [abstract]. *European Urology Supplements* 2008;**7**(3):247. [DOI: 10.1016/S1569-9056(08)60704-6] [Biosis Previews: PREV200800283210]

Kotoula A, Gardikis S, Tsalkidis A, Mantadakis E, Zissimopoulos A, Deftereos S, et al. Comparative efficacies of procalcitonin and conventional inflammatory markers for prediction of renal parenchymal inflammation in pediatric first urinary tract infection. *Urology* 2009;**73**(4):782-6. [MEDLINE: 19152962]

Kotoula A, Gardikis S, Tsalkidis A, Mantadakis E, Zissimopoulos A, Kambouri, K, et al. Procalcitonin for the early

prediction of renal parenchymal involvement in children with UTI: preliminary results. *International Urology & Nephrology* 2009;**41**(2):393-9. [MEDLINE: 18836845]

Krzemien 2019 *{published data only}*

Krzemien G, Panczyk-Tomaszewska M, Kotula I, Demkow U, Szmigielska A. Diagnostic accuracy of urine neutrophil gelatinase-associated lipocalin and urine kidney injury molecule-1 as predictors of acute pyelonephritis in young children with febrile urinary tract infection. *Central-European Journal of Immunology* 2019;**44**(2):174-80. [MEDLINE: 31530987]

Krzemien G, Panczyk-Tomaszewska M, Kotula I, Demkow U, Szmigielska A. Serum neutrophil gelatinase-associated lipocalin for predicting acute pyelonephritis in infants with urinary tract infection. *Central-European Journal of Immunology* 2019;**44**(1):45-50. [MEDLINE: 31114436]

Kuzmanovska 2008 *{published data only}*

Kuzmanovska D, Sahpazova E, Bogdanovska A, Konstadinova R. Parenchymal renal damage in children with urinary tract infection [Parenhimna bubrezna ostecenja u djece sa infekcijom mokracnog sustava]. *Paediatria Croatica, Supplement* 2008;**52**(1):212-7. [EMBASE: 351830973]

Levtchenko 2001 *{published and unpublished data}*

* Levtchenko E, Lahy C, Levy J, Ham H, Piepsz A. Treatment of children with acute pyelonephritis: a prospective randomized study. *Pediatric Nephrology* 2001;**16**(11):878-84. [MEDLINE: 11685593]

Levtchenko EN, Lahy C, Levy J, Ham HR, Piepsz A. Role of Tc-99m DMSA scintigraphy in the diagnosis of culture negative pyelonephritis. *Pediatric Nephrology* 2001;**16**(6):503-6. [MEDLINE: 11420916]

Mahyar 2014 *{published data only}*

Mahyar A, Ayazi P, Ahmadi R, Daneshi-Kohan MM, Hashemi HJ, Dalirani R, et al. Are serum procalcitonin and interleukin-1 beta suitable markers for diagnosis of acute pyelonephritis in children? *Prague Medical Report* 2014;**115**(1-2):16-23. [MEDLINE: 24874931]

Martin Aguado 2000 *{published data only}*

Martín Aguado MJ, Canals Baeza A, Vioque López J, Tarazona JL, Flores Serrano J. Technetium-99m-dimercaptosuccinic acid (DMSA) scintigraphy in the first febrile urinary tract infection in children [Gammagrafía con tecnecio-99m-ácido dimercaptosuccínico en el estudio de la primera infección urinaria febril del niño]. *Anales Espanoles de Pediatria* 2000;**52**(1):23-30. [MEDLINE: 11003855]

Melis 1992 *{published data only}*

Melis K, Vandevivere J, Hoskens C, Vervaet A, Sand A, Van Acker KJ. Involvement of the renal parenchyma in acute urinary tract infection: the contribution of 99mTc dimercaptosuccinic acid scan. *European Journal of Pediatrics* 1992;**151**(7):536-9. [MEDLINE: 1327798]

Mohkam 2010 *{published and unpublished data}*

Mohkam M, Maham S, Rahmani A, Naghi I, Otokesh B, Raiiati H, et al. Technetium Tc 99m dimercaptosuccinic acid renal scintigraphy in children with acute pyelonephritis: correlation with other imaging tests. *Iranian Journal of Kidney Diseases* 2010;**4**(4):297-301. [MEDLINE: 20852370]

Montini 2007 *{published and unpublished data}*

* Montini G, Toffolo A, Zucchetta P, Dall'Amico R, Gobber D, Calderan A, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. *BMJ* 2007;**335**(7616):386. [MEDLINE: 17611232]

Nikfar 2010 *{published data only}*

Nikfar R, Khotaee G, Ataee N, Shams S. Usefulness of procalcitonin rapid test for the diagnosis of acute pyelonephritis in children in the emergency department. *Pediatrics International* 2010;**52**(2):196-8. [MEDLINE: 20500474]

Printza 2012 *{published and unpublished data}*

Printza N, Farmaki E, Piretzi K, Arsos G, Kollios K, Papachristou F. Acute phase 99mTc-dimercaptosuccinic acid scan in infants with first episode of febrile urinary tract infection. *World Journal of Pediatrics* 2012;**8**(1):52-6. [MEDLINE: 22282382]

Seo 2014 *{published data only}*

Seo WH, Nam SW, Lee EH, Je BK, Yim HE, Choi BM. A rapid plasma neutrophil gelatinase-associated lipocalin assay for diagnosis of acute pyelonephritis in infants with acute febrile urinary tract infections: a preliminary study. *European Journal of Pediatrics* 2014;**173**(2):229-32. [MEDLINE: 23918295]

Shaikh 2019 *{published data only}*

Shaikh N, Martin JM, Hoberman A, Skae M, Milkovich L, Nowalk A, et al. Host and bacterial markers that differ in children with cystitis and pyelonephritis. *Journal of Pediatrics* 2019;**209**:146-53.e1. [MEDLINE: 30905425]

Sheu 2007 *{published and unpublished data}*

* Sheu JN, Chen MC, Cheng SL, Lee IC, Chen SM, Tsay GJ. Urine interleukin-1beta in children with acute pyelonephritis and renal scarring. *Nephrology* 2007;**12**(5):487-93. [MEDLINE: 17803473]

Sheu JN, Chen MC, Lue KH, Cheng SL, Lee IC, Chen SM, et al. Serum and urine levels of interleukin-6 and interleukin-8 in children with acute pyelonephritis. *Cytokine* 2006;**36**(5-6):276-82. [MEDLINE: 17374489]

Sheu 2011 *{published data only}*

Sheu JN, Chang HM, Chen SM, Hung TW, Lue KH. The role of procalcitonin for acute pyelonephritis and subsequent renal scarring in infants and young children. *Journal of Urology* 2011;**186**(5):2002-8. [MEDLINE: 21944121]

Taskinen 2005 *{published and unpublished data}*

Taskinen S, Ronnholm K. Post-pyelonephritic renal scars are not associated with vesicoureteral reflux in children. *Journal of Urology* 2005;**173**(4):1345-8. [MEDLINE: 15758798]

Tekin 2015 *{published data only}*

Tekin M, Konca C, Gulyuz A, Uckardes F, Turgut M. Is the mean platelet volume a predictive marker for the diagnosis of acute

pyelonephritis in children? *Clinical & Experimental Nephrology* 2015;**19**(4):688-93. [MEDLINE: 25367868]

Tuerlinckx 2005 *{published and unpublished data}*

Tuerlinckx D, Vander Borght T, Glupczynski Y, Galanti L, Roelants V, Krug B, et al. Is procalcitonin a good marker of renal lesion in febrile urinary tract infection? *European Journal of Pediatrics* 2005;**164**(10):651-2. [MEDLINE: 16025299]

Wu 2012 *{published data only}*

Wu JH, Chiou YH, Chang JT, Wang HP, Chen YY, Hsieh KS. Urinary tract infection in infants: a single-center clinical analysis in Southern Taiwan. *Pediatrics & Neonatology* 2012;**53**(5):283-8. [MEDLINE: 23084719]

Xu 2014 *{published data only}*

Xu RY, Liu HW, Liu JL, Dong JH. Procalcitonin and C-reactive protein in urinary tract infection diagnosis. *BMC Urology* 2014;**14**:45. [MEDLINE: 24886302]

Yun 2018 *{published data only}*

Yun BA, Yang EM, Kim CJ. Plasma neutrophil gelatinase-associated lipocalin as a predictor of renal parenchymal involvement in infants with febrile urinary tract infection: a preliminary study. *Annals of Laboratory Medicine* 2018;**38**(5):425-30. [MEDLINE: 29797812]

Zaki 1996 *{published data only}*

Zaki M, Al Mutari G, Al Saleh Q, Ramadan DG. Febrile urinary tract infection in children: role of 99mTc-dimercaptosuccinic acid (DMSA) scan and other imaging techniques. *Annals of Saudi Medicine* 1996;**16**(4):410-3. [EMBASE: 1996271418]

References to studies excluded from this review

Agrawal 2013 *{published data only}*

Agrawal P, Pandey A, Sompura S, Pursnani ML. Role of blood C - reactive protein levels in upper urinary tract infection and lower urinary tract infection in adult patients (>16 years). *Journal of the Association of Physicians of India* 2013;**61**(7):462-3. [MEDLINE: 24772749]

Al Kholi 2010 *{published data only}*

Al Kholi UM, Mostafa M, Gaballa A. The role of urinary interleukin-8 level in diagnosis and differentiation between different types of urinary tract infection in children. *Current Urology* 2010;**4**(4):203-7. [EMBASE: 2010698409]

Andersson 2009 *{published data only}*

Andersson L, Preda I, Hahn-Zoric M, Hanson LA, Jodal U, Sixt R, et al. Urinary proteins in children with urinary tract infection. *Pediatric Nephrology* 2009;**24**(8):1533-8. [MEDLINE: 19352723]

Andreola 2007 *{published data only}*

Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt, L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. *Pediatric Infectious Disease Journal* 2007;**26**(8):672-7. [MEDLINE: 17848876]

Arambasic 2016 *{published data only}*

Arambasic J, Mandic S, Debeljak Z, Mandic D, Horvat V, Seric V. Differentiation of acute pyelonephritis from other febrile states in children using urinary neutrophil gelatinase-associated lipocalin (uNGAL). *Clinical Chemistry & Laboratory Medicine* 2016;**54**(1):55-61. [MEDLINE: 26053013]

Asom 1996 *{published data only}*

Asom AA, Bardfeld PA, Kaskel FJ, Katz SP. Clinical value of renal cortical scintigraphy (RCS) in localizing urinary tract infections (UTI) in adolescent females [abstract]. *Journal of the American Society of Nephrology* 1996;**7**(9):616.

