Inflammatory markers: are they reliable predictors of severe bacterial infections in children?

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Abstract

Children arriving at the emergency department with fever is a fairly common problem in pediatric practice and the pediatrician has to detect the minority of those children with severe bacterial infection. Rapid diagnosis and treatment of these severe infections is essential since a delay in the management may lead to poorer outcome. The inflammatory markers: procalcitonin and C-reactive protein are reliable markers of severe bacterial infections such as bacteremia, meningitis, pyelonephritis and bacterial pneumonia. We created a score utilizing both procalcitonin and C-reactive protein. This Lab-score has been tested and validated as the best marker of severe bacterial infections in children with fever without a source.

Reference


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Inflammatory markers: are they reliable predictors of severe bacterial infections in children?

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I) Introduction:

Description of a clinical case:

A 4-month-old baby is seen at the Emergency Department with fever of 39.5°C and there is no focus on the clinical examination. There are no respiratory signs and no clinical signs of meningitis. He does not appear septic. You wonder if this child has a benign common viral infection or a bacterial infection such as pyelonephritis or an occult bacteremia. Which laboratory test would be a good screening test to exclude a severe bacterial infection?

Children presenting to the Emergency Department (ED) with fever is a fairly common problem in paediatric practice. The majority of these children have a source for their infection, but 20 % of those younger than 36 months have no apparent source for their fever. In this group of children with fever without source (FWS), between 10 % to 26 % \(^{1-7}\) suffer from severe bacterial infection (SBI). Even for experienced paediatricians it is a challenge to identify children with SBI from those with a localised bacterial or viral infection. Moreover, in young children, symptoms of bacterial infection are usually non-specific. Paucity of specific signs and symptoms makes the diagnosis of these infections even more problematic. For instance, babies younger than 12 months with meningitis rarely have neck stiffness and in the same age group, babies with pneumonia often presents only tachypnea without pathologic pulmonary auscultation. Limited signs are also seen in older children, for example, children younger than 24 months with pyelonephritis almost never suffer flank pain. Indeed, the occult SBI clinical picture evolves with age.

Rapid diagnosis and treatment of systemic bacterial infections is essential in paediatrics since a delay in the management of SBI may lead to a poorer outcome. It
is in any case, important to limit the use of antibiotics in order to reduce the development of resistance of bacteria to antibiotics and also to reduce the costs and prevent unnecessary admission to hospital.

The principal aim in evaluating febrile children is therefore: how to identify children at risk of SBI?

Numerous researchers are trying to find the ideal marker, which would identify with accuracy bacterial infections amongst a majority of viral infections. This marker should have a high sensibility, so as not to fail to identify SBI and an excellent specificity, so as not to overtreat viral infection with antibiotics. Moreover the level of the marker should raise very rapidly, probably in less than 12 hours from the beginning of the fever, to be used in the environment of the ED where the decision to treat or not should be promptly taken. Furthermore, this laboratory marker should be easily and rapidly available and certainly not too expensive.

In this review, I will briefly describe the most clinically relevant predictors of SBI in febrile children. Firstly, I will introduce the clinical evaluation, then the white blood cell count (WBC), C-reactive protein (CRP) and finally Procalcitonin (PCT). Other markers such as IL-6, TNF-alpha or sedimentation rate have been insufficiently tested for the moment, in the paediatric population to be used in clinical practice.

**Clinical evaluation**

An assessment of the child’s overall appearance is critical, since ill-appearing children are more likely than well-appearing children to have SBI. For children with a toxic appearance, a complete septic work-up, antibiotic treatment, and hospitalisation are required regardless of age or risk factors. Moreover, the physical
examination may reveal the source of infection and may decrease the need for additional testing. In many situations, clinical evaluation is not sufficient to accurately identify SBI, especially for younger children. Many clinical scoring systems have been developed for predicting bacterial infection in febrile children \(^{10-12}\). These clinical scoring system, such as the Infant Observational Scale \(^{11}\), are designed to quantify toxicity in pediatric patients. They stratify a child as either ill or well depending on his social response, colour, hydration status, arousability and strength of cry. Nevertheless, when tested in febrile infants, a high Infant Observational Scale has reasonable specificity but low sensitivity in detecting SBI\(^1\). As clinical signs and symptoms are not always highly predictive of a serious infection in young children, biological markers of infection need to be considered.

**White blood cell count**

One of the first indicators of SBI examined by researchers was the WBC. It is universally available and historically useful as an indicator of serious infections. Algorithms commonly used to evaluate young infants with fever usually include the interpretation of WBC \(^{13-17}\). However, recent literature indicates that WBC is not a reliable indicator of SBI in febrile children \(^{18 \, 19-22}\). For this reason researchers continue to look for more applicable and sensitive markers of inflammation in children with fever.
**C-reactive protein**

The CRP is an acute phase protein released by the liver after the onset of inflammation or tissue damage. Synthesis of CRP by hepatocytes is modulated by cytokines. Interleukins 1b and 6 and tumor necrosis factor are the most important regulators of CRP synthesis. CRP is produced within 4 to 6 hours after onset of tissue injury or inflammation, doubling every 8 hours before peaking around 36 hours. Its half-life is short, in the order of 4 to 8 hours.

Due to its early rapid rise, CRP has been studied by investigators as an early marker of bacterial infections. In general, CRP elevations in invasive acute bacterial infections tend to be in the range of 150 to 350 mg/L. Invasive bacterial infection without marked CRP elevation is unlikely but may be encountered, depending on when the specimen was drawn. In contrast CRP values in most acute viral infections tend to be much lower, ranging from < 20 up to 40 mg/L. Unfortunately, this distinction is not absolute, and CRP values > 100 mg/L can occur in uncomplicated infections caused by adenovirus, cytomegalovirus, and other virus. However CRP has potential as a reliable indicator of bacterial infections.

**Procalcitonin**

PCT is a 116 – aminoacid peptide and one of the precursors of calcitonin. From an endocrinological point of view, mature calcitonin is produced in neuro-endocrine C-cells of the thyroid. In these cells, the mature hormone is processed and stored in secretory granules. A microbial infection induces an ubiquitous increase of CALC-1
gene-expression and a constitutive release of PCT from all parenchymal tissues and differentiated cells types through the body. CALC- gene products can thus follow either a classical hormonal production in neuro-endocrine C-cells or alternatively, a cytokine-like ubiquitous expression pathway in numerous cell types. The release of PCT can be induced either directly from endotoxins or indirectly via different cytokines (eg, IL-1 Beta, TNF-alpha, IL-6). The induction can also be attenuated by cytokines released during a viral infection (eg, interferon–gamma). In sepsis, the predominance of PCT as opposed to mature calcitonin is indicative of a constitutive pathway within cells lacking secretory granules.

Other investigators observed that significant production of PCT was present only in adherent monocytes and in tissue, but not in circulating leukocytes. Adherent monocytes produce PCT for a limited time only and PCT acts as a chemokine during the initial period. The chemoattractant effect of PCT on monocyctic cells and the production in monocytes lasts only a few hours. Cells of the tissue, currently only investigated in adipocytes at this time, begin to produce PCT only after crosstalk with adherent monocytes.

The findings of other studies support the hypothesis of hepatic production of PCT. Significant quantities of PCT were not measurable in an anhepatic animal with septic shock and PCT concentrations in hepatic venous blood were higher than those measured in arterial blood. Another study showed that hepatocytes produced large quantities of PCT following stimulation with TNF-alpha and IL-6. Thus, the liver seems to produce substantial amounts of PCT during sepsis and infection.

An other PCT-mediated effect is that PCT stimulates inducible nitric oxide synthetase induction in cells prestimulated by lipopolysaccharides, tumor necrosis factor alpha and interferon gamma.
In conclusion, local or systemic inflammation affecting tissue and monocytes adhesion are a prerequisite for PCT production. This explains why PCT is induced by local and systemic bacterial infection, but also after tissue trauma. Thereafter, other cells types (such as adipocytes or hepatocytes) are capable of producing PCT and may substantially contribute to PCT synthesis during sepsis.

In bacterial infections, PCT increases from concentrations in the pictogram range to plasma concentrations ranging from 1 to 1000 ng/ml. In healthy subjects PCT concentration are below 0.5 ng/ml. Values range from 0.5 to 2 ng/ml in moderate localize bacterial infections and are above 2 in sepsis. This increase often correlates with the severity of the disease and with mortality. Increases in PCT occur more rapidly than increases in CRP. PCT can be detected in the plasma 2 hours after the injection of endotoxins. Within 6-8 hours, PCT concentrations rise and a plateau is reached after approximately 12 hours. The plasma concentration remains high as long as an adequate stimulus persists. With its fast elevation due to bacterial stimulus, in conjunction with a rapid downfall of its concentration 48 hours after the administration of an effective antibiotic therapy, PCT is a precocious and sensitive marker for SBI. It may be used not only for diagnostic purposes but also for patients' monitoring and response to therapy.

PCT can be measured with a quantitative immunoluminometric assay (LUMItest PCT, Brahms Diagnostica, Berlin, Germany) in 2 hours. A rapid semiquantitative chromatographic test (Brahms PCT-Q, Brahms Diagnostica) can also be used at the bedside of patients and gives an indication of PCT concentration in 30 min. PCT measurement is now possible at an ultra-sensitive level, by the time-resolved amplified cryptate emission (TRACE) technique (Kryptor® PCT, Brahms, Hennigsdorf, Germany). It is based on a sheep polyclonal anti-calcitonin antibody
and a monoclonal anti-katacalcin antibody, which binds to the calcitonin and katacalcin sequence of calcitonin precursor molecules. The assay has a functional assay sensitivity of 0.06 ng/ml. Using this lower threshold, exclusion of bacterial infection could be possible with a much higher negative predictive value and in conditions other than overt sepsis. This increase in sensitivity could perhaps guide diagnostic and therapeutic procedures in the future.

**Clinical Prediction rule**

Despite the promising value of inflammatory markers, a unique test would probably never be perfect. One way to improve both sensitivity and specificity is to combine different markers in a prediction rule to assess SBI with more accuracy in children with fever. To construct such a prediction rule, investigators began to list potential predictors of the outcome of interest

These potential predictors are then tested by statistical analysis, typically by logistic regression, to determine which predictors are most powerful in this given population. Investigators would then determine the best single independent predictor of an illness. Secondly, these independent predictors were combined together in a risk index score and tested on the same “derivation population”. But the success of the prediction rule would be applicable only to a particular population of patients. Therefore, the rule must also be validated on a population different from the derivation population; called the validation population. Finally, the prediction rule must be tested by an impact analysis. Ideally, an impact study would randomize patients to the application or non application of the rule and follow-up patients for all relevant outcomes. This study must demonstrate changes in clinician behaviour with beneficial consequences.
There are many methods of describing the value of a prediction rule. These include sensitivity, specificity, likelihood ratios (LR), positive and negative predictive values. Sensitivity refers to the proportion of patients with the relevant outcome, for whom the results of the prediction rule are abnormal. Specificity refers to the proportion of patients who do not have the relevant outcome for whom the results are normal. But clinicians are usually more interested in the likelihood that their patients will develop the relevant outcome. What the clinician wants to know, is how strong is the post test probability of illness in each given patient. The characteristics that determine this, are the positive and negative predictive values, in other words; the post-test probabilities if the test is either positive or negative. Estimating pre-test probability and then applying the LR to determine post-test predictive value is the optimal method to use a test. Treatment decisions are then based on post-test probability and how serious the outcome would be if the illness was left untreated.

A diagnostic test to differentiate between SBI from more common viral infections has long been sought. Perhaps it will be constituted by an association of inflammatory markers combined in a prediction rule. Indeed, emergency physicians recently determined that the top clinical priority for the development of new clinical decision rules is in the investigation of the febrile child under 36 months of age.
II) Clinical Application

What is known about the validity of predictors of severe bacterial infections?

II.1) Fever without source

Introduction:

Most febrile children have an apparent source of infection, for example, a viral respiratory infection or acute otitis media. Twenty percent of febrile children have fever without an apparent source of infection after a careful history and physical examination. Of these, from 10 to 25% have an occult SBI including bacteremia, urinary tract infection (UTI), occult pneumonia or early bacterial meningitis (BM). Occult bacteremia occurs in approximately 3% of children younger than 3 years of age with FWS and with a temperature of 39 °C. The introduction of the pneumococcal vaccine will probably lower this incidence to approximately 1% for children older than 3 months. UTIs are almost always occult in children younger than 2 years. UTI occur in 3 to 4% of febrile boys younger than 1 year and in 8 to 9% of febrile girls younger than 2 years of age. Sixteen percent of girls less than 2 years old with FWS had UTI. Concerning pneumonia, seven percent of all febrile children aged younger than 2 years will have a pulmonary infection and Murphy et al. detected 5% occult pneumonia in children with fever but without respiratory distress, tachypnea, hypoxia or lower respiratory tract abnormalities on examination.
**Current algorithm of management**

If no focal infection is identified and the origin of the infection is not believed to be viral, diagnostic testing is undertaken in order to identify occult bacterial infections. Many algorithms \(^{13-17}\) propose to check first the clinical appearance of the child either using a clinical score, for example the Infant Observation Scale\(^ {11}\), or applying the National Institute for Health and Clinical Excellence (NICE) traffic light system ([http://www.nice.org.uk/nicemedia/pdf/CG47NICEGuideline.pdf](http://www.nice.org.uk/nicemedia/pdf/CG47NICEGuideline.pdf)) or simply evaluating the overall child’s toxic appearance. If the child appears toxic, has a positive Infant Observation Scale or has any “red features” at the NICE traffic light system, a complete work-up with parenteral antibiotic is recommended. For the detection of occult bacteremia in a well appearing child, the guidelines depend on the immunization status ([http://www.uptodate.com/contents/fever-without-a-source](http://www.uptodate.com/contents/fever-without-a-source)). If the child is incompletely immunized with conjugate vaccines for *Haemophilus influenzae type b* and *Streptococcus pneumoniae* (less than three doses), it is recommended to perform a WBC. If the WBC is superior to 15 G, a sepsis work-up is completed and cultures are drawn and antibiotic is administrated (Figure 1). For completely immunized child, given the decreased overall incidence of pneumococcal bacteremia, no laboratory evaluation is recommended. For the identification of the child with pneumonia, the guidelines propose to perform chest radiography if the child is tachypneic or in respiratory distress or if WBC is superior to 20G/L. Finally, to identify urinary tract infection, guidelines propose rapid urine test and culture in girls under 24 months of age and in uncircumcised boy under 12 months of age. The recommendation is to treat with antibiotic children with positive rapid tests.
These guidelines suggest that the laboratory screening has the aim of not only identifying those children at risk of occult pneumococcal bacteremia but also those at risk of occult SBI such as pyelonephritis, pneumonia, early meningitis or other invasive infection. It would be useful to evaluate the risk for a child to have SBI by using an initial screening marker which may help to decide which child needs complete sepsis work-up. Such a screening marker could assist the clinician in making a decision, for example, which child with mild tachypnea requires that a chest radiography be performed. Also in the case of UTI, the sensitivity of the leucocyturia to detect UTI is only 80%, therefore the screening marker could help the clinician to determine, which child without leucocyturia, requires to complete the work-up by conducting urethral catheterization for urinary culture. Moreover, it would also provide supplementary information to the clinician in which baby without meningeal signs, a lumbar puncture should be performed. Accurate markers of SBI would be extremely precious to the pediatric clinician.

Infants younger than 3 months are especially at risk of SBI. They have decreased immunologic function and are commonly infected with more virulent organisms. Additionally, the physical examination is more difficult as these younger children have a limited behavioural repertoire. For these infants, there are many strategies and management guidelines: The Boston, Rochester or Philadelphia criteria, have all attempted to use both clinical and laboratory data to identify febrile infants at low risk of SBI. Low risk criteria have included non toxic clinical appearance, previously healthy term infant, no focal bacterial infection on clinical examination and normal laboratory screening test results using primarily the WBC. Using the Rochester criteria, Jaskiewicz et al. found that 5 of 437 children younger than 60 days old who met low-risk criteria had indeed SBI. However, Ferrera et al. found that 6 % of
neonates who were retrospectively classified as low risk by the Rochester criteria had SBI $^{57}$. Therefore the sensitivity of the Rochester criteria to detect a SBI is only 86.4 %. Kadish et al. found a 3.5 % rate of SBI in neonates categorized as low risk by both the Boston and the Philadelphia criteria $^{58}$ and Garra et al. found similar rates of SBI in infants younger than 8 weeks classified as low risk by the Philadelphia and Rochester criteria $^{59}$. One recent retrospective study examined the reliability of low risk criteria to exclude SBI in 450 febrile neonate $^{60}$. The low risk criteria were defined as not ill appearing, WBC between 5 and 15 G/L, the absence of leucocyturia or < 23 WBC in the cerebrospinal fluid (CFS). The prevalence of SBI was 20 % and incidence of SBI was similar among the neonates classified by week of age. The prevalence of SBI in the group of low risk criteria was rather high at 6 %. The negative predictive value of the low risk criteria was 93.8 %.

The sensitivity of these different criteria is not ideal and moreover, their positive predictive values are rather low, ranging from 18 to 26 % $^{58,61,62}$. In conclusion, these different “low risk criteria” are not sufficiently reliable to exclude SBI in this population of young infants.

It is notable, that all the proposed screening criteria include WBC to stratify the risk of SBI, despite that WBC does not seem to have the best predictive value. Therefore, many studies are aimed at identifying better predictor criteria.

**Bacterial infections in children younger than 16 years**

Two studies have analysed the predictive value of CRP and PCT in febrile children younger than 16 years. The largest study on PCT was the one of Gendrel et al. $^{63}$. They determined the PCT value upon admission to hospital for 700 children aged 1
month to 15 years with fever. In this sample, an infectious etiology for the fever was determined in just over half of the patients (360) and the remaining 340 were excluded from the analysis. Using the final diagnosis, they assigned children to three different groups: invasive bacterial infections (n=46), localized bacterial infections (n=78) and viral infections (n=236). Septicemia and meningitis were recorded as invasive infection and UTI and otitis media as localized infections. Gendrel noted a statistically significant difference between the mean PCT levels of the different groups. The mean PCT level of the invasive bacterial infection was 45.9 ng/ml, while it was only 4.2 ng/ml for localized infections and 0.4 ng/ml for viral infections. Only three patients with viral infection had a PCT > 2 ng/ml, while 44/46 children with invasive bacterial infection had a PCT > 2 ng/ml. PCT was the most useful test, with an area under the receiver operating characteristic curve (AUC) of 0.94, that is 0.05 higher than the next best indicator which was CRP. An optimal cut off of 1 ng/ml was calculated to distinguish bacterial from viral infection with a sensitivity of 83% and a specificity of 93%. When differentiating only between invasive bacterial infection and all other infections, a PCT cut off of 2 ng/ml had a 96% sensitivity and 87% sensitivity. Only patients with a definite diagnosis were included, thereby excluding a large number of patients in this study. All patients were hospitalised; therefore care should be taken before drawing conclusions on the usefulness of PCT as a screening tool for a broad range of patients.

Putto et al. studied prospectively 151 children with more than 12 hours of fever duration to determine the diagnostic value of CRP. Twenty seven (18%) children had a bacterial infection. The sensitivity of CRP (cut off 20 mg/L) was 100% and the specificity 75% for the detection of bacterial infection. The predictive value of WBC
(cut off 15 G/L) was inferior, that is, the sensitivity was only 67 % and the specificity 66 %.

**Fever without source in children younger than 36 months**

**Clinical evaluation:**

The clinical assessment of the child remains essential. Many clinical scoring systems have been elaborated to incorporate the clinical assessment. However, they are not widely used in practice because they lack sensitivity. Andreola et al. have evaluated the Infant Observational Scale $^{11}$, a clinical score often proposed in the US guidelines for the management of FWS. They reported a sensitivity of only 38% to detect SBI $^1$. Fernandez et al. also found a similar percentage of children with irritability or with feeding refusal between those having bacterial infections or viral infections $^{21}$. Nevertheless, the association of vital signs with specific symptoms such as grunting, tachypnea or neck stiffness improve the likelihood of a severe infection $^{65,66}$. Thompson et al. reported in a prospective study that having one or more of the following: temperature $\geq 39^0$ C, saturation $\leq 94\%$, tachycardia and/or tachypnoea was 80% sensitive (95% CI 75% to 85%) and 39% specific (95% CI 34% to 44%) for serious or intermediate bacterial infection $^{67}$. This study provided comparable sensitivity to more complicated systems such as the Manchester Triage System (84% sensitive, 38% specific) $^{68}$, and the National Institute for Health and Clinical Excellence (NICE) traffic light system (85% sensitive, 29% specific).

C-reactive protein

The CRP has been studied as a SBI marker in numerous studies. Pulliam et al. reported the results of a prospective study in 2001 examining the utility of CRP in evaluating febrile children. Seventy-seven patients of 1 to 36 months of age were enrolled, all with fever > 39°C. In addition to CRP, WBC, blood and urine cultures were performed. Fifteen (18%) had SBI (6 UTI, 4 pneumonia, 5 S pneumoniae bacteremia). Comparison of the groups with SBI and without SBI were indistinguishable in age, sex, temperature, duration of fever and the Infant Observation Scale. The CRP concentration, WBC and ANC were significantly different between the two groups. But in a multivariate logistic regression analysis, only CRP remained a predictor of SBI. The cut off value for the CRP of 70 mg/L, had a sensitivity of 79 % and specificity of 91 %. One limitation, however, of this study was that enrolled patients were a convenience sample.

