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

Shaikh N, Borrell JL, Evron J, Leeflang MMG

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[Diagnostic Test Accuracy Review]

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

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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.

Objectives

The objectives of this review were to 1) determine whether procalcitonin, 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 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 (procalcitonin, CRP, ESR) against the results of an acute-phase 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 cutoff values were used for the primary analysis: 0.5 ng/mL for procalcitonin, 20 mg/L for CRP and 30 mm/h 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 24 studies met our inclusion criteria. Seventeen studies provided data for the primary analysis: six studies (434 children) included data on procalcitonin, 13 studies (1638 children) included data on CRP, and six studies (1737 children) included data on ESR (some studies had data on more than one test). The summary sensitivity estimates (95% CI) for the procalcitonin, CRP, ESR tests at the aforementioned

cutoffs were 0.86 (0.72 to 0.93), 0.94 (0.85 to 0.97), and 0.87 (0.77 to 0.93), respectively. The summary specificity values for procalcitonin, CRP, and ESR tests at these cutoffs were 0.74 (0.55 to 0.87), 0.39 (0.23 to 0.58), and 0.48 (0.33 to 0.64), 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

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. Accordingly, 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 24 relevant studies of which 17 provided data for our primary outcome. Six studies (434 children) provided data for the procalcitonin test; 13 studies (1638 children) provided data for the C-reactive protein test, and six studies (1737 children) provided data for the erythrocyte sedimentation rate test. We found all three tests to be sensitive (summary sensitivity values ranged from 86% to 95%), but not very specific (summary specificity values ranged from 38% to 71%). 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. Summary of findings table

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 (cutoff)	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
PCT (0.5 ng/mL)	6 (434)	0.86 (0.72 to 0.93)	0.74 (0.55 to 0.87)	84	104	83%	22%	Very high
CRP (20 mg/L)	13 (1638)	0.94 (0.85 to 0.97)	0.39 (0.23 to 0.58)	36	244	70%	19%	High
ESR (30 mm/h)	6 (1737)	0.87 (0.77 to 0.93)	0.48 (0.32 to 0.64)	78	208	71%	29%	Moderate

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

DMSA - ⁹⁹Tc-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 ($> 39^{\circ}\text{C}$) is suggestive of pyelonephritis (Shaikh 2007), many children with cystitis also have fever. Despite that ^{99}Tc -dimercaptosuccinic acid (DMSA) scan has been shown to be accurate in identifying pyelonephritis (sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 0.86, 0.91, 9.5, and 0.15, 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 previous UTIs or dysplasia; 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, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)) can be used to accurately differentiate children with pyelonephritis from children with cystitis.

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 systemic 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/h) 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.

Alternative test(s)

Although several other tests have been proposed (e.g. urinary interleukin-6 and interleukin-8), 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 in the near future, 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. Another individual patient data meta-analysis examining the accuracy of procalcitonin in predicting pyelonephritis is currently underway (Leroy 2012). 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:

- $\geq 10^4$ CFU/mL from a catheterized specimen, or
- $\geq 10^5$ 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 sensitivity analysis 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. Searches were carried out 14 June 2011, and updated 13 February 2013 using search strategies developed in consultation with the Cochrane Renal Group's Trials Search Co-ordinator.

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 questionnaire to independently assess the quality of all studies that met our inclusion criteria (Whiting 2003). Disagreements were resolved by discussion. See Appendix 2 for a description of the QUADAS items that were used and criteria for scoring each item.

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 cutoff 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 cutoff (per test). We chose the latter option because the majority of the studies we found reported data for the following cutoffs: 0.5 ng/mL for procalcitonin; 20 mg/L for CRP, and 30 mm/h for ESR. Early studies established that a cutoff of 20 mg/L for CRP was ideal for discriminating between cystitis and pyelonephritis (Hanson 1983; Pytkkanen 1981). Therefore, this was the cutoff most commonly reported and the cutoff which we used for the primary analysis. For procalcitonin, a cutoff of 0.5 ng/mL has been recommended by the manufacturer and is widely accepted. In contrast, for the ESR test, no cutoff has been established. A value of > 10 mm/h is considered abnormal but very few studies used this cutoff. Accordingly, for the primary analysis, we used the cutoff most commonly reported in the studies meeting our inclusion criteria: 30 mm/h. Authors of papers using other cutoffs were contacted for data relative to the cutoffs listed. Articles for which no data could be obtained for the above cutoffs 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 cutoffs 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 within 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 9.2 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 cutoffs 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 in which the spectrum of patients was felt to be non-representative of the population of children with UTI (QUADAS item 1).