Ataei 2009 *{published data only}*

Ataei N, Safaian B, Madani A, Esfahani ST, Ataei F. Renal parenchymal changes in children with acute pyelonephritis using DMSA scan and the relationship with certain biologic factors. *Tehran University Medical Journal* 2009;**67**(2):125-31. [EMBASE: 2009456653]

Ayazi 2009 *{published data only}*

Ayazi P, Mahyar A, Hashemi HJ, Daneshi MM, Karimzadeh T, Salimi F. Comparison of procalcitonin and C-reactive protein tests in children with urinary tract infection. *Iranian Journal of Pediatrics* 2009;**19**(4):381-6. [EMBASE: 2010034009]

Ayazi 2013 *{published data only}*

Ayazi P, Mahyar A, Daneshi MM, Hashemi HJ, Pirouzi M, Esmailzadehha N. Diagnostic accuracy of the quantitative C-reactive protein, erythrocyte sedimentation rate and white blood cell count in urinary tract infections among infants and children. *Malaysian Journal of Medical Sciences* 2013;**20**(5):40-6. [MEDLINE: 24643248]

Azab 2016 *{published data only}*

Azab S, Zakaria M, Raafat M, Seief H. The combination of urinary IL - 6 and renal biometry as useful diagnostic tools to differentiate acute pyelonephritis from lower urinary tract infection. *International Braz J Urol* 2016;**42**(4):810-6. [MEDLINE: 27564295]

Banuelos-Andrio 2017 *{published data only}*

Banuelos-Andrio L, Espino-Hernandez M, Ruperez-Lucas M, Villar-Del Campo MC, Romero-Carrasco CI, Rodriguez-Caravaca G. Usefulness of analytical parameters in the management of paediatric patients with suspicion of acute pyelonephritis. Is procalcitonin reliable? *Revista Espanola de Medicina Nuclear e Imagen Molecular* 2017;**36**(1):2-6. [MEDLINE: 27329559]

Belhadj-Tahar 2008 *{published data only}*

Belhadj-Tahar H, Coulais Y, Tafani M, Bouissou F. Procalcitonin implication in renal cell apoptosis induced by acute pyelonephritis in children. *Infection & Drug Resistance* 2008;**1**:17-20. [MEDLINE: 21694876]

Benador 1994 *{published data only}*

Benador D, Benador N, Slosman DO, Nussle D, Mermillod B, Girardin E. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. *Journal of Pediatrics* 1994;**124**(1):17-20. [MEDLINE: 8283371]

Benador 1998 *{published data only}*

Benador N, Siegrist C, Gendrel D, Greder C, Benador D, Assicot M, et al. Procalcitonin is a marker of severity of renal lesions in pyelonephritis. *Pediatrics* 1998;**102**(6):1422-5. [MEDLINE: 9832579]

Benador 2001 *{published data only}*

Benador D, Neuhaus TJ, Papazyan JP, Willi UV, Engel-Bicik I, Nadal D, et al. Randomised controlled trial of three day versus 10 day intravenous antibiotics in acute pyelonephritis: effect on renal scarring. *Archives of Disease in Childhood* 2001;**84**(3):241-6. [MEDLINE: 11207174]

Benigno 1986 *{published data only}*

Benigno V, Di Peri S, Distefano F, Como G, Boncori R. Laboratory parameters as a guide for the radiologic study of infections of the urinary tract in childhood [I parametri di laboratorio come guida allo studio radiologico delle infezioni delle vie urinarie in eta pediatrica]. *Pediatria Medica e Chirurgica* 1986;**8**(1):91-3. [MEDLINE: 3725620]

Bouissou 1994 *{published data only}*

Bouissou F, Belmonte D, Danet B, Baunin C, Raynaud N, Salles JP, et al. Value of DMSA renal scintigraphy in acute pyelonephritis in pediatric patients [Interet de la scintigraphie renale au DMSA dans les pyelonephritis aigues de l'enfant]. *Annales de Pediatrie* 1994;**41**(1):7-13. [EMBASE: 1994068022]

Bouissou 2008 *{published data only}*

Bouissou F, Munzer C, Decramer S, Roussel B, Novo R, Morin D, et al. Prospective, randomized trial comparing short and long intravenous antibiotic treatment of acute pyelonephritis in children: dimercaptosuccinic acid scintigraphic evaluation at 9 months. *Pediatrics* 2008;**121**(3):e553-60. [MEDLINE: 18267977]

Brouhard 1997 *{published data only}*

Brouhard BH. Early (99m)Tc dimercaptosuccinic acid (DMSA) scintigraphy in symptomatic first-time urinary tract infection. *Clinical Pediatrics* 1997;**36**(6):366-7. [MEDLINE: 9196240]

Buyan 1993 *{published data only}*

Buyan N, Bircan ZE, Hasanoglu E, Ozturk E, Bayhan H, Rota S. The importance of 99mTc DMSA scanning in the localization of childhood urinary tract infections. *International Urology & Nephrology* 1993;**25**(1):11-7. [MEDLINE: 8390412]

Capdevila 2001 *{published data only}*

Capdevila Cogul E, Martin Ibanez I, Mainou Cid C, Toral Rodriguez E, Cols Roig Mf, Agut Quijano T, et al. First urinary tract infection in healthy infants: epidemiology, diagnosis and treatment [Primera infeccion urinaria en el lactante sano: epidemiologia y pautas de diagnostico y tratamiento]. *Anales Espanoles de Pediatria* 2001;**55**(4):310-4. [MEDLINE: 11578537]

Castello 1995 *{published data only}*

Castello Girona F, Vilaplana Canto E, Yeste Fernandez D, Roca Bielsa I, Enriquez Civico G. 99mTc dimercaptosuccinic scan in the study of the first urinary tract infection in infants [Gamamarafia con 99mTecnecio-acido dimercaptosuccinico en el estudio de la primera infeccion urinaria del lactante]. *Anales Espanoles de Pediatria* 1995;**42**(2):118-22. [EMBASE: 1995091284]

Chiou 2010 *{published data only}*

Chiou YY, Chen MJ, Chiu NT, Lin CY, Tseng CC. Bacterial virulence factors are associated with occurrence of acute pyelonephritis but not renal scarring. *Journal of Urology* 2010;**184**(5):2098-102. [MEDLINE: 20850815]

Christian 2000 *{published data only}*

Christian MT, McColl JH, MacKenzie JR, Beattie TJ. Risk assessment of renal cortical scarring with urinary tract infection by clinical features and ultrasonography. *Archives of Disease in Childhood* 2000;**82**(5):376-80. [MEDLINE: 10799427]

Connell 1993 *{published data only}*

Connell H, de Man P, Jodal U, Lincoln K, Svanborg C. Lack of association between hemolysin production and acute inflammation in human urinary tract infection. *Microbial Pathogenesis* 1993;**14**(6):463-72. [MEDLINE: 7692210]

Craig 1998 *{published data only}*

Craig JC, Irwig LM, Knight JF, Sureshkumar P, Roy L. Symptomatic urinary tract infection in preschool Australian children. *Journal of Paediatrics & Child Health* 1998;**34**(2):154-9. [MEDLINE: 9588640]

de Man 1988 *{published data only}*

de Man P, Jodal U, Lincoln K, Eden CS. Bacterial attachment and inflammation in the urinary tract. *Journal of Infectious Diseases* 1988;**158**(1):29-35. [MEDLINE: 3292665]

Doganis 2007 *{published data only}*

Doganis D, Siafas K, Mavrikou M, Issaris G, Martirosova A, Perperidis G, et al. Does early treatment of urinary tract infection prevent renal damage? *Pediatrics* 2007;**120**(4):e922-8. [MEDLINE: 17875650]

Dura Trave 1997 *{published data only}*

Dura Trave T, Gonzalez Montero R, Juste Ruiz M, Gonzalez de Dios J, Carratala Marco F, Moya Benavent M, et al. Usefulness of renal scintigraphy in the assessment of the first febrile urinary infection in children [Utilidad de la gammagrafia renal en la valoracion de la primera infeccion urinaria febril en la edad pediatrica]. *Anales Espanoles de Pediatria* 1997;**47**(4):378-82. [MEDLINE: 9499305]

Ehsanipour 2017 *{published data only}*

Ehsanipour F, Noorbakhsh S, Zarabi V, Movahedi Z, Rahimzadeh N. Comparison the serum STREM1 levels between children with upper and lower UTI. *Current Pediatric Review* 2017;**13**(2):152-6. [MEDLINE: 28215176]

Elo 1985 *{published data only}*

Elo J, Tallgren LG, Vaisanen V, Korhonen TK, Svenson SB, Makela PH. Association of P and other fimbriae with clinical pyelonephritis in children. *Scandinavian Journal of Urology & Nephrology* 1985;**19**(4):281-4. [MEDLINE: 2868520]

Eremeeva 2016 *{published data only}*

Eremeeva A, Dlin V, Korsunsky A, Orekhova S, Bondarenko E, Gurbanova S. Lipocalin-2 associated with neutrophilic gelatinases (uNGAL) as the marker of microbial inflammatory diseases of kidneys and urinary tract in children [abstract]. *Pediatric Nephrology* 2016;**31**(10):1767-8. [EMBASE: 612479409]

Fang 2017 *{published data only}*

Fang J, Luan J, Zhu GH, Qi C, Wang D. Detection of PCT and urinary beta$_2$ -MG enhances the accuracy for localization diagnosing pediatric urinary tract infection. *Journal of Clinical Laboratory Analysis* 2017;**31**(5):e22088. [MEDLINE: 27801524]

Fang 2020 *{published data only}*

Fang C, Wang Z, Dai Y, Chang W, Sun L, Ma X. Serum human neutrophil lipocalin: An effective biomarker for diagnosing bacterial infections. *Clinical Biochemistry* 2020;**75**:23-9. [MEDLINE: 31672644]

Fernandez 2001 *{published data only}*

Fernandez Lopez A, Luaces Cubells C, Valls Tolosa C, Ortega Rodriguez J, Garcia Garcia J J, Mira Vallet A, et al. Procalcitonin in the early diagnosis of invasive bacterial infection in febrile infants [Procalcitonina para el diagnostico precoz de infeccion bacteriana invasiva en el lactante febril]. *Anales Espanoles de Pediatria* 2001;**55**(4):321-8. [MEDLINE: 11578539]

Fernandez 2003 *{published data only}*

Fernandez Lopez A, Luaces Cubells C, Garcia Garcia JJ, Fernandez Pou J, Spanish Society of Pediatric Emergencies. Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker. *Pediatric Infectious Disease Journal* 2003;**22**(10):895-903. [MEDLINE: 14551491]

Fernandez-Menendez 2003 *{published data only}*

Fernandez-Menendez JM, Malaga S, Matesanz JL, Solis G, Alonso S, Perez-Mendez C. Risk factors in the development of early technetium-99m dimercaptosuccinic acid renal scintigraphy lesions during first urinary tract infection in children. *Acta Paediatrica* 2003;**92**(1):21-6. [MEDLINE: 12650294]

Figueiredo 1999 *{published data only}*

Figueiredo S, Rocha P, Coelho E, Alexandrino AM, Rocha H. Retrospective study of urinary tract infection in infants [Estudo retrospectivo de infeccao urinaria alta em lactentes]. *Nascer e Crescer* 1999;**8**(2):89-92. [EMBASE: 1999270461]

Friedman-Gruszczynska 2008 *{published data only}*

Friedman-Gruszczynska J. Assessment of clinical relevance of CRP levels in infectious diseases in children [Ocena przydatnosci klinicznej oznaczania stezenia bialka CRP w chorobach infekcyjnych u dziec]. *Pediatria Polska* 2008;**83**(1):49-53. [EMBASE: 2008097172]

Galetto-Lacour 2002 *{published data only}*

Galetto-Lacour A, Zamora S, Gervaix A. Blood markers of severe bacterial infections [abstract]. In: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; Sep 27-30 2002; San Diego, USA. 2002.