Pratt et al. studied 124 patients between the ages of 1 and 36 months with FWS. They reported the superiority of CRP compared to WBC and ANC in the detection of SBI: better sensitivity and specificity. They compared the predictive values of these markers between fever duration of less than 12 hours with duration of more than 12 hours. All markers performed significantly better when the fever duration was more than 12 hours and all 3 markers had extremely poor sensitivities when fever was less than 12 hours. In this study, the CRP remained the best predictor regardless of fever duration (table 1).

Isaacman et al. have assessed the utility of CRP in detecting SBI in 256 children with FWS. They found a comparable predictive value for CRP and WBC with the AUC
of 0.71 for CRP and 0.69 for WBC (table 1). This is the only study which does not conclude CRP to be superior when compared to WBC.

Berger et al. enrolled prospectively 138 children younger than 12 months with fever with or without focus. A multivariate logistic regression defined CRP and other clinical variables as independent predictors of SBI. However, the WBC was not determined as an independent predictor of SBI in this multivariate analysis.

A recent systematic review analysed the diagnostic accuracy of CRP to detect SBI in children with fever. They included 6 studies that compared the predictive values of CRP in the detection of SBI. The 6 studies included enrollement of 1040 children and the cut off of CRP ranged from 20 to 70 mg/L. In differentiating between SBI and benign or non bacterial infections, the pooled estimated sensitivity of CRP in the 6 studies was 77 % and the specificity 79 % with a positive LR of 3.64 and a negative LR of 0.29. In the multivariate analysis, the CRP was an independent predictor of SBI. The authors concluded that CRP provides moderate and independent information for both ruling in and ruling out SBI in children with fever. The poor sensitivity however means that CRP cannot be used alone to exclude all bacterial infections.

**Procalcitonin**

The CRP appears to have potential as a reliable indicator of bacterial infection in a paediatric population. Investigators speculated that if CRP was helpful, PCT might be even more an sensitive indicator of SBI. PCT rises only slightly in viral infections but may increase a thousand-fold in bacterial infections. PCT levels rise more rapidly when stimulated by infection than do CRP levels.
A large multicenter, ED study evaluating PCT and CRP in 352 febrile infants between the ages of 1 and 36 months was conducted by Fernandez Lopez et al. in 2003. The study included children with fever who were required to undergo blood analysis to rule out the possibility of bacterial infection and who were hospitalised. Infants were divided into 3 groups: viral infection (n=122), localized bacterial infection (n=80) and invasive bacterial infection (n=150). In this study, the diagnostic performances for detecting SBI were excellent for PCT (AUC of 0.95) and for CRP (AUC of 0.81) and were superior to those of WBC (AUC of 0.65). Using a cut off of 0.59 ng/ml the authors noted a sensitivity of PCT to detect SBI of 91.3 % and a specificity of 93.5 %, much better than the CRP sensitivity of 78% and its specificity of 75% with a cut off at 27.5 mg/L. In infants in whom the duration of the fever was < 12 hours (n=104), the diagnostic performance of PCT was greater than that of the CRP (AUC, 0.93 for PCT and 0.69 for CRP; p<0.001). The excellent performance of the inflammatory markers was partly explained by the fact that patients who could not be classified in any of the three groups were excluded from the study causing a potential bias. This bias of selection could restrain the applicability of the good performance of PCT to a broad population of children.

We performed two prospective studies which enrolled all children younger than 3 years who were consecutively admitted to the ED with FWS. These works were published in 2001 and 2003. They are mentioned in table 1 but they will be presented in more detail in the next section of this manuscript. Thayyil et al. enrolled prospectively 72 children with FWS to compare the accuracy of different markers for early diagnosis of SBI. PCT, with a cut off level of 0.5 ng/L, had the best sensitivity compared to CRP and WBC (table 1). A combination of PCT,
CRP and WBC generated a positive LR of 10.6 changing the post-test probability to 54 %.

A recent Italian study enrolled 408 children and SBI was diagnosed in 94 children (23.1%) \(^1\). In a multiple regressive model, only PCT and CRP were retained as significant predictors of SBI. The AUC was similar for PCT (0.82) and for CRP (0.85) but superior to the area of WBC (0.71) and of ANC (0.74). For infants with fever < 8 hours, the AUC for PCT (0.92) was superior to the AUC of CRP (0.75). The authors concluded that PCT and CRP are valuable markers in predicting SBI in children with FWS and that they perform better than WBC and ANC. PCT appears more accurate when used early on in the infection.

Guen et al. conducted a prospective study on 215 children with FWS to study the best predictor of bacteremia \(^72\). Seven (3.3%) children had bacteremia. PCT had again the best sensitivity (86 %) and the authors determined that the association of PCT and WBC had the best predictive value for detecting bacteremia due to the poor performance of CRP in this study.

Table 1 summarizes the results of 9 studies collecting the data of 1743 patients on the sensitivity and specificity of WBC, CRP and PCT to detect SBI in children with FWS \(^1, 3, 4, 6, 7, 21, 22, 70, 71\). In all studies, the sensitivity of WBC count to detect SBI was low, ranging from 50 to 69% and the specificity from 53 to 80%. Pratt et al. determined a lower sensitivity (17%) for children with < 12 hours of fever duration and a higher sensitivity (82%) for those with > 12 hours of fever \(^4\). For the CRP, the sensitivity ranged from 63 to 100 %. In all studies, the AUC were systematically superior for CRP compared to WBC. Five prospective trials evaluated the accuracy of PCT to predict SBI in children with FWS \(^1, 3, 21, 70, 71\). In this group of children younger than 36 months of age, the prevalence of SBI varied between 11 to 34% and the cut
off values of PCT used in these studies varied from 0.5 to 0.9 ng/ml. The sensitivity of PCT to detect SBI ranged from 88 to 93%, except in the study of Andreola et al. (77%) and the specificity ranged from 74 to 94% except in the study of Thayyl et al. (50%). Globally, the diagnostic performance of PCT was greater than WBC count and comparable to the performance of CRP. However, in infants in whom the duration of fever was < 12 hours, the diagnostic performance of PCT was greater than that of CRP and of WBC count with an AUC of 0.93 compared to 0.69 for CRP. Almost all of these studies showed constantly better predictive value for PCT and CRP than WBC. In 5 studies using multivariate analysis, CRP was an independent predictor of SBI in all five, WBC only in one study and PCT was the best predictor in the two studies where it was tested.

Concern to compare studies relates to the fact that the cut off values for the same biological marker differ, impacting on the sensitivity and specificity of the test. For markers in FWS, the determination of a low cut off value for positivity increases the sensitivity but decreases the specificity of the test. To alleviate this problem, the calculation of LR is useful because it integrates in the same equation the sensitivity and the specificity of the test. (positive LR = sensitivity/1-specificity; negative LR = 1-sensitivity)/specificity). Starting from a pre-test probability of disease that is equal to the prevalence, the LR will generate a post-test probability of disease. The further LRs are from the one value, the stronger the evidence for the presence or the absence of a disease.

We recently published a report which calculates the positive and negative LRs for WBC count, CRP and PCT from nine prospective studies in children with FWS. Results clearly suggest that PCT has better discriminative values, i.e better positive and negative LRs, than the WBC count. CRP is in an intermediate position (figure 2).
Fever without source in children younger than 3 months

Infants younger than 3 months with FWS have the highest risk of SBI and to accurately identify SBI in this group is even more challenging. Two studies evaluated the value of WBC as a predictor of SBI or bacteremia in febrile neonates. Schwartz et al. retrospectively analysed the data of 449 neonates and detected 19.4 % SBI. The sensitivity of the WBC to detect SBI was 38 % and the specificity 81 %. Bonsu et al. examined retrospectively the data of 3810 infants < 3 months. They calculated for WBC a sensitivity to detect bacteremia of 45 % and a specificity of 78 % (table 2). They both concluded that WBC is not sufficiently reliable to exclude invasive infections by neonates.

Gajdos et al. published a retrospective study in 315 febrile infants less than three months old. SBI was diagnosed in 79 (25.1%) infants. The AUC was 0.87 for CRP. Multivariate analysis of clinical and laboratory predictors retained only CRP (OR:13.4) and WBC with >50% neutrophils (OR: 2.92) as independent predictors. CRP <20 mg/l and < 50 % neutrophils had a negative predictive value of 93.1 % for the presence of SBI.

Hsiao et al. studied prospectively the usefulness of screening tests in 429 infants of 2 to 4 months of age. They diagnosed 10 % of SBI and 1 % bacteremia in this population of pneumococcal vaccinated infants. WBC, CRP, duration of fever and the Infant Observation Scale were elevated in infants with SBI however the difference for WBC and the Infant Observational Scale between infants with and without SBI were at the limit of significance. The sensitivity of WBC was 52 % with a cut off of 15 G/L
and the sensitivity of CRP was 100 % with a cut off of 20 mg/L. CRP performed also better than WBC in this population of infants.

Bressan et al. assessed the diagnostic accuracy of WBC and CRP in detecting SBI in neonates with early onset fever. Ninety-nine patients were studied and SBI was documented in 25% patients. The AUC was 0.78 for CRP and 0.59 for WBC.

Neonates with normal laboratory markers on initial determination underwent repeated blood examination at > 12 hours from fever onset. The AUC for repeated laboratory tests showed higher scores: 0.99 for CRP and 0.79 for WBC.

Olaciregui et al. evaluated the potential predictor of SBI in a retrospective study published in 2009 on 347 infants of less than three months with FWS. The multivariate analysis found that leucocytes count (OR 1.1), CRP (O.R 6.3) and PCT (O.R 6.6) had intrinsic predictive value for SBI but CRP and PCT are superior predictors of SBI than WBC. For neonates with fever of short duration and for the more invasive infections PCT performed better than the two other markers.

A recent study included 234 prospectively enrolled infants of less than 90 days with FWS. Thirty (12.8%) infants had SBI. For the diagnosis of SBI, the AUC was 0.82 for PCT. A PCT cut off value of 0.12 ng/ml had a sensitivity of 95 % and a specificity of 26 % with a negative predictive value of 96 %. One should note, that with this relative low cut off value, only 27 % of the infants were classified as low risk, but that all cases of bacteremia were detected. PCT performed better than WBC and ANC.

One infant with culture proven Escheria Coli bacteremia had a relatively low level of PCT: 0.44 ng/mL. The authors reanalysed the results of the same population of infants comparing infants who received or not recent immunization. They concluded that PCT levels are increased among infants with recent immunization
compared to infants without recent immunization. Despite this increase, PCT can still reliably discriminate infants with SBI from those without SBI.

Table 2 reviews the predictive value of inflammatory markers for identifying SBI in infants younger than 3 months in five studies. The data collected was for 1558 infants. The sensitivity of WBC was relatively poor and ranged from 38 to 52 % \(^5\), \(^6\), \(^0\), \(^7\). The sensitivity of CRP was very different between the two studies where it was available: 64 and 100 % \(^5\), \(^7\). Bressan et al. determined lower sensitivities for neonates with < 12 hours of fever duration (WBC: 28%; CRP: 48%) and higher sensitivities for those with > 12 hours of fever (WBC:80%; CRP: 100%) \(^7\). Finally the sensitivity of PCT fluctuated and depended on the selected cut off: 63 % (cut off: 0.5 ng/mL) \(^7\) and 95 % (cut off 0.12 ng/ml) \(^2\). The predictive values were again higher for CRP and PCT than for WBC. One should note that these markers performed less accurately for this population of very young infants compared to older children. More studies are therefore needed for a better evaluation of these inflammatory markers and their predictive value and usefulness in the management of children under 3 months.

**Combination of markers**

Several studies have attempted to combine markers of SBI in prediction rules in order to better predict SBI in children. Craig et al. evaluated 40 clinical features to construct a multivariate model to identify SBI in 15’781 febrile children younger than 5 years \(^6\). Their diagnostic model retained 26 relevant clinical items. The authors concluded that the performance of their model was acceptable with an AUC between 0.8 and 0.9. However, most other investigations tend to associate clinical items with laboratory markers.
A retrospective analysis on laboratory and clinical items was performed on 572 febrile children aged less than 36 months to develop a model to predict bacteremia. A logistic regression formula was developed and the model retained predictors based on temperature, gender and ANC. This very complex model had a sensitivity of 76 % and a specificity of 74 % at a risk value that maximizes sensitivity and specificity. This model was further validated on a second data set of 9465 children and the model confirmed a high predictive value. 80

The same group of investigators completed a retrospective study on 5279 febrile infants younger than 3 months 18. There was a 7 % rate of SBI. The model, created by recursive portioning, used 4 clinical parameters to define high risk patients: positive urine analysis, WBC, high temperature and age of less than 13 days. The sensitivity of the model for SBI was 82 % and the specificity 76 %.

Berger et al. prospectively enrolled 138 febrile children aged 2 weeks to 1 year 7. A multivariate logistic regression defined CRP, duration of fever, clinical score with focal signs of infection and a history of diarrhea as independent predictors of SBI. The WBC was not retained as an independent predictor. The authors then constructed a complex table to predict post test probabilities according to the various values of the variables retained in the diagnostic model. This complex model assessed the probability of SBI in individual infants but seems difficult to apply in the context of the evaluation of a febrile child in an ED.

Bleeker et al. performed a retrospective study on 231 children aged less than 36 months with FWS 81. They determined by multivariate analysis the predictors of SBI. The clinical parameters retained as independent predictors were: duration of fever, poor micturition, vomiting, age, temperature, chest wall retraction, and poor peripheral circulation. The AUC of these clinical parameters was 0.75. They then
determined laboratory predictors: WBC, CRP and leucocyturia. In adding these laboratory parameters to the clinical parameters, they obtained an AUC of 0.83. In a second study, they prospectively enrolled 150 children to validate the previously developed rule in children with FWS \(^{82}\). However, the overall applicability of the prediction rule appeared inferior with an AUC of 0.6 for the “clinical model” and 0.78 for the “clinical and laboratory model”. They decided to construct an updated rule, with the following independent predictors: duration of fever, vomiting, ill appearance, chest wall retraction and poor peripheral circulation with an AUC of 0.69. After including the laboratory parameters (WBC, CRP, urinary analysis) to the updated prediction rule, the AUC obtained increased to 0.83.

In conclusion, the models constructed by multivariate logistic regression appear to be robust models and have good predictive values. It now seems logical to implement new models using the best current markers of SBI such as CRP and PCT. These models must be easily applicable in the context of the emergency evaluation of a febrile child.
II.2) Urinary tract infections:

Renal cortical scintigraphy with 99m Tc-dimercaptosuccinic acid (DMSA) has emerged as the gold standard for the detection and evaluation of acute pyelonephritis and renal scarring in children. DMSA also confirmed that scarring only occurs at sites which correspond to scintigraphic abnormalities revealed during the initial scan, validating the reliability of acute-phase scans in identifying those kidneys at risk of late clinical sequelae of renal scarring.

Investigators have attempted to identify markers to differentiate pyelonephritis from lower UTI. The main purpose is to detect predictors of the presence of a renal lesion, seen at the initial DMSA, and thereby identify those children, who are at risk of renal scarring and complications.

Numerous studies (table 3) have evaluated retrospectively or prospectively the predictive value of different markers to identify among children, with febrile UTI, those with acute lesions at the initial DMSA. The thirteen studies collected the data of 1440 children. In the ten prospective studies, the authors enrolled children with febrile UTI and they diagnosed acute renal lesions in 28 to 80 % of the children 83-92.

Several of the studies evaluated the predictive value of the WBC as a marker of acute renal lesions. In four studies, the mean WBC showed no difference between children with or without renal lesions 85,86,88,92. Four studies evaluated the predictive value of WBC in the diagnosis of pyelonephritis. The sensitivity was low and ranged from 62 to 74 %, except for the study by Huang et al. (89%) which used a very low cut off, and the specificity ranged from 27 to 72 %. The WBC thus appears not to be a good predictor of acute renal lesions.
All thirteen studies determined the value of CRP to predict a renal lesion at the initial scintigraphy. The cut off used to differentiate the origin of the UTI was similar for the majority of studies: from 20 to 40 mg/L except for the studies by Garin, which used 0.5mg/L. All studies found high sensitivity ranging from 66 to 100 % in the prediction of acute renal lesions but relatively low specificity ranging from 18 to 66 % except for the study by Kotoula et al. which had a specificity of 90%. The CRP appears to have a good sensitivity for identifying pyelonephritis. However, its low specificity limits its clinical feasibility, as its use will consider many UTIs without renal lesions as pyelonephritis.

More recent studies are aimed at determining if PCT could predict renal involvement in UTI. The sensitivity of PCT ranged from 68 to 100 % except for the study by Gurgoeze et al. This study determined a poor sensitivity for PCT, only 58 %. However, in the multivariate analysis, PCT had the best odds ratio (12) compared to the odds ratio of Il-1 beta (1.2), which was the only other marker retained as an independent predictor. A recent meta-analysis included 10 studies involving 627 children with UTI to assess the prognostic value of PCT. Using a cut off value of 0.5 to 0.6 ng/ml, the authors determined a pooled diagnostic odds ratio for PCT of 14.25 (95 % confidence interval, 4.70 to 43.23).

The conclusion derived from these different studies is that both PCT and CRP are excellent markers of early renal lesions. Both CRP and PCT showed a very high sensitivity, which confers to these markers a very high predictive value. Low levels of PCT and CRP virtually ruled out pyelonephritis. Nevertheless, PCT, compared to CRP, demonstrated a better ability to discriminate febrile UTI with renal involvement from those without. This was due to the lower specificity of CRP. This is an essential
aspect, not only for treatment, but especially for the follow-up and the long term prognosis of these children.

To integrate both the specificity and the sensitivity of a test, we calculated the positive and negative LR values (figure 3). The LR values of WBC were constantly lower than for CRP and PCT, establishing that WBC is not a good predictor of renal lesions. PCT and CRP had both excellent LR values. Positive LR values were higher for PCT than for CRP in 7 of the 10 studies where the two markers were compared, confirming that PCT is a good predictor of the presence of renal lesions in UTI. On the contrary, the negative LR values for CRP were lower in 5 of the 10 studies and comparable in 4 of the 10 studies where it was analysed, which validates the good value of CRP to exclude renal lesions in UTI.

When levels of PCT were correlated with the extension of renal involvement, assessed by DMSA, a high correlation was found in three studies 84, 86, 91.

Karanavaki et al. determined that levels of PCT increased in parallel with the severity of renal lesions 91. Inversely, the levels of CRP broadly overlap, in this study, among the groups with different degrees of severity of renal lesions. Consequently, PCT had a higher reliability in this clinical setting.

Five studies evaluated the usefulness of inflammatory markers to distinguish between uncomplicated UTI and pyelonephritis with renal scarring (table 3) 86, 91, 96-98.

Prat et al. performed DMSA 6 months after UTI in 77 children. Renal scars were detected in 13/77 children (16%) 96. High sensitivity (92%) but low specificity (34%) was confirmed for CRP in detecting scarring, unlike PCT, which showed an equivalent sensitivity of 92% but a higher specificity of 62%. The authors concluded that PCT had a high negative predictive value of renal damage and that a low PCT level at the time of diagnosis of UTI was prognostic for a low risk of renal scarring.
Bressan et al. confirmed the high sensitivity of PCT to predict renal scarring (86%) but did not observe a positive correlation between CRP and renal scarring. Pecile et al. also studied the relationship between PCT levels and scarring. PCT levels were higher in children with lesions on follow-up scans. In contrast, there was no significant correlation between CRP levels and scarring. Ghiro et al. investigated retrospectively the management of pyelonephritis in 1333 patients of which 540 had a DMSA scan. They found a positive association between CRP and renal scarring. PCT was not evaluated in this retrospective study. In another study, Karanavaki et al. concluded that PCT, but not CRP, was able to differentiate within the group those children with totally reversible lesions from partially reversible lesions on follow-up scans.

As high levels of PCT have been demonstrated to be associated with severe pyelonephritis and renal scars, both of which are correlated to vesicoureteral reflux (VUR), the direct relationship between PCT and VUR has been analysed in three studies (table 3). These studies intended to evaluate if a discriminative approach would select those children at risk of VUR and thereby required cystourethrography testing. Leroy et al. demonstrated a correlation between PCT levels and the presence of and the grade of VUR. In their first study, the sensitivity of PCT (cut off 0.5 ng/ml) to detect high grade VUR was 92%. We confirmed this high sensitivity in a European multicentric study that gathered an extensive population with a sensitivity to detect high grade VUR of 100%. Soylu et al. have determined the correlation between CRP and VUR. They also found for CRP (cut off 5 mg/L) a sensitivity of 100% in detecting high grade reflux.

In conclusion, PCT has demonstrated some specific characteristics that make it more reliable than CRP in predicting those patients with renal lesions during UTI. It
has a better specificity compared to CRP in detecting renal involvement during febrile UTI. It also appears to show a progressive blood concentration increase in relation to the increased risk and extension of an acute renal lesion and consequent scarring. Therefore PCT can be considered an accurate and reliable biological marker to be used in the clinical decision making process in the treatment of febrile UTI.
II.3) Meningitis:

Acute meningitis in children is predominantly aseptic and therefore requires no specific treatment. It is estimated, however, that approximately 5% of patients in western countries will have BM and that these children are at risk of death or severe neurological sequelae, particularly when the diagnosis and/or antibiotic administration are delayed. As distinguishing between bacterial and aseptic meningitis in the pediatric ED is sometimes difficult, guidelines recommend that antibiotics be started immediately in children with clinical evidence of acute meningitis or with CFS pleocytosis and continued until bacterial culture results become available. Distinguishing between bacterial and aseptic meningitis could help reduce unnecessary antibiotic use and consequently the number of hospital admissions.