RESULTS

Results of the search

The results of the search strategy are shown in [Figure 1](#). Of the 2850 records were identified, 147 records were retrieved and reviewed. A total of 24 studies (29 records) met our inclusion criteria; 13 authors were successfully contacted for clarification and additional data. Seventeen studies provided data for the primary analysis: six studies (434 children) included data on procalcitonin ([Bigot 2005](#); [Bressan 2009](#); [Kotoula 2009a](#); [Nikfar 2010](#); [Sheu 2011](#); [Tuerlinckx 2005](#)), 13 studies included data on CRP (1638 children) ([Benador 1997](#); [Bigot 2005](#); [Bressan 2009](#); [Hoberman 1999](#); [Kotoula 2009a](#); [Levtchenko 2001](#); [Martin Aguado 2000](#); [Montini 2007](#); [Nikfar 2010](#); [Printza 2012](#); [Sheu 2007](#); [Taskinen 2005](#); [Tuerlinckx 2005](#)), and six studies (1737 children) included data on ESR tests ([Donoso 2004](#); [Fretzayas 2000](#); [Hoberman 1999](#); [Kotoula 2009a](#); [Mohkam 2010](#); [Montini 2007](#)). Some studies had data on more than one test.

Figure 1. Study flow diagram

CRP - C-reactive protein; DMSA - ⁹⁹Tc-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 of the included studies was that the population of children studied did not appear to be representative of the larger population of children with UTIs; of the 24 included studies, only 13 had populations that were clearly representative ([Figure 2](#)). Radiologists were blinded to the test

results in only six 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 and or reference standard. Some of these aforementioned limitations are not reflected in the QUADAS 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

	Representative spectrum?	Acceptable reference standard?	Acceptable delay between tests?	Partial verification avoided?	Differential verification avoided?	Incorporation avoided?	Index test results blinded?	Reference standard results blinded?	Relevant clinical information?	Uninterpretable results reported?	Withdrawals explained?
Ansari Gilani 2010	?	+	+	+	+	+	+	+	+	+	+
Benador 1997	-	+	+	+	+	+	+	?	+	+	+
Biggi 2001	?	+	+	+	+	+	+	+	+	+	+
Bigot 2005	?	+	+	+	+	+	+	+	+	+	-
Bressan 2009	-	+	+	+	+	+	+	?	+	+	+
Donoso 2004	-	+	+	+	+	+	+	?	+	+	+
Fretzayas 2000	+	+	+	+	+	+	+	+	+	+	+
Garin 2007	+	+	+	+	+	+	+	?	?	+	+
Hoberman 1999	+	+	+	+	+	+	+	+	+	+	+
Kotoula 2009a	+	+	+	+	+	+	+	?	+	+	+
Kuzmanovska 2008	+	+	+	+	+	+	+	?	?	?	?
Levtchenko 2001	-	+	+	+	+	+	+	+	+	+	+
Martin Aguado 2000	+	+	+	+	+	+	+	?	+	+	+
Melis 1992	+	+	?	+	+	+	+	?	+	+	+
Mohkam 2010	+	+	+	+	+	+	+	?	+	+	-
Montini 2007	-	+	+	+	+	+	+	?	+	+	+
Nikfar 2010	+	+	+	+	+	+	+	?	+	+	+
Printza 2012	+	+	+	+	+	+	+	?	+	+	+
Sheu 2007	?	+	+	+	+	+	+	?	+	+	+
Sheu 2011	+	+	+	+	+	+	+	?	+	+	+
Taskinen 2005	-	+	+	+	+	+	+	?	+	+	+
Tuerlinckx 2005	?	?	+	+	+	+	+	?	+	+	+
Wu 2012	+	+	+	-	+	+	+	?	?	+	+
Zaki 1996	+	+	+	+	+	+	+	?	?	+	+

Figure 2. (Continued)

Findings

For the procalcitonin test, six studies reported data for the 0.5 ng/mL cutoff. The summary sensitivity and specificity estimates were 0.86 (0.72 to 0.93) and 0.74 (0.55 to 0.87), 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 close to 90% (i.e., comparable to the DMSA), but the remainder of the studies reported much lower accuracy values. Sensitivity

analysis (Table 1) was limited because of the small number of studies. Heterogeneity appeared less marked (and the test seemed to more accurate) when only studies with a representative population were included; however, because of the small number of studies (3) with representative populations, no firm conclusions can be drawn. Meta-regression was not feasible because of the small number of studies. Three studies reported data using cutoffs other than 0.5 ng/mL; a forest plot of the sensitivity and specificity at these cutoffs is shown in Figure 4. As expected, the test appeared to be more specific at cutoff 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)

Figure 4. Procalcitonin at cutoffs other than 0.5 ng/mL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Kotoula (PCT 0.85 ng/mL)	24	1	3	29	0.89 [0.71, 0.98]	0.97 [0.83, 1.00]		
Kotoula (PCT 1.2 ng/mL)	23	0	4	30	0.85 [0.66, 0.96]	1.00 [0.88, 1.00]		
Sheu (PCT 1 ng/mL)	62	3	14	33	0.82 [0.71, 0.90]	0.92 [0.78, 0.98]		
Sheu (PCT 1.5 ng/mL)	57	2	21	34	0.73 [0.62, 0.82]	0.94 [0.81, 0.99]		
Sheu (PCT 2 ng/mL)	49	1	27	35	0.64 [0.53, 0.75]	0.97 [0.85, 1.00]		
Tuerlinckx (PCT 1.7 ng/mL)	23	3	27	10	0.46 [0.32, 0.61]	0.77 [0.46, 0.95]		