Galetto-Lacour 2003 *{published data only}*

Galetto-Lacour A, Zamora SA, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. *Pediatrics* 2003;**112**(5):1054-60. [MEDLINE: 14595045]

Garcia de Guadiana 2011 *{published and unpublished data}*

Garcia de Guadiana L, Gonzalez J, Gonzalez M, Martin E, Albaladejo M, Cortes P. Usefulness of C-reactive protein in admission to localize site of urinary infection in children [abstract]. *Clinical Chemistry & Laboratory Medicine* 2011;**49**(Suppl 1):S637. [EMBASE: 70517512]

Gendrel 1998 *{published data only}*

Gendrel D. Urinary tract infection and biological markers: C-reactive protein, interleukins and procalcitonin [Infection urinaire biologiques: proteine C reactive, interleukine et procalcitonine]. *Archives de Pediatrie* 1998;**5 Suppl 3**:269-73S. [MEDLINE: 9759316]

Gervaix 2001 *{published data only}*

Gervaix A, Galetto-Lacour A, Gueron T, Vadas L, Zamora S, Suter S, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatric Infectious Disease Journal* 2001;**20**(5):507-11. [MEDLINE: 11368108]

Ghasemi 2013 *{published data only}*

Ghasemi K, Montazeri S, Pashazadeh AM, Javadi H, Assadi M. Correlation of 99mTc-DMSA scan with radiological and laboratory examinations in childhood acute pyelonephritis: a time-series study [abstract]. *European Journal of Nuclear Medicine & Molecular Imaging* 2013;**40**(Suppl 2):S279. [DOI: https://doi.org/10.1007/s00259-013-2535-3]

Ghasemi 2016 *{published data only}*

Ghasemi K, Esteghamati M, Borzoo S, Parvaneh E. Predictive accuracy of urinary neutrophil gelatinase associated lipocalin (NGAL) for renal parenchymal involvement in children with acute pyelonephritis. *Electron Physician [Electronic Resource]* 2016;**8**(2):1911-7. [MEDLINE: 27053998]

Girardin 2000 *{published data only}*

Girardin E. Pyelonephritis in children: new tools for evaluation [Pyelonephrites de l'enfant: nouveaux moyens d'evaluation]. *Medecine Therapeutique Pediatrie* 2000;**3**(5):376-80. [EMBASE: 30944096]

Giunta 2014 *{published data only}*

Giunta F, Forfori F, Seri G. Molecular markers for urinary tract infections. *Official Gazette of the United States Patent & Trademark Office Patents* 2014. [US Patent US 2013/0084650 A1]

Grouteau 1999 *{published data only}*

Grouteau E, Fauvel J, Blum G, Ouhayoun E, Salles J, Decramer S, et al. Phospholipase A2 (Pla2) and C reactive protein (CRP) in acute pyelonephritis in children. Correlation with DMSA scan [abstract no: P92]. *Pediatric Nephrology* 1999;**13**.

Guermazi 1993 *{published data only}*

Guermazi F, Lenoir P, Verboven M, Smets A, Braeckman J, Jonckheer M, et al. Technetium 99m labeled dimercaptosuccinic acid (99m Tc-DMSA) scintigraphy in the diagnosis and follow-up of urinary infections in children [Apport de la scintigraphie a l'acide dimercaptosuccinque marque au technetium 99m (99mTC-DSA) dans le diagnostic et le suivi des infections urinaires de l'enfant]. *Archives Francaises de Pediatrie* 1993;**50**(5):391-8. [MEDLINE: 8239890]

Gurgoze 2005 *{published data only}*

Gurgoze M, Akarsu S, Yilmaz E, Godekmerdan A, Akca Z, Ciftci I, et al. Proinflammatory cytokines and procalcitonin in children with acute pyelonephritis. *Pediatric Nephrology* 2005;**20**(10):1445-8. [MEDLINE: 16079986]

Guven 2006 *{published data only}*

Guven AG, Kazdal HZ, Koyun M, Aydn F, Gungor F, Akman S, et al. Accurate diagnosis of acute pyelonephritis: How helpful is procalcitonin? *Nuclear Medicine Communications* 2006;**27**(9):715-21. [MEDLINE: 16894326]

Hahn 2003 *{published data only}*

Hahn H, Moon DH, Yang YJ, Park YS. Renal scarring after acute pyelonephritis in children under the age of 5 years is primarily related to the extent and severity of acute inflammatory changes [abstract]. *Journal of Nuclear Medicine* 2003;**44**(5 Suppl):358. [BIOSIS Previews: PREV200300383499]

Han 2016 *{published data only}*

Han SY, Lee IR, Park SJ, Kim JH, Shin JI. Usefulness of neutrophil-lymphocyte ratio in young children with febrile urinary tract infection. *Korean Journal of Pediatrics* 2016;**49**(3):139-44. [MEDLINE: 27186221]

Shin JI, Han SY. Usefulness of neutrophil lymphocyte ratio in young children with febrile urinary tract infection [abstract]. *Pediatric Nephrology* 2015;**39**(9):1579. [EMBASE: 72033275]

Hellerstein 1981 *{published data only}*

Hellerstein S, Duggan E, Welchert E, Mansour F. Localization of the site or urinary tract infections using serum C reactive protein [abstract]. *Pediatric Research* 1981;**15**(4 Pt 2):694. [DOI: 10.1203/00006450-198104001-01528] [BIOSIS Previews: PREV198121026875]

Hellerstein 1982 *{published data only}*

Hellerstein S, Duggan E, Welchert E, Mansour F. Serum C-reactive protein and the site of urinary tract infections. *Journal of Pediatrics* 1982;**100**(1):21-5. [MEDLINE: 7057312]

Hewitt 2008 *{published data only}*

Hewitt IK, Zucchetta P, Rigon L, Maschio F, Molinari PP, Tomasi L, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. *Pediatrics* 2008;**122**(3):486-90. [MEDLINE: 18762516]

Hitzel 2002 *{published data only}*

Hitzel A, Liard A, Vera P, Manrique A, Menard JF, Dacher JN. Color and power Doppler sonography versus DMSA scintigraphy in acute pyelonephritis and in prediction of renal scarring. *Journal of Nuclear Medicine* 2002;**43**(1):27-32. [MEDLINE: 11801699]

Hsu 2016 *{published data only}*

Hsu CC, Tsai JD, Ku MS, Chen SM, Liao PF, Hung TW, et al. Antimicrobial resistance and diagnostic imaging in infants younger than 2 months old hospitalized with a first febrile urinary tract infection: a population-based comparative study. *Pediatric Infectious Disease Journal* 2016;**35**(8):840-5. [MEDLINE: 27100129]

Huang 2007 *{published data only}*

Huang DT, Huang FY, Tsai TC, Tsai JD, Chiu NC, Lin CC. Clinical differentiation of acute pyelonephritis from lower urinary tract infection in children. *Journal of Microbiology, Immunology & Infection* 2007;**40**(6):513-7. [MEDLINE: 18087632]

Hubert-Dibon 2018 *{published data only}*

Hubert-Dibon G, Danjou L, Feildel-Fournial C, Vrignaud B, Masson D, Launay E, et al. Procalcitonin and C-reactive protein may help to detect invasive bacterial infections in children who have fever without source. *Acta Paediatrica* 2018;**107**(7):1262-9. [MEDLINE: 29385638]

Ilyas 2002 *{published data only}*

Ilyas M, Mastin ST, Richard GA. Age-related radiological imaging in children with acute pyelonephritis. *Pediatric Nephrology* 2002;**17**(1):30-4. [MEDLINE: 11793131]

Jakobsson 1992a *{published data only}*

Jakobsson B, Söderlundh S, Berg U. Diagnostic significance of 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy in urinary tract infection. *Archives of Disease in Childhood* 1992;**67**(11):1338-42. [MEDLINE: 1335226]

Jakobsson 1992b *{published data only}*

Jakobsson B, Nolstedt L, Svensson L, Soderlundh S, Berg U. ^{99m}Technetium-dimercaptosuccinic acid scan in the diagnosis of acute pyelonephritis in children: relation to clinical and radiological findings. *Pediatric Nephrology* 1992;**6**(4):328-34. [MEDLINE: 1343562]

Jakobsson 1994 *{published data only}*

Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Archives of Disease in Childhood* 1994;**70**(2):111-5. [MEDLINE: 8129430]

Jakobsson 1997 *{published data only}*

Jakobsson B, Svensson L. Transient pyelonephritic changes on 99mTechnetium-dimercaptosuccinic acid scan for at least five months after infection. *Acta Paediatrica* 1997;**86**(8):806-7. [MEDLINE: 9307157]

Jaksic 2011 *{published data only}*

Jaksic E, Bogdanovic R, Artiko V, Saranovic DS, Petrasinovic Z, Petrovic M, et al. Diagnostic role of initial renal cortical scintigraphy in children with the first episode of acute pyelonephritis. *Annals of Nuclear Medicine* 2011;**25**(1):37-43. [MEDLINE: 21080122]

Jantausch 1994 *{published data only}*

Jantausch BA, Rifai N, Getson P, Akram S, Majd M, Wiedermann BL. Urinary N-acetyl-beta-glucosaminidase and beta-2-microglobulin in the diagnosis of urinary tract infection in febrile infants. *Pediatric Infectious Disease Journal* 1994;**13**(4):294-9. [MEDLINE: 8036046]

Jodal 1975 *{published data only}*

Jodal U, Lindberg U, Lincoln K. Level diagnosis of symptomatic urinary tract infections in childhood. *Acta Paediatrica Scandinavica* 1975;**64**(2):201-8. [MEDLINE: 1093351]

Johnson 1985 *{published data only}*

Johnson CE, Shurin PA, Marchant CD, Strieter CM, Murdell-Panek D, Debaz BP, et al. Identification of children requiring radiologic evaluation for urinary infection. *Pediatric Infectious Disease* 1985;**46**(6):656-63. [MEDLINE: 3909120]

Kanellopoulos 2005 *{published data only}*

Kanellopoulos TA, Vassilakos PJ, Kantzis M, Ellina A, Kolonitsiou F, Papanastasiou DA. Low bacterial count urinary tract infections in infants and young children. *European Journal of Pediatrics* 2005;**164**(6):355-61. [MEDLINE: 15739109]

Kangari 2015 *{published data only}*

Kangari G, Esteghamati M, Ghasemi K, Mahboobi H. Predictive accuracy of urinary beta2-microglobulin for kidney injury in children with acute pyelonephritis. *Iranian Journal of Kidney Diseases* 2015;**9**(1):19-24. [MEDLINE: 25599732]

Karakatsani 1997 *{published data only}*

Karakatsani Z, Kipuru C, Stefanidis C. Is C-reactive protein reliable for the prediction of renal lesions in infants with urinary tract infection (UTI)? [abstract]. *Pediatric Nephrology* 1997;**11**(5):C56. [BIOSIS Previews: PREV199799837360]

Karavanaki 2007 *{published data only}*

Karavanaki K, Angelos Haliotis F, Sourani M, Kariyiannis C, Hantzi E, Zachariadou L, et al. DMSA scintigraphy in febrile urinary tract infections could be omitted in children with low procalcitonin levels. *Infectious Diseases in Clinical Practice* 2007;**15**(6):377-81. [EMBASE: 350135450]

Kassir 2001 *{published data only}*

Kassir K, Vargas-Shiraishi O, Zaldivar F, Berman M, Singh J, Arrieta A. Cytokine profiles of pediatric patients treated with antibiotics for pyelonephritis: potential therapeutic impact. *Clinical & Diagnostic Laboratory Immunology* 2001;**8**(6):1060-3. [MEDLINE: 11687440]

Katz 1993 *{published data only}*

Katz SP, Barfeld PA, Kaskel FJ. Clinical value of DMSA scan in differentiating acute pyelonephritis (APN) from other urinary tract infections (UTI) in adolescent females [abstract]. *Journal of the American Society of Nephrology* 1993;**4**.

