Association of Procalcitonin With Acute Pyelonephritis and Renal Scars in Pediatric UTI

WHAT’S KNOWN ON THIS SUBJECT: Prompt, high-quality diagnosis of acute pyelonephritis and later identification of children with scarring are important to prevent future complications. Examination by dimercaptosuccinic acid scan is the current clinical gold standard but is not routinely performed.

WHAT THIS STUDY ADDS: Procalcitonin demonstrated a more robust predictive ability, compared with C-reactive protein or white blood cell count, to selectively identify both children who had acute pyelonephritis during the early stage of urinary tract infections, as well as those with late scarring.

abstract

BACKGROUND AND OBJECTIVE: Urinary tract infections (UTIs) are common childhood bacterial infections that may involve renal parenchymal infection (acute pyelonephritis [APN]) followed by late scarring. Prompt, high-quality diagnosis of APN and later identification of children with scarring are important for preventing future complications. Examination via dimercaptosuccinic acid scanning is the current clinical gold standard but is not routinely performed. A more accessible assay could therefore prove useful. Our goal was to study procalcitonin as a predictor for both APN and scarring in children with UTI.

METHODS: A systematic review and meta-analysis of individual patient data were performed; all data were gathered from children with UTIs who had undergone both procalcitonin measurement and dimercaptosuccinic acid scanning.

RESULTS: A total of 1011 patients (APN in 60.6%, late scarring in 25.7%) were included from 18 studies. Procalcitonin as a continuous, class, and binary variable was associated with APN and scarring (P < .001) and demonstrated a significantly higher (P < .05) area under the receiver operating characteristic curve than either C-reactive protein or white blood cell count for both pathologies. Procalcitonin ≥0.5 ng/mL yielded an adjusted odds ratio of 7.9 (95% confidence interval [CI]: 5.8–10.9) with 71% sensitivity (95% CI: 67–74) and 72% specificity (95% CI: 67–76) for APN. Procalcitonin ≥0.5 ng/mL was significantly associated with late scarring (adjusted odds ratio: 3.4 [95% CI: 2.1–5.7]) with 79% sensitivity (95% CI: 71–85) and 50% specificity (95% CI: 45–54).

CONCLUSIONS: Procalcitonin was a more robust predictor compared with C-reactive protein or white blood cell count for selectively identifying children who had APN during the early stages of UTI, as well as those with late scarring. Pediatrics 2013;131:870–879.

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KEY WORDS: acute pyelonephritis, children, procalcitonin, renal scarring, urinary tract infection.

ABBREVIATIONS: APN—acute pyelonephritis, AUC—area under the curve, CI—confidence interval, CRP—C-reactive protein, DCA—decision curve analysis, DMSA—dimercaptosuccinic acid, LR—likelihood ratio, OR—odds ratio, PCT—procalcitonin, ROC—receiver operating characteristic, UTI—urinary tract infection, VUR—vesicoureteral reflux, WBC—white blood cell.

scan this to watch a video about PCT and infections.
Urinary tract infections (UTIs) are the most common invasive bacterial infections among young febrile children.1 UTIs can occur as simple bladder infections (lower UTI; bacteriuria only) but can also involve the kidneys (acute pyelonephritis [APN], in which bacteriuria is associated with infectious renal parenchymal involvement), leading to renal scarring.2 The belief that persisting APN effects followed by late renal scarring, sometimes with recurrences, may lead to future complications such as hypertension and/or end-stage renal failure has been the major driving force behind the aggressive investigation and treatment of first-occurrence UTIs.3 The prompt and high-quality diagnosis of APN and differentiation from lower UTI is therefore of key importance. A dimercaptosuccinic acid (DMSA) scan is considered the gold standard in imaging for both renal parenchymal involvement during acute infection and for late renal damage left by the infection.4 However, DMSA scans are not performed in most children with UTI due to the limited availability of nuclear medicine departments compared with the high number of children with UTIs. Thus, a more practical and accessible tool that could assist clinicians in determining the presence of renal parenchymal involvement and/or late renal damage would be of great clinical value.