For the CRP test, we found 13 studies that reported data for the 20 mg/L cutoff. There was considerable heterogeneity among accuracy values from the various studies (Data table 2). The summary sensitivity and specificity estimates were 0.94 (0.85 to 0.97) and 0.39 (0.23 to 0.58), respectively (Figure 5). Heterogeneity appeared less marked when we included only studies in which 1) the DMSA scan was conducted during the first week in all children, 2) excluded children with genitourinary abnormalities, and 3) excluded children who were afebrile. The specificity of the test was somewhat improved when we limited the analysis to studies in which children were judged to be representative of the larger population of children with UTI or to studies in which bag collection

was not used (Table 1). None of the covariates investigated (fever, use of bags to collect urine samples, delay in performance of the DMSA) was significant ($P < 0.05$) in the meta-regression analysis. However, because of the small number of studies, we had limited power to detect differences. Accordingly, it seems important to note that studies in which bags were not used tended to report higher specificity levels: 0.53 (0.30 to 0.75) versus 0.30 (0.15 to 0.52) ($P = 0.16$, Table 1). Fourteen studies reported data using cutoffs other than 20 mg/L; a forest plot showing the sensitivity and specificity at these cutoffs 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)

Figure 6. C-reactive protein at cutoffs other than 20 mg/L

For the ESR test, we found six studies that reported data for the 30 mm/h cutoff. 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. The summary (95% CI) sensitivity and specificity estimates were 0.87 (0.77 to 0.93), and 0.48 (0.33 to

0.64), respectively Figure 7. Exclusion of Mohkam 2010 did not alter the pooled accuracy estimates considerably. Sensitivity analysis (Table 1) and meta-regression were limited because of the small number of studies. Eight studies reported data using cutoffs other than 30 mm/h; a forest plot showing the sensitivity and specificity at these cutoffs 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/h (solid point = pooled accuracy; dotted oval = 95% confidence region)

Figure 8. ESR at cutoffs other than 30 mm/h

Direct comparison was only possible for the procalcitonin versus CRP (five studies). Although the differences in the accuracy estimates were not significant for either sensitivity ($P = 0.13$) or

specificity ($P = 0.14$), the procalcitonin test had higher specificity values than the CRP test in 4/5 studies (Figure 9).

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

DISCUSSION

Summary of main results

In this review we examined the accuracy of procalcitonin, CRP, and ESR, in predicting pyelonephritis. We found all three tests to be sensitive (summary sensitivity values ranged from 0.83 to 0.94), but not very specific (summary specificity values ranged from 0.39 to 0.74). There was limited data to allow for a direct comparison between the three tests. Furthermore, the number of studies particularly on the ESR and procalcitonin tests was very limiting. 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, non-representative patient populations, 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 cutoffs 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 (1/6 studies for procalcitonin, 0/13 studies for CRP, and 0/6 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 cutoffs 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). Assuming a pre-test probability of pyelonephritis of 60% (Shaikh 2010), a test would have to have a positive likelihood ratio of at least 3.8 to rule in pyelonephritis (i.e., to increase the probability of cystitis from 60% to > 85%, with 85% being the threshold above which clinicians would be reasonably confident in their diagnosis of pyelonephritis). The pooled positive likelihood ratio for the procalcitonin test comes close to this value, and given the unexplained heterogeneity between studies, it is possible that this test, especially at higher cutoff values, could be useful in ruling in pyelonephritis if future studies support its use in this population (Implications for research). To rule out pyelonephritis (that is, to reduce the post-test probability of pyelonephritis to < 20%, with 20% being a threshold below which most clinicians would feel confident in their diagnosis of cystitis), a test would have to have a negative likelihood ratio of less than 0.17. The summary negative likelihood ratio for the CRP test was 0.16 (0.11 when we focused on studies in which bag specimen were not used, Table 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. Second, let us examine the utility of the tests in a lower risk population (with a 30% probability of pyelonephritis), such as one would encounter in older febrile children with urinary symptoms. In this population, a test would have to have a positive likelihood ratio of 13.2 and a negative likelihood ratio of 0.58 to rule in and rule out pyelonephritis, respectively. Accordingly, at the cutoffs examined, none of the tests would be useful in ruling in pyelonephritis in this

population. The CRP test, which has the lowest negative likelihood ratio, could be useful in ruling out pyelonephritis if future research supports this.

In summary, the ESR test does not appear to be useful in differentiating cystitis from pyelonephritis at the cutoff 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 unexplained heterogeneity of the results prevents us from making 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 cutoff 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 cutoffs 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 cutoffs 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 utilize representative populations (see [Appendix 2](#), QUADAS item 1), avoid the use of bag samples, and present results stratified by age. Since accuracy is best studied in populations suspected of having the target condition, studies should be limited to febrile children. Children with known 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 report data for cutoffs higher 0.5 ng/mL.