Katz 2002 *{published data only}*

Katz SP, Gromisch DS, Balbi HJ, Vilela MG, Constantatos C, Affan AA. A seven year retrospective review of patients diagnosed with urinary tract infection (UTI) from birth to twenty-four months of age [abstract]. *Pediatric Research* 2002;**51**.

Kiker 1982 *{published data only}*

Kiker JD, Woodside JR, Reed WP, Borden TA, Woodside MD. Urinary lactic dehydrogenase and serum C-reactive protein as means of localizing the site of urinary tract infection in patients with ileal conduits. *Journal of Urology* 1982;**128**(4):749-51. [MEDLINE: 7143596]

Kilicaslan 2015 *{published data only}*

Kilicaslan B, Alp H, Yildirim M, Inandi T. Diagnostic value of MAG3 scintigraphy and DMSA scintigraphy in renal parenchyma damage and acute pyelonephritis of children. *Cukurova Medical Journal* 2016;**41**(3):464-471. [DOI: 10.17826/cukmedj.237484]

Kilicaslan 2016 *{published data only}*

Kilicaslan B, Noyan A, Cengiz N, Sariturk C, Parmaksiz G, Baskin E. Can we differentiate pyelonephritis and cystitis without 99mTc-dimercaptosuccinic acid scan in children? *Cukurova Medical Journal* 2015;**40**(3):495-503. [DOI: https://doi.org/10.17826/cutf.21897]

Kim 2001 *{published data only}*

Kim S, Kim I, Kim E, Yoo I, Chung Y, Sohn H, et al. Planar and pinhole renal cortical scintigraphic findings correlated to consolidated clinical parameters in acute urinary tract infection [abstract]. *Journal of Nuclear Medicine* 2001;**42**.

Koufadaki 2014 *{published data only}*

Koufadaki AM, Karavanaki KA, Soldatou A, Tsentidis Ch, Sourani MP, Sdogou T, et al. Clinical and laboratory indices of severe renal lesions in children with febrile urinary tract infection. *Acta Paediatrica* 2014;**103**(9):e404-9. [MEDLINE: 24862642]

Krzemien 2004 *{published data only}*

Krzemien G, Roszkowska-Blaim M, Kostro I, Szmigielska A, Karpinska M, Sieniawska M, et al. Urinary levels of interleukin-6 and interleukin-8 in children with urinary tract infections to age 2. *Medical Science Monitor* 2004;**10**(11):CR593-7. [MEDLINE: 15507849]

Krzemien 2016 *{published data only}*

Krzemien G, Szmigielska A, Turczyn A, Panczyk-Tomaszewska M. Urine interleukin-6, interleukin-8 and transforming growth factor beta1 in infants with urinary tract infection and asymptomatic bacteriuria. *Central-European Journal of Immunology* 2016;**41**(3):260-7. [MEDLINE: 27833443]

Krzemien 2017 *{published data only}*

Krzemien G, Panczyk-Tomaszewska M, Adamczuk D, Kotula I, Demkow U, Szmigielska A. Neutrophil gelatinase-associated lipocalin: a biomarker for early diagnosis of urinary tract infections in infants. *Advances in Experimental Medicine & Biology* 2018;**1047**:71-80. [MEDLINE: 28980274]

Kupperman 2019 *{published data only}*

Kuppermann N, Dayan PS, Levine DA, Vitale M, Tzimenatos L, Tunik MG, et al. A clinical prediction rule to identify febrile infants 60 days and younger at low risk for serious bacterial

infections. *JAMA Pediatrics* 2019;**173**(4):342-51. [MEDLINE: 30776077]

Lai 2003 *{published data only}*

Lai SW, Ng KC. Retrospective analysis of inflammatory parameters in acute pyelonephritis. *Scandinavian Journal of Urology & Nephrology* 2003;**37**(3):250-2. [MEDLINE: 12775285]

Lee 2006 *{published data only}*

Lee JH, Son CH, Lee MS, Park YS. Vesicoureteral reflux increases the risk of renal scars: a study of unilateral reflux. *Pediatric Nephrology* 2006;**21**(9):1281-4. [MEDLINE: 16791609]

Lee 2009 *{published data only}*

Lee HY, Soh BH, Hong CH, Kim MJ, Han SW. The efficacy of ultrasound and dimercaptosuccinic acid scan in predicting vesicoureteral reflux in children below the age of 2 years with their first febrile urinary tract infection. *Pediatric Nephrology* 2009;**24**(10):2009-13. [MEDLINE: 19593590]

Lee 2015 *{published data only}*

Lee IR, Shin JI, Park SJ, Oh JY, Kim JH. Mean platelet volume in young children with urinary tract infection. *Scientific Reports* 2015;**5**:10872. [MEDLINE: 26666588]

Lee 2017 *{published data only}*

Lee JW, Kim SH, Park SJ, Lee KH, Park JH, Kronbichler A, et al. The value of delta neutrophil index in young infants with febrile urinary tract infection. *Scientific Reports* 2017;**7**:41265. [MEDLINE: 28169298]

Lee 2017a *{published data only}*

Lee JW, Park JS, Park KB, Yoo GH, Kim SS, Lee SM. Prediction of renal cortical defect and scar using neutrophil-to-lymphocyte ratio in children with febrile urinary tract infection. *Nuklear-Medizin* 2017;**56**(3):109-14. [MEDLINE: 28488726]

Lee 2018 *{published data only}*

Lee JW, Her SM, Kim JH, Lee KH, Eisenhut M, Park SJ, et al. D-dimer as a marker of acute pyelonephritis in infants younger than 24 months with urinary tract infection. *Pediatric Nephrology* 2018;**33**(4):631-7. [MEDLINE: 29306986]

Lee 2018a *{published data only}*

Lee JH, Jang SJ, Rhie S. Antinatriuretic phenomena seen in children with acute pyelonephritis may be related to the activation of intrarenal RAAS. *Medicine* 2018;**97**(36):e12152. [MEDLINE: 30200111]

Lee 2018b *{published data only}*

Lee IS, Park YJ, Jin MH, Park JY, Lee HJ, Kim SH, et al. Usefulness of the procalcitonin test in young febrile infants between 1 and 3 months of age. *Korean Journal of Pediatrics* 2018;**61**(9):285-90. [EMBASE: 625077903]

Lee 2019 *{published data only}*

Lee JH. Discrimination of culture negative pyelonephritis in children with suspected febrile urinary tract infection and negative urine culture results. *Journal of Microbiology, Immunology & Infection* 2019;**52**(4):598-603. [MEDLINE: 29100793]

Leroy 2012 *{published data only}*

Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervaix A, et al. Procalcitonin predicts well acute pyelonephritis and renal scars in children with urinary tract infection [abstract]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii547.

Levine 2018 *{published data only}*

Levine AR, Tran M, Shepherd J, Naut E. Utility of initial procalcitonin values to predict urinary tract infection. *American Journal of Emergency Medicine* 2018;**36**(11):1993-7. [MEDLINE: 29530360]

Lin 2000 *{published data only}*

Lin DS, Huang SH, Lin CC, Tung YC, Huang TT, Chiu NC, et al. Urinary tract infection in febrile infants younger than eight weeks of age. *Pediatrics* 2000;**105**(2):E20. [MEDLINE: 10654980]

Linne 1994 *{published data only}*

Linne T, Fituri O, Escobar-Billing R, Karlsson A, Wikstad I, Aperia A, et al. Functional parameters and 99mtechnetium-dimercaptosuccinic acid scan in acute pyelonephritis. *Pediatric Nephrology* 1994;**8**(6):694-9. [MEDLINE: 7696107]

Lomberg 1992 *{published data only}*

Lomberg H, Jodal U, Leffler H, De Man P, Svanborg C. Blood group non-secretors have an increased inflammatory response to urinary tract infection. *Scandinavian Journal of Infectious Diseases* 1992;**24**(1):77-83. [MEDLINE: 1589729]

Lucas-Saez 2014 *{published data only}*

Lucas-Saez E, Ferrando-Monleon S, Marin-Serra J, Bou-Monterde R, Fons-Moreno J, Peris-Vidal A, et al. Predictive factors for kidney damage in febrile urinary tract infection. Usefulness of procalcitonin. *Nefrologia* 2014;**34**(4):451-7. [MEDLINE: 25036058]

Mahyar 2013 *{published data only}*

Mahyar A, Ayazi P, Maleki MR, Daneshi-Kohan MM, Sarokhani HR, Hashemi HJ, et al. Serum levels of interleukin-6 and interleukin-8 as diagnostic markers of acute pyelonephritis in children. *Korean Journal of Pediatrics* 2013;**56**(5):218-23. [MEDLINE: 23741236]

Majd 1991 *{published data only}*

Majd M, Rushton HG, Jantausch B, Wiedermann BL. Relationship among vesicoureteral reflux, P-fimbriated Escherichia coli, and acute pyelonephritis in children with febrile urinary tract infection. *Journal of Pediatrics* 1991;**119**(4):578-85. [MEDLINE: 1681043]

Majd 1992 *{published data only}*

Majd M, Rushton HG. Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. *Seminars in Nuclear Medicine* 1992;**22**(2):98-111. [MEDLINE: 1317065]

Malaga 1978 *{published data only}*

Malaga S, Matesanz JL, Dieguez MA, Crespo M. Value of the C reactive protein, urinary lactic dehydrogenase and renal capacity of concentration in the topographic diagnosis of the urinary infection in infancy (author's transl) [Valor de la

proteina C reactiva, lactilo-dehidrogenasa urinaria y capacidad renal de concentracion en el diagnostico topografico de la infeccion urinaria en la infancia]. *Anales Espanoles de Pediatria* 1978;**11**(6-7):485-96. [MEDLINE: 697217]

Masajtis-Zagajewska 2015 *{published data only}*

Masajtis-Zagajewska A, Kurnatowska I, Wajdlich M, Nowicki M. Utility of copeptin and standard inflammatory markers in the diagnostics of upper and lower urinary tract infections. *BMC Urology* 2015;**15**:67. [MEDLINE: 26152182]

Mazigh Mrad 2002 *{published data only}*

Mazigh Mrad S, Fetni I, Rabeh O, Oubich F, Boukthir S, Barsaoui S. Contribution of clinical, biological and radiological parameters in the diagnosis of urinary infection localization [Apport des parametres cliniques biologiques et radiogiques dans le diagnostic de localisation de l'infection urinaire]. *Tunisie Medicale* 2002;**80**(10):28-32. [MEDLINE: 12632757]

Mohkam 2008 *{published data only}*

Mohkam M, Karimi A, Karimi H, Sharifian M, Armin S, Dalirani R, et al. Urinary interleukin-8 in acute pyelonephritis of children: a before-after study. *Iranian Journal of Kidney Diseases* 2008;**2**(4):193-6. [MEDLINE: 19377236]