Numerous studies have compared the predictive value of inflammatory markers such as WBC, CRP and more recently PCT to the predictive value of CFS markers (protein and glucose levels and pleocytosis or neutrophil count) to differentiate bacterial from viral meningitis (table 4). These studies have compared mean values of the inflammatory markers in bacterial and aseptic meningitis. They all concluded that PCT and CRP levels are statistically higher in children with BM than with aseptic meningitis.\textsuperscript{102-110}

Some studies calculated the predictive values of CRP\textsuperscript{102, 103, 105, 108, 109}. The CRP sensitivity ranged from 80 to 95%, clearly higher than the sensitivity range of the WBC (40 to 62%) and even of the traditionally used CFS markers (33 to 88%). Tatara et al. analysed retrospectively 192 children with meningitis. They determined
the AUC of different markers and concluded that CRP had the best AUC (0.97) compared to WBC (0.63), CFS-WBC (0.81), CFS-protein (0.84) and CFS-glucose (0.79) \(^{108}\). False negative cases among the CRP test results were found to have less than 6 hours of illness.

Four studies evaluated the predictive value of PCT \(^{105-107,111}\). PCT had the higher range of sensitivity (89 to 100 %) and specificity (83 to 100 %) compared to the other markers. Gendrel et al. found that PCT is highly discriminative of BM with no overlap between PCT values of bacterial vs aseptic meningitis \(^{106}\). Dubos et al. processed a logistic-regression analysis with various markers and the only biologic tests independently and statistically associated with BM were PCT (OR: 108) and CFS protein (OR 34) \(^{105}\).

Figure 4 represents graphically the LRs of the different markers calculated from the six studies which enrolled children with meningitis \(^{102,105-109}\). PCT and CRP have clearly better LRs than WBC. PCT also had a better discriminative value than the CFS markers (protein, glucose and WBC levels) and than CRP. The CRP seemed to have slightly better LR than CFS-WBC and comparable LRs than the ones of CFS protein concentration. CFS-glucose concentration was not represented in this graph due to poorer predictive values.

Sormuren et al. studied 237 children with meningitis and Gram stain-negative CFS with the objective to distinguish bacterial from viral meningitis \(^{104}\). They calculated the predictive value for WBC, CRP and CFS markers. Of the tests investigated in this study, only CRP was capable of identifying BM with high sensitivity (96%), high specificity (93%) and with a high negative predictive value (99 %).

All of these studies concluded that CRP and PCT are excellent predictors of BM, and are superior to CFS markers.
Two studies evaluated the predictive values of markers to identify BM and septicaemia in children in an intensive care unit\textsuperscript{112,113}. They both confirmed a high sensitivity of PCT (100 %) and a high specificity (62 and 100%), with better predictive values than CRP (table 4).

Ménager et al. used a blood PCT level $< 0.5$ ng/ml to withhold antibiotic treatment during an outbreak of enterovirus meningitis\textsuperscript{114}. The dosage of PCT contributed to a shortened hospitalisation duration and in reducing antibiotic treatment in the group of children with PCT dosage compared to the group control without PCT dosage.

Given the potentially severe consequences of a delayed diagnosis of BM, any diagnostic tool must achieve, as close as possible, a 100 % sensitivity.

Used alone, no single clinical criteria or individual laboratory marker offers 100 % sensitivity with high specificity in identifying BM. Only combinations of clinical and laboratory criteria together in clinical decision rules could have such high predictive values. A recent review examined the performance and levels of validation of different decision rules\textsuperscript{115}. The authors concluded that two rules are highly promising and have been validated retrospectively in large populations: the Bacterial Meningitis Score (BMS)\textsuperscript{111,116} and the Meningitest\textsuperscript{117}. These two scores (table 5) have similar criteria excluding the cut off for CFS protein which is higher in the BMS and as well the Meningitest includes PCT in the score, which is considered the best single marker of BM. The Meningitest seemed to have a slightly superior sensitivity than the BMS, in this study, but this needs to be confirmed in other studies. We recently have externally validated the meningitest in a study regrouping 198 children with acute meningitis from 5 european countries\textsuperscript{118}. The BMS and the Meningitest both reached 100% sensitivities (95% CI= 96-100%) in this population of children.
It seems, that associating clinical and laboratory markers to predict BM in children has a greater accuracy and therefore predicts better who needs antibiotic treatment. It is certain that a sensitivity close to 100 % is essential to identify all cases of BM. Associating to these prediction rules the PCT, which appears to be the best single predictor of BM, seems promising. It is now necessary to validate these rules on prospective studies, where it can be determined, according to the score value, if children should receive antibiotics or not.
II.4.) Pneumonia

Bacterial pneumonia cannot be differentiated from viral pneumonia on the basis of a patient’s characteristics, routine laboratory tests or radiographic findings. However, early indicators of cause and severity would help with the decision of whether to prescribe or withhold antibiotics. To evaluate the predictive values of a marker, the etiologic agent of the pneumonia must be determined accurately. This is however a difficult challenge in children, since the appropriate specimen can rarely be obtained from the lower respiratory tract, as children are not able to expectorate efficiently. Moreover, children are frequently colonized by *Streptococcus pneumonia* in the naso-pharynx and consequently the urinary antigen is frequently positive due only to this colonization.

The studies investigating the accuracy of different markers unfortunately define the etiology of pneumonia in a non-uniform manner, that is, there is no golden standard for the definition of pneumonia etiology. The criteria for confirming a pneumococcal pneumonia vary from positive naso-pharyngeal culture to positive antigen assays in either urine or blood culture. Some studies have used serological testing to determine the diagnosis of pneumococcal infection in paired sera. The results of the studies therefore depend on the procedural accuracy in the etiological diagnosis of lower respiratory tract infection.
Etiological diagnosis of pneumonia by bacterial culture

Three prospective studies have defined bacterial pneumonia by positive culture, either blood culture, pleural fluid or valid sputum\textsuperscript{119-121} (table 6). Moulin et al. assessed the predictive value of PCT in differentiating bacterial and viral causes of pneumonia\textsuperscript{119}. The study enrolled 72 children with an etiological diagnosis in a population of 82 children with community acquired pneumonia. The diagnosis of pneumococcal pneumonia was confirmed by positive blood culture in ten patients and the recovery of \textit{Streptococcus pneumonia} from valid sputum or naso-pharyngeal aspirate in 15 patients. With a cut off of 1, PCT had a sensitivity of 86 % and a specificity of 87 %. PCT performed better than CRP and WBC. Prat et al. enrolled a selected group of 85 children with pneumonia in whom an etiological diagnosis could be determined\textsuperscript{120}. The diagnosis of pneumococcal pneumonia was established by positive blood culture and/or pleural fluid culture in 7 children and by urinary pneumococcal capsular polysaccharide antigen in 24 children. The sensitivity was 90 % and the specificity was 74 % for PCT (cut off: 2 ng/ml) and the sensitivity was 90 % and the specificity 60 % for CRP (cut off: 65 mg/l) to distinguish pneumococcal infection from all other etiologies. The predictive values were rather high and the AUC of PCT (0.873) and CRP (0.888) were superior to that of WBC (0.678).

Hatzistilianou et al. also compared the predictive value of PCT in a selected group of 73 children with pneumonia in whom an etiological diagnosis could be determined in a population of 124 children with community acquired pneumonia\textsuperscript{121}. The pneumococcal pneumonia was defined by a positive blood culture. The authors concluded that the sensitivity of PCT was 100 % for bacterial pneumonia with a specificity of 98 %, if the cut off was fixed at 2 ng/l. The sensitivity of PCT was 100 %
and the specificity was 60%, if the cut off was fixed at 0.5 ng/l. The predictive value of PCT was higher than either CRP or WBC. These three studies based their etiological diagnosis mainly on positive culture and their results published very good predictive values for both PCT and CRP. However, there are limitations to the interpretation of these data. Firstly, the enrolled patients were a selection of patients in whom a definite diagnosis was determined and did not include the general population of children who also had pneumonia. Secondly, an important proportion of the patients had invasive disease (ie. positive blood culture or pleural fluid culture). In consequence, this population of children may not necessarily represent children with community acquired pneumonia. Finally, the accuracy of urinary pneumococcal antigen in the diagnosis of pneumococcal pneumonia is subject to debate, as previously described, due to colonization.

The predictive value of CRP in the diagnosis of bacterial pneumonia was evaluated in three studies. Flood et al. performed a meta analysis in 2008, which included 1230 patients in whom criteria was applied to differentiate bacterial from non bacterial etiology such as positive culture from blood, respiratory secretion or pleural fluids. Children with bacterial pneumonia were more likely to have a CRP concentration exceeding 30 to 60 mg/L than children with non bacterial infections (odds ratio= 2.58, 95% CI: 1.20-5.55). There was a pooled incidence of 41 % for bacterial pneumonia, using the mean odds ratio in the different studies as the positive LR. The positive predictive value of CRP exceeding 40-60 mg/L was 64 %. One retrospective study from Singapore included 1702 children with community acquired pneumonia. Etiology of bacterial pneumonia was defined by a positive culture of blood, pleural fluid or sputum. The CRP level was again higher for bacterial pneumonia (median: 103 mg/l) than for viral pneumonia (median: 44.3 mg/l) (p<0.001) and 20 % of the
bacterial pneumonia patients had positive blood culture or pleural fluid. In one study with 50 children having pneumonia enrolled prospectively, bacterial pneumonia was defined as a positive chest radiography with lobar, lobular or alveolar condensation suggestive of bacterial pneumonia (36/50 patients) \(^{124}\). The CRP was significantly higher in bacterial pneumonia (mean: 121 mg/l) versus viral pneumonia (mean: 27 mg/l), \(p<0.01\). The CRP had a superior AUC (0.79) compared to WBC and elevated CRP level had a positive predictive value of 70 % for bacterial pneumonia. Once again, the definition of the etiological origin of pneumonia was controversial in this study.

**Etiological diagnosis of pneumonia by serological diagnosis**

The following studies have diagnosed pneumococcal etiology using antibody assays to capsular C-polysaccharides (C-PS), to type specific capsular polysaccharides (CPS) and to protein antigen pneumolysin (PNL) in paired sera and by immune complex assays measuring circulating complexes containing C-PS, CPS or PNL. Korppi et al. studied a cohort of 201 children with pneumonia enrolled from 1981-1982 in Finland and they used sero-diagnosis, as defined previously. In 1997, they analysed the predictive value of CRP and WBC in a sub-group of 161 children from the 201 children of the 1981-1982 cohort \(^{125}\). The diagnosis of pneumonia was based on the presence of pulmonary infiltration on the chest radiograph. The CRP and ANC results differed significantly between pneumococcal and viral infection. With a cut off of CRP at 60 mg/l, the sensitivity was 26 % and the specificity was 83 %. In 2001, Korppi et al. analysed a subgroup of 131 children with sera available for PCT measurement from the same previous cohort of 161 children \(^{126}\). They evaluated the
predictive value of PCT. With a cut off at 0.5 ng/ml, the sensitivity of PCT to detect a pneumococcal etiology was 55 % and the specificity 70 %. The authors concluded that, although marginally higher in pneumococcal pneumonia, the PCT could not be used to discriminate pneumococcal pneumonia from viral pneumonia. In 2004, Korppi et al. tested the possibility of using a combination of markers (CRP, WBC, PCT and ESR) and whether this combination would differentiate better between pneumococcal from viral etiology. They analysed the same 132 children from the previous cohort of children published in 2001. They found that the highest LR (1.74) was achieved using a combination of CRP (80 mg/L), WBC (17X G/L), PCT (0.84) and ESR (63 mm/h). This combination had a sensitivity of 61% and a specificity of 65 %. They concluded that no combination using these markers was sufficiently sensitive to be used in clinical practice. In 2003, Korppi et al. measured PCT values in sera of 190 patients from the initial Finland cohort of 201 patients published in 1981. The median of PCT in pneumococcal versus viral pneumonia was not significantly different while the sensitivity of PCT (cut off at 0.5 ng/ml) was 46 % and the specificity was 52 %. In an Italian study by Don and Korppi et al., they enrolled prospectively 100 children with radiologically confirmed pneumonia. They defined pneumococcal pneumonia as positive serodiagnosis with antibodies to pneumolysin and to capsular C-polysaccharide. In 2007, Don et al. analysed the usefulness of PCT in assessing the severity, as well as the etiology of pneumonia. The PCT was higher in admitted patients compared to outpatients (median 17 vs 0.72) and higher in alveolar compared to interstitial pneumonia (median 9.43 vs 0.53). However, the PCT level was not different between pneumococcal and viral etiology. At a cut off at 0.5 ng/ml, the sensitivity was 78 % and the specificity 35 % for the detection of pneumococcal
pneumonia. The authors concluded that although PCT was related to the severity of the pneumonia, PCT was not capable to differentiate between bacterial and viral etiology. In 2008, Korppi et al. assessed the value of clinical features with PCT in differentiating viral, pneumococcal and atypical pneumonia. No significant associations were found between any of the clinical signs or symptoms and the etiology of pneumonia. In the multivariate analysis, the only independent predictors of bacterial etiology were children aged over 5 years and PCT above 1 ng/ml.

Virkki et al. enrolled prospectively 215 children in 1993, in Finland, with community acquired pneumonia. Pneumococcal pneumonia was defined using the identical sero-diagnosis as in the previous studies. They investigated the differential diagnostic role of WBC, ESR and CRP. The WBC and ESR did not differ between the bacterial and viral etiology, however the CRP levels differed between the two groups. Regrettably, the sensitivity for detecting bacterial pneumonia was too low for use in clinical practice. Toikka et al. studied 126 children with sera available for retrospective PCT determination, from the previous Finland cohort of 215 children published in 1993. Children with bacterial pneumonia had significantly higher PCT (median 2.09 ng/ml versus 0.56 ng/ml) and CRP concentrations (96 mg/L versus 54 mg/l) than those with an isolated viral etiology. However, the values markedly overlapped between the two etiologies. The sensitivity for PCT was 70 % (cut off 0.5 ng/ml) with a specificity of 48 % while the sensitivity was 77 % for CRP (cut off 40 mg/L).

In a study by Michelow et al., they enrolled prospectively 154 hospitalised children with pneumonia. Pneumococcal pneumonia was defined by identical serodiagnosis and by blood pneumolysin-based PCR. The author found an association for both positive PCR assay and positive serology with PCT levels.
In conclusion, the evaluation of inflammatory markers as predictors of pneumococcal etiology in pneumonia shows conflicting results in the studies reviewed. Studies using bacteriological culture, however, demonstrated a good predictive value for both CRP (range of sensitivity: 88-96 % and positive predictive value of 64 %) \(^{122}\) and PCT (range of sensitivity 86-100 % with specificity from 60 to 98 %) \(^{119-121}\). Perhaps these better results reflect a selection of children with more invasive disease; a population in which these markers may be more reliable. On the other hand, the studies based on sero-diagnosis showed conflicting results with a low predictive value using the Finland cohort of Korppi et al. \(^{125-128}\). The studies from Toikka et al. and Don et al. indicate better sensitivity for CRP (77 %) and PCT (70 and 78 %) but with poor specificity \(^{129,132}\). One assumption is that CRP and PCT are effectively faulty predictors in the etiology of pneumonia, even if both markers predict accurately bacterial pneumonia when the diagnosis is defined by culture. On the contrary, one may assume that serodiagnosis does not reliably identify pneumococcal infection. A seroconversion of pneumococcal antibodies may be the consequence of simple colonization of the naso-pharynx and not of true pulmonary infection. In addition, perhaps pneumococcal pneumonia was not always detected using the conversion of assayed antibodies, as was done in these studies. Perhaps a lower cut off for these inflammatory markers should be used in order to exclude bacterial etiology and thus isolate a group of patients with markers of lower levels and in whom the bacterial etiology is very unlikely. It could be perhaps possible to withhold antibiotic treatment in this sub-population of patients as opposed to prescribe antibiotics to the vast majority of children. A retrospective study by Schutzle et al. included 327 children with acute respiratory infection \(^{134}\). The authors used a lower cut off for PCT of 0.1 ng/ml below which antibiotic treatment could be safely
withheld for 132 children. More prospective intervention trials are necessary in order to confirm the safety for PCT set at this limit.
II.5) Other infections

The predictive value of PCT during infectious illness has also been studied in other domains of pediatrics concerns such as neonatal infections and fever in oncology patients.

**Neonatal infections:**
Analyzing the value of PCT is complicated due to a physiological increase of PCT during the first days of life. Therefore results of studies on the use of PCT as an early marker are contradictory. However, Chiesa et al. concluded that the magnitude of PCT response to infection is much greater than the physiologic increase after birth. Both the specificity and the sensitivity of PCT were greater than those obtained for CRP.

**Fever in oncology:**
In neutropenic cancer patients, early markers of infection are needed, ones which are released into the circulating blood independently from the leucocyte count. Fleishhack et al. concluded that the overall diagnostic efficiency of PCT was superior to that of CRP in the early detection of Gram-negative bacteremia. However, both sensitivity and specificity of PCT are low compared with other studies in children with sepsis. The use of PCT in febrile neutropenic children has yet to be established in future studies.
III) Personal Works:


Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs.


In this first study, we asked the question whether the determination of PCT, CRP and other inflammatory markers (IL-6, IL-8 and IL-1Ra) was superior to the commonly used markers for the prediction of SBI in children with FWS. One hundred and twenty-four febrile children, aged 7 days to 36 months, were included in the study. Twenty-eight (23%) had SBI. The PCT, CRP and IL-6 values were higher in children with SBI but IL-8 and IL-1Ra were comparable between both groups, that is those with SBI and those without. The PCT had a sensitivity of 93 % and a specificity of 78 % for the detection of SBI while CRP had a sensitivity of 89% and a specificity of 75%. Both markers performed better than WBC, than a clinical score (the Infant Observational Scale) and than all other inflammatory markers tested (IL-6, IL-8 and IL-1Ra). Moreover, in children aged less than 12 months, who are more difficult to evaluate, PCT and CRP maintained a high sensitivity (94%). The PCT and CRP seem to be promising markers of bacterial infections in children with FWS.
Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identifiers of serious bacterial infections in children with fever without localising signs

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Abstract  Fever without localising signs in very young children remains a diagnostic problem. Until present, a clinical scoring system combined with leucocyte count, urine analysis and determination of CRP are recognised as being helpful to identify patients at risk of serious bacterial illness. In this study we asked the question whether the determination of procalcitonin (PCT), interleukin (IL)-6, IL-8 and interleukin-1 receptor antagonist (IL-1Ra) was superior to these commonly used markers for the prediction of a serious bacterial infection (SBI). Children, 7 days to 36 months of age, with a rectal temperature above 38 °C and without localising signs of infection were prospectively enrolled. For each infant, we performed a physical examination, a clinical score according to McCarthy, a complete white cell count, an urine analysis and a determination of CRP. We further determined PCT, IL-6, IL-8, and IL-1Ra concentrations and compared their predictive value with those of the usual management of fever without localising signs. Each infant at risk of SBI had blood culture, urine and cerebrospinal fluid cultures when indicated, and received antibiotics until culture results were available. A total of 124 children were included of whom 28 (23%) had SBI. Concentrations of PCT, CRP and IL-6 were significantly higher in the group of children with SBI but IL-8 and IL-1Ra were comparable between both groups. PCT showed a sensitivity of 93% and a specificity of 78% for detection of SBI and CRP had a sensitivity of 89% and a specificity of 75%.

Conclusion  Compared to commonly used screening methods such as the McCarthy score, leucocyte count and other inflammatory markers such as interleukin-6, interleukin-8 and interleukin-1 receptor antagonist, procalcitonin and C-reactive protein offer a better sensitivity and specificity in predicting serious bacterial infection in children with fever without localising signs.

Key words  Bacterial infection · C-reactive protein · Interleukin-6 · Paediatrics · Procalcitonin

Abbreviations  DMSA dimercaptosuccinic acid · IL interleukin · IL-1Ra interleukin-1 receptor antagonist · PCT procalcitonin · ROC receiver operating characteristics · SBI serious bacterial infection

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Introduction

Fever without localising signs in young children remains a difficult diagnostic problem, since clinical signs and symptoms are often unreliable predictors of a serious bacterial infection (SBI) which requires rapid therapeutic intervention with intravenous antibiotic therapy. Many clinical studies [3, 10, 14, 18] have addressed this problem and the combination of a clinical scoring system such as that of McCarthy [19] combined with a total and differential leucocyte count and a determination of the CRP concentration are commonly used screening methods. More recently, the concentration of procalcitonin (PCT), a prohormone of calcitonin [2, 5, 15] and of cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), as well as the cytokine antagonist interleukin-1 receptor antagonist (IL-1Ra) [8, 11, 16, 22] have been reported to lead to a better diagnostic accuracy when used in specific clinical situations. For instance, IL-1Ra and IL-6 were superior to circulating intercellular adhesion molecule 1 and CRP in predicting neonatal sepsis [16], whereas PCT was the best predictor in other clinical situations such as bacteremic infections in adults or children [1, 6, 9, 12, 13]. The time course of changes among these various parameters is very different: IL-6 reaches peak concentrations in bacteremic patients several hours before the rise in CRP concentration occurs [4, 7]. PCT starts to rise 2 h after experimental endotoxin administration and reaches peak levels within 6–8 h [4, 7]. From many studies [14, 25], it is known that CRP becomes a relatively reliable predictor of SBIs in fever of more than 12 h duration. Therefore it is to be expected that the predictive value of each of these markers depends on the duration between the invasion by the infectious agent and the concentration of the inflammatory marker. Furthermore, the spectrum of infectious agents possibly involved in the generation of fever varies from newborn to children below 3 years of age or even older children and adults. The diagnostic accuracy of these parameters may therefore well vary in these different clinical situations.