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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]

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]

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]

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 niños con primera pielonefritis aguda: correlación con exámenes de laboratorio, ecografía y la presencia de reflujo vesico ureteral]. *Revista Médica 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, et al. 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]

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](https://doi.org/10.1016/S1569-9056(08)60704-6); Biosis Previews: PREV200800283210]

Kotoula A, Gardikis S, Tsalkidis A, Mantadakis E, Zisimopoulos 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, Zisimopoulos 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]

Kuzmanovska 2008 {published data only}

Kuzmanovska D, Sahpazova E, Bogdanovska A, Konstadinova R. Parenchymal renal damage in children with urinary tract infection [Parenhimna bubrežna oštećenja u djece sa infekcijom mokraćnog sustava]. *Paediatrica Croatica, Supplement* 2008;**52**(Suppl 1):212-7. [EMBASE: 2010638845]

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]

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 Pediatría* 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, Raiati 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, Zucchetto 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, Khotae 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]

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]

Tuerlinckx 2005 {published and unpublished data}

Tuerlinckx D, Vander Borgh 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]

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
Abamor 2005 {published data only}

Abamor E. Accurate diagnosis of acute pyelonephritis in children: How helpful is procalcitonin?. *Nephrology Dialysis Transplantation* 2005;**20**.

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]

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]

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. [PUBMED: 3108721]

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]

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]

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 dzieci]. *Pediatrica Polska* 2008;**83**(1):49-53. [EMBASE: 2008097172]

Galetto-Lacour 2002 {published data only}

Galetto-Lacour A, Zamora S, Gervais A. Blood markers of severe bacterial infections [abstract]. 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, Gervais 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. *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 3:269S-73S. [MEDLINE: 9759316]

Gervais 2001 {published data only}

Gervais 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]

Girardin 2000 {published data only}

Girardin E. Pyelonephritis in children: new tools for evaluation [Pyelonephrites de l'enfant: nouveaux moyens d'evaluation]. *Medicine Therapeutique Pediatrie* 2000;**3**(5):376-80. [EMBASE: 2000414072]

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 dimercaptosuccinique marque au technetium 99m (99mTC-DMSA) 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 A, Kazdal H, 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]

Hellerstein 1981 {published data only}

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

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]

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, Nølstedt L, Svensson L, Soderlundh S, Berg U. 99mTechnetium-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]

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, Kariyannis 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: 2007563970]

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]

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**.

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]

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):350-2. [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]

Leroy 2012 {published data only}

Leroy S, Fernandez-Lopez A, Nikfar R, Romanello C, Bouissou F, Gervais 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.

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]

Majd 1991 {published data only}

Majd M, Rushton HG, Jantusch 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]

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 radiologiques 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]

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 scintigraphic 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]

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]

Oh 2010 {published data only}

Oh Mm, Cheon J, Kang SH, Park HS, Lee JG, Moon DG. 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]

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 zakażeniem układu moczowego - Doniesienie wstępne]. *Pediatrica Polska* 2004;**79**(2):111-4. [EMBASE: 2004143727]

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, Falletti 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, Falletti 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: 2005271359]

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, Reiniers 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 Groupin 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-Michalczyk 2008 {published data only}

Puczko-Michalczyk A, Zoch-Zwierz W, Wasilewska A, Porowska T, Korzeniecka-Kozerska A. Evaluation of inflammatory and renal injury markers in youngest children with pyelonephritis [Ocena wskaźników zapalenia i uszkodzenia nerek u najmłodszych dzieci chorych na odmiedniczkowe zapalenie nerek]. *Polski Merkurusz 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 ninios]. *Revista Espanola de Pediatria* 2005;**61**(5):358-63. [EMBASE: 2006003054]

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]

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]

Sharifian 2005 {published data only}

Sharifian MD, Akbarian M. Accurate diagnosis of acute pyelonephritis in children: how helpful is procalcitonin? [abstract]. *Nephrology Dialysis Transplantation* 2005;**20**(Suppl 5):250.

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]

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: 2004251416]

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. *Paediatrica Croatica* 1998;**42**(3-4):165-72. [EMBASE: 1999052133]

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]

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]

Additional references

Bossuyt 2006

Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. *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]

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]

Shaikh 2010

Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics* 2010;**126**(6):1084-91. [MEDLINE: 21059720]

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 2003

Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology* 2003;**3**:25. [MEDLINE: 14606960]

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. [DOI: [10.1002/14651858.CD009185](https://doi.org/10.1002/14651858.CD009185)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ansari Gilani 2010

Clinical features and settings	Setting not well described
Participants	119 children with a first UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	CRP, ESR
Follow-up	
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Setting not described
Acceptable reference standard? All tests	Yes	It seems that pyelonephritis defined as the presence of abnormalities on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 7 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Yes	Radiologists were blinded to patient's histories
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported

Ansari Gilani 2010 (Continued)

Withdrawals explained?	Yes	Able to account for all patients
All tests		

Benador 1997

Clinical features and settings	Hospitalised children with suspected pyelonephritis
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Participants	201 children with febrile UTI
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Study design	Prospective
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Target condition and reference standard(s)	Pyelonephritis, DMSA
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Index and comparator tests	CRP
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Follow-up	
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Notes	Additional information provided by authors
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Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	No	CRP > 10 mg/L required for inclusion
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)

Benador 1997 (Continued)

Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Biggi 2001

Clinical features and settings	Children referred to radiology	
Participants	101 children with a first UTI	
Study design	Prospective	
Target condition and reference standard(s)	Pyelonephritis, DMSA	
Index and comparator tests	ESR, CRP	
Follow-up		
Notes	Additional information provided by authors	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Referred population
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard

Biggi 2001 (Continued)

Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Yes	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Bigot 2005

Clinical features and settings	Emergency department
Participants	42 children with a febrile UTI (not necessarily the first UTI)
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	Procalcitonin, CRP
Follow-up	
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	80 patients who did not have complete data were excluded
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan

Bigot 2005 (Continued)

Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Yes	DMSA scan interpreted blind to status of other tests
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	No	80 patients who did not have complete data were excluded

Bressan 2009

Clinical features and settings	Emergency department
Participants	72 children with a first febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	Procalcitonin, CRP
Follow-up	
Notes	Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	No	CRP part of inclusion criteria
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA

Bressan 2009 (Continued)

Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Donoso 2004

Clinical features and settings	Children hospitalised for presumed pyelonephritis and referred for a DMSA
Participants	143 children with a first episode of pyelonephritis
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP (200 mg/L cutoff)
Follow-up	
Notes	Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
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Donoso 2004 (Continued)

Representative spectrum? All tests	No	Referred population, CRP may have been used to determine inclusion
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Fretzayas 2000

Clinical features and settings	First symptomatic UTI
Participants	Children < 14 years with a first UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP (200 mg/L cutoff)

Fretzayas 2000 (Continued)

Follow-up

Notes Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Yes	DMSA scan interpreted blind to status of other tests
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Garin 2007

Clinical features and settings	Children 3 months to 2 years admitted to 2 hospitals
Participants	185 children with UTI

Garin 2007 (Continued)

Study design	Retrospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP
Follow-up	
Notes	Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 5 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Unclear	Standard cutoffs used for ESR; unusual cutoff for CRP
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Hoberman 1999

Clinical features and settings	Patients presenting to hospital or emergency department with a UTI
Participants	306 children 1 to 24 months old with a first febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP
Follow-up	
Notes	Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Yes	DMSA scan interpreted blind to status of other tests
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported?	Yes	All test results were reported

Hoberman 1999 (Continued)

All tests

Withdrawals explained? All tests	Yes	Able to account for all patients
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Kotoula 2009a

Clinical features and settings	Children hospitalized for UTI
Participants	57 children 2 to 108 months of age with a first UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP, Procalcitonin
Follow-up	
Notes	Children with lesions that did not partially regress at 6 months excluded; additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded?	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)

Kotoula 2009a (Continued)

All tests

Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Kuzmanovska 2008

Clinical features and settings	Children treated at the clinic of children's diseases in Skopje	
Participants	282 children with a febrile UTI	
Study design	Prospective	
Target condition and reference standard(s)	Pyelonephritis, DMSA	
Index and comparator tests	ESR, CRP	
Follow-up		
Notes	Additional information provided by authors	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided?	Yes	DMSA alone was used as the reference standard

Kuzmanovska 2008 (Continued)

All tests

Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Unclear	Unusual cutoffs used for test result interpretation, probably influenced by clinical data
Uninterpretable results reported? All tests	Unclear	All test results were reported
Withdrawals explained? All tests	Unclear	Able to account for all patients

Levtchenko 2001

Clinical features and settings	Children admitted to hospital because of suspected pyelonephritis	
Participants	92 children with febrile UTI	
Study design	Prospective	
Target condition and reference standard(s)	Pyelonephritis, DMSA	
Index and comparator tests	CRP	
Follow-up		
Notes	Additional information provided by authors	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	No	CRP part of inclusion criteria
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided?	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan

Levtchenko 2001 (Continued)

All tests

Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Yes	DMSA scan interpreted blind to status of other tests
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Martin Aguado 2000

Clinical features and settings	Children presenting to a hospital centre
Participants	103 children 1 to 10 years of age with a first febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	CRP
Follow-up	
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard?	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA

Martin Aguado 2000 (Continued)

All tests

Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Melis 1992

Clinical features and settings	Children 1 week to 16 years admitted for a UTI
Participants	146 children with UTI
Study design	Retrospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP
Follow-up	
Notes	

Table of Methodological Quality

Melis 1992 (Continued)

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Unclear	Timing of DMSA not clear
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Mohkam 2010