Moldovan 2015 *{published data only}*

Moldovan DA, Baghiu MD, Balas A, Truta ST. The value of the "Lab-Score" method in identifying febrile infants at risk for serious bacterial infections. *The Journal of Critical Care Medicine* 2015;**1**(1):11-7. [MEDLINE: 29967810]

Montini 2008 *{published data only}*

Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics* 2008;**122**(5):1064-71. [MEDLINE: 18977988]

Montini 2009 *{published data only}*

Montini G, Zucchetta P, Tomasi L, Talenti E, Rigamonti W, Picco G, et al. Value of imaging studies after a first febrile urinary tract infection in young children: data from Italian renal infection study 1. *Pediatrics* 2009;**123**(2):e239-46. [MEDLINE: 19139086]

Moon 2009 *{published data only}*

Moon DG, Oh MM, Nam SG, Jin MH, Park HS, Cheon J, et al. Predictive factors for acute scintingraphic lesion and ultimate scar formation in patients with acute febrile UTI [abstract]. *Journal of Urology* 2009;**181**(4 Suppl 1):380. [EMBASE: 70113158]

Mussap 2006 *{published data only}*

Mussap M, Cataldi L, Plebani M, Fanos V. Laboratory investigation for the early diagnosis and monitoring of neonatal urinary tract infections: The present situation and future perspectives. *Journal of Chemotherapy* 2006;**18 Spec no 3**:9-13. [MEDLINE: 16789365]

Naseri 2008 *{published data only}*

Naseri M. Alterations of peripheral leukocyte count, erythrocyte sedimentation rate, and C-reactive protein in febrile urinary tract infection. *Iranian Journal of Kidney Diseases* 2008;**2**(3):137-42. [MEDLINE: 19377227]

Naseri 2017 *{published data only}*

Naseri M, Banihasan M, Alamdaran SA. Prediction of renal cortical involvement using serum and urinary inflammatory markers in children with febrile urinary tract infection. *Iranian Journal of Radiology* 2017;**14**(2):e41485. [EMBASE: 617759856]

Neuhaus 2008 *{published data only}*

Neuhaus TJ, Berger C, Buechner K, Parvex P, Bischoff G, Goetschel P, et al. Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. *European Journal of Pediatrics* 2008;**167**(9):1037-47. [MEDLINE: 18074149]

Nickavar 2015 *{published data only}*

Nickavar A, Safaeian B, Biglari Abhari M. Radiologic and clinical evaluation of children with first febrile urinary tract infection. *International Journal of Pediatrics & Adolescent Medicine* 2015;**2**(1):24-8. [MEDLINE: 30805432]

Oh 2010 *{published data only}*

Oh MM, Cheon J, Kang SH, Park HS, Lee JG, Moon du G. Predictive factors for acute renal cortical scintigraphic lesion and ultimate scar formation in children with first febrile urinary tract infection. *Journal of Urology* 2010;**183**(3):1146-50. [MEDLINE: 20096887]

Oh 2011 *{published data only}*

Oh M, Moon DG, Bae JH, Kang SH, Kim JJ, Lee JG, et al. The role of therapeutic delay time in acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI; is there difference according to the presence of vesico-ureteral reflux? [abstract]. *Journal of Urology* 2011;**185**(4 Suppl 1):e230-1. [EMBASE: 70377836]

Ohta 2019 *{published data only}*

Ohta N, Yasudo H, Mizutani M, Matsushige T, Fukano R, Kittaka S, et al. Serum soluble ST2 as a marker of renal scar in pediatric upper urinary tract infection. *Cytokine* 2019;**120**:258-63. [MEDLINE: 31153005]

Orlowska 2004 *{published data only}*

Orlowska H, Roszkowska-Blaim M. Procalcitonin - a new inflammatory marker in children with urinary tract infection - a preliminary study [Prokalcytonina - Nowy marker stanu zapalnego u dzieci z zakazeniem ukladu moczowego - Doniesienie wstepne]. *Pediatria Polska* 2004;**79**(2):111-4. [EMBASE: 38404888]

Otto 2005 *{published data only}*

Otto G, Burdick M, Strieter R, Godaly G. Chemokine response to febrile urinary tract infection. *Kidney International* 2005;**68**(1):62-70. [MEDLINE: 15954896]

Otukesh 2009 *{published data only}*

Otukesh H, Fereshtehnejad SM, Hoseini R, Hekmat S, Chalian H, Chalian M, et al. Urine macrophage migration inhibitory factor (MIF) in children with urinary tract infection: a possible predictor of acute pyelonephritis. *Pediatric Nephrology* 2009;**24**(1):105-11. [MEDLINE: 18800229]

Paripovic 2011 *{published data only}*

Paripovic A, Stajic N, Putnik J, Slavkovic B, Jaksic E, Bogdanovic R. Interleukin-6 (IL-6) and interleukin-8 (IL-8) in urine of children with acute pyelonephritis [abstract]. *Pediatric Nephrology* 2011;**26**(9):1691-2. [EMBASE: 70530833]

Pecile 2004 *{published data only}*

Pecile P, Miorin E, Romanello C, Falleti E, Valent F, Giacomuzzi F, et al. Procalcitonin: a marker of severity of acute pyelonephritis among children. *Pediatrics* 2004;**144**(2):e249-54. [MEDLINE: 15286264]

Pecile 2005 *{published data only}*

Pecile P, Miorin E, Romanello C, Falleti E, Valent F, Giacomuzzi F, et al. Procalcitonin: a marker of severity of acute pyelonephritis among children: commentary. *Archives de Pediatrie* 2005;**12**(7):1155-6. [EMBASE: 40835238]

Pecile 2007 *{published data only}*

Pecile P, Romanello C. Procalcitonin and pyelonephritis in children. *Current Opinion in Infectious Diseases* 2007;**20**(1):83-7. [MEDLINE: 17197887]

Piepsz 1998 *{published data only}*

Piepsz A, Tamminen-Mobius T, Reiners C, Heikkila J, Kivisaari A, Nilsson NJ, et al. Five-year study of medical or surgical treatment in children with severe vesico-ureteral reflux dimercaptosuccinic acid findings. International Reflux Study Group in Europe. *European Journal of Pediatrics* 1998;**157**(9):753-8. [MEDLINE: 9776536]

Prat 2003 *{published data only}*

Prat C, Dominguez J, Rodrigo C, Gimenez M, Azuara M, Jimenez O, et al. Elevated serum procalcitonin values correlate with renal scarring in children with urinary tract infection. *Pediatric Infectious Disease Journal* 2004;**22**(5):438-42. [MEDLINE: 12792386]

Prat 2004 *{published data only}*

Prat C, Dominguez J, Rodrigo C, Gimenez M, Azuara M, Blanco S, et al. Use of quantitative and semiquantitative procalcitonin measurements to identify children with sepsis and meningitis. *European Journal of Clinical Microbiology & Infectious Diseases* 2004;**23**(2):136-8. [MEDLINE: 14689316]

Preda 2011 *{published data only}*

Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Imaging strategy for infants with urinary tract infection: a new algorithm. *Journal of Urology* 2011;**185**(3):1046-52. [MEDLINE: 21247606]

Printza 2008 *{published data only}*

Printza N, Papachristou F, Piretzi K, Goga C, Arsos G. Neither clinical nor biological data can predict renal involvement in infants with febrile urinary tract infection [abstract]. *Pediatrics* 2008;**121**(Suppl 2):S143.

Puczko-Michalczuk 2008 *{published data only}*

Puczko-Michalczuk A, Zoch-Zwierz W, Wasilewska A, Porowska T, Korzeniecka-Kozerska A. Evaluation of inflammatory and renal injury markers in youngest children with pyelonephritis [Ocena wskaznikow zapalenia i uszkodzenia nerek u najmlodszych dzieci chorych na odmiedniczkowe zapalenie nerek]. *Polski Merkuriusz Lekarski* 2008;**25**(150):451-4. [MEDLINE: 19205372]

Putnik 2011 *{published data only}*

Putnik J, Stajic N, Paripovic A, Jaksic E, Bogdanovic R. Procalcitonin as a predictor of acute pyelonephritis and risk for renal scarring in children with a first febrile urinary tract infection [abstract]. *Pediatric Nephrology* 2011;**26**(9):1701-2. [EMBASE: 70530865]

Repetto 2004 *{published data only}*

Repetto HA, Alarcon PA, Pellegrini M. Procalcitonin as a marker of acute pyelonephritis. *Pediatric Nephrology* 2004;**18**(7):726. [MEDLINE: 12721819]

Robles 2005 *{published data only}*

Robles Garcia B, Rodriguez Fernandez LM, Suarez Rodriguez MA, Marugan De Miguelsanz JM, Fernandez Castano M, Fuentes Acebes MC. Comparison of the utility of fever and some laboratory parameters to diagnose acute pyelonephritis in children [Comparacion de la utilidad de la fiebre y de algunos parametros analiticos para el diagnostico de pielonefritis aguda en ninos]. *Revista Espanola de Pediatria* 2005;**61**(5):358-63. [EMBASE: 43010352]

Sadeghi 2011 *{published data only}*

Sadeghi BS, Hashemi M. Diagnostic evaluation of procalcitonin in children with acute pyelonephritis [abstract]. *Iranian Journal of Kidney Diseases* 2011;**5**(Suppl 1):15. [EMBASE: 70539635]

Sellem 2013 *{published data only}*

Sellem A, Elajmi W, Mahjoub Y, Hammami H. Interest of DMSA renal scintigraphy in acute pyelonephritis in children [Interet de la scintigraphie renale au DMSA dans les pyelonephrites aigues de l'enfant]. *Medecine Nucleaire* 2013;**37**(10-11):455-61. [EMBASE: 52833969]

Sevketoglu 2010 *{published data only}*

Sevketoglu E, Yilmaz A, Gedikbasi A, Karyagar S, Kiyak A, Mulazimoglu M, et al. Urinary macrophage migration inhibitory factor in children with urinary tract infection. *Pediatric Nephrology* 2010;**25**(2):299-304. [MEDLINE: 19841948]

Sheu 2009 *{published data only}*

Sheu JN, Chen SM, Meng MH, Lue KH. The role of serum and urine interleukin-8 on acute pyelonephritis and subsequent renal scarring in children. *Pediatric Infectious Disease Journal* 2009;**28**(10):885-90. [MEDLINE: 19687772]

Sim 2015 *{published data only}*

Sim JH, Yim HE, Choi BM, Lee JH, Yoo KH. Plasma neutrophil gelatinase-associated lipocalin predicts acute pyelonephritis

in children with urinary tract infections. *Pediatric Research* 2015;**78**(1):48-55. [MEDLINE: 25790277]

Simren 2018 *{published data only}*

Simrén Y, Valdimarsson S, Stokland E, Lagerstrand KM, Sixt R, Hansson S. Renal swelling indicates renal damage in infants with their first urinary tract infection. *Acta Paediatrica* 2018;**107**(11):2004-10. [MEDLINE: 29972698]

Simsek 2004 *{published data only}*

Simsek E, Kologlu N, Yugunt I, Kocabay K. Comparison of imaging studies and diagnostic tests for the diagnosis and follow-up of recurrent urinary tract infection in children. *International Pediatrics* 2004;**19**(2):109-13. [EMBASE: 38747472]