Procalcitonin (PCT), a 116-amino acid propeptide of calcitonin without hormonal activity, is an early, sensitive, and specific marker of bacterial infection.5,6 PCT is almost undetectable under physiologic conditions or during viral infections but rises in response to bacterial endotoxins; the extent of this increase seems to be proportional to the severity of the infection.6 However, its exact role, if any, in the inflammatory response and in the cytokine cascade remains unknown.5 It seems like this has already been done, so why do it here? Read on...

In febrile UTI, the predictive ability of high PCT concentrations for both APN and late renal scarring has been previously investigated by several teams. A review7 and a recent systematic review and meta-analysis8 showed that a serum PCT >0.5 ng/mL predicts early renal parenchymal involvement reasonably well (diagnostic odds ratio [OR]: 14.3 [95% confidence interval (CI): 4.7–43.2]); however, heterogeneity made these results inconclusive. Moreover, results concerning late renal scarring were controversial, with no pooled measurements provided.9 Most of this heterogeneity and these discrepancies may be due to threshold effects because the initial studies chose different PCT cutoff values due to population variation; unfortunately, any effects from the latter could not be fully explored with only pooled data from the studies. Under these circumstances, the only way to analyze PCT as a continuous biomarker without a priori threshold choice, simultaneously controlling for potential individual-level confounders, and then provide robust conclusions concerning PCT as a predictor of APN and/or scarring would be to obtain individual data unaltered by thresholds.9 How most meta-analyses don’t get to the actual data, but the results

We thus aimed to perform an updated systematic review and meta-analysis on individual patient data to investigate PCT as a predictor for both APN and renal scarring in children with a febrile UTI. The most appropriate threshold values of PCT were simultaneously studied. 2 objectives

METHODS

We performed a systematic review and meta-analysis on individual patient data, in accordance with international standards (Centre for Reviews and Dissemination guidelines,10 PRISMA,11 and STARD12). We electronically and manually searched for all cohort studies of children with UTI, a PCT measurement, and a renal DMSA scintigraphy published between January 1993 and September 2011.

All cohort studies of consecutively included children with a febrile UTI, a PCT measurement, and an early (ie, within 14 days) and a late (ie, repeated at least 43.2) interval between the 2 measurements were included, representing 13 centers as follows: Afula (Israel),19 Ahvaz (Iran),20 Antalya (Turkey),21 Athens (Greece),22 Barcelona (Spain),19 Elazig (Turkey),26 Geneva (Switzerland),17,21,31 Lille (France),23 Padova (Italy),32 Thrace (Greece),29,30 Toulouse (France),16 Udine (Italy),13 and Yvoir (Belgium).24

**think of the study population in a meta-analysis as individual studies. Just like you need to evaluate how patients are selected in a RCT, you need to evaluate how studies are selected to include in a meta-analysis. Was their search complete? What was inclusion/exclusion criteria? Classic rookie mistakes are just searching PubMed, or searching only using keywords, or just using English articles. Articles are not included if they don’t directly contribute to the key statistic in a meta-analysis. If the main results in a bunch of smaller studies vary too much, they can’t really be combined well.**
population characteristics according to each center

this shows whether there were significant differences between studies. were there?

3 months later available renal DMSA scan results of each study and reflux values for each donor were calculated from the

we asked the authors to send us their data files (duplicates were discarded). for each study, we also collected méthodological information (e.g., clinical quality evaluation, reference values).

the discriminative ability of each biomarker for APN and then late renal damage was evaluated by drawing ROC curves, as well as by calculating performance (true-positives) were added and the harms (false-positives) were subtracted.