Clinical features and settings	Hospitalised children with UTI
Participants	Children 1 to 14 years of age with a UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA

Mohkam 2010 (Continued)

Index and comparator tests ESR, CRP

Follow-up

Notes Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	No	Able to account for all patients

Montini 2007

Clinical features and settings Children hospitalised for UTI

Montini 2007 (Continued)

Participants	502 children with a first febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP, procalcitonin
Follow-up	
Notes	Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	No	ESR/CRP part of inclusion
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Nikfar 2010

Clinical features and settings	Children admitted with a UTI
Participants	100 children 1 month to 14 years with a febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	CRP, Procalcitonin
Follow-up	
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported?	Yes	All test results were reported

Nikfar 2010 (Continued)

All tests

Withdrawals explained? All tests	Yes	Able to account for all patients
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Printza 2012

Clinical features and settings	Children admitted to hospital for UTI
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Participants	98 infants < 12 months of age with a first febrile UTI
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Study design	Prospective
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Target condition and reference standard(s)	Pyelonephritis, DMSA
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Index and comparator tests	CRP, ESR
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Follow-up	
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Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded?	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)

Printza 2012 (Continued)

All tests

Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Sheu 2007

Clinical features and settings	Recruitment source not specified	
Participants	78 children 1 month to 10 years with a first febrile UTI	
Study design	Prospective	
Target condition and reference standard(s)	Pyelonephritis, DMSA	
Index and comparator tests	CRP	
Follow-up		
Notes	Additional information provided by authors	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Recruitment source not specified
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided?	Yes	DMSA alone was used as the reference standard

Sheu 2007 (Continued)

All tests

Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results.
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Sheu 2011

Clinical features and settings	Children admitted to hospital for UTI	
Participants	112 children < 2 years of age with a first febrile UTI	
Study design	Prospective	
Target condition and reference standard(s)	Pyelonephritis, DMSA	
Index and comparator tests	Procalcitonin	
Follow-up		
Notes	Unclear whether Sheu 2007 and Sheu 2011 overlap. If so, direct comparison may be possible	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided?	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan

Sheu 2011 (Continued)

All tests

Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Taskinen 2005

Clinical features and settings	Children referred to hospital because of suspected pyelonephritis	
Participants	64 children with a first febrile UTI	
Study design	Prospective	
Target condition and reference standard(s)	Pyelonephritis, DMSA	
Index and comparator tests	CRP	
Follow-up		
Notes	Additional information provided by authors	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	No	CRP part of inclusion
Acceptable reference standard?	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA

Taskinen 2005 (Continued)

All tests

Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Tuerlinckx 2005

Clinical features and settings	Children admitted to hospital for UTI
Participants	63 children 2 months to 14 years of age first febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	CRP, procalcitonin
Follow-up	
Notes	

Table of Methodological Quality

Tuerlinckx 2005 (Continued)

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Population not described in detail
Acceptable reference standard? All tests	Unclear	Details regarding DMSA scan procedure not described
Acceptable delay between tests? All tests	Yes	DMSA conducted within 15 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Yes	Standard cutoffs used for test result interpretation, not influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Wu 2012

Clinical features and settings	Children less than 4 months of age with a UTI
Participants	156 children with a first UTI
Study design	Retrospective
Target condition and reference standard(s)	Pyelonephritis, DMSA

Wu 2012 (Continued)

Index and comparator tests CRP

Follow-up

Notes

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 3 to 5 days of diagnosis
Partial verification avoided? All tests	No	16 patients did not received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Unclear	Unusual cutoff used for test result interpretation
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

Zaki 1996

Clinical features and settings Children 6 months to 12 years admitted to hospital

Zaki 1996 (Continued)

Participants	50 children with a first diagnosed febrile UTI
Study design	Prospective
Target condition and reference standard(s)	Pyelonephritis, DMSA
Index and comparator tests	ESR, CRP
Follow-up	
Notes	Additional information provided by authors

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Patients with UTI systematically enrolled from primary care setting without additional inclusion/exclusion population restrictions
Acceptable reference standard? All tests	Yes	Pyelonephritis defined as the presence of photopenia on planar DMSA
Acceptable delay between tests? All tests	Yes	DMSA conducted within 7 days of diagnosis
Partial verification avoided? All tests	Yes	All patients (or random selection of patients) received verification of diagnosis with DMSA scan
Differential verification avoided? All tests	Yes	Patients received verification of pyelonephritis using DMSA regardless of index test result
Incorporation avoided? All tests	Yes	DMSA alone was used as the reference standard
Index test results blinded? All tests	Yes	Index test results were interpreted without knowledge of the DMSA scan results
Reference standard results blinded? All tests	Unclear	No mention of whether radiologists were aware of clinical information (including the index test results)
Relevant clinical information? All tests	Unclear	Unusual cutoffs used for test result interpretation, possibly influenced by clinical data
Uninterpretable results reported? All tests	Yes	All test results were reported
Withdrawals explained? All tests	Yes	Able to account for all patients