Smolkin 2002 *{published data only}*

Smolkin V, Koren A, Raz R, Colodner R, Sakran W, Halevy R. Procalcitonin as a marker of acute pyelonephritis in infants and children. *Pediatric Nephrology* 2002;**17**(6):409-12. [MEDLINE: 12107804]

Soylu 2007 *{published data only}*

Soylu A, Kasap B, Demir K, Turkmen M, Kavukcu S. Predictive value of clinical and laboratory variables for vesicoureteral reflux in children. *Pediatric Nephrology* 2007;**22**(6):844-8. [MEDLINE: 17273861]

Stokland 1996a *{published data only}*

Stokland E, Hellstrom M, Jacobsson B, Jodal U, Lundgren P, Sixt R. Early 99mTc dimercaptosuccinic acid (DMSA) scintigraphy in symptomatic first-time urinary tract infection. *Acta Paediatrica* 1996;**85**(4):430-6. [MEDLINE: 8740300]

Stokland 1998 *{published data only}*

Stokland E, Hellstrom M, Jacobsson B, Jodal U, Sixt R. Evaluation of DMSA scintigraphy and urography in assessing both acute and permanent renal damage in children. *Acta Radiologica* 1998;**39**(4):447-52. [MEDLINE: 9685836]

Subat-Dezulovic 1998 *{published data only}*

Subat-Dezulovic M, Katalinic-Franulovic J, Cekada S. Epidemiological and clinical characteristics of the first documented urinary infection in children [Epidemioloske i klinicke osobitosti prve dokazane urinarne infekcije u djece]. *Paediatria Croatica* 1998;**42**(3-4):165-72. [EMBASE: 29067766]

Sun 2013 *{published data only}*

Sun HL, Wu KH, Chen SM, Chao YH, Ku MS, Hung TW, et al. Role of procalcitonin in predicting dilating vesicoureteral reflux in young children hospitalized with a first febrile urinary tract infection. *Pediatric Infectious Disease Journal* 2013;**32**(9):e348-54. [MEDLINE: 23584577]

Swerkersson 2007 *{published data only}*

Swerkersson S, Jodal U, Sixt R, Stokland E, Hansson S. Relationship among vesicoureteral reflux, urinary tract infection and renal damage in children. *Journal of Urology* 2007;**178**(2):647-1. [MEDLINE: 17574623]

Tealab 2011 *{published data only}*

Tealab AA, Kholy O, Saad M, Gaballah A. The role of urinary IL 8 level in diagnosis and differentiation between different types of urinary tract infection in children [abstract]. *European Urology, Supplements* 2011;**10**(2):111. [EMBASE: 70375789]

Thayyil 2005 *{published data only}*

Thayyil S, Shenoy M, Hamaluba M, Gupta A, Frater J, Verber IG. Is procalcitonin useful in early diagnosis of serious bacterial infections in children? *Acta Paediatrica* 2005;**94**(2):155-8. [MEDLINE: 15981747]

Valavi 2011 *{published data only}*

Valavi E, Ahmadzadeh A, Ziaee KT, Nicfar R, Aminzadeh M, Najafi R. Clinical correlation between findings of renal scintigraphy and clinical / laboratory findings in children with febrile UTI [abstract]. *Iranian Journal of Kidney Diseases* 2011;**5**(Suppl 1):10. [EMBASE: 70539623]

Verboven 1990 *{published data only}*

Verboven M, Ingels M, Delree M, Piepsz A. 99mTc-DMSA scintigraphy in acute urinary tract infection in children. *Pediatric Radiology* 1990;**20**(7):540-2. [MEDLINE: 2170901]

Vujevic 2017 *{published data only}*

Vujevic M, Benzon B, Markic J. New prediction model for diagnosis of bacterial infection in febrile infants younger than 90 days. *Turkish Journal of Pediatrics* 2017;**59**(3):261-8. [MEDLINE: 29376570]

Wang 2005 *{published data only}*

Wang YT, Chiu NT, Chen MJ, Huang JJ, Chou HH, Chiou YY. Correlation of renal ultrasonographic findings with inflammatory volume from dimercaptosuccinic acid renal scans in children with acute pyelonephritis. *Journal of Urology* 2005;**173**(1):190-4. [MEDLINE: 15592072]

Yen 1999 *{published data only}*

Yen CW, Chen DH. Urinary tract infection in children. *Journal of Microbiology, Immunology & Infection* 1999;**32**(3):199-205. [MEDLINE: 10637719]

Zhang 2013 *{published data only}*

Zhang L, Yu Q, Guo KP, Yi SW, Li S, Mo LY. Role of procalcitonin in the diagnosis of acute pyelonephritis in children. *Zhongguo Dangdai Erke Zazhi [Chinese Journal of Contemporary Pediatrics]* 2013;**15**(2):85-7. [MEDLINE: 23428117]

Additional references

Bossuyt 2006

Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways.[Erratum in: BMJ. 2006 Jun 10;332(7554):1368]. *BMJ* 2006;**332**(7549):1089-92. [MEDLINE: 16675820]

Coulthard 2009

Coulthard MG, Lambert HJ, Keir MJ. Do systemic symptoms predict the risk of kidney scarring after urinary tract infection?

Archives of Disease in Childhood 2009;**94**(4):278-81. [MEDLINE: 19015216]

Craig 2000

Craig JC, Wheeler DM, Irwig L, Howman-Giles RB. How accurate is dimercaptosuccinic acid scintigraphy for the diagnosis of acute pyelonephritis? A meta-analysis of experimental studies. *Journal of Nuclear Medicine* 2000;**41**(6):986-93. [MEDLINE: 10855622]

Freedman 2005

Freedman AL, Urologic Diseases in America Project. Urologic diseases in North America Project: trends in resource utilization for urinary tract infections in children. *Journal of Urology* 2005;**173**(3):949-54. [MEDLINE: 15711347]

Hanson 1983

Hanson LA, Jodal U, Sabel KG, Wadsworth C. The diagnostic value of C-reactive protein. *Pediatric Infectious Disease* 1983;**2**(2):87-9. [MEDLINE: 6856495]

Hayen 2010

Hayen A, Macaskill P, Irwig L, Bossuyt P. Appropriate statistical methods are required to assess diagnostic tests for replacement, add-on, and triage. *Journal of Clinical Epidemiology* 2010;**63**(8):883-91. [MEDLINE: 20079607]

Hoberman 1994

Hoberman A, Wald ER, Reynolds EA, Penchansky L, Charron M. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. *Journal of Pediatrics* 1994;**124**(4):513-9. [MEDLINE: 8151463]

Huang 2011

Huang YY, Chen MJ, Chiu NT, Chou HH, Lin KY, Chiou YY. Adjunctive oral methylprednisolone in pediatric acute pyelonephritis alleviates renal scarring. *Pediatrics* 2011;**128**(3):e496-504. [MEDLINE: 21844061]

Leroy 2013

Leroy S, Fernadez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervaix A, et al. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. *Pediatrics* 2013;**131**(5):870-9. [MEDLINE: 23629615]

Mantadakis 2009

Mantadakis E, Plessa E, Vouloumanou EK, Karageorgopoulos DE, Chatzimichael A, Falagas ME. Serum procalcitonin for prediction of renal parenchymal involvement in children with urinary tract infections: a meta-analysis of prospective clinical studies. *Journal of Pediatrics* 2009;**155**(6):875-81. [MEDLINE: 19850301]

Pylkkanen 1981

Pylkkanen J Vilska J, Koskimies O. The value of level diagnosis of childhood urinary tract infection in predicting renal injury. *Acta Paediatrica Scandinavica* 1981;**70**(6):879-83. [MEDLINE: 7324941]

SAS 2011

SAS Software [computer program]. SAS Institute Inc., North Carolina USA, 2011.

Shaikh 2007

Shaikh N, Morone NE, Lopez J, Chianese J, Sangvai S, D'Amico F, et al. Does this child have a urinary tract infection? *JAMA* 2007;**298**(24):2895-904. [MEDLINE: 18159059]

Shaikh 2008

Shaikh N, Morone NE, Bost JE, Farrell MH. Prevalence of urinary tract infection in childhood: a meta-analysis. *Pediatric Infectious Disease Journal* 2008;**27**(4):302-8. [MEDLINE: 18316994]

Stokland 1996

Stokland E, Hellstrom M, Jacobsson B, Jodal U, Sixt R. Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. *Journal of Pediatrics* 1996;**129**(6):815-20. [MEDLINE: 8969722]

Whiting 2011

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011;**155**(8):529-36. [MEDLINE: 22007046]

References to other published versions of this review

Shaikh 2011

Shaikh N, Evron J, Leeflang MM. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No: CD009185. [DOI: 10.1002/14651858.CD009185]

Shaikh 2015

Shaikh N, Borrell JL, Evron J, Leeflang MM. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No: CD009185. [DOI: 10.1002/14651858.CD009185.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ansari Gilani 2010

Study characteristics

Ansari Gilani 2010 *(Continued)*

Patient Sampling	Prospective
Patient characteristics and setting	119 children with a first UTI Setting not well described Setting not described
Index tests	CRP, ESR
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Ansari Gilani 2010 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Barati 2016

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	95 patients with first febrile UTI Patients admitted to hospital with first febrile UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	
Methodological quality	

Barati 2016 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Benador 1997

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	201 children with febrile UTI Hospitalised children with suspected pyelonephritis CRP > 10 mg/L required for inclusion		
Index tests	CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Benador 1997 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Biggi 2001

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	101 children with a first UTI Children referred to radiology Referred population
Index tests	ESR, CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	
Methodological quality	

Biggi 2001 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Bigot 2005

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	42 children with a febrile UTI (not necessarily the first UTI) Emergency department 80 patients who did not have complete data were excluded		
Index tests	PCT, CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported 80 patients who did not have complete data were excluded		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Bigot 2005 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Bouguila 2013

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	75 children with first febrile UTI Children admitted with first episode of febrile UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP, PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Bouguila 2013 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Bressan 2009

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	72 children with a first febrile UTI Emergency department CRP part of inclusion criteria
Index tests	PCT, CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Bressan 2009 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Chen 2013

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	136 enrolled children Children< 10 years old admitted to hospital with febrile UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP, PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	

Chen 2013 *(Continued)*

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Donoso 2004

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	143 children with a first episode of pyelonephritis Children hospitalised for presumed pyelonephritis and referred for a DMSA Referred population, CRP may have been used to determine inclusion
Index tests	ESR, CRP (200 mg/L cutoff)
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Donoso 2004 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Fretzayas 2000

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	Children < 14 years with a first UTI First symptomatic UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	ESR, CRP (200 mg/L cutoff)
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	

Fretzayas 2000 *(Continued)*

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Garin 2007

Study characteristics			
Patient Sampling	Retrospective		
Patient characteristics and setting	185 children with UTI Children 3 months to 2 years admitted to 2 hospitals Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	ESR, CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes	Standard cutoffs used for ESR; unusual cutoff for CRP		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Garin 2007 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Hoberman 1999

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	306 children 1 to 24 months old with a first febrile UTI Patients presenting to hospital or emergency department with a UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	ESR, CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients

Hoberman 1999 *(Continued)*

Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Hoberman 1999 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Jung 2016

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	150 infants experiencing first febrile UTI and 100 control with other febrile illnesses Infants admitted to the hospital with febrile illnesses CRP part of inclusion		
Index tests	CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA Incorporation avoided? Yes. DMSA alone was used as the reference standard Acceptable reference standard? Yes. Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Jung 2016 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Kim 2017