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RESULTS

Study Characteristics

Following the aforementioned criteria, we retrieved 227 abstracts by electronic searching; 19 were potentially suitable (Fig 1). After full text review, 1 study was not included because of absence of DMSA scan data, leaving 18 articles to be included.16–33 The 13 corresponding study authors were contacted; all agreed to participate and send data. A total of 1011 (97.9%) patients fully met the inclusion criteria. All studies had a high methodologic quality (Supplemental Appendix Tables 1 and 2). Nine (69.2%) centers performed both early and late DMSA scans. All centers performed the early DMSA scan within 7 days; 5 of 9 centers performed the late scan at 6 months, and the other centers varied between 3 and 24 months (Table 1). Among the 9 centers performing late DMSA scans, late scanning was systematically conducted regardless of early-scan results in only 1 (11.1%) center (Elazığ, Turkey). Nine (69.2%) centers collected urine samples following high-quality standard operating procedures (suprapubic aspiration, urethral catheterization for non–toilet-trained children, and clean-voided midstream for the other patients). All centers measured PCT by using the LUMITest PCT immunoluminometric assay or the BRAHMS PCT-Q semiquantitative rapid test (BRAHMS, Hennigsdorf, Germany). All centers included hospitalized children with UTI. No adverse events had been reported in performing PCT measurement, DMSA scanning, or cystography. Table 1 provides details on the characteristics of each center’s population.

Analysis of APN and late renal scars involved 1011 and 525 patients, respectively. APN by grade was analyzed in 357 patients. PCT as a continuous variable involved only 883 (87.3%) patients, as PCT was measured by the PCT-Q semiquantitative test for 128 patients. Analysis of CRP and WBC count involved 959 (94.9%) and 962 (95.2%) patients, respectively. VUR was examined in 772 (76.4%) patients.

Predicting APN

APN was demonstrated in 613 children (60.6%) of the 1011 patients included. The mean ± SD age of the children was 25.2 ± 32.8 months (median: 10.5; interquartile range: 4.3–32.3); 332 (32.8%) were boys. VUR was diagnosed in 182 (23.6%) and in 80 children (10.4%). PCT as a continuous, class, or binary variable was significantly associated with APN (Table 2, Fig 2). The strength of the association increased when the PCT category (when ordinal variable) increased (Table 2). PCT ≥0.5 ng/mL (current threshold used in the literature) yielded an adjusted OR of 7.9 (95% CI: 5.8–10.9). CRP and WBC count were also significantly related to APN, with similar OR values for CRP as previously described; however, lower OR values were obtained for WBC count (Table 2). PCT as a continuous variable offered an area under the ROC curve (AUC ROC) of 0.82 (95% CI: 0.79–0.84), after adjusting according to the chosen model. The AUC ROCs for CRP and WBC count were significantly lower (P < .0001: 0.72 (95% CI: 0.69–0.76) and 0.62 (95% CI: 0.57–0.65), respectively, once adjusted by using the model (Fig 3). (The DCA demonstrated that PCT provided a more statistically robust test than CRP, WBC count, or extreme systematic strategies (ie, DMSA for everyone or no one) (Fig 3). PCT ≥0.5 ng/mL had a 79% of sensitivity (95% CI: 71–85), with a 50% specificity (95% CI: 45–54) (Table 3).

Predicting Late Renal Scars

Late scars were demonstrated in 135 (25.7%) of the 525 children included. The mean ± SD patient age was 26.6 ± 33.8 months (median: 11.0; interquartile range: 4–36); 162 (31%) were male. VUR was present in 107 (22.0%) of the 486 patients who underwent cystography; VUR ≥3 was diagnosed in 51 (10.5%) children. PCT as a continuous and binary variable was significantly associated with renal scars (Table 2, Fig 2). PCT ≥0.5 ng/mL yielded an adjusted OR of 3.4 (95% CI: 2.1–5.7). CRP and WBC count were also significantly related to renal scarring (Table 2, Fig 2). PCT as a continuous variable resulted in an AUC ROC of 0.75 (95% CI: 0.70–0.80) once adjusted according to the model built and was significantly higher (P = .02) than those values observed for CRP and WBC count (0.70 [95% CI: 0.65–0.76] and 0.66 [95% CI: 0.60–0.72], respectively) (Fig 3). According to DCA, PCT was better than CRP, WBC count, and both extreme systematic strategies (ie, DMSA for everyone or no one) (Fig 3). PCT ≥0.5 ng/mL had a 79% of sensitivity (95% CI: 71–85), with a 50% specificity (95% CI: 45–54) (Table 3).