Until present, we used the clinical scoring system of McCarthy [19] combined with a total and differential leucocyte count and CRP concentration to decide whether a patient with fever without localising signs below 3 years of age (but beyond 7 days of age) required further diagnostic work-up and antimicrobial therapy. In this study, we asked the question, whether the determination, in addition to the previously used parameters, of PCT, IL-6, IL-8 or IL-1Ra offered an advantage in terms of sensitivity and specificity, with which a SBI could be predicted.

Patients and methods

The study protocol was approved by the Ethical Committee of the Department of Paediatrics, University Hospitals of Geneva.

Children aged 7 days to 36 months of age consulting the Emergency Department of the University Children’s Hospital of Geneva with a rectal temperature above 38 °C and without localising signs of infection in their history or at physical examination were prospectively enrolled. Each infant was examined by a paediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever and determined a clinical score according to McCarthy [19]. This scoring system allows to identify seriously ill children. Children with fever lasting longer than 7 days, neonates of less than 1 week and all children treated with antibiotics during the 2 previous days as well as those with known immunodeficiencies (like neutropenia due to chemotherapy or HIV-infected children) were excluded. All children had a urine analysis and blood drawn for a white blood cell count and for determination of CRP, PCT, IL-6, IL-8 and IL-1Ra concentrations.

White blood cell count and CRP determination were performed in blood samples mixed with EDTA. CRP was determined by a rapid immunometric kit method (Nycoearn CRP). For the determination of PCT, IL-8, IL-6 and IL-1Ra, the blood sample was centrifuged to sediment red cells and serum frozen at −20 °C within 1 h. PCT was measured in a blinded manner by an immunoluminometric assay (Lumitest PCT, Brahms Diagnostica, Berlin). This assay requires 20 µl of sample and can be performed within 2 h. IL-6, IL-8 and IL-1Ra were measured using commercially available quantitative sandwich enzyme immunoassays (R&D Systems Europe, UK). Due to the limited amount of plasma available, samples were diluted in sample buffer prior to the assays. IL-6 was measured using a highly sensitive immunoassay specific for IL-6 whose sensitivity is 0.1 pg/ml (Quantikine HS human IL-6). Serum samples were assayed at a 1:40 dilution and therefore the limit of detection was 4 pg/ml. Coefficients of variation are less than 12% and 30% for intra-assay and interassay variation respectively. IL-8 was measured using an immunoassay specific for IL-8 (Quantikine human IL-8). The sensitivity of the assay is 8 pg/ml. Serum samples were assayed at a 1:5 dilution and the limit of detection was then 40 pg/ml. Coefficients of variation are less than 7% and 10% for intra-assay and interassay variations respectively. IL-1Ra was measured using an immunoassay specific for IL-1Ra. The sensitivity of the assay is 14 pg/ml. Serum samples were assayed at a 1:20 dilution and the limit of detection was then 280 pg/ml. Coefficients of variation are less than 1% for intra-assay and interassay variations.

Children with leucocytes >15,000/mm³, band counts >1500/mm³, leucocyturia or CRP >40 mg/l had a blood culture, an urine culture, and a spinal tap when meningitis was suspected. They also received antibiotics for 48–72 h until the results of the cultures were known. All children had a clinical follow-up with physical examination by a paediatrician within the following 48 h by or telephone contact. The diagnosis was registered at the end of the clinical follow-up. Infections requiring intravenous antibiotic therapy, such as bacteraemia (positive blood culture), pyelonephritis (positive urine culture with >10⁷ colonies/ml and a positive Jendrassik 99M-dmrciprocepsཧecine (DMSA) renal scintigraphy at 4 days with a reversible cortical defect on the control scintigraphy at 90 days), lobar pneumonia (radiological diagnosis of lobar infiltrate by the radiologist in a blinded manner), meningitis (pleocytosis of >5 cells/µl and a positive culture of cerebrospinal fluid) or osteo-arthritis were defined as SBI. The remaining patients suffered from infections classified as benign for the purpose of this study on the basis that they did neither require oral antibiotic therapy at follow-up (probable viral infections) nor parenteral therapy for infections such as acute otitis media, lower urinary tract infection (negative renal DMSA scintigraphy), gastroenteritis or adenitis (local infections).

Statistics

Demographic characteristics and laboratory values of children with and without SBI were compared using the Fischer exact test for frequencies, the Student’s-t test for normally distributed continuous variables and the Mann-Whitney U test otherwise. The sensitivity,
specificity, negative and positive predictive values for the detection of a SBI were determined for the McCarthy score and the different laboratory parameters. Binominal exact 95% confidence intervals were calculated for sensitivity and specificity. The diagnostic accuracy of the different parameters and the best cut off points were determined with a receiver operating characteristics (ROC) curve. For PCT and CRP, likelihood ratios were determined. The likelihood ratio for a positive test expresses the odds that a positive test result would be expected in a patient with (as opposed to one without) a SBI, and is calculated as sensitivity/(1 – specificity) [24]. In order to calculate 95% confidence intervals around the likelihood ratio, a Taylor series expansion was used to determine the variance of this ratio [21].

Results

A total of 133 children were included from March 1998 to August 1999. Nine children were excluded because they did not present at clinical follow-up or suffered from immunodeficiencies and the data of 124 children were analysed. Patients with and without serious infections were comparable for the median age, the height of fever and the McCarthy score [19] with a slight increase in the median duration of fever for patients with SBI (Table 1). In children with fever above 40 °C recorded during this febrile episode, there was a tendency to an increased percentage of SBI (43% versus 23%, \( P = 0.06 \)). Of 62 (50%) children who were hospitalised, 37 (92%) were treated with antibiotics (54 i.v. and 3 i.m.) and among those sent home, antibiotics were prescribed for 20 (32%) (12 oral, 4 i.m. and 4 i.v.). A blood culture was performed in 91 (73%) children, an urine culture specimen in 103 (83%) and a cerebrospinal fluid culture in 13 (11%).

There was a comparable incidence of SBI in infants <3 months (8/31 = 26%), in those 3–12 months old (10/49 = 20%) and >12 months (10/44 = 23%) (\( P = 0.8 \)). The final diagnosis was SBI in 28 children (23%) (4 bacteremia, 19 pyelonephritis, 5 lobar pulmonary condensation), focal bacterial infection in 13 children (10%) (7 cystitis, 4 otitis, 1 adenitis, 1 Campylobacter gastro-enteritis) and probable viral infection in 83 children (67%) (negative culture and no signs for focal infection at clinical follow-up).

The concentrations of PCT, CRP and IL-6 were significantly higher in the group of children with SBI (\( P < 0.001 \)). IL-8 and IL-1Ra values were comparable between both groups (Table 1). PCT concentrations were comparable in the group of probable viral compared to focal infection; median (range): 0.40 ng/ml (0.11–3.30 ng/ml) versus 0.44 ng/ml (0.16–1.00 ng/ml), respectively.

Box plots of the distribution of PCT, CRP and IL-6 concentrations are shown in Fig. 1. PCT and CRP effectively discriminated between benign infections and SBI with a slight advantage for PCT (area under ROC curve 0.8824 and 0.8767, respectively) and both were superior to IL-6 (area under the ROC curve: 0.7781, IL-1Ra (0.5327) and IL-8 (0.4404). The likelihood ratio for a positive PCT was 4.24 (95% CI: 2.58–5.90) and for a positive CRP 3.57 (95% CI: 2.25–4.89). In Table 2, the sensitivity, specificity and predictive values of other parameters routinely used in the management of children with SBI are compared with those of PCT and cytokines. The PCT concentration had the best sensitivity (93%) and specificity (78%). The four bacteraemic patients had PCT values superior to 3 ng/ml with a value of 360 ng/ml for a patient with an Escherichia coli bacteremia. Among the 28 children with SBI, 2 had a PCT concentration below the cut-off level (0.9 ng/ml). CRP had a sensitivity of 89% and a specificity of 75%. The other parameters used routinely (total and differential leucocyte count, McCarthy score) had a lower sensitivity ranging from 20%–68%. When PCT and CRP were associated, the sensitivity of the combination increased but the specificity decreased (Table 2). Table 3 compares the predictive value of PCT and CRP between subjects below or above 12 months of age, both parameters had a trend towards poorer specificity in older children.

Discussion

Among our population of 124 children below the age of 3 years presenting at the emergency room with fever without localising signs, 28 suffered from a SBI such as bacteremia, pyelonephritis or lobar pneumonia. In terms of age and level of the initial temperature, the groups were comparable (Table 1). The sensitivity and the specificity for predicting a SBI were calculated for the various inflammatory markers measured, the PCT values were better than CRP. However, in this study, both tests were not significantly different, this could be

| Table 1 Comparison of different parameters and of the mean concentrations of PCT, CRP, IL-6, IL-8 and IL-1Ra (as mean ± standard error or median and range) between children with benign infections and SBI. (ND non detectable, NS not significant) |
|-------------------------------------------------|-----------------|------------------|
| Age (months) | 10.9 ± 0.9 | 11.2 ± 1.8 | NS |
| Fever duration (h) | 24 (1–240) | 27 (2–140) | 0.02 |
| Temperature (°C) | 39.0 ± 0.1 | 39.1 ± 0.2 | NS |
| PCT (ng/ml) | 40 (0.11–43.3) | 3.6 (0.25–566) | <0.01 |
| CRP (mg/l) | 20 (10–200) | 108 (10–200) | <0.01 |
| IL-6 (pg/l) | 14.7 (1.5–801) | 69 (10–801) | <0.01 |
| IL-8 (pg/l) | ND (ND–3869) | 43.5 (ND–145) | NS |
| IL-1Ra (pg/l) | 5173 (435–74868) | 8381 (689–49917) | NS |

*IL-8 values were below the detection level (40 pg/ml) in 50 subjects with a benign infection and in 7 subjects with a serious infection.*
Fig. 1 Logarithm of PCT, CRP, IL-6 concentrations in children with SBI or benign infections (BI). The box plots show the 25th, 50th and 75th percentiles of the distribution. The upper and lower limits correspond to the highest and lowest value within 1.5 times the interquartile range above the 75th percentile and below the 25th percentile respectively. Points outside these limits are outliers and are graphically represented.

Table 2 Sensitivity, specificity and predictive values of the different markers for the prediction of a SBI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Negative predictive value (%)</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (0.9 ng/ml)*</td>
<td>93 (77-99)</td>
<td>78 (69-86)</td>
<td>97</td>
<td>55</td>
</tr>
<tr>
<td>CRP (40 mg/l)*</td>
<td>89 (72-98)</td>
<td>75 (65-83)</td>
<td>96</td>
<td>51</td>
</tr>
<tr>
<td>Leucocytes &gt; 15,000/mm³</td>
<td>68 (48-84)</td>
<td>77 (67-85)</td>
<td>89</td>
<td>46</td>
</tr>
<tr>
<td>Band &gt; 1500/mm³</td>
<td>29 (13-49)</td>
<td>91 (83-96)</td>
<td>81</td>
<td>46</td>
</tr>
<tr>
<td>McCarthy score &gt; 10</td>
<td>20 (3-56)</td>
<td>86 (76-93)</td>
<td>79</td>
<td>29</td>
</tr>
<tr>
<td>IL-6 (50 pg/l)*</td>
<td>79 (59-92)</td>
<td>66 (55-75)</td>
<td>91</td>
<td>40</td>
</tr>
<tr>
<td>IL-1Ra (9500 pg/l)*</td>
<td>71 (51-87)</td>
<td>63 (52-72)</td>
<td>88</td>
<td>36</td>
</tr>
<tr>
<td>IL-8 (70 pg/l)*</td>
<td>38 (15-65)</td>
<td>79 (69-87)</td>
<td>81</td>
<td>34</td>
</tr>
<tr>
<td>PCT (0.9 ng/ml)* or CRP (40 mg/l)*</td>
<td>96 (82-100)</td>
<td>67 (56-76)</td>
<td>98</td>
<td>46</td>
</tr>
<tr>
<td>PCT (0.9 ng/ml)* or Leucocytes &gt; 15,000/mm³*</td>
<td>100 (88-100)</td>
<td>62 (51-71)</td>
<td>100</td>
<td>43</td>
</tr>
</tbody>
</table>

* Cut off level

Table 3 Sensitivity, specificity and predictive value (%) for a SBI of PCT and CRP in relation to age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age (months)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative predictive value (%)</th>
<th>Positive predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>&lt; 12 (n = 80)</td>
<td>94</td>
<td>87</td>
<td>98</td>
<td>68</td>
</tr>
<tr>
<td>(0.9 ng/ml)*</td>
<td>&gt; 12 (n = 44)</td>
<td>90</td>
<td>62</td>
<td>96</td>
<td>41</td>
</tr>
<tr>
<td>CRP</td>
<td>&lt; 12 (n = 80)</td>
<td>94</td>
<td>84</td>
<td>98</td>
<td>63</td>
</tr>
<tr>
<td>(40 mg/l)*</td>
<td>&gt; 12 (n = 44)</td>
<td>80</td>
<td>59</td>
<td>91</td>
<td>36</td>
</tr>
</tbody>
</table>

* Cut off level

due to the small size of the study and larger cohorts of patients would be necessary to identify a statistically significant advantage of PCT over CRP. The other markers IL-6, IL-8 and IL-1Ra as well as the total and differential leucocyte count, were all below PCT and CRP. Only 2 infants among the 28 with a SBI had a PCT concentration below the cut-off value of 0.9 ng/ml. At follow-up examination, one had pyelonephritis with a minimal renal lesion on DMSA scintigraphy and another a classical pyelonephritis. For the former patient, it is possible that the inflammatory reaction at the moment when PCT was determined was too weak. In children below the age of 1 year, in whom clinical signs and symptoms are often unreliable, PCT and CRP were more predictive than in older children (Table 3).

Interestingly, IL-1Ra, IL-6 or IL-8 concentrations did not offer any advantage over PCT and performed less well than CRP. In newborn children, Küster et al. [16] showed that IL-1Ra and IL-6 increased significantly earlier than CRP, but no data on PCT were obtained, whereas in a recent study in newborns, PCT determination detected early-onset sepsis with a sensitivity of 93% and a specificity of 98% [6]. These excellent results were not confirmed by another group reporting on newborns [17]. However, a population of hospitalised newborns, in whom clinical signs and symptoms as well as inflammatory markers were studied prospectively, is not comparable to our study population in which the clinician saw the child only at the time when it was brought in by the parents and after onset of fever. Furthermore, hospitalised newborn infants very rarely suffer from post-natally acquired viral diseases in contrast to older children presenting with fever without localising signs. Our study clearly does not address the
question in newborn infants, but it is the first one in children with fever without localising signs in which PCT, IL-6 and IL-1Ra, are measured simultaneously.

How can we explain the striking difference between PCT (sensitivity 93%, specificity 78%) and CRP (sensitivity 89%, specificity 75%) on the one hand and IL-6 (sensitivity 79%, specificity 66%) and IL-1Ra (sensitivity 71%, specificity 63%) on the other? First, for IL-6 and IL-1Ra, their concentrations indeed increase early, i.e. within 6 h, but it may already have dropped when our patients presented at the emergency room, whereas PCT remains longer in the circulation [7]. Second, it is possible that PCT, more than IL-1Ra and IL-6, allows to distinguish between bacterial and viral infections, which are frequent in groups of children such as the one we studied. IL-6, IL-8 and IL-1Ra are indeed activated by various viruses [23, 26, 27, 28]. Finally, PCT is a molecule with a remarkable stability without significant influence of the blood sampling technique and of repeated freezing and thawing cycles [20] which is less the case for the cytokines.

On the basis of our data, PCT offers only a modest advantage over CRP, which at present is more easily measurable in an outpatient setting. If CRP is used by taking into account the kinetics of parameters of inflammation, it still offers a good prediction of a SBI. However, PCT determination has recently been simplified and, after careful testing with regard to accuracy of the rapid test, it may offer an advantage over CRP in children with fever without localising signs, especially in those of younger age. Since the number of children below the age of 1 year tested in our study was rather small, this problem should be further addressed. Moreover, because PCT rises earlier than CRP after a bacterial stimulus, this test may prove to be more accurate at the beginning of an infection. Total and differential leukocyte count, which is commonly used in the decision algorithm, performed poorly compared to PCT and CRP raising the question of its utility. We therefore suggest that it may be abandoned as a routine first screening method.

Our study showed that in comparison to commonly used screening methods, such as the clinical score of McCarthy [19], the total and differential leukocyte count and CRP as well as to other inflammatory markers such as IL-6, IL-1Ra and IL-8, PCT offers a slightly better sensitivity (93%) and specificity (78%) in predicting a SBI in children with fever without localising signs and may be used alone in the initial screening.

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References


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Galetto-Lacour A, Zamora SA, Gervaix A.

Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center.

*Pediatrics* 2003;112(5):1054-60.

In this second article, we intended to assess the value of bedside tests for PCT, CRP and IL-6 in predicting SBI in children with FWS. Blood PCT, CRP and IL-6 values were determined using rapid tests available in 20 minutes. Ninety-nine children with FWS were included in the study and 29 (29%) had a SBI. The PCT had the best sensitivity (93%) and negative predictive value (96%). The sensitivity of CRP was 79 % and the negative predictive value was 90 %. After calculating the LR, PCT and CRP performed much better than WBC. In children with PCT < 0.5 ng/mL, the risk of SBI was decreased from 29 % to 3 % supporting the absence of antibiotic treatment in these children. Children with PCT > 2 ng/mL had a post test probability of SBI of 68 %, which justified beginning antibiotic treatment pending the results of cultures. The rapid CRP test also gave useful information. Below 40 mg/L, the risk of SBI was decreased from 29 % to 10 %. On the contrary, the probability of SBI with a WBC count < 15 G/L was barely unchanged, decreasing only from 29 to 21 %.

Furthermore, the ease and the rapidity of these tests were key considerations for their practical use in the ED, where decisions need to be taken rapidly.
Bedside Procalcitonin and C-Reactive Protein Tests in Children With Fever Without Localizing Signs of Infection Seen in a Referral Center
Annick Galetto-Lacour, Samuel A. Zamora and Alain Gervaix

*Pediatrics* 2003;112;1054-1060
DOI: 10.1542/peds.112.5.1054

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.pediatrics.org/cgi/content/full/112/5/1054
Bedside Procalcitonin and C-Reactive Protein Tests in Children With Fever Without Localizing Signs of Infection Seen in a Referral Center

Annick Galetto-Lacour, MD; Samuel A. Zamora, MD; and Alain Gervaix, MD

ABSTRACT. Objective. To assess the value of bedside tests for predicting the occurrence of severe bacterial infections (SBIs) in children with fever without source.

Methods. We conducted a prospective study of 99 children, aged 7 days to 36 months, who were seen for fever >38°C and no localizing sign of infection at the emergency department of the University Children’s Hospital of Geneva. Blood procalcitonin (PCT), C-reactive protein (CRP), and interleukin-6 (IL-6) values were determined using rapid tests and were compared with the total white blood cell (WBC) count with differential and clinical score. Specificity, sensitivity, predictive values, and multilevel likelihood ratios (LRs) with posttest probabilities of disease were calculated.

Results. Twenty-nine (29%) children received a diagnosis of having an SBI. PCT had the best sensitivity (93%) and negative predictive value (96%). Band count had the best specificity (93%), but its positive predictive value was only 38%. Multilevel LRs revealed that a PCT concentration <0.5 ng/mL (LR: 0.093) almost ruled out SBI (posttest probability of disease: 3.7%) in 54 (54%) subjects, whereas a value >2 ng/mL (LR: 5.2) increased the probability of SBI to 68% in 19 (19%) children. For CRP, values <40 mg/L (LR: 0.263) and >100 mg/L (LR: 144.83) generated posttest probabilities for SBI of 9% (61 subjects) and 86.5% (14 subjects), respectively. For WBC count, the posttest probabilities of SBI were modestly changed from the pretest prevalence.

Conclusions. PCT and CRP performed better than IL-6, WBC, and/or band count in predicting the occurrence of SBI. PCT and CRP bedside tests may be useful tools for emergency and private practice doctors and should be considered in the initial work-up of children with fever without source. *Pediatrics* 2003;112:1054–1060; interleukin-6, procalcitonin, C-reactive protein, bacterial infection, fever without source, pediatrics, pyelonephritis.

ABBIETIATIONS. ED, emergency department; SBI, serious bacterial infection; FWS, fever without source; WBC, white blood cell; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin 6; EDTA, ethylenediaminetetraacetic acid; DMISA, 99M-dimercaptosuccinic acid; CSF, cerebrospinal fluid; LR, likelihood ratio; UTI, urinary tract infection.
different rapid tests and the WBC count for predicting SBI s in children with FWS.