Study characteristics	
Patient Sampling	Retrospective
Patient characteristics and setting	138 children with febrile UTI Retrospective review of medical records of UTI patients admitted to Department of pediatrics Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP, PCT, pNGAL
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA

Kim 2017 *(Continued)*

Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Kim 2017 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Kotoula 2009a

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	57 children 2 to 108 months of age with a first UTI Children hospitalized for UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	ESR, CRP, PCT		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients Children with lesions that did not partially regress at 6 months excluded (additional information provided by authors)		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Kotoula 2009a *(Continued)*

Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		Unclear risk	

Krzemien 2019

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	54 febrile children 1 to 24 months of age with first UTI
Index tests	CRP, PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA within 10 days

Krzemien 2019 *(Continued)*

	DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	DMSA within 10 days		
Comparative			
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Krzemien 2019 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Kuzmanovska 2008

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	282 children with a febrile UTI Children treated at the clinic of children's diseases in Skopje Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	ESR, CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan Unclear whether uninterpretable results reported Unclear about reasons for withdrawals		
Comparative			
Notes	Unusual cutoffs used for test result interpretation, probably influenced by clinical data		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	

Kuzmanovska 2008 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Could the patient flow have introduced bias?		Unclear risk	

Levtchenko 2001

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	92 children with febrile UTI Children admitted to hospital because of suspected pyelonephritis CRP part of inclusion criteria
Index tests	CRP

Levtchenko 2001 *(Continued)*

Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	

Levtchenko 2001 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Mahyar 2014

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	79 children with first episode of proven UTI Children hospitalized with first proven UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	CRP, ESR, PCT		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Mahyar 2014 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Martin Aguado 2000

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	103 children 1 to 10 years of age with a first febrile UTI Children presenting to a hospital centre

Martin Aguado 2000 *(Continued)*

	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Martin Aguado 2000 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Melis 1992

Study characteristics	
Patient Sampling	Retrospective
Patient characteristics and setting	146 children with UTI Children 1 week to 16 years admitted for a UTI Representative spectrum? Yes. Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	ESR, CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Melis 1992 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Mohkam 2010

Study characteristics

Mohkam 2010 *(Continued)*

Patient Sampling	Prospective
Patient characteristics and setting	Children 1 to 14 years of age with a UTI Hospitalised children with UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	ESR, CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Not able to account for all patients
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Mohkam 2010 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Could the patient flow have introduced bias?		Unclear risk	

Montini 2007

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	502 children with a first febrile UTI Children hospitalised for UTI ESR/CRP part of inclusion
Index tests	ESR, CRP, PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	
Methodological quality	

Montini 2007 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Nikfar 2010

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	100 children 1 month to 14 years with a febrile UTI Children admitted with a UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP, PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Nikfar 2010 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Printza 2012

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	98 infants < 12 months of age with a first febrile UTI Children admitted to hospital for UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP, ESR
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	

Printza 2012 *(Continued)*

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Seo 2014

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	47 infants aged 1 to 12 months with first febrile UTI Children admitted to Department of Pediatrics with first episode of febrile UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Seo 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Shaikh 2019

Study characteristics	
Patient Sampling	Convenience sample, prospective
Patient characteristics and setting	61 febrile children with suspected UTI
Index tests	PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA within 2 weeks of diagnosis DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	DMSA within 2 weeks
Comparative	
Notes	
Methodological quality	

Shaikh 2019 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sheu 2007

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	78 children 1 month to 10 years with a first febrile UTI Recruitment source not specified
Index tests	CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			

Sheu 2007 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sheu 2011

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	112 children < 2 years of age with a first febrile UTI Children admitted to hospital for UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	PCT
Target condition and reference standard(s)	Pyelonephritis, DMSA Incorporation avoided? Yes. DMSA alone was used as the reference standard Acceptable reference standard? Yes. Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	Unclear whether Sheu 2007 and Sheu 2011 overlap. If so, direct comparison may be possible

Sheu 2011 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Taskinen 2005

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	64 children with a first febrile UTI Children referred to hospital because of suspected pyelonephritis CRP part of inclusion
Index tests	CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Taskinen 2005 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Tekin 2015

Study characteristics	
Patient Sampling	Prospective
Patient characteristics and setting	94 patients aged 2 months to 12 years with first episode of UTI Children admitted Department of pediatrics with first episode of UTI patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP, ESR
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients

Tekin 2015 *(Continued)*

Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Tekin 2015 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Tuerlinckx 2005

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	63 children 2 months to 14 years of age first febrile UTI Children admitted to hospital for UTI Population not described in detail		
Index tests	CRP, PCT		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Details regarding DMSA scan procedure not described		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Tuerlinckx 2005 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Wu 2012

Study characteristics	
Patient Sampling	Retrospective
Patient characteristics and setting	156 children with a first UTI Children less than 4 months of age with a UTI Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Index tests	CRP
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA
Flow and timing	16 patients did not received verification of diagnosis with DMSA scan (partial verification) All test results were reported

Wu 2012 *(Continued)*

	Able to account for all patients		
Comparative			
Notes	Unusual cutoff used for test result interpretation		

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Unclear		
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Wu 2012 *(Continued)*

Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Xu 2014

Study characteristics			
Patient Sampling	Retrospective		
Patient characteristics and setting	46 patients with suspected APN Retrospective analysis of 46 patients who underwent DMSA renal scan Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	CRP, PCT		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			

Xu 2014 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Yun 2018

Study characteristics	
Patient Sampling	Infants hospitalised for febrile UTI
Patient characteristics and setting	Hospitalised febrile infants < 12 months of age
Index tests	
Target condition and reference standard(s)	Photopenia on DMSA scan
Flow and timing	Timing of the DMSA unclear
Comparative	
Notes	

Yun 2018 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	

Zaki 1996

Study characteristics			
Patient Sampling	Prospective		
Patient characteristics and setting	50 children with a first diagnosed febrile UTI Children 6 months to 12 years admitted to hospital Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions		
Index tests	ESR, CRP		
Target condition and reference standard(s)	Pyelonephritis, DMSA DMSA alone was used as the reference standard Pyelonephritis defined as the presence of photopenia on planar DMSA		
Flow and timing	All patients (or random selection of patients) received verification of diagnosis with DMSA scan All test results were reported Able to account for all patients		
Comparative			
Notes	Unusual cutoffs used for test result interpretation, possibly influenced by clinical data		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (All tests)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	No		

Zaki 1996 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Unclear risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

CRP - C-reactive protein; DMSA - ^{99}Tc-dimercaptosuccinic acid; ESR - erythrocyte sedimentation rate; NGAL - neutrophil gelatinase-associated lipocalin; PCT - procalcitonin; UTI - urinary tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agrawal 2013	Adult data only
Al Kholi 2010	Not relevant - No data in paper
Andersson 2009	Not relevant - No data in paper
Andreola 2007	Insufficient data in paper to determine 2 x 2 table
Arambasic 2016	Insufficient data in paper to determine 2 x 2 table
Asom 1996	Not relevant - No data in paper
Ataei 2009	Insufficient data in paper to determine 2 x 2 table
Ayazi 2009	Urine culture criteria not met
Ayazi 2013	Urine culture criteria not met

Study	Reason for exclusion
Azab 2016	Not relevant - No DMSA
Banuelos-Andrio 2017	Urine culture criteria not met
Belhadj-Tahar 2008	Insufficient data in paper to determine 2 x 2 table
Benador 1994	Not relevant - No PCT, CRP, or ESR
Benador 1998	Urine culture criteria not met
Benador 2001	Not relevant - All children had a positive DMSA
Benigno 1986	Not relevant - No DMSA
Bouissou 1994	DMSA not within 30 days
Bouissou 2008	DMSA not within 30 days
Brouhard 1997	Not relevant - No data in paper
Buyan 1993	Used SPECT DMSA
Capdevila 2001	DMSA not within 30 days
Castello 1995	Urine culture criteria not met
Chiou 2010	Not relevant - No data in paper
Christian 2000	DMSA not within 30 days
Connell 1993	Not relevant - No DMSA
Craig 1998	Not relevant - No PCT, CRP, or ESR
de Man 1988	Not relevant - No DMSA
Doganis 2007	Not relevant - No data in paper
Dura Trave 1997	Not relevant - No data in paper
Ehsanipour 2017	Not relevant - No DMSA
Elo 1985	Not relevant - No DMSA
Eremeeva 2016	Insufficient data in paper to determine 2 x 2 table
Fang 2017	Not relevant - No DMSA
Fang 2020	Insufficient data in paper to determine 2 x 2 table
Fernandez 2001	Insufficient data in paper to determine 2 x 2 table
Fernandez 2003	Insufficient data in paper to determine 2 x 2 table
Fernandez-Menendez 2003	Insufficient data in paper to determine 2 x 2 table

Study	Reason for exclusion
Figueiredo 1999	Not relevant - No data in paper
Friedman-Gruszczynska 2008	Not relevant - No DMSA
Galetto-Lacour 2002	Not relevant - No data in paper
Galetto-Lacour 2003	Insufficient data in paper to determine 2 x 2 table
Garcia de Guadiana 2011	Insufficient data in paper to determine 2 x 2 table
Gendrel 1998	Not relevant - No data in paper
Gervaix 2001	Urine culture criteria not met
Ghasemi 2013	Urine culture criteria not met
Ghasemi 2016	Used SPECT DMSA
Girardin 2000	Not relevant - No data in paper
Giunta 2014	Adult data only
Grouteau 1999	Not relevant - No data in paper
Guermazi 1993	Not relevant - No data in paper
Gurgoze 2005	Urine culture criteria not met
Guven 2006	Urine culture criteria not met
Hahn 2003	Not relevant - All children had a positive DMSA
Han 2016	Insufficient data in paper to determine 2 x 2 table
Hellerstein 1981	Not relevant - No DMSA
Hellerstein 1982	Not relevant - No DMSA
Hewitt 2008	Not relevant - All children had a positive DMSA
Hitzel 2002	Not relevant - No PCT, CRP, or ESR
Hsu 2016	Insufficient data in paper to determine 2 x 2 table
Huang 2007	Insufficient data in paper to determine 2 x 2 table
Hubert-Dibon 2018	Not relevant - No DMSA
Ilyas 2002	Not relevant - No data in paper
Jakobsson 1992a	Insufficient data in paper to determine 2 x 2 table
Jakobsson 1992b	Insufficient data in paper to determine 2 x 2 table, also Index test part of inclusion criteria
Jakobsson 1994	Insufficient data in paper to determine 2 x 2 table, also urine culture criteria not specified