DISCUSSION

We demonstrated that the measurement of serum PCT can provide considerable predictive value for the development of APN and renal scars, and that this predictive capacity is better than that provided by either CRP or WBC count regardless of considered thresholds. Because the related medical decision process is binary (to perform or not to perform a DMSA scan), our goal was to provide an alternative
A model was separately derived for each biomarker (PCT, CRP, or WBC count). Univariate and multivariate analysis used different multivariable regressions (DMSA for everyone or no one) adjusting for intercenter variability due to the significant heterogeneity found within these studies. We avoided these issues by working with individual data, adjusting for intercenter variability modeling with multilevel regressions, as well as accounting for all covariates of interest at the individual level. Moreover, the study design (a meta-analysis of individual patient data) allowed us to study the impact of different threshold levels, to perform DCA, and to draw conclusions without the usual threshold effect that often affects diagnostic accuracy assessed by meta-analysis, thus confounding results. Our approach was complementary to that of Mantadakis et al, who performed a nonsystematic review of the potential of PCT to predict late renal scarring, without computing pooled estimates, as they were confronted with different studies and cutoffs. With our systematic meta-analysis, assay that could contribute to diagnosis and investigate the optimal threshold by which these clinical decisions could be made. PCT ≥ 0.5 ng/mL seemed to offer the optimal compromise of sensitivity and specificity for both APN and late renal scars: 71% sensitivity (95% CI: 67–74) with a 72% specificity (95% CI: 67–76) for APN; 79% sensitivity (95% CI: 71–85) with a 50% of specificity (95% CI: 45–54) for late scarring. Furthermore, DCA showed that PCT offered the best benefit/harm balance irrespective of the chosen threshold, compared with CRP, WBC count, or systematic strategies (DMSA for everyone or no one) for the selective identification of children who might benefit from a DMSA scan.

Our findings add evidence to those of Mantadakis et al. Together, they suggest a reasonably strong predictive value based on PCT levels; however, data from studies using pooled estimates lead to a more cautious interpretation due to the significant heterogeneity found within these study pools. We avoided these issues by working with individual data, adjusting for intercenter variability modeling with multilevel regressions, as well as accounting for all covariates of interest at the individual level. Moreover, the study design (a meta-analysis of individual patient data) allowed us to study the impact of different threshold levels, to perform DCA, and to draw conclusions without the usual threshold effect that often affects diagnostic accuracy assessed by meta-analysis, thus confounding results. Our approach was complementary to that of Mantadakis et al, who performed a nonsystematic review of the potential of PCT to predict late renal scarring, without computing pooled estimates, as they were confronted with different studies and cutoffs. With our systematic meta-analysis,
we offer further evidence to support their results, updating the review in a systematic manner and providing pooled estimates of the predictive ability of PCT, leading to a robust conclusion.

The use of imaging in this field has been largely debated in the last decade. However, the decision as to which tests, if any, should be routinely conducted in children with UTIs necessarily depends on many factors. The “top-down” approach uses early DMSA scanning as a screening test. Although children with a negative acute-phase DMSA scan are unlikely to develop scarring, DMSA scans are expensive, invasive, and expose children to radiation. However, the top-down strategy raises 2 concerns: first, it requires DMSA scan availability across countries and settings, which is not currently the case, and second, the identification of late renal scarring results in only a more careful follow-up of affected children. Therefore, PCT may occupy an intermediate position useful for identifying children at high risk for APN and renal scarring, and for whom a DMSA scan can be selectively proposed to confirm parenchymal involvement. The reported sensitivity and specificity values may not appear very convincing (~70%). However, PCT is not meant to replace DMSA scanning, which remains the gold standard for assessing parenchymal involvement (APN or scarring). PCT could be used as an intermediate strategy, based on a single biomarker, easier to set up than a nuclear imaging process, which can help discriminate between lower UTI and APN, even in settings in which DMSA scans are not available. Interestingly, PCT offered the best benefit/harm balance irrespective of the chosen threshold, compared with systematic strategies (DMSA for everyone or no one) for the selective identification of children who might benefit from a DMSA scan. Later in the imaging evaluation, a cystography could be proposed for children with a proven APN, to diagnose or rule out VUR, and treat it if necessary. Moreover, PCT may also be helpful when choosing between oral or intravenous antibiotic treatments during the early infectious phase, depending on the severity of the UTI (lower UTI or APN). PCT could find a place in the debated process of UTI imaging and treatment, as a key point test in the decisonal flowchart.