METHODS
In the ED of the University Children’s Hospital of Geneva, we prospectively enrolled children, aged 7 days to 36 months, who had a rectal temperature ≥38°C and no localizing signs of infection in their history or at physical examination. Informed consent was obtained from the parents. Excluded from the study were children with fever longer than 7 days, children who were treated with antibiotics during the 2 previous days, and those with known immunodeficiencies. The study protocol was approved by the Ethics Committee of the Department of Pediatrics, University Hospital of Geneva.

Children were examined by a pediatric resident who took a complete history, performed a physical examination, recorded the degree and duration of fever, and determined a clinical score according to McCarthy.15 All children had a WBC count with differential and a determination of CRP, PCT, and IL-6 values. Toxic-appearing children had a full sepsis workup, were admitted to the hospital, and were given parenteral antibiotics. Nontoxic-appearing children, from 1 week to 90 days of age or from 91 days to 36 months of age with fever ≥38°C, had a urine collection by suprapubic aspiration, transurethral bladder catheterization, or midstream catch for analysis and culture. Blood was systematically cultured in children with leukocytes >15 g/L or band counts >1.5 g/L. In children from 91 days to 36 months of age with fever ≥38°C but <39°C, urine and blood culture were not performed unless biological risk factors (leukocytes >15 g/L, band counts >1.5 g/L, or leukocytosis) were present.16 A spinal tap was performed when meningitis was suspected. Erythrocyte, platelet, and WBC counts were performed in blood samples mixed with ethylenediaminetetraacetic acid (EDTA) using an automated cell counter. Band form was counted manually by trained technicians. CRP value was determined in 50 μL of EDTA-blood with a rapid (15 minutes) immunometric method (Nyocard CRP) according to the instructions of the manufacturer. Procalcitonin was measured by a rapid semi-quantitative immunochromatographic test (Beadlyte PCT Plus Diagnostics, Berlin, Germany) in plasma samples (range of results: <0.5 ng/mL, ≥0.5 ng/mL, ≥2 ng/mL, and ≥10 ng/mL). Briefly, 200 μL of plasma-EDTA was applied onto the test strip. PCT in the sample is bound by mouse monoclonal antibodies conjugated with colloidal gold to form a complex. This complex moves by means of capillarity through an area containing fixed anti-calcitonin antibodies to form a sandwich complex that can be seen as a reddish band. The color intensity of the band is directly proportional to the PCT concentration of the sample. IL-6 was measured using a lateral flow semi-quantitative immunoassay (Milenia Quickline Interleukin-6; Milenia Biotech, Bad Nauheim, Germany) in 20 minutes (range of results: <100 ng/mL, ≥100 ng/mL, ≥500 ng/mL, ≥1000 ng/mL). Briefly, 100 μL of plasma-EDTA was pipetted onto the test strip. IL-6 present in the sample binds to a monoclonal anti-IL-6 antibody conjugated to gold particles, flows through the test system, and finally overlying a test band coated with a second monoclonal antibody specific for IL-6. The accumulated gold particles are immobilized on the test band and become visible as a red-blue band. Color intensity is directly proportional to the concentration of IL-6 in the sample. Results of both assays were read by 2 investigators (A.L.C., A.G.) in a blinded manner, and the similarity of results was 99%.

Decisions on antibiotic treatment and hospitalization were made by the resident in charge of the patient, based on clinical assessment and the presence of biological risk factors. All children had a clinical follow-up with physical examination by a pediatrician in the following 48 hours or by telephone contact. Antibiotics were discontinued after 48 to 72 hours if the results of the cultures were negative. The diagnosis was registered at the end of the clinical follow-up.

Definition and criteria of SBI s were 1) bacteremia, 2) positive blood culture; 2) pyelonephritis, positive urine culture with >105 colony-forming units/mL, and cortical defect seen at the technetium 99m-dimercaptosuccinic acid (DMSA) renal scintigraphy; 3) lobar pneumonia, lobar consolidation diagnosed on a chest radiograph by a pediatric radiologist unaware of the study; 3) bacterial meningoitis, cerebrospinal fluid (CSF) pleocytosis of >20 cells/μL and positive culture of CSF; 4) deep abscesses, assessed by computed tomography scan and surgical exploration. Children were classified as having a benign infection for the purpose of this study on the basis of 1) negativity of blood or CSF culture, 2) positive urine culture with a normal DMSA renal scintigraphy, 3) clinical improvement without antibiotics, and 4) the presence of a focal infection at the follow-up visit such as otitis media or gastroenteritis.

Statistics
Demographic characteristics and laboratory values of children with benign infection and SBI were compared using the Fisher exact test for frequencies, the t test for normally distributed continuous variables, and the Mann-Whitney U test otherwise. The sensitivity, specificity, and negative and positive predictive values for the detection of an SBI were determined for the McCarthy score and the different laboratory parameters using the cutoff points listed in Table 1. For additional insights into the interpretation of diagnostic test data, likelihood ratios (LR) were also determined for PCT, CRP, and leukocytes. The LR for a positive test expresses the odds that the test result would be expected in a patient with (as opposed to one without) an SBI and is calculated as sensitivity/(1 – specificity).17 The LR indicates the value of the test for increasing certainty about a positive diagnosis. Starting from a pretest probability of disease that is equal to the prevalence, the LR will generate a posttest probability of disease. Three ranges of values were used to generate LR for PCT (<0.5, 0.5–2, >2 ng/mL), CRP (<40, 40–100, >100 ng/mL), and leukocytes (<15, 15–20, >20 G/L). To calculate 95% confidence intervals for the LR, we used a Taylor series expansion to determine the variance of this ratio.17

RESULTS
This study included 110 children. Eleven children were excluded (4 were older than 3 years, 2 received antibiotics, 1 had a temperature <36°C, 2 had focal symptoms already at the inclusion, and 2 had insufficient blood samples), so the data of 99 children were analyzed. A blood culture was performed in 88

| TABLE 1. Sensitivity, Specificity, and Predictive Values of Markers of SBI |
|-----------------|------------------|------------------|--------------|--------------|
| PCT (0.5 ng/mL) | 93 (77–99)       | 74 (62–84)       | 96           | 60           |
| CRP (40 ng/L)   | 79 (60–92)       | 79 (67–88)       | 80           | 61           |
| Leukocytes ≥15 G/L | 77 (64–89)     | 76 (64–84)       | 80           | 61           |
| Band ≥1.5 G/L   | 11 (2–28)        | 72 (61–83)       | 80           | 61           |
| Leukocytes ≥15 G/L | 71 (56–86)     | 70 (55–85)       | 80           | 61           |
| or band ≥1.5 G/L | 72 (56–86)     | 70 (55–85)       | 80           | 61           |
| IL-6 (100 pg/L) | 36 (13–65)       | 80 (64–91)       | 77           | 38           |
| YOS score > 50  | 23 (5–84)        | 82 (67–92)       | 76           | 30           |

NPV indicates negative predictive value; PPV, positive predictive value; YOS, Yale observation scale; CI, confidence interval. * Cutoff.
(89%) children, a urine culture in 89 (90%), and a CSF culture in 17 (17%). Of 40 (40%) children who were hospitalized, 35 (88%) were treated with antibiotics, only by intravenous route, and among those sent home, antibiotics were prescribed for 36 (61%); 10 oral, 1 intramuscularly, and 25 intravenously). SBIs were diagnosed in 29 (29%) children and included 4 occult bacteremia, 21 pyelonephritis, 2 lobar pneumonia, 1 mastoiditis, and 1 retropharyngeal abscess. Streptococcus pneumoniae and Streptococcus agalactiae were the causative organisms of 3 and 1 occult bacteremia, respectively. Escherichia coli was the organism recovered from 90% of all urinary tract infections (UTIs). Benign infection was diagnosed in 70 (71%) children. Eleven subjects had lower UTI, 4 developed acute otitis media diagnosed at the follow-up visit, and 3 had aseptic meningitis. Fifty-two (52%) children were considered as having a probable viral infection based on negative bacterial cultures and no sign of a focal infection (except nonbloody diarrhea) at the clinical follow-up visit. Demographic characteristics and laboratory parameters of patients with and without serious bacterial infections are compared in Table 2. The duration of fever before consultation was significantly longer for patients with SBI ($P = .026$; Table 2). Leukocytes, band form, CRP, and PCT were also significantly increased in children with SBI compared with children with benign infection.

In Table 1, the sensitivity, the specificity, and the predictive values of parameters routinely recommended in the treatment of children with FWS are compared with those of PCT, CRP, and IL-6 rapid tests for the diagnosis of SBI. PCT and band form showed the best sensitivity and specificity, respectively, with values >90%. PCT and CRP had comparable positive predictive values for SBI of 61% and 60%, respectively, and performed better than the other clinical or biologic parameters. PCT showed an excellent negative predictive value of 96%. Combination of PCT (>0.5 ng/mL) and CRP (>40 mg/L) increased the sensitivity to 97% but decreased the specificity to 61% (data not shown). Among the 29 children with SBI, 2 had a PCT concentration below the limit of detection of the test (<0.5 mg/L). One had occult pneumococcal bacteremia and came to the ED with a fever lasting <10 hours. The second case had pyelonephritis with minimal but positive changes at the DMSA renal scintigraphy. Six (6%) and 14 (14%) children with SBI had a CRP value <40 mg/L and a leukocyte count <15 G/L, respectively (Fig 1).

LRs and the generated posttest probabilities of diseases for PCT, CRP, and leukocytes are presented in Table 3. For a better visual understanding, the pretest probability, the LR for specified range of values, and the probability of having an SBI after measuring PCT, CRP, and the leukocyte count were plotted on a nomogram (Fig 2). For PCT, >70% of the population was distributed in clinically useful ranges, either narrowing the probability of SBI to 3% in 54 subjects with PCT <0.5 ng/mL or increasing the probability to 68% in 19 children with PCT >2 ng/mL. These figures were similar for CRP, but for leukocytes, the posttest generated probabilities were modestly changed from the pretest prevalence in the specified ranges (Table 3, Fig 2).

**DISCUSSION**

Our study demonstrates that determination of blood PCT and CRP using rapid tests is superior to WBC and band counts for predicting an SBI in children aged <3 years with FWS. The ease of use and the rapidity of the tests assayed in this study are other key considerations for the office practitioner and the emergency doctor.

The treatment of children younger than 3 years with fever without localizing signs of infection remains a debated question. Although wide-scale *Haemophilus influenzae* type b vaccination has dramatically decreased the incidence of occult bacteremia and meningitis in young children, *S pneumoniae* is still a leading cause of severe sepsis and death in this population, especially in countries where conjugated vaccines against pneumococci are not yet routinely recommended. Although the heptavalent conjugate pneumococcal vaccine is licensed for use in young children, pneumococcal disease caused by a serotype not in the vaccine, as a result of vaccine failure, or occurring in children who were not immunized or partially immunized will continue to be the most frequent cause of occult bacteremia. As emphasized recently by Klein, the treatment of febrile infants with FWS aged 3 months to 3 years should not be changed on the basis of vaccine status until more extensive experience with heptavalent conjugate pneumococcal vaccine is available. UTI is also a major bacterial cause of fever in young chil-

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**Table 2.** Demographic Characteristics and Laboratory Parameters of Children With Benign and Serious Bacterial Infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Benign Infection (Median [Range])</th>
<th>SBI (Median [Range])</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>7.2 (0.4-31.1)</td>
<td>9.7 (0.7-34)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>39/51</td>
<td>14/15</td>
<td>NS</td>
</tr>
<tr>
<td>Fever duration (h)</td>
<td>24 (1-140)</td>
<td>49 (6-140)</td>
<td>0.02</td>
</tr>
<tr>
<td>Fever (°C)</td>
<td>39.5 (38.4-38.6)</td>
<td>39.4 (38.3-41)</td>
<td>NS</td>
</tr>
<tr>
<td>PCT (≥&lt;20.5 ng/mL)</td>
<td>52/18</td>
<td>2/27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>16 (10-200)</td>
<td>100 (10-200)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6 (≥&lt;100 ng/L)</td>
<td>31/9</td>
<td>8/5</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocytes (G/L)</td>
<td>10.2 (3-29.3)</td>
<td>15.1 (3.8-46.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Band (G/L)</td>
<td>0.2 (0-2.7)</td>
<td>0.7 (0-13)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NS indicates nonsignificant.
TABLE 3. LRs for Selected Range of Values of PCT, CRP, and Leukocyte Counts and Posttest Probability of SBI in Children With FWS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>LR (95% CI)</th>
<th>Posttest Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5 ng/mL</td>
<td>54</td>
<td>0.09 (0.02-0.36)</td>
<td>3</td>
</tr>
<tr>
<td>0.5-2</td>
<td>26</td>
<td>2.8 (1.49-5.33)</td>
<td>54</td>
</tr>
<tr>
<td>&gt;2</td>
<td>19</td>
<td>5.2 (2.20-12.42)</td>
<td>68</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 mg/L</td>
<td>61</td>
<td>0.26 (0.13-0.54)</td>
<td>10</td>
</tr>
<tr>
<td>40-100</td>
<td>22</td>
<td>2.0 (1.04-4.01)</td>
<td>45</td>
</tr>
<tr>
<td>&gt;100</td>
<td>16</td>
<td>14.5 (3.46-60.70)</td>
<td>86</td>
</tr>
<tr>
<td>Leukocyte</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 G/L</td>
<td>66</td>
<td>0.65 (0.44-0.97)</td>
<td>21</td>
</tr>
<tr>
<td>15-20</td>
<td>15</td>
<td>1.6 (0.63-4.11)</td>
<td>40</td>
</tr>
<tr>
<td>&gt;20</td>
<td>18</td>
<td>2.4 (1.07-5.46)</td>
<td>49</td>
</tr>
</tbody>
</table>

Pretest probability: 29%.

dren with a prevalence of 5% to 20%. If cystitis is not associated with long-term sequelae, then delay in the initiation of antibiotics in children with pyelonephritis can lead to permanent, serious renal damage such as chronic hypertension and renal insufficiency. Several experts state that careful daily observation of a nontoxic-appearing child should suffice to correctly treat children with FWS, pending the results of urine and blood culture. Despite these statements, antibiotics are still largely prescribed in private office and in EDs. Factors that urge physicians to give antibiotics include the absence of an adequate diagnostic marker of bacterial infections, the concern about lack of patient follow-up, and the time pressure. Furthermore, the results of a survey of pediatricians found that parental pressure, rather than concerns about legal liability or the need to be efficient in practice, was the major reason that antimicrobials are prescribed inappropriately. For example, in this study, the decision to give an antibiotic treatment was taken by the resident in charge of the patient. Of 40 nontoxic-appearing children without biological risk factors, 20 (50%) were given antibiotics. In those children, the only measurable significant parameter associated with antibiotic prescription was a younger age (6.8 months ± 7.0 vs 12.3 months ± 8.2; P = .03). As a consequence, the widespread use of antibiotics favors the selection of resistant bacteria and increases the risk of drug-related adverse events and the cost of care.

If algorithms are used to select patients who are the most likely to benefit from an antibiotic treatment, then they must be accurate and applicable in all medical settings where time pressure is important. In previously published guidelines, total WBC and differential counts were the most common laboratory tests recommended in children with FWS. They can be obtained in <30 minutes in most EDs but are seldom obtained in this time frame by office practitioners, who do not have a laboratory and a skilled technician. Although these tests are rapidly obtained, our results showed that the sensitivity of the total leukocyte and band count or the combination of both was between 11% and 55%, with negative predictive values ranging from 72% to 79%. These results are in accordance with those published recently by Pulliam et al. By contrast, serum PCT showed better sensitivity (93%) and negative predictive value (96%). Regarding the LR, the rapid PCT test performed much better than leukocyte count. A WBC count superior to 20 G/L increased only the probability of SBI from 29% to 49%. The probability of SBI with a WBC count <15 G/L was barely unchanged, decreasing from 29% to 21%. By contrast, in children with a PCT value <0.5 ng/mL, which represented half of the study population, the risk of SBI
was considerably decreased from 29% (pretest probability) to 3%, supporting the absence of antibiotic treatment in such children. Children with a PCT value >2 ng/mL had a posttest probability of SBI of 68%, which in our opinion justifies antibiotic treatment pending the results of cultures. In the quarter of the study population with PCT values between 0.5 and 2 ng/mL, the uncertainty remained with a posttest risk of SBI of 54%. However, 11 of the 25 children with a PCT value in this range also had a pathologic urinalysis, and a pyelonephritis was confirmed in 10. In a previous study, we showed that a PCT value >0.5 ng/mL and a positive urinalysis predicted a pyelonephritis in 87% of cases. Similar advantage of PCT over leukocyte count and other blood markers has also been reported in febrile neutropenic children and in critically ill children.

The rapid CRP test also gave more useful information than the WBC count. Its sensitivity and negative predictive value were 79% and 90%, respectively, for a cutoff value of 40 mg/L. The LRs that we calculated were comparable to those obtained in the same settings in a recently published study. Below 40 mg/L, the risk of SBI was decreased from 29% to 10%.

In the present study, we chose to examine the utility of rapid tests in predicting the occurrence of SBI, not limited to occult bacteremia. We believed that this would be more representative of typical clinical scenarios in which clinicians must decide in all children with FWS what work-up is necessary and whether antibiotic therapy is indicated. However, the rate of SBI (29%) used as the pretest probability was higher than previously reported. There are 2 reasons for this difference: 1) our ED is a referral center for sicker children and, 2) children with a positive urine culture (n = 32) underwent a DMSA renal scintigraphy that was positive in 63% of cases. This high rate of renal involvement in children with UTI has been reported in several studies from different countries where such sensitive methods were used and accounted for 50% to 67% of all UTIs. We can assume that in previous studies, where a distinction between lower and upper UTI was not performed accurately, most of the children were classified in the non-SBI group. However, this distinction is important because the oral or parenteral administration of antibiotics is still debated for the treatment of pyelonephritis. Although the overall prevalence of SBI was high in this study per-
formed in a referral center, the rate of occult bacteremia (4%) was similar to previously published data.20 Nevertheless, as LRs are independent of disease prevalence, we can extrapolate our figures using an SBI rate of 10%, as reported in the general population of children with FWS. In this scenario, PCT <0.5 ng/mL or CRP <40 mg/L almost rules out SBI with a posttest probability <1% and <3%, respectively, whereas using a leukocyte count <15 G/L, the posttest probability stays at approximately 6%.

In several studies, IL-6 was shown to be a good marker of bacterial infection and superior to intercellular adhesion molecule 1 and CRP in predicting neonatal sepsis.11,13 However, in our study, IL-6 did not allow an accurate determination of children with SBI. The poor sensitivity of this marker is probably attributable to its rapid kinetics. Indeed, blood IL-6 increases in the first few hours after bacterial endotoxemia and starts already to decrease after 12 hours.37 This can explain why, in our study, the higher IL-6 concentrations were found in children with SBI and a short duration of fever before consultation. Compared with IL-6, PCT increases in blood 6 hours after a stimulus, reaches a plateau between 12 and 48 hours, and then decreases if the stimulus stops.37 Finally, CRP increases later than PCT, explaining why, for several authors, it is important to be cautious with the interpretation of CRP values in children with fever lasting <12 hours.12 Comparing the 3 rapid tests, PCT seems to have a slight advantage over CRP because of its earlier increase after stimulation and a better negative predictive value. Nonetheless, although this test seems promising, it has been investigated less than CRP in children and needs additional investigation. Both CRP and PCT performed better than IL-6 in this study.

Although these rapid tests look promising, this study has been performed in a specific ED setting, on a relatively small number of children, and with the specific aim to compare their values with the ones of WBC and band counts to detect SBI. Therefore, larger studies in private offices are needed and should also be undertaken to assess the reliability of these tests in physicians who do them occasionally and to evaluate their cost-effectiveness.

CONCLUSIONS

The algorithms published >10 years ago by Barraff et al20 and still largely cited in recent literature takes into account clinical scores and biological parameters, especially WBC and band counts. However, the difficulty in obtaining timely results in addition to the low predictive values of leukocytes make them difficult to use in practice. CRP and PCT rapid tests can be performed at the bedside, have good predictive values, and deserves additional investigations in the initial treatment of children with fever without localizing signs of infection.

REFERENCES


Galetto-Lacour A, Zamora SA, Gervaix A.

A Score Identifying Serious Bacterial Infections in Children With Fever Without Source.


Despite the promising predictive value of PCT and CRP, a unique test would probably never be perfect. One way to improve the predictive value of a single test would be to combine different markers in a risk index score. In this study, we analysed the predictive value of different markers in a multivariate logistic regression analysis to determine which predictors were the most powerful. We then constructed a Lab-score using only the predictive variables that were independently associated with SBI.