Study	Reason for exclusion
Jakobsson 1997	Urine culture criteria not met
Jaksic 2011	Insufficient data in paper to determine 2 x 2 table
Jantausch 1994	Not relevant - No PCT, CRP, or ESR
Jodal 1975	Not relevant - No DMSA
Johnson 1985	Not relevant - No DMSA
Kanellopoulos 2005	Not relevant - No PCT, CRP, or ESR
Kangari 2015	Urine culture criteria not met
Karakatsani 1997	Insufficient data in paper to determine 2 x 2 table
Karavanaki 2007	Insufficient data in paper to determine 2 x 2 table
Kassir 2001	Not relevant - No data in paper
Katz 1993	Not relevant - No data in paper
Katz 2002	Not relevant - No data in paper
Kiker 1982	Not relevant - No data in paper
Kilicaslan 2015	Used SPECT DMSA
Kilicaslan 2016	Used SPECT DMSA
Kim 2001	Not relevant - No data in paper
Koufadaki 2014	Mild DMSA abnormalities considered normal
Krzemien 2004	DMSA not within 30 days
Krzemien 2016	Insufficient data in paper to determine 2 x 2 table
Krzemien 2017	Not relevant - No DMSA
Kupperman 2019	Not relevant - No DMSA
Lai 2003	Not relevant - All children had a positive DMSA
Lee 2006	Not relevant - No data in paper
Lee 2009	Not relevant - No PCT, CRP, or ESR
Lee 2015	Insufficient data in paper to determine 2 x 2 table
Lee 2017	Insufficient data in paper to determine 2 x 2 table
Lee 2017a	Insufficient data in paper to determine 2 x 2 table
Lee 2018	Urine culture criteria not met

Study	Reason for exclusion
Lee 2018a	Insufficient data in paper to determine 2 x 2 table
Lee 2018b	Not relevant - No DMSA
Lee 2019	Insufficient data in paper to determine 2 x 2 table
Leroy 2012	Insufficient data in paper to determine 2 x 2 table
Levine 2018	Adult data only
Lin 2000	Not relevant - No DMSA
Linne 1994	Not relevant - No PCT, CRP, or ESR
Lomberg 1992	Not relevant - No DMSA
Lucas-Saez 2014	Urine culture criteria not met
Mahyar 2013	Urine culture criteria not met
Majd 1991	Insufficient data in paper to determine 2 x 2 table
Majd 1992	Not relevant - No data in paper
Malaga 1978	Not relevant - No DMSA
Masajtis-Zagajewska 2015	Not relevant - No DMSA
Mazigh Mrad 2002	Urine culture criteria not met
Mohkam 2008	Not relevant - All children had a positive DMSA
Moldovan 2015	Not relevant - No DMSA
Montini 2008	Not relevant – No data in paper
Montini 2009	Not relevant – No data in paper
Moon 2009	Not relevant - No data in paper
Mussap 2006	Not relevant - No data in paper
Naseri 2008	Not relevant - No DMSA
Naseri 2017	Urine culture criteria not met
Neuhaus 2008	Not relevant - No data in paper
Nickavar 2015	Insufficient data in paper to determine 2 x 2 table
Oh 2010	Not relevant - No data in paper
Oh 2011	Not relevant - No data in paper
Ohta 2019	Not relevant – No data in paper

Study	Reason for exclusion
Orlowska 2004	Urine culture criteria not met
Otto 2005	Adult data only
Otukesh 2009	Insufficient data in paper to determine 2 x 2 table
Paripovic 2011	Insufficient data in paper to determine 2 x 2 table
Pecile 2004	Used SPECT DMSA
Pecile 2005	Not relevant - No data in paper
Pecile 2007	Not relevant - No data in paper
Piepsz 1998	Not relevant - No PCT, CRP, or ESR
Prat 2003	DMSA not within 30 days
Prat 2004	Not relevant - No data in paper
Preda 2011	Not relevant - No data in paper
Printza 2008	Not relevant - No data in paper
Puczko-Michalczuk 2008	Not relevant - All children had a positive DMSA
Putnik 2011	Insufficient data in paper to determine 2 x 2 table
Repetto 2004	Not relevant - No data in paper
Robles 2005	Insufficient data in paper to determine 2 x 2 table
Sadeghi 2011	Insufficient data in paper to determine 2 x 2 table
Sellem 2013	Urine culture criteria not met
Sevketoglu 2010	Not relevant - No data in paper
Sheu 2009	Not relevant - No data in paper
Sim 2015	Insufficient data in paper to determine 2 x 2 table
Simren 2018	Insufficient data in paper to determine 2 x 2 table
Simsek 2004	Not relevant - No data in paper
Smolkin 2002	Urine culture criteria not met
Soylu 2007	Not relevant - No DMSA
Stokland 1996a	DMSA not within 30 days
Stokland 1998	DMSA not within 30 days
Subat-Dezulovic 1998	Not relevant - No DMSA

Study	Reason for exclusion
Sun 2013	Not relevant – No data in paper
Swerkersson 2007	Not relevant - No data in paper
Tealab 2011	Not relevant - No data in paper
Thayyil 2005	Not relevant - No data in paper
Valavi 2011	Insufficient data in paper to determine 2 x 2 table
Verboven 1990	Not relevant - No PCT, CRP, or ESR
Vujevic 2017	Not relevant - No DMSA
Wang 2005	Urine culture criteria not met
Yen 1999	Not relevant - No data in paper
Zhang 2013	Not relevant – No data in paper

CFU - colony forming units; CRP - C-reactive protein; DMSA - ^{99}Tc-dimercaptosuccinic acid; ESR - erythrocyte sedimentation rate; PCT - procalcitonin; SPECT - single-photon emission computed tomography; UTI - urinary tract infection

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 PCT > 0.5 ng/mL	12	1000
2 CRP > 20 mg/L	16	1895
3 ESR ≥ 30 mm/hour	8	1910

ADDITIONAL TABLES

Table 1. Summary of sensitivity analysis

	PCT > 0.5	CRP > 20	ESR ≥ 30
All studies			
Summary sensitivity	0.81	0.93	0.83
Summary specificity	0.76	0.37	0.57

Table 1. Summary of sensitivity analysis *(Continued)*

Studies that included only children with a first UTI			
Summary sensitivity	0.82	0.94	0.86
Summary specificity	0.75	0.32	0.58
Studies in which perineal bags were not used			
Summary sensitivity	0.83	0.93	0.82
Summary specificity	0.78	0.49	0.68
Studies that included only febrile children			
Summary sensitivity	0.80	0.92	--
Summary specificity	0.78	0.38	--
Studies in which DMSA was conducted with 7 days of diagnosis			
Summary sensitivity	0.83	0.93	0.82
Summary specificity	0.77	0.43	0.64
Studies in which children with genitourinary anomalies were excluded			
Summary sensitivity	0.83	0.91	0.81
Summary specificity	0.80	0.40	0.49
Studies with low risk of bias			
Summary sensitivity	0.80	0.93	0.79
Summary specificity	0.77	0.42	0.67

-- Insufficient number of studies available or model would not converge
CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; PCT - procalcitonin; UTI - urinary tract infection

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
MEDLINE (OvidSP)	1. procalcitonin.tw. 2. procalcitonin.nm. 3. PCT.tw. 4. or/1-3 5. c-Reactive Protein/ 6. c-reactive protein.tw. 7. CRP.tw.

(Continued)

	8. or/5-7 9. Blood Sedimentation/ 10.erythrocyte sedimentation rate.tw. 11.ESR.tw. 12.blood sedimentation.tw. 13.or/9-12 14.or/4,8,13 15.Technetium Tc 99m Dimercaptosuccinic Acid/ 16.DMSA.tw. 17.dimercaptosuccin$.tw. 18.scintigra$.tw. 19.Radionuclide Imaging/ 20.Succimer 21.Kidney/dg 22.or/15-21 23.or/14,22 24.Urinary Tract Infections/ 25.Pyelonephritis/ 26.urinary tract infection$.tw. 27.pyelonephritis.tw. 28.(UTI or UTIs).tw. 29.or/24-28 30.and/23,29
EMBASE (OvidSP)	1. Procalcitonin/ 2. procalcitonin.tw. 3. PCT.tw. 4. or/1-3 5. C reactive protein/ 6. c-reactive protein.tw. 7. CRP.tw. 8. or/5-7 9. Erythrocyte Sedimentation Rate/ 10.erythrocyte sedimentation rate.tw. 11.blood sedimentation.tw. 12.ESR.tw. 13.or/9-12 14.or/4,8,13 15.succimer tc 99m/ 16.succimer/ 17.dimercaptosuccin$.tw. 18.DMSA.tw. 19.Scintigraphy/ 20.scintigra$.tw. 21.Scintiscanning/ 22.Radioisotope Diagnosis/ 23.or/16-22 24.or/15,23 25.Urinary Tract Infection/ 26.Pyelonephritis/ 27.urinary tract infection$.tw. 28.pyelonephritis.tw.

(Continued)

	29.(UTI or UTIs).tw. 30.or/25-29 31.and/24,30
BIOSIS Previews	#9 #8 OR #7 #8 #6 AND #5 #7 #6 AND #4 #6 TS=(urinary tract infection* OR pyelonephritis OR UTI or UTIs) #5 TS=(dimercaptosucc* OR DMSA OR scintiscan* OR scintigra* OR radionuclide OR radioisotope) #4 #3 OR #2 OR #1 #3 TS=(procalcitonin or PCT) #2 TS=(erythrocyte sedimentation rate OR blood sedimentation OR ESR) #1 TS=(c-reactive protein OR c reactive protein OR CRP)

Appendix 2. QUADAS-2

Domain 1: Patient selection

Risk of bias (could the selection of patients have introduced bias?)

1. Was a consecutive or random sample of patients enrolled?
2. Was a case-control design avoided?
3. Did the study avoid inappropriate exclusions?

Applicability (are there concerns that the included patients and setting do not match the review question?

Domain 2: Index test

Risk of bias (could the conduct or interpretation of the index test have introduced bias?)

1. Were the index test results interpreted without knowledge of the results of the reference standard?
2. If a threshold was used, was it prespecified?

Applicability (are there concerns that the index test, its conduct, or interpretation differ from the review question?)

Domain 3: Reference standard

Risk of bias (could the reference standard, its conduct, or its interpretation have introduced bias?)

1. Is the reference standard likely to correctly classify the target condition?
2. Were the reference standard results interpreted without knowledge of the results of the index test?

Applicability (are there concerns that the target condition as defined by the reference standard does not match the question?)

Domain 4: Flow and timing

Risk of bias (could the patient flow have introduced bias?)

1. Was there an appropriate interval between the index test and the reference standard?
2. Did all the patients receive the same reference standard?
3. Were all patients included in the analysis

WHAT'S NEW

Date	Event	Description
10 September 2020	New citation required but conclusions have not changed	12 new studies added, no change to conclusions
10 September 2020	New search has been performed	New search undertaken 17 December 2019

HISTORY

Protocol first published: Issue 6, 2011
Review first published: Issue 1, 2015

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: NS
- Study selection, assessment of methodology: KS, VO, NS
- Extract data from studies: KS, VO, NS
- Enter data into RevMan: KS, VO, NS
- Carry out the analysis: NS, ML
- Interpret the analysis: KS, NS, VO, ML
- Draft the final review: KS, NS, VO, ML
- Disagreement resolution: NS, ML
- Update the review: NS, KS, VO, ML

DECLARATIONS OF INTEREST

- Kai J Shaikh: none known
- Victor A Osio: none known
- Nader Shaikh: none known
- Mariska MG Leeflang: none known

SOURCES OF SUPPORT

Internal sources

- None, USA

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We followed the same methods as in the previous version of this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Biomarkers [blood]; *Blood Sedimentation; C-Reactive Protein [*analysis]; Calcitonin [*blood]; Cystitis [blood] [*diagnosis]; Diagnosis, Differential; Procalcitonin [*blood]; Pyelonephritis [blood] [complications] [*diagnosis]; Randomized Controlled Trials as Topic; Sensitivity and Specificity; Urinary Tract Infections [blood]

MeSH check words

Child; Humans