C-reactive protein - CRP; DMSA - ⁹⁹Tc-dimercaptosuccinic acid; ESR - Erythrocyte sedimentation rate; UTI - urinary tract infection

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

Study	Reason for exclusion
Abamor 2005	Citation incorrect
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
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
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. Used 1000 CFU/mL as the cutoff for catheterized specimens. Also, unlike the rest of the studies in this review, the reference standard was based on a combination of the results of both the early and late DMSA scans (instead of just the early scan)
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

Study	Reason for exclusion
Elo 1985	Not relevant - No DMSA
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
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
Gervais 2001	Urine culture criteria not met
Girardin 2000	Not relevant - No data in paper
Grouteau 1999	Not relevant - No data in paper
Guermazi 1993	Not relevant - No data in paper
Gurgoze 2005	Urine culture criteria not met
Guyen 2006	Urine culture criteria not met
Hahn 2003	Not relevant - All children had a positive DMSA
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
Huang 2007	Insufficient data in paper to determine 2 x 2 table
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
Jakobsson 1997	Urine culture criteria not met
Jaksic 2011	Insufficient data in paper to determine 2 x 2 table

Study	Reason for exclusion
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
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
Kim 2001	Not relevant - No data in paper
Krzemien 2004	DMSA not within 30 days
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
Leroy 2012	Insufficient data in paper to determine 2 x 2 table
Lin 2000	Not relevant - No DMSA
Linne 1994	Not relevant - No PCT, CRP, or ESR
Lomberg 1992	Not relevant - No DMSA
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
Mazigh Mrad 2002	Urine culture criteria not met.
Mohkam 2008	Not relevant - All children had a positive DMSA
Montini 2008	Possible duplicate report of Montini 2007 study
Montini 2009	Possible duplicate report of Montini 2007 study
Moon 2009	Not relevant - No data in paper
Mussap 2006	Not relevant - No data in paper

Study	Reason for exclusion
Naseri 2008	Not relevant - No DMSA
Neuhaus 2008	Not relevant - No data in paper
Oh 2010	Not relevant - No data in paper
Oh 2011	Not relevant - No data in paper
Orlowska 2004	Culture criteria (used 1000 to define a positive culture)
Otto 2005	Not relevant - 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
Sevketoglu 2010	Not relevant - No data in paper
Sharifian 2005	Citation incorrect
Sheu 2009	Not relevant - No data in paper
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

Study	Reason for exclusion
Stokland 1998	DMSA not within 30 days
Subat-Dezulovic 1998	Not relevant - No DMSA
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
Wang 2005	Urine culture criteria not met
Yen 1999	Not relevant - No data in paper

CFU - colony forming units; DMSA - ⁹⁹Tc-dimercaptosuccinic acid; 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	6	434
2 CRP > 20 mg/L	13	1638
3 ESR ≥ 30 mm/h	6	1737
4 PCT: cutoff other than 0.5 ng/mL	3	232
5 CRP: cutoff other than 20 mg/L	14	1674
6 ESR: cutoff other than 30 mm/h	8	1781

Test 1. PCT > 0.5 ng/mL.

Test 2. CRP > 20 mg/L.

Test 3. ESR $\geq$ 30 mm/h.

Test 4. PCT: cutoff other than 0.5 ng/mL.

Test 5. CRP: cutoff other than 20 mg/L.

Test 6. ESR: cutoff other than 30 mm/h.

ADDITIONAL TABLES

Table 1. Summary of sensitivity analysis

	PCT > 0.5	CRP > 20	ESR $\geq$ 30
All studies			
Summary sensitivity	0.86	0.94	0.87
Summary specificity	0.74	0.39	0.48
Summary positive likelihood ratio	3.24	1.55	1.67
Summary negative likelihood ratio	0.20	0.16	0.27
Studies with representative populations			
Summary sensitivity	--	0.89	--
Summary specificity	--	0.57	--
Summary positive likelihood ratio	--	2.08	--
Summary negative likelihood ratio	--	0.19	--
Studies that included only children with a first UTI			
Summary sensitivity	0.88	0.94	0.91
Summary specificity	0.69	0.36	0.46
Summary positive likelihood ratio	2.86	1.47	1.69
Summary negative likelihood ratio	0.18	0.16	0.20
Studies in which perineal bags were not used			
Summary sensitivity	0.85	0.94	--

Table 1. Summary of sensitivity analysis (Continued)

Summary specificity	0.72	0.53	--
Summary positive likelihood ratio	3.00	1.96	--
Summary negative likelihood ratio	0.21	0.11	--
Studies that included only febrile children			
Summary sensitivity	--	0.93	--
Summary specificity	--	0.42	--
Summary positive likelihood ratio	--	1.59	--
Summary negative likelihood ratio	--	0.18	--
Studies in which DMSA was conducted with 7 days of diagnosis			
Summary sensitivity	0.86	0.94	--
Summary specificity	0.74	0.44	--
Summary positive likelihood ratio	3.24	1.69	--
Summary negative likelihood ratio	0.20	0.14	--
Studies in which children with genitourinary anomalies were excluded			
Summary sensitivity	--	0.90	0.86
Summary specificity	--	0.42	0.40
Summary positive likelihood ratio	--	1.56	1.44
Summary negative likelihood ratio	--	0.23	0.34