We performed a combined analysis of data collected from our two previous prospectively and consecutively enrolled cohorts of children with FWS. The study population was divided using randomized stratification into a derivation set (2/3) and into a validation set (1/3). In the multivariate analysis, only PCT (OR: 37.6), CRP (OR: 7.8) and urine dipstick (OR: 23.2) remained significantly associated with SBI. The WBC was not an independent predictor when these 3 variables were taken into account. Based on the results of the logistic regression analysis, we developed a risk index score named the Lab-score. Two points were attributed to PCT or CRP above the cut off values (PCT: 0.5 ng/mL and CRP: 40 mg/L) and 4 points for values of PCT above 2 ng/mL, and for CRP above 100 mg/L. One point was attributed for a positive urine dipstick. The sensitivity of the Lab-score for the identification of SBI was 94 % and the specificity 81 %. In the validation set the sensitivity of the score was 94 % and the specificity 78 %. When compared to the other parameters commonly used to
predict SBI, the Lab-score had the best accuracy associating good sensitivity and specificity. The good specificity of the Lab-score should enable its use in the decision of antibiotic treatment in a sub-population of children, without over treating those children with viral infection.
Two hundred two children were studied of whom 54 (27%) had SBI. In the multivariate analysis, only procalcitonin [odds ratio (OR): 37.6], C-reactive protein (OR: 7.8), and urine dipstick (OR: 23.2) remained significantly associated with SBI. The sensitivity of the score for the identification of SBI was 94% and the specificity 81%. In the validation set the sensitivity of the score was 94% and the specificity 78%.

Key Words: scoring system, fever without a source, serious bacterial infection

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Fever without source (FWS) in young children remains a difficult diagnostic problem, because clinical signs and symptoms are often unreliable predictors of a serious bacterial infection (SBI). Many clinical studies have addressed this problem, and the combination of a clinical evaluation associated with a total and differential leukocyte count are commonly used screening methods. The relatively poor specificity of the markers used to identify SBI, taken independently, urges physicians to give antibiotics to the majority of patients. In our study, we analyzed the predictive values of different markers in a multivariate logistic regression analysis. Our goal was to develop a simple score, which could be easily performed in the emergency room or in the office to predict SBI in a pediatric population with FWS.

MATERIALS AND METHODS

We performed a combined analysis of data collected from 2 prospectively and consecutively enrolled cohorts of children with FWS in a single university center. Both cohort studies had the same inclusion and exclusion criteria and had followed similar methodology. The study protocol was approved by the Ethical Committee of the Child and Adolescent Department, University Hospitals of Geneva. The study included all children aged from 7 days to 36 months who were consecutively admitted to the Emergency Department of the University Children’s Hospital of Geneva with a rectal temperature above 38°C and without localizing signs of infection in their history or at physical examination. Criteria of exclusion are notified in the previous studies. All children had a clinical score based on the Infant Observation Scale (IOS), a urine analysis with culture and blood drawn for white cell count, determination of C-reactive protein (CRP), procalcitonin (PCT), and culture. Lumbar puncture was performed when meningitis was suspected. The pediatric resident in charge of the patient decided which child should receive antibiotics. All children had a clinical follow-up with physical examination by a pediatrician in the following 48 hours or by a telephone contact. The diagnosis was registered at the end of the clinical follow-up. Technical laboratory determinations and definition of SBIs: bacteremia, pyelonephritis, lobar pneumonia, bacterial meningitis, and criteria of benign infection are described elsewhere.

Statistics. The study population was divided by stratified randomization in a derivation set (2/3) and a validation set (1/3). The sensitivity, specificity, negative, and positive predictive values for the detection of a SBI were determined in the derivation set for the different laboratory parameters using the cutoff points derived from our previous studies. Univariate logistic regression was performed considering the dichotomized predictive parameters as independent values and SBI as the outcome value. Then, parameters significantly

A SCORE IDENTIFYING SERIOUS BACTERIAL INFECTIONS IN CHILDREN WITH FEVER WITHOUT SOURCE

Annick Galetto Lacour, MD, Samuel A. Zamora, MD, and Alain Gervaix, MD

Abstract: The objective of the study was to develop a simple clinical tool to identify serious bacterial infection (SBI) in children with fever without a source. For each child, a clinical assessment, a white blood cell count, a urine analysis, a determination of C-reactive protein, procalcitonin, and appropriate cultures were performed.
associated with SBI were entered forward stepwise into a multiple regression model and only those remaining independently significantly (P < 0.05) associated with SBI were retained. For ease of use in the clinical setting, we then created a Laboratory-score using only the predictive variables independently associated with SBI. The sensitivity, specificity, and predictive values of the Laboratory-score were determined in the derivation set and in the validation set.

RESULTS

Two hundred twenty-two children were consecutively included from March 1998 to February 2002. Twenty children were excluded. The data of 202 children were analyzed. The final diagnosis was: SBI in 54 children (27%) (7 bacteremia, 40 pneumonia, 5 lobar pulmonary condensation, 1 retropharyngeal abscess, and 1 mastoiditis), benign focal infection in 26 children (13%) (cystsitis, acute otitis media, adenitis, Campylobacter gastroenteritis), and probable viral infection in 122 children (60%) (negative culture and no signs for focal infection at clinical follow-up). One hundred thirty-four of 202 (66%) of the children received antibiotics. The study population was divided in a derivation set (n = 135) and a validation set (n = 67). The 2 sets were comparable in terms of age, fever, incidence of SBI, clinical observational scores, and laboratory parameters. The sensitivity, specificity, and predictive values for the different parameters associated with SBI are listed in Table 1.

Logistic regression was performed in the logistic regression with variables potentially associated with SBI. PCT (odds ratio (OR)) 35.6 showed the strongest association followed by CRP (OR: 12.9), urine dipstick (OR: 9.7), and leukocytosis (OR: 3). Left shift and IOS score were not statistically associated with SBI.

Then PCT, CRP, urine dipstick, and leukocytosis were entered into a forward stepwise multiple logistic regression model to identify independent predictor of SBI. The PCT value remained the most significant predictor of SBI (OR: 37.6; 95% CI: 5.8–243). The other variables independently associated with SBI in this analysis were CRP (OR: 7.8; 95% CI: 2.304) and urine dipstick (OR: 23.2; 95% CI: 5.4–104.8). Leukocytosis was not independently associated with the occurrence of SBI (P = 0.49).

Laboratory Score. Based on the results of the logistic regression analysis, we developed a risk index score, named Laboratory-score. The relative weighting of each component variable of the Laboratory-score was based on its odds ratio in the univariate analysis. Two points were attributed to PCT or CRP above the cutoff values (0.5 mg/mL and 40 mg/L, respectively) and 4 points for values of PCT above 2 mg/mL and for CRP above 100 mg/L. One point was attributed for a positive urine dipstick (Table 2).

The performance of the Laboratory-score was then tested both on the derivation population and the validation set (Table 1). In the derivation set, the Laboratory-score (≥2) had a sensitivity of 94% and a specificity of 81%. When compared with the other parameters commonly used to predict SBI, the Laboratory-score had the best accuracy associating good sensitivity and specificity. In the validation set the Laboratory-score had similar performances with a sensitivity of 94% (95% CI: 74–99) and a specificity of 78% (95% CI: 64–87) (Table 1).

DISCUSSION

Our data showed that PCT, CRP, and urine dipstick are independent predictors of SBI in this population of children with FWS. In our study, the IOS score and left shift were not statistically different between children with and without SBI. Moreover, leukocytosis was not an independent predictor of SBI when PCT, CRP, and urine dipstick have been taken into account.

We have developed a scoring system (Laboratory-score) based on the 3 predictive variables independently associated with SBI: PCT, CRP, and urinary dipstick. The principal advantage of the Laboratory-score is its good specificity (81%) for the prediction of SBI associated with the severity of a high sensitivity (94%). The good specificity of the Laboratory-score should enable the reliable selection of children who need antibiotic treatment, without over treating children with viral infection. Based on this study, if antibiotics had solely been administered for children with a positive score, only 40% of the population would have received antibiotics. In comparison, based on the clinician's decisions, more than 65% of the studied population received antibiotics. The use of the Laboratory-score could, thus, substantially reduce antibiotic use.

Potential limitations of our study should be considered. Our study population is relatively small explaining the width of the confidence intervals around the estimates of sensitivity and specificity. The incidence of SBI (27%) in our study seems higher than reported in other studies but similar to the incidence of a recent study from Italy (23%) that analyzed comparable populations of children in a tertiary hospital. This likely reflects referral bias, as pediatricians refer ill-appearing children to our hospital for initial work-up. Because this bias

<table>
<thead>
<tr>
<th>TABLE 2. Laboratory Score</th>
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<tbody>
<tr>
<td>Predictor</td>
</tr>
<tr>
<td>PCT (mg/mL)</td>
</tr>
<tr>
<td>&lt;0.5</td>
</tr>
<tr>
<td>≥0.5</td>
</tr>
<tr>
<td>≥2</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
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<tr>
<td>&lt;40</td>
</tr>
<tr>
<td>40–100</td>
</tr>
<tr>
<td>≥100</td>
</tr>
<tr>
<td>Urine dipstick</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
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</tbody>
</table>

Possible laboratory scores range from 0 to 9.

*Positive urine dipstick: positive leukocytes, or acute test result.

<table>
<thead>
<tr>
<th>TABLE 1. Predictive Value (%) of Different Variables Between Children With and Without Severe Bacterial Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictor</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>PCT (0.5 mg/mL)</td>
</tr>
<tr>
<td>CRP (40 mg/L)</td>
</tr>
<tr>
<td>Leukocytosis (15 GL)</td>
</tr>
<tr>
<td>Left shift (1.5 GL)</td>
</tr>
<tr>
<td>Laboratory score (≥2)</td>
</tr>
</tbody>
</table>

*Cut-off level.

PPV indicates positive predictive value; NPV, negative predictive value.
affects the prevalence of SBI in our patient population, the predictive values of the Laboratory-score must be interpreted with caution, and the performance of the Laboratory-score might vary if applied to other cohorts of children. In contrast, the sensitivity and specificity of our scoring system are not affected by this potential bias. An internal validation of the score was performed on a subset of the population. However, this sample is small and the potential bias associated with our entire population remains.

In conclusion, PCT, CRP, and urine dipstick are independent predictors of SBI in this study. White blood cell count is not an independent predictor, when these 3 variables are taken into account. A Laboratory-score including PCT, CRP, and urine dipstick provides a security equivalent to the standard work-up, is easier to use, and could considerably diminish antibiotic use in children with benign infection. However, children should be carefully followed up, to identify the small proportion with SBI not initially detected by a positive score. Finally, the Laboratory-score should be prospectively validated and evaluated in different clinical settings before its use in clinical guidelines of children with FWS.

REFERENCES

Annick Galetto Lacour¹, Samuel A. Zamora¹, Barbara Andreola², Silvia Bressan², Laurence Lacroix¹, Liviana Da Dalt², Alain Gervaix¹

Validation of a laboratory risk index score for the identification of severe bacterial infection in children with fever without source

Arch Dis Child 2010;95:968-973

The success of the risk index score in our previous study could be only applicable to the particular population of patients and clinicians involved in this derivation study. Internal validation is not a guarantee for generalization of a risk index score to other populations. Therefore, we planned a study to externally validate the Lab-score. External validation aims to address the accuracy of a model in patients from a distinct but plausibly related population. The validation population must have similar inclusion and exclusion criteria but involves children from a different time period and location. For this reason, we applied the Lab-score to a large population of children with FWS enrolled in a previous Italian study conducted in a Pediatric ED. The predictive values of the Lab-score in this validation set population were comparable with those of the derivation population. The sensitivity of a score ≥ 3 was 86 % and the specificity 83 %. The AUC for the Lab-score was significantly superior to that of any single parameter. The Lab-score performed better than other laboratory markers, even when applied to children of a different age group.
Validation of a laboratory risk index score for the identification of severe bacterial infection in children with fever without source

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Validation of a laboratory risk index score for the identification of severe bacterial infection in children with fever without source

Annick Galetto-Lacour,1 Samuel A Zamora,1 Barbara Andreola,2 Silvia Bressan,2 Laurence Lacroix,1 Liviana Da Dalt,2 Alain Gervaix1

ABSTRACT

Objective The identification of severe bacterial infection (SBI) in children with fever without source (FWS) remains a diagnostic problem. The authors previously developed in their Swiss population a risk index score, called the Lab-score, associating three independent predictors of SBI, namely C reactive protein (CRP), procalcitonin (PCT) and urinary dipstick. The objective of this study was to validate the Lab-score in a population of children with FWS different from the derivation model.

Methods A prospective study, conducted in Padova, on 408 children aged 7 days to 36 months with FWS was recently published. PCT, CRP, white blood cell count (WBC) and urinary dipstick were determined in all children. The Lab-score was applied to this population and the diagnostic characteristics for the detection of SBI were calculated for the Lab-score and for any single variable used in the Italian study.

Results For the identification of SBI, the sensitivity of a score ≥3 was 86% (95% CI 77% to 92%) and the specificity 83% (95% CI 79% to 87%). The area under the receiver operating characteristic curve for the Lab-score (0.91) was significantly superior to that of any single variable: 0.71 for WBC, 0.86 for CRP and 0.84 for PCT. The Lab-score performed better than other laboratory markers, even when applied to children of different age groups (<3 months, 3–12 months and >12 months). The results obtained in this validation set population were comparable with those of the derivation set population.

Conclusions This study validated the Lab-score as a valuable tool to identify SBI in children with FWS.

What is already known on this topic

► Current US guidelines in the management of young children with fever without source (FWS) are rarely followed by paediatricians because of time constraints.

► Biological markers such as procalcitonin (PCT) and C reactive protein (CRP) have been shown to be quick and reliable predictors of severe bacterial infection (SBI).

► A risk index score of SBI associating PCT, CRP and urinary dipstick has been recently published and showed to be superior to any individual markers.

What this study adds

► This risk index score has been now validated in a large external cohort of young children with FWS.

► This risk index score of SBI is a quick and useful tool for the management of FWS in emergency departments.

In young children with fever without source (FWS), one challenge is to identify those with a severe bacterial infection (SBI) among a majority suffering from a benign viral infection. The commonly used screening method to discriminate non-toxic children at risk of SBI combines a clinical evaluation associated with laboratory variables; a white blood cell count (WBC) with differential, and a urine analysis.1–4 More recently, the determination of C reactive protein (CRP) and procalcitonin (PCT) concentrations has been reported to have a better diagnostic accuracy.5–8

However, the considerable overlap of these variables in patients with and without SBI limits their discriminative ability when applied as single predictors. We have recently developed a laboratory risk index score called the “Lab-score” combining three markers—PCT, CRP and urinary dipstick.9

METHODS

The purpose of this study was to validate the Lab-score on an external population. This population has to be comparable to the derivation set: it must have similar inclusion and exclusion criteria to those used in the derivation one. But, it
We recently developed a laboratory risk index score for SBI, called the Lab-score, based on data from 202 children aged less than 3 years with FWS.9 We classified children on the basis of their final diagnosis into two groups, patients with SBI or without SBI, and we used the same diagnostic criteria as the Italian study. Briefly, this score took into account only predictive variables independently associated with SBI in this group of children, namely PCT, CRP and urinary dipstick. The relative weight of each variable was based on the OR in univariable analysis. Two points were attributed to PCT and CRP above the cut-off values of 0.5 ng/ml and 40 mg/l, respectively, and 4 points for values of PCT above 2 ng/ml and for CRP above 100 mg/l. One point was attributed for a positive urine dipstick (ie, positive leucocyte esterase and/or positive nitrite). Consequently, Lab-score values ranged from 0 to 9 points (table 1). We calculated that a cut-off value of 5 points best differentiated children with and without SBI with a sensitivity of 94% (95% confidence interval (CI) 82% to 99%), and a specificity of 81% (95% CI 72% to 88%). To validate our Lab-score on a different population, we applied it to the data obtained from the study performed in Italy.

### Statistical analysis

We compared demographic characteristics between our population and the Italian cohort using the Mann–Whitney U test for continuous values and the Fisher’s exact test for frequencies with Stata 7.0. The diagnostic performance of the Lab-score and the other laboratory variables considered were compared using a receiver operating characteristic (ROC) analysis with MedCalc 9.5.

We determined the sensitivity, specificity and negative and positive predictive values for the detection of a SBI both for the different laboratory variables and for the Lab-score using the cut-off points derived from our previous studies.\(^{15}^{16}\)

We determined the predictive values of the Lab-score for all patients and for subsets of patients of different age groups: <3 months, 3–12 months and >12 months of age. For all variables, we also calculated positive and negative likelihood ratios.

Informed consent was obtained from the parents or legal guardians for the additional blood sampling. The study protocol was approved by the Padova Hospital Ethics Committee.

### RESULTS

Four hundred and six patients were considered for analysis. Two hundred and three (50%) were female. The median age was 9.6 months (range 0.2–36); 106 (26%) were younger than 3 months, 150 (34%) aged from 3 months to 12 months and 162 (40%) were older than 12 months.

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**Table 1: Lab-score**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ng/ml)</td>
<td></td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>0</td>
</tr>
<tr>
<td>≥0.5</td>
<td>2</td>
</tr>
<tr>
<td>≥2</td>
<td>4</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>0</td>
</tr>
<tr>
<td>40–99</td>
<td>2</td>
</tr>
<tr>
<td>≥100</td>
<td>4</td>
</tr>
<tr>
<td>Urine dipstick*</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>1</td>
</tr>
</tbody>
</table>

*Positive urine dipstick: positive leucocytes esterase or nitrite test result.
CRP, C reactive protein; PCT, procalcitonin.

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SBI was diagnosed in 92 (22.7%) children and non-SBI in 314 children. Among SBI, the main diagnoses were pyelonephritis in 50 (12.3%) and pneumonia in 24 (5.9%) children (table 2). Six (1.5%) patients had occult bacteremia. In the non-SBI group of children, the diagnoses were focal bacterial infection in 64 (16%), proved viral infection in 56 (9%) and probable viral infection in 214 (53%).

The median age and the diagnosis distribution were comparable between our derivation set population and these 406 children used as the validation set (table 2).

A higher proportion of children were seen after 24 h of the onset of fever in the Italian population compared to our original population (65% vs 46%, p<0.001).

The area under the ROC curve (AUC) for the Lab-score, 0.91 (95% CI 0.87 to 0.93), was significantly higher than the AUC for PCT, 0.84 (95% CI 0.80 to 0.87) (p=0.002), than the AUC for CRP, 0.86 (95% CI 0.82 to 0.89) (p=0.02), than the AUC for WBC, 0.71 (95% CI 0.66 to 0.75) (p<0.001) (figure 1).

The diagnostic characteristics of the Lab-score and the other laboratory variables are reported in table 3. The sensitivity of a positive score (≥3) for the identification of SBI was 86% (95% CI 77% to 92%) and the specificity 83% (95% CI 79% to 87%). The diagnostic accuracy of the Lab-score was superior to any single variable, such as WBC (sensitivity 52%, specificity 75%), procalcitonin (PCT), C reactive protein (CRP) and white blood cell count (WBC) for prediction of severe bacterial infection.

**DISCUSSION**

This study demonstrates that the Lab-score developed for young children with FWS in our population can be applied in other settings with similar study population characteristics with the same accuracy. Indeed, as we previously showed, the combination of PCT, CRP and urinary dipstick variables included in the Lab-score, is significantly superior to any single variable and to WBC count, in terms of sensitivity but also specificity and predictive values for SBI detection in children less than 3 years of age.

Even though the populations of the derivation and validation set belong to different countries, it is noteworthy how the SBI prevalence (26.7% vs 22.7%) and the diagnosis distribution are very similar: occult bacteremia (both at 1.5%), focal bacterial infection (12.8% vs 15.8%) and probable viral infection (60.4% vs 61.6%) (table 2). Having proved that the aetiology of FWS in young children is comparable in different places, at least in countries with similar socio-economic levels, the Lab-score can be applied as a useful tool for the management of these children, even in settings other than the one of origin. As the good performance of the Lab-score in the derivation set could only be due to chance, the external validation of this prediction rule is an important step to demonstrate its wider efficacy and applicability.

In this validation study, the Lab-score sensitivity was slightly lower: 86% (95% CI 77% to 92%) and the specificity slightly higher 83% (95% CI 79% to 87%) than previously reported but remained in the 95% CI of the derivation population. Although we showed that the sensitivity of the Lab-score seemed to increase with the age of the child, going from 78% in infants less than 3 months of age to 97% in those more than 12 months of age, and that the specificity decreased with age going from 90% in infants less than 3 months to 77% beyond the age of 1 year, no statistical difference could
be found between the derivation and the validation population set regarding the mean age of the studied populations who could have explained the difference of the sensitivity and the specificity between the two populations.

As we have demonstrated the validity of the Lab-score in a different setting, what could be the main advantages of its use in the management of young children with FWS? First, current published guidelines still propose to use a clinical score and the WBC as screening methods to identify SBI in non-toxic children with FWS. However, even though a trained paediatrician performs a clinical score, it remains subjective and variable with time. In contrast, the Lab-score is an objective tool that takes into account laboratory values at a specific time point. Furthermore, the predictive values of the Lab-score were considerably higher than those of WBC to identify SBI. By calculating the likelihood ratios to determine post-test probabilities, we showed that a WBC >15'000 cells/mm³ increased the probability of SBI from 23% to only 38% in the studied population, whereas a Lab-score ≥3 increased this probability from 23% to 60%. Moreover, the Lab-score performed better than WBC also for ruling out SBI (figure 2).