There are several potential limitations to our study that should be addressed.

First, despite the extensive electronic and hand searches performed, a publication bias is possible, especially because test accuracy studies are more...
easily conducted and abandoned than randomized controlled trials, and are then particularly susceptible to publication bias. However, our current knowledge about the precise effects of publication bias on meta-analytic estimates, as well as how to assess the extents of these possible limitations, are limited. Therefore, due to the complexity of accurately assessing this issue, we can provide no estimates of the effect of a probable publication bias. Secondly, a participation bias related to the response and voluntary participation of the centers also might be possible but seems unlikely because all authors contacted responded positively to our

![Figure 3: ROC curve and DCA for PCT, CRP, and WBC count.](image)

The curve that is highest is best. But it may not be best in every situation.

Here are the basics of a ROC. The point closest to the upper left corner is the best cut-off for an imperfect test. It also means the highest area under the curve (AUC).
requests for patient data sets. Thirdly, the possibility of a classification bias seems unlikely because PCT was measured by using validated techniques (immunoluminometric assay or semiquantitative PCT-Q assay), while blinded to the outcome. Fourthly, we assumed that patients who had a normal DMSA had no late lesions even if late DMSA was not performed. However, this assumption is commonplace in the literature, and we verified this assumption in the only center (Elazığ, Turkey) in which all patients systematically underwent both late and early DMSA: none of the negative early DMSA cases were followed by a positive late DMSA. This outcome gives an indication on the robustness of our assumption. Fifthly, we addressed heterogeneity issues due to data pooling from different centers (including different time frames for the late DMSA scan) by analyzing them as hierarchical data and using multilevel modeling. We chose to analyze the data set as a meta-analysis of individual patient data because this method provides the least biased and most reliable means of addressing the questions at hand. Sixthly, technical concerns, such as the collection of urine from non-toilet-trained children in sterile bags at 4 of the selected centers (not a recommended method) could have led to selection bias. Lastly, the delay between the first indications of infection and PCT level measures was not taken into account, and this might have introduced a bias in the results but only by underestimating the relationship between APN or late scarring and PCT, because this marker increases as early as 6 hours postinfection and also decreases just as quickly at the end of infection.

CONCLUSIONS

We demonstrated that PCT has a robust predictive ability to selectively identify children who had APN in the early stages of UTI and those that developed later renal scarring. The use of serum PCT measurements has the potential to aid the clinical decision-making process regarding the appropriate acute management of children with UTI. In particular, due to limited resources and technical availability, it may be helpful to use such an assay to selectively identify children who may benefit from a DMSA scan at the early and late stages of infection. The impact of PCT measurements on the currently debated practice of UTI examinations needs to be evaluated by a well-designed impact study and may lead to possible refinement of the decisional process.

ACKNOWLEDGMENTS

The authors thank Dr Gardikis and Dr Defteros (Department of Pediatric Surgery and Radiology, Alexandroupoulous University Hospital, Democritus University of Thrace School of Medicine, Thrace, Greece), Dr Galetto-Lacour (Department of Pediatrics, University Hospital of Geneva, Geneva, Switzerland), Dr Ellero (Department of Pediatrics, University of Udine, Udine, Italy), Professor Da Dalt (Department of Pediatrics, University of Padova, Italy) for participation in data collection/sharing, Dr Bacchetta (Department of Pediatric Nephrology–Reference Centre for Rare Renal Diseases, Feme Mère Enfant Hospital, University of Lyon, Lyon, France) for helpful discussions, and Melissa Laird (Inserm U818, Institut Pasteur, Paris, France) for pertinent comments and corrections.

REFERENCES


9. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet. 1993;341 (8842):418–422


Here are the basic components of a DCA curve: the x and y axis, and the 2 standard curves (treat everyone, treat noone). The results of the test are plotted with these.

X-Axis is 'Threshold Probability' – abbreviated Pt

It's the probability of disease derived from a test that a clinician would act i.e. cut out a tumor, do a bronch, admit for IV antibiotics, etc.

Ranges from 0 to 100%