-- 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)	<ol style="list-style-type: none"> 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.Techetium Tc 99m Dimercaptosuccinic Acid/
- 16.DMSA.tw.
- 17.dimercaptosuccin\$.tw.
- 18.scintigra\$.tw.
- 19.Radionuclide Imaging/
- 20.Succimer/du
- 21.Kidney/ri
- 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/26-30

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 items

1. Was the spectrum of patients representative of the patients with UTI?

The judgement should be based on both the method of recruitment and the characteristics of those recruited. Thus, if most of the children were systematically enrolled from a primary care setting (general practice, hospital outpatient clinic, urgent care clinic, or emergency department), and the inclusion and exclusion criteria did not restrict the population further, then code "yes." Studies that recruited a group of healthy controls and a group with pyelonephritis, this item should be coded as "no". Studies in which children were enrolled mostly from specialty clinics (e.g., urology or nephrology) or who were required to have additional findings for inclusion (e.g., VUR, other labs required for inclusion) should be coded as "no." If >20% of the children in the study were likely not to have had UTI, code a "no". If there is insufficient information available to make a judgement then it should be scored as "unclear".

2. Is the DMSA likely to correctly classify the target condition?

If the presence of photopenia on planar DMSA was used to define a DMSA scan as abnormal then this item should be scored "yes". If criteria other than photopenia (e.g., difference in perfusion) were used, then this item should be marked as "no". If the criteria used to define an abnormal scan are not specified, then this item should be scored as "unclear".

3. Prolonged period between reference standard and index test.

If the DMSA was conducted in the first 15 days of diagnosis, then it is likely to have detected most cases of pyelonephritis, and this item should be scored "yes". If the DMSA was conducted within 15 to 30 days of the index UTI, code "no."

4. Did the whole sample or a random selection of the sample, receive verification using a DMSA?

Partial verification bias occurs when not all participants receive confirmation of the diagnosis by the reference standard. If it is clear from the study that all patients, or a random selection of patients, who received the index test (procalcitonin, erythrocyte sedimentation rate, C-reactive protein) went on to receive verification of pyelonephritis using a DMSA, then this item should be scored as "yes". This item should be scored as yes even if the reference standard was not the same for all patients. If some of the patients who received the index test did not receive verification of their true disease state, and the selection of patients to receive the reference standard was not random, then this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear". Record the proportion of the sample not verified.

5. Did patients receive the same reference standard regardless of the index test result?

Differential verification bias occurs when some of the index test results are verified by a different reference standard. If it is clear that patients received verification of their true disease status using a planar DMSA then this item should be scored as "yes". Otherwise this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

6. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

If the scan DMSA alone was used as the reference standard, then this item should be scored as "yes". If it appears that the index test formed part of the reference standard then this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

7. Were the index test results interpreted without knowledge of the results of the reference standard?

8. Were the reference standard results interpreted without knowledge of the results of the index test?

If the study clearly states that the test results (index or reference standard) were interpreted blind to the results of the other test then these items should be scored as "yes". If this does not appear to be the case they should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?

Clinical data is not usually used in practice when interpreting results of erythrocyte sedimentation rate, procalcitonin, and C-reactive protein (standard cutoffs are used). If the same occurred in the study, then this item should be scored as "yes". If this is not the case then this item should be scored as "no". If this information is not reported by the study then it should be scored as "unclear".

10. Were uninterpretable/ intermediate test results reported?

If it is clear that all test results, including uninterpretable/indeterminate/intermediate are reported then this item should be scored as "yes". If you think that such results occurred but have not been reported then this item should be scored as "no". If it is not clear whether all study results have been reported then this item should be scored as "unclear".

11. Were withdrawals from the study explained?

If it is clear what happened to all patients who entered the study, for example if a flow diagram of study participants is reported, then this item should be scored as "yes". If it appears that some of the participants who entered the study did not complete the study, i.e. did not receive both the index test and reference standard, and these patients were not accounted for then this item should be scored as "no". If it is not clear whether all patients who entered the study were accounted for then this item should be scored as "unclear".

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- None, USA.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The main difference between the protocol and the review was in the cutoffs to be analysed for the ESR and CRP tests. In addition, we had proposed an additional QUADAS item (in addition to the usual 11 items) in the protocol (relating to indeterminate DMSA tests). After assessing the trials, it became clear that this item was redundant (covered in QUADAS item 4), and it was therefore dropped. In addition, we had planned to use an ESR level of 10 mm/h as our cutoff level. Because very few studies used this cutoff, for the primary analysis, we used a value of 30 mm/h, which was the cutoff most commonly reported in the studies meeting our inclusion criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Child; Humans