### Table 3: Sensitivity, specificity, positive and negative predictive and likelihood ratio values of the Lab-Score, WBC, CRP and PCT for SBI detection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab-score*≥3 (n=406)</td>
<td>86 (77 to 92)</td>
<td>83 (79 to 87)</td>
<td>60 (51 to 68)</td>
<td>95 (92 to 97)</td>
<td>5.1 (3.9 to 6.6)</td>
<td>0.17 (0.10 to 0.28)</td>
</tr>
<tr>
<td>&lt; 3 months (n=106)</td>
<td>78 (59 to 89)</td>
<td>90 (61 to 95)</td>
<td>72 (54 to 85)</td>
<td>92 (84 to 96)</td>
<td>7.7 (3.9 to 15.3)</td>
<td>0.25 (0.12 to 0.50)</td>
</tr>
<tr>
<td>3–12 months (n=138)</td>
<td>79 (62 to 90)</td>
<td>85 (78 to 91)</td>
<td>59 (43 to 73)</td>
<td>94 (87 to 97)</td>
<td>5.4 (3.3 to 8.8)</td>
<td>0.24 (0.12 to 0.50)</td>
</tr>
<tr>
<td>&gt;12 months (n=162)</td>
<td>97 (86 to 100)</td>
<td>77 (69 to 84)</td>
<td>55 (43 to 67)</td>
<td>99 (94 to 100)</td>
<td>4.2 (3.1 to 5.8)</td>
<td>0.04 (0.01 to 0.25)</td>
</tr>
<tr>
<td>WBC*≥15'000 cells/mm³</td>
<td>52 (42 to 62)</td>
<td>75 (70 to 80)</td>
<td>38 (30 to 47)</td>
<td>84 (80 to 88)</td>
<td>2.1 (1.6 to 2.7)</td>
<td>0.64 (0.52 to 0.80)</td>
</tr>
<tr>
<td>CRP* (40 mg/l)</td>
<td>73 (63 to 81)</td>
<td>81 (77 to 85)</td>
<td>53 (45 to 62)</td>
<td>91 (87 to 94)</td>
<td>3.8 (3.0 to 5.0)</td>
<td>0.34 (0.24 to 0.47)</td>
</tr>
<tr>
<td>PCT* (0.5 ng/ml)</td>
<td>75 (65 to 83)</td>
<td>76 (71 to 81)</td>
<td>48 (40 to 56)</td>
<td>91 (87 to 94)</td>
<td>3.1 (2.5 to 4.0)</td>
<td>0.33 (0.23 to 0.47)</td>
</tr>
</tbody>
</table>

*Cut-off level.
CRP, C reactive protein; LR, likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; WBC, white blood cell count.
we conclude that WBC is not a good predictor of SBI or even of bacteremia.22

Second, the good specificity of the Lab-score for the detection of SBI especially in children during the first year of life enables a reliable selection of children who need antibiotic treatment. It is actually commonly accepted that antibiotics are too often prescribed to young children with viral infections,23 and reducing antibiotic prescription is now a general goal for diminishing microbial resistance and treatment costs.24 In a recent meta-analysis on antimicrobial control strategies, studies using rapidly available ancillary tests were associated with the greatest reduction in antibiotic use25 and hospitalisation. If children in the validation set received antibiotics based on a positive Lab-score, only 33% would have been treated, compared to the 67% who were given antibiotics in the derivation population, according to clinician's decisions. The use of the Lab-score could thus substantially reduce antibiotic prescription and could achieve cost saving without compromising patient care.

Finally, if algorithms are used to select patients who are the most likely to benefit from antibiotic treatment, then they must be accurate and applicable in all medical settings where time pressure is important. If WBC count and differential can be obtained in less than 30 min in most emergency departments, they are seldom obtained in this time frame by office practitioners, who do not have skilled technicians. It is therefore not surprising that compliance with the actual guidelines is low and varies widely between private office settings and hospital emergency departments. Thus, according to many authors, the recommendations are inadequate and do favour overhospitalisation and overprescription of antibiotics.25–28 On the contrary, the Lab-score is very time-sparring since results are available in less than 20 min and it is simple to use since anyone can perform these tests without referring to an external laboratory. CRP and PCT values are obtained from less than 200 μl of blood by rapid determination tests and urine dipstick by direct reading. Moreover, the score itself is simple to calculate and easy to remember.

Potential limitations of our study should be considered. As for the derivation set population, the validation of this score has been performed in a population recruited in the emergency departments of a reference tertiary care hospital. Therefore, the incidence of SBI was high (22.7%). This bias could influence the positive and negative predictive values of the Lab-score, but not its sensitivity and specificity. As the majority of children with FWS are seen primarily by private practitioners, who refer sicker children to reference hospitals, the incidence of SBI is supposed to be lower in the general population. Thus, to extrapolate the predictive values of the Lab-score to a standard population of children with a 10% incidence of SBI, we calculated the post-test probabilities using likelihood ratios, which remain uninfluenced by the incidence of the disease. In this situation, the post-test probability would be 1.9% for a score <3, and 37% for score ≥3. However, it is necessary to further validate the Lab-score in a population of children seen in general practice to assess its feasibility, its performance and how it can influence antibiotic prescription and referral to hospital for management and hospitalisation. Furthermore, the sensitivity and specificity of the score could vary if this population of children had a different proportion of SBI than the population of reference.

In conclusion, this study validated the performance of the Lab-score on an external population and confirmed its superiority compared with WBC and to the single markers as predictor of SBI in children less than 3 years of age with FWS. However, as the sensitivity of this score is not 100%, close follow-up should be ensured in order to identify the small proportion of children with SBI not initially detected by a positive score. Using the Lab-score to identify children at risk of SBI might allow a substantial reduction in antibiotic prescription. Finally, further studies are needed to establish its performance in settings other than referral hospitals.

Competing interests None.

Ethics approval The study protocol was approved by the Padova Hospital Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Galetto-Lacour A, Gervaix A.

Identifying severe bacterial infection in children with fever without source

*Expert Rev Anti Infect Ther 2010;8:1231-7.*

This article reviewed the value of different markers in the prediction of SBI. This work calculated the positive and negative LRs of WBC, CRP and PCT in nine prospective studies in children with FWS. The results clearly suggested that CRP and PCT have better discriminative values than WBC. Despite these encouraging predictive values, a single marker will probably never be perfect. Therefore, one way to improve predictive value is the combination of different tests associating clinical and laboratory markers in prediction rules. This report discussed several clinical decision rules, which adequately assessed the probability of SBI but seem difficult to implement in practice due to their complexity. Recently, PCT, CRP and urinary dipstick were combined in a simple risk index score that displayed promising predictive value in SBI in children. This review concluded that impact analyses using these prediction rules have still to be performed to show improved quality of care in this setting.
Acute febrile illnesses are common in children under 5 years of age and the single most common indication seen by primary care practitioners and emergency physicians. In most cases, the origin of the febrile illness is a self-limiting infection, probably of viral origin. However, up to 20% of children younger than 3 years of age experience an acute febrile episode with no apparent source for their fever. Among those children with a fever without source (FWS), 10–15% of infants less than 3 months of age and 5–7% of children between 3 and 36 months old have a severe bacterial infection (SBI) [1–7], such as urinary tract infection, pneumonia, bacteremia, meningitis, or bone or joint infection. Urinary tract infections are almost always occult in children younger than 2 years of age, and occur in 3–4% of febrile boys younger than 1 year of age and in 8–9% of febrile girls younger than 2 years of age [8]. In total, 16% of white girls less than 2 years old with FWS have urinary tract infection and 7% have pneumonia [9–11]. Furthermore, Murphy et al. detected 5% occult pneumonia in children with fever but without respiratory distress, tachypnea, hypoxia or lower respiratory tract abnormalities on examination [12]. Occult bacteremia occurs in approximately 3% of children under 3 years of age with FWS and a temperature of 39°C [13–15]; however, in populations that have access to conjugated Haemophilus influenzae type b and pneumococcal vaccines this incidence has decreased to approximately 1% [16,17].

The paucity of specific signs and symptoms in young children with a FWS makes the diagnosis of these bacterial infections difficult to distinguish from viral infection. Even for experienced pediatricians the management of FWS is a challenge as the consequences of a delayed or missed diagnosis may be serious and, occasionally, fatal. It is, therefore, not surprising that the top clinical priority, recently determined by emergency physicians, is the development of clinical decision rules for the investigation of the febrile child under 36 months of age [18]. To overcome clinical uncertainty, many investigators searched for biological markers, which could accurately identify the few, but serious, bacterial infections amongst the majority of self-limiting viral infections. The ideal marker should have a high sensitivity to not miss SBI, together with a high specificity to avoid overtreating viral infections with antibiotics. It should also possess characteristics for decades, many investigators have attempted to identify clinical or laboratory markers that can accurately differentiate severe bacterial from self-limiting viral infections in young children with fever without source. Unfortunately, no perfect marker has been discovered so far. Many guidelines recommend white blood cell count as a screening marker in fever without source, whereas compelling evidence in the literature emphasizes the superior characteristics of C-reactive protein and procalcitonin. One way to improve predictive value is the combination of prediction rules of different tests for clinical and laboratory markers. Several clinical decision rules, reviewed in this article, have been suggested but seem to be difficult to implement in practice due to their complexity. Recently, procalcitonin, C-reactive protein and urinary dipstick were combined in a simple risk index score that displayed promising predictive value in severe bacterial infections in children. Ultimately, impact analyses still have to be performed to show improved quality of care in this setting.

**Keywords:** clinical decision rules • C-reactive protein • fever without source • pediatrics • procalcitonin • severe bacterial infections
such as rapid kinetics with a significant increase in the first 6–12 h after the beginning of the fever, be easy to use by medical and nurse staff, have a short running time and reasonable cost for use in emergency departments and private practices. To this aim, the white blood cell (WBC) count, C-reactive protein (CRP) and, more recently, procalcitonin (PCT) have been investigated.

Clinical decision rules for the management of young children with FWS must take into account clinical assessment, including history and biological markers of infection.

**Clinical assessment**

An assessment of the child’s overall appearance is critical. Ill-appearing children are more likely to have SBI than well-appearing children. For children who look ill, an aggressive work-up, antibiotic treatment and hospitalization are required regardless of age or risk factors. Many clinical scoring systems have been developed for predicting bacterial infection in well-appearing febrile children [19–21] but they are not widely used in practice because of a lack of sensitivity. Andreola et al. [2] have evaluated the Infant Observational Scale [20], a clinical score often proposed in the US guidelines for the management of FWS, and reported only a 38% sensitivity to detect SBI [2]. Fernandez et al. also found a similar percentage of children with irritability and feeding refusal in those with bacterial or viral infection [22]. Even though unwell appearance, high fever or parental concerns are more often associated with severe infection, several large studies have clearly demonstrated the limited diagnostic value of individual signs in FWS. This is not surprising, since uniform pathophysiological disturbance in all serious infections is unlikely.

Therefore, association of vital signs together with specific symptoms such as grunting, tachypnea or neck stiffness increase the likelihood of a severe infection [23,24]. In a prospective study, Thompson et al. reported that having one or more of the following: temperature of 39°C or higher, saturation of 94% or less, and tachycardia and/or tachypnea, was 80% (95% CI: 75–85%) sensitive and 39% (95% CI: 34–44%) specific for serious or intermediate infection [25]. This study provided comparable sensitivity to more complicated systems such as the Manchester Triage System (84% sensitive, 38% specific) [26] and the NICE traffic light system (85% sensitive, 29% specific) [101].

As clinical signs and symptoms are not highly predictive of a serious infection in young children, biological markers of infection must be considered.

**Biological markers**

One of the first markers of SBI investigated was the WBC count. It is universally available and historically considered as an indicator of serious infection when increased above 15,000/mm³ in children [27]. Algorithms commonly used to manage young infants with fever usually still include the WBC count [28–32]. However, compelling evidence in the recent literature indicates that WBC is not a reliable indicator of SBI in febrile children. Bonsu et al. retrospectively analyzed 3810 febrile infants aged less than 90 days and concluded that the WBC count had a sensitivity of 45% and a specificity of 78% at a cutoff of 15,000/mm³ and thus was not an accurate predictor of bacteremia in infants [33]. Nine prospective studies also analyzed the predictive value of WBC count as an indicator of SBI in different populations of febrile children [1–7,22,34]. In all of them, the sensitivity of WBC count to detect SBI was low, ranging from 50 to 69% and the specificity from 53 to 80% (Table 1). Pratt and Attia determined a lower sensitivity (17%) for children with less than 12 h of fever duration and higher sensitivity (82%) for those with more than 12 h of fever [3].

Numerous reports have assessed the usefulness of the CRP for detecting SBI in children with FWS. This protein is produced by liver cells in response to inflammatory stimuli. Nine prospective studies [1–7,22,34] were aimed at determining the predictive value of this marker in SBI. Apart from in one study [7], the areas under the receiver operating characteristic curve (AUC) were systematically superior for CRP compared with WBC count.

A recent systematic review analyzed the diagnostic accuracy of CRP to detect SBI in children with fever [35]. The investigators included six studies that compared the predictive values of CRP in SBI [2,4–7,34]. A total of 1040 children were included and the cutoff value for CRP varied from 20 to 70 mg/l. The pooled estimated sensitivity and specificity of CRP was 77 and 79%, respectively, with a positive likelihood ratio (LR) of 3.64 and a negative LR of 0.29. The authors concluded that CRP provided moderate and independent information for both ruling in and ruling out SBI in children with fever.

Another recent marker of bacterial infection is PCT. PCT is a 116-amino acid peptide precursor of calcitonin that is shown to be increased in patients with sepsis [36]. PCT rises slightly in viral infections but can increase 1000-fold in bacterial infections. Furthermore, PCT shows favorable kinetics with a detection threshold starting 3–6 h after bacterial challenge whereas almost 12–24 h is required for CRP to be produced and measurable in blood [37].

Five prospective trials were performed to evaluate the accuracy of PCT to predict SBI in children with FWS [1,2,4,5,22]. In this group of children younger than 36 months of age, the prevalence of SBI varied between 11 and 34% and the cutoff values of PCT determined in those studies ranged from 0.5 to 0.9 µg/l. The sensitivity of PCT to detect SBI ranged from 88 to 93%, except in the study of Andreola et al. [77%] [2] and specificity ranged from 74 to 94% except in the study of Thayyil et al. [50%] [1]. Globally, the diagnostic performance of PCT was greater than WBC count and comparable to the performance of CRP. However, in infants in whom the duration of fever was less than 12 h, the diagnostic performance of PCT was greater than that of CRP and of WBC count with an AUC of 0.93 compared with 0.69 for CRP [2,22].

Table 1 summarizes the results of nine studies collecting the data of 1743 patients on the sensitivity and specificity of WBC, CRP and PCT to detect SBI in children with FWS [1–7,22,34]. Almost all of them showed consistently better predictive value of PCT and CRP compared with WBC. In five studies using multivariate analysis [2,6,7,34,38], CRP was an independent predictor of SBI in all five, WBC only in one study and PCT was the best predictor in the two studies where it was tested.
Often, concern about comparing studies relates to the fact that the cutoff values for the same biological marker differ, impacting on the sensitivity and specificity of the test. For markers in FWS, the determination of a low cutoff value for positivity increases the sensitivity but decreases the specificity of the test. To alleviate this problem, the calculation of LRs is useful because it integrates the sensitivity and the specificity of the test in the same equation (positive LR = sensitivity/1-specificity; negative LR = 1-sensitivity/specificity). The LR indicates how many times more (or less) likely patients with the disease are to have that particular result than patients without disease. Starting from a pre-test probability of disease that is equal to the prevalence, the LR will generate a post-test probability of disease. The further LRs are from 1, the stronger the evidence for the presence or the absence of a disease. Figure 1 illustrates the positive and negative LRs of the WBC count, CRP and PCT in nine prospective studies in children with FWS. The results clearly suggest that PCT has better discrimi-

Table 1. Predictive values of white blood cell count, C-reactive protein and procalcitonin for identifying severe bacterial infections in children less than 36 months of age with fever without source.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>% SBI</th>
<th>Cutoff</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreola et al. (2007)</td>
<td>408</td>
<td>23</td>
<td>15</td>
<td>40</td>
<td>0.5</td>
<td>52</td>
</tr>
<tr>
<td>Thayyil et al. (2005)</td>
<td>72</td>
<td>11</td>
<td>15</td>
<td>50</td>
<td>0.5</td>
<td>50</td>
</tr>
<tr>
<td>Fernandez Lopez et al. (2003)</td>
<td>445</td>
<td>34</td>
<td>17</td>
<td>28</td>
<td>0.59</td>
<td>54</td>
</tr>
<tr>
<td>Pulliam et al. (2001)</td>
<td>77</td>
<td>18</td>
<td>15</td>
<td>70</td>
<td>64</td>
<td>79</td>
</tr>
<tr>
<td>Pratt and Attia (2007)</td>
<td>119</td>
<td>14</td>
<td>15</td>
<td>30</td>
<td>17/82</td>
<td>67/100</td>
</tr>
<tr>
<td>Isaacman and Burke (2002)</td>
<td>256</td>
<td>11</td>
<td>17</td>
<td>44</td>
<td>69</td>
<td>63</td>
</tr>
<tr>
<td>Berger et al. (1996)</td>
<td>138</td>
<td>24</td>
<td>15</td>
<td>20</td>
<td>52</td>
<td>83</td>
</tr>
<tr>
<td>Galetto-Lacour et al. (2001)</td>
<td>124</td>
<td>23</td>
<td>15</td>
<td>40</td>
<td>0.9</td>
<td>68</td>
</tr>
<tr>
<td>Galetto-Lacour et al. (2003)</td>
<td>99</td>
<td>29</td>
<td>15</td>
<td>40</td>
<td>0.5</td>
<td>52</td>
</tr>
</tbody>
</table>

†Results are for <12 h fever/>12 h fever.
‡×1000/mm³.
AUC: Area under the receiver operation characteristic curve; CRP: C-reactive protein; n: Number of patients; PCT: Procalcitonin; SBI: Severe bacterial infection; WBC: White blood cell count.

Identification of severe bacterial infection in children with fever

Prediction rules

Despite the promising characteristics of PCT and CRP, a unique marker will never be perfect. One way to improve predictive value is the combination of different tests in prediction rules. Independent predictors of the illness of interest are selected using logistic regression analysis or recursive partitioning, combined in a rule and tested on the population they are derived from. Then the rule must be validated on a population different from the derivation set and, ultimately, tested by an impact analysis. Several studies have attempted to combine factors in prediction rules to better predict SBI. Craig et al. evaluated 40 clinical features to construct a multivariate model to identify SBI in 15,781 febrile children younger than 5 years [24]. Their diagnostic model retained 26 clinically relevant items. The authors et al. performed multivariate analysis in this specific population and concluded that WBC count (odds ratio [OR]: 1.1), CRP (OR: 6.3) and PCT (OR: 6.6) had intrinsic predictive value for SBI but that CRP and PCT were superior predictors of SBI compared with WBC [40]. Table 2 shows the sensitivity, specificity and the AUC characteristics of WBC, CRP and PCT in children younger than 3 months of age [40-44].
concluded that the performance of their model was acceptable with an AUC between 0.8 and 0.9. However, most investigations have associated clinical and laboratory markers. Isaacman et al. and Bachur and Harper developed models from retrospective studies, using temperature, gender and age as clinical predictors of SBI and absolute neutrophil count, WBC and urinary analysis [46,47]. These models had a sensitivity ranging from 76 to 82% and a specificity ranging from 74 to 76%. Bleeker et al. also developed a prediction rule in which several clinical and laboratory predictors including CRP were retained. Results showed an AUC of 0.75 for the ‘clinical model’ and 0.83 for the ‘clinical and laboratory model’. However, the overall applicability of the rule appeared inferior with an AUC of 0.6 for the clinical model and 0.78 for the clinical and laboratory model in a second study in which 150 children were prospectively enrolled [48,49].

Overall, the models constructed by multivariate logistic regression appear to be robust and display better predictive values than single parameters. Because PCT and CRP are valuable indicators of SBI they should be implemented in new models. Therefore, in a recent publication, Galetto-Lacour et al. performed a combined analysis of data collected from two previous prospectively and consecutively enrolled cohorts of children with FWS to determine independent laboratory predictors of SBI [4,5]. In the multivariate analysis, only PCT (OR: 37.6; 95% CI: 5.8–243), CRP (OR: 7.8; 95% CI: 2–30.4) and urine dipstick (OR: 23.2; 95% CI: 5.1–104.8) remained significantly associated with SBI, whereas WBC did not. These markers were combined in a risk index score named the Lab-score. Two points were attributed to PCT and CRP if above the cutoff values (PCT: 0.5 µg/l and CRP: 40 mg/l) and four points for values of PCT and CRP if above 2 µg/l and 100 mg/l, respectively. One point was attributed for a positive urine dipstick. The study population was divided by stratified randomization in a derivation set (2/3) and a validation set (1/3). The sensitivity of the Lab-score for the identification of SBI was 94% (95% CI: 82–99) and the specificity 81% (95% CI: 72–88) in the derivation set. The sensitivity of the score was 94% (95% CI: 74–99) and the specificity 78% (95% CI: 64–87) in the validation set [38]. When compared with parameters commonly used to predict SBI, such as WBC count and CRP alone, the Lab-score proved to have better predictive value. External validation of the Lab-score was performed in a large population, different but comparable, of children with FWS enrolled in a study conducted in a pediatric emergency department.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Age (months)</th>
<th>Type of study</th>
<th>n</th>
<th>% SBI</th>
<th>WBC (15’)</th>
<th>CRP (mg/l)</th>
<th>PCT (µg/l)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bressan et al. (2010)</td>
<td>&lt;1</td>
<td>Pro</td>
<td>408</td>
<td>99†</td>
<td>25</td>
<td>15</td>
<td>20</td>
<td>28</td>
<td>48</td>
<td>88</td>
<td>0.59</td>
</tr>
<tr>
<td>Maniaci et al. (2008)</td>
<td>&lt;3</td>
<td>Pro</td>
<td>72</td>
<td>234</td>
<td>13</td>
<td>0.12</td>
<td>95</td>
<td>26</td>
<td>61</td>
<td>0.61</td>
<td>0.76</td>
</tr>
<tr>
<td>Olaciregui et al. (2009)</td>
<td>&lt;3</td>
<td>Retro</td>
<td>445</td>
<td>347</td>
<td>24</td>
<td>15</td>
<td>20</td>
<td>38</td>
<td>64</td>
<td>63</td>
<td>0.67</td>
</tr>
<tr>
<td>Hsiao et al. (2006)</td>
<td>2–4</td>
<td>Pro</td>
<td>77</td>
<td>429</td>
<td>10</td>
<td>15.7</td>
<td>20</td>
<td>52</td>
<td>100</td>
<td>79</td>
<td>0.72</td>
</tr>
<tr>
<td>Schwartz et al. (2009)</td>
<td>&lt;1</td>
<td>Retro</td>
<td>99</td>
<td>449</td>
<td>19</td>
<td>15</td>
<td>38</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Value of LR: 0.
†Children with fever <12 h.

<table>
<thead>
<tr>
<th>Ref.</th>
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<tbody>
<tr>
<td>[44]</td>
</tr>
<tr>
<td>[42]</td>
</tr>
<tr>
<td>[40]</td>
</tr>
<tr>
<td>[43]</td>
</tr>
</tbody>
</table>

Overall, the models constructed by multivariate logistic regression appear to be robust and display better predictive values than single parameters. Because PCT and CRP are valuable indicators of SBI they should be implemented in new models. Therefore, in a recent publication, Galetto-Lacour et al. performed a combined analysis of data collected from two previous prospectively and consecutively enrolled cohorts of children with FWS to determine independent laboratory predictors of SBI [4,5]. In the multivariate analysis, only PCT (OR: 37.6; 95% CI: 5.8–243), CRP (OR: 7.8; 95% CI: 2–30.4) and urine dipstick (OR: 23.2; 95% CI: 5.1–104.8) remained significantly associated with SBI, whereas WBC did not. These markers were combined in a risk index score named the Lab-score. Two points were attributed to PCT and CRP if above the cutoff values (PCT: 0.5 µg/l and CRP: 40 mg/l) and four points for values of PCT and CRP if above 2 µg/l and 100 mg/l, respectively. One point was attributed for a positive urine dipstick. The study population was divided by stratified randomization in a derivation set (2/3) and a validation set (1/3). The sensitivity of the Lab-score for the identification of SBI was 94% (95% CI: 82–99) and the specificity 81% (95% CI: 72–88) in the derivation set. The sensitivity of the score was 94% (95% CI: 74–99) and the specificity 78% (95% CI: 64–87) in the validation set [38]. When compared with parameters commonly used to predict SBI, such as WBC count and CRP alone, the Lab-score proved to have better predictive value. External validation of the Lab-score was performed in a large population, different but comparable, of children with FWS enrolled in a study conducted in a pediatric emergency department.
in Padova, Italy [2]. The characteristics of the Lab-score in this
distinct population were comparable with those of the deriva-
tion population. The sensitivity for a score of 3 or higher was
86% (95% CI: 77–92) and the specificity 83% (95% CI: 79–87).
When using the LRs to calculate the post-test probabilities, results
showed that if the Lab-score was less than 3, the risk of SBI was
decreased from 23% (pre-test probability) to 4.8% and if more
than 3, it increased from 23 to 60%. By comparison, the WBC
count (cutoff fixed at 15,000/mm³) offered very modest modifi-
cations of the post-test probabilities increasing from 23 to 38%
when superior to the cutoff, or decreasing to 16% when inferior
to the cutoff [50]. When the performance of the Lab-score was
stratified by age, a trend towards higher sensitivity (p = 0.03) and
lower specificity (p = 0.04) was associated with increasing age.

Expert commentary
Identifying SBI in young children with FWS remains a chal-
lenge for physicians for the following reasons: SBIs are relatively
rare compared with self-limiting viral infections; these infections
encompass a wide spectrum of diseases ranging from pyelone-
phritis to joint and bone infection; they are not associated with
specific signs and symptoms and are not easily distinguished with
biological markers.

In this peculiar situation of uncertainty, only the combina-
tion of clinical signs and biological markers – both independent
predictors of SBI in multivariate analysis – in clinical decision
rules will help to accurately rule in or rule out severe infections
in children.

Many guidelines still recommend the WBC count as a screen-
ning marker in FWS, whereas compelling evidence in the literature
emphasizes the better characteristics of CRP and PCT. Both CRP
and PCT are available as rapid tests (20–40 min to obtain results),
do not require trained technicians for determination and are not
more expensive than a WBC count. Furthermore, sparing antibiot-
c use and unnecessary hospitalization in children with low risk of SBI
by the use of more appropriate markers, will improve medical prac-
tice and save money. We believe that the time has come to abandon
the use of WBC count in screening algorithms in determining SBI.

Five-year view
Clinical decision rules using independent clinical or laboratory
markers of SBI in young children with FWS have been developed
recently. However, no study has combined new promising mark-
ers such as PCT with clinical signs clearly associated with spe-
cific diseases that are mainly encountered in children with FWS,
namely pyelonephritis, pneumonia and occult bacteremia. In the
next 5 years, such studies have to be performed and validated in
different populations and settings. Whether such blood tests are
always justified in children fully vaccinated with bacterial conjugate
vaccines should be evaluated to tailor treatment on an individual
basis. Finally, impact studies have to prove that these strategies can
be implemented in practice, improve the quality of care and are
cost effective. At the end of this process, new guidelines for the
management of children with FWS must be released.

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The authors have no relevant affiliations or financial involvement with any
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employment, consultancies, honoraria, stock ownership or options, expert
testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues
- Among children with a fever without source, 10–25% have severe bacterial infection difficult to distinguish initially from self-limiting
  viral infections.
- Many guidelines recommend white blood cell count as a screening marker in fever without source, whereas compelling evidence in the
  literature emphasizes the better characteristics of C-reactive protein and procalcitonin.
- Several decision rules have linked clinical and laboratory markers and assessed the probability of severe bacterial infection adequately.
- Procalcitonin, C-reactive protein and urinary dipstick were recently combined in a risk index score that displayed better predictive values
  than single parameters.
- Ultimately, impact analyses of the application of these clinical decision rules have to be performed to show improved quality of care.

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  without source. Determination of the
  predictive values of procalcitonin,
  C-reactive protein and white blood cell
  count for severe bacterial infection.
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  as identifiers of serious bacterial
  infections in children with fever without
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  bedside procalcitonin and C-reactive protein
  tests in children with fever without
  localizing signs of infection seen in a


**Large series comparing the predictive value of biological markers for the diagnosis of severe bacterial infections in febrile children.**


**First study on the development of a prediction rule associating C-reactive protein, procalcitonin and urinary dipstick.**
Identification of severe bacterial infection in children with fever


Website

101 NICE clinical guideline 47: feverish illness in children
Gervaix A, Galetto Lacour A, Gueron T, Vadas L, Zamora SA, Suter S Girardin E.

Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection.

*Pediatr Infect Dis J 2001 20 (5):507-511*

The objective of this study was to determine the accuracy of PCT and CRP rapid tests to predict renal involvement in children with febrile UTI. Fifty-four children with a proven UTI were enrolled; in which 63 % had renal involvement assessed by a Tc-DMSA renal scan conducted during the acute phase. The WBC and band form counts were not different between children with cystitis and those with pyelonephritis. The CRP (cut off: 40 mg/dL) had a sensitivity of 68 % and a specificity of 55 % while PCT (cut off: 0.5 ng/mL) had a sensitivity of 74 % and a specificity of 85 %. There was an excellent correlation between Lumitest (a quantitative test for the PCT dosage) and PCT-Q test (a rapid semi-quantitative test that can be used at the bedside of patients). Children with PCT values above the cut off had a post-test probability of having pyelonephritis at 89 % and with CRP values above the cut off, had a 72 % probability of having pyelonephritis. The PCT and CRP perform better than WBC and band form counts in the detection of renal lesion in children with UTI.
Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection

ALAIN GERVAIX, MD, ANNICK GALETTO-LACOUR, MD, THIERRY GUERON, MD, LASZLO VADAS, PHD, SAMUEL ZAMORA, MD, SUSANNE SUTER, MD AND ERIC GIRAUDIN, MD

Background. Urinary tract infection (UTI) is a common problem in children. Because clinical findings and commonly used blood indices are nonspecific, the distinction between lower and upper urinary tract infection cannot be made easily in this population. However, this distinction is important because renal infection can induce parenchymal scarring. The objective of this study was to determine the accuracy of procalcitonin (PCT) compared with C-reactive protein (CRP) rapid tests to predict renal involvement in children with febrile UTI.

Methods. PCT and CRP were measured in the blood of children admitted to the emergency room with fever, signs and symptoms of urinary tract infection and/or a positive urine dipstick analysis. Renal parenchymal involvement was assessed by a 99mTc-labeled dimercaptosuccinic acid renal scan in the acute phase of infection in all children. Sensitivity, specificity and likelihood ratios were determined for both tests.

Results. Fifty-four children with a proven urinary tract infection were enrolled: 63% had renal involvement; and 37% had infection restricted to the lower urinary tract. No difference was found for age, sex and total white blood cell count between the groups. The calculated likelihood ratios of procalcitonin and C-reactive protein rapid tests were between 3.8 and 7 and 1.5 and 2.8, respectively. A positive PCT value predicted renal involvement in 87 to 92% of children with febrile UTI, compared with 44 to 83% using CRP values.

Accepted for publication Jan. 4, 2001.
From the Department of Pediatrics, University Hospital of Geneva, Geneva, Switzerland.
Key words. Urinary tract infection, children, procalcitonin, C-reactive protein, pyelonephritis.
Reprints not available.
Conclusions. A rapid determination of procalcitonin concentration could be useful for the management of children with febrile UTI in the emergency room.

INTRODUCTION

Urinary tract infection (UTI) is a common problem in infants and children with a prevalence of 6.5% and 3.3% in girls and boys younger than 1 year of age, respectively. In childhood UTI is 2- to 4-fold more prevalent in girls than in boys, and ~5% of schoolgirls have urinary tract infection during their school years. The general route of infection of the urinary tract is ascending, and the pathogens originate from the perineal flora. Infection can be restricted to the bladder (i.e., cystitis) or spread to the kidneys to cause pyelonephritis. Infants and young children are at high risk for incurring acute renal injury, although older children can be affected as well. Cystitis is not associated with long term sequelae. Early initiation of appropriate treatment is the cornerstone of successful outcome of children with pyelonephritis as demonstrated by clinical and experimental data showing that delay in instituting antibiotics in acute upper urinary tract infection increases the risk of kidney damage. Therefore if cystitis can be treated orally with antibiotics, the parenteral route is often recommended in children with pyelonephritis.

Procalcitonin (PCT), a 116-amino acid propeptide of calcitonin, is elevated in patients with septic shock and normal in patients with noninfectious inflammatory conditions or viral infections. More interestingly Gendrel et al. showed high plasma concentrations of procalcitonin in children with invasive bacterial infections, moderate elevation in localized bacterial infections and normal values in viral infections. Our group also showed that the plasma procalcitonin concentration is correlated with the severity of renal scars in children with pyelonephritis. A new 30-min rapid semiquantitative test is now available for determining procalcitonin values and may be a useful tool at the emergency room.

The purpose of this prospective study was to determine the correlation between the quantitative and the rapid semiquantitative PCT tests and the accuracy of PCT compared with C-reactive protein (CRP) to predict renal involvement in children with febrile UTI.

PATIENTS AND METHODS

Children 1 week to 16 years old attending the Emergency Unit at the University Children Hospital of Geneva with fever (rectal temperature >38.0°C), signs and symptoms suggestive of a urinary tract infection and/or a positive urine dipstick analysis (positive leukocyte esterase and/or nitrite) were consecutively enrolled after written consent was obtained from the parents. Children who received antibiotics in the previous week were excluded from the study.

Urine samples were obtained by clean-void midstream catch, by suprapubic aspiration or by sterile collection bags and sent for culture within 1 h after standard procedures.

At admission white blood cell count, plasma C-reactive protein and procalcitonin values were determined in all children. CRP was measured in EDTA-blood samples by a rapid immunometric method (NycoCard CRP; Nycomed Pharma, Oslo, Norway) following the instructions of the manufacturer. PCT was measured quantitatively in EDTA-blood samples by an immunoluminometric assay (Lumitest PCT; Brahms Diagnostica, Berlin, Germany) in a blinded manner following the instructions of the manufacturer. PCT values were also determined by a rapid semiquantitative immunochromatographic test (Brahms PCT-Q; Brahms Diagnostica) by two observers. Briefly 200 μl of EDTA-plasma were applied to the test strip. PCT in the sample is bound by mouse anti-calcitonin antibodies conjugated with colloidal gold to form a complex. This complex moves by means of capillarity through an area containing fixed anti-calcitonin antibodies to form a sandwich complex that can be seen as a reddish band. The color intensity of the band is directly proportional to the PCT concentration of the sample.

At Days 3 to 5 renal cortical scintigraphy (CS) was performed in all children with a positive urine culture (considered positive if ≥10^6, ≥10^4, and ≥10^3 colony-forming units/ml of a urinary tract pathogen for suprapubic aspiration, midstream catch and collection bag samples, respectively). The CS was considered to be abnormal if a focal or diffuse decrease or absence of 99mTc-dimercaptosuccinic acid (DMSA) uptake was noted in at least two projections. The radiologists who interpreted CS were blinded for CRP values, PCT values and patient status. Children with abnormal CS were considered to have pyelonephritis. All children were given antibiotics intravenously until the results of the renal cortical scintigraphy. The therapy of those with normal CS was changed to oral antibiotics for a total duration of treatment of 7 days.

The protocol of this study has been accepted by the Ethical Committee of the Department of Pediatrics, University Hospital of Geneva.

Demographic characteristics and laboratory values of children with UTI were compared with the Fisher exact test for frequencies, the Mann-Whitney U test and the t-test for continuous values. P ≤ 0.05 was considered as significant.

Sensitivity and specificity for the detection of acute pyelonephritis were determined for the CRP and PCT
rapid tests, and binominal exact 95% confidence intervals were calculated. The best cutoff points of both tests were determined with a receiver operating characteristic curve. The likelihood ratio for a positive PCT or CRP test to predict an acute pyelonephritis was calculated as \( A / \text{total number of pyelonephritis} / B / \text{total number of cystitis} \), in which \( A \) is the number of pyelonephritis detections and \( B \) the number of cystitis detections in a specified range of values.\(^{15}\) The pretest probability for children with UTI to have renal involvement was considered to be 63% based on our results of positive CS. The pretest probability and the likelihood ratio were used to calculate the posttest probability.\(^{15}\)

RESULTS

Fifty-four children with proved urinary tract infection were analyzed. Eighteen were boys and 36 were girls. *Escherichia coli* was cultured as a single organism in 50 children, and *Enterococcus faecalis* was cultured in 2 children. Mixed infection with these 2 organisms was found in 2 infants. All urine cultures were negative 48 to 72 h after initiation of therapy. No UTI-associated bacteremia was recorded. Thirty-four children (63.9%) had a positive renal DMSA scan (CS) compatible with an acute pyelonephritis and 20 (37.1%) with normal CS were diagnosed as having lower urinary tract infection. Comparison of children with cystitis and those with pyelonephritis showed no statistically significant difference for age (51 vs. 27 months, \( P = 0.36 \)), sex (M/F 9/11 vs. 9/25, \( P = 0.2 \)), duration of symptoms before admission (28 vs. 32 h, \( P = 0.06 \)), white blood cell count (11.7 vs. 14.5 \( \times 10^9/L \), \( P = 0.07 \)) and band count (0.2 vs. 0.4 \( \times 10^9/L \), \( P = 0.12 \)).

Figure 1 shows the values of PCT by two assays in children with UTI. After processing blood samples in the laboratory by well-trained technicians, the Lumitest provides quantitative values of PCT, whereas Brahms PCT-Q is a rapid semiquantitative test that can be used at the bedside by physicians or nurses. No interobserver variability was noticed with this latter assay. Values of PCT are displayed in four different ranges: \(< 0.5; 0.5 \text{ to } 2; 2 \text{ to } 10; \text{ and } > 10 \text{ ng/ml} \) (threshold of detection, 0.5 ng/ml). Comparison of both methods showed a good correlation between tests. In three patients PCT quantitative values of 0.32, 0.40 and 0.43 ng/ml appeared to be slightly positive on the semiquantitative test and therefore considered in the range of 0.5 to 2 ng/ml by the two persons who performed the test. In the upper range (>10 ng/ml) the rapid test overestimated the values of PCT.

Figure 2 shows the values of CRP and procalcitonin assessed by rapid tests in children with lower and upper urinary tract infection. The median value of CRP was significantly higher in children with pyelonephritis than in children with lower tract infection (85.0 vs. 27.5 mg/dl, \( P = 0.007 \)). However, in 11 children (32.3%) with a cortical defect on renal DMSA scan, the CRP values were normal or only slightly elevated (i.e. <40 mg/dl). Furthermore CRP was frankly elevated (>40 mg/dl) in 45% (9/20) of children in whom renal cortical involvement was absent. By comparison blood PCT was below the limit of detection (<0.5 ng/ml) in 26% (9 of 34) of children with pyelonephritis and positive in 15% (3 of 20) of children with cystitis. Sensitivity and specificity of both CRP and PCT tests are shown in Table 1. However, the clinical usefulness of a diagnostic test is largely determined by the accuracy with which it identifies its target disorders and is best approached by the calculation of the likelihood ratio for specified ranges of results. With PCT-Q, the likelihood ratios were 3.8 in the range of 0.5 to 2.0 ng/ml and 7.0 for a value >5 ng/ml, predicting pyelonephritis in 87 and 92% of children, respectively. With CRP the likelihood ratios were 1.5 (range, 20 to 40 mg/dl), 0.5 (range, >40 to 80 mg/dl) and 2.8 (range, >80 mg/dl), predicting renal involvement in 71, 44 and 83% of children, respectively (Table 1).

**Fig. 1.** Comparison of blood procalcitonin values determined by a quantitative test (Lumitest) and a semiquantitative test (Brahms PCT-Q) in 54 children with febrile UTI. ●, positive cortical scintigraphy; ○, negative cortical scintigraphy.

**Fig. 2.** Quantitative determination of CRP and semiquantitative determination of PCT concentrations in blood of children with cystitis (negative CS) and acute pyelonephritis (positive CS). \( P \) values were determined using Fisher’s exact test for frequencies.
TABLE 1. Sensitivity, specificity and likelihood ratios of PCT and CRP rapid tests in children with pyelonephritis

<table>
<thead>
<tr>
<th>Range</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio</th>
<th>Probability of Pyelonephritis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT:Q (≥0.6 ng/ml)</td>
<td>74</td>
<td>86</td>
<td>4.0</td>
<td>83</td>
</tr>
<tr>
<td>&lt;0.5 ng/ml</td>
<td>(55.0–77.1)</td>
<td>(62.1–96.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.5–2 ng/ml</td>
<td>88</td>
<td>95</td>
<td>3.82</td>
<td>87</td>
</tr>
<tr>
<td>&gt;2.0 ng/ml</td>
<td>68</td>
<td>76</td>
<td>7.6</td>
<td>92</td>
</tr>
<tr>
<td>CRP (≥40 ng/dl)</td>
<td>55</td>
<td>1.61</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>0–20 mg/dl</td>
<td>(49.5–32.5)</td>
<td>(31.5–76.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20–40 mg/dl</td>
<td>0.69</td>
<td>1.37</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>&gt;40–80 mg/dl</td>
<td>0.47</td>
<td>1.41</td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>&gt;80 mg/dl</td>
<td>2.79</td>
<td>1.39</td>
<td></td>
<td>83</td>
</tr>
</tbody>
</table>

* Cutoff determined by receiver operating characteristic curve analysis.
† Numbers in parentheses, 95% confidence interval.

DISCUSSION

The distinction between lower and upper urinary tract infection is important because renal involvement can induce parenchymal scarring that may lead to arterial hypertension and chronic renal failure.16 In this study we used a very sensitive technique to assess renal parenchymal involvement. DMSA renal scan (CS) performed during the acute phase of infection showed that 63% of children had parenchymal defects. These results are in accordance with two studies in which 67.0% and 61.9% of infants and children with symptomatic febrile UTI had renal involvement4,17 and they confirm that infection of the lower tract spreads to the upper tract and kidneys more frequently than expected in children. In one study CS performed 2 to 3 months after the acute episode showed the presence of renal scars in two-thirds of children.4

We tried to find out a blood marker that could correlate with CS. We showed in a previous study that PCT, determined by an immunoluminometric quantitative test, was elevated in children with acute pyelonephritis and often normal in cystitis.12 A new rapid semiquantitative test for PCT has become available and could be a useful tool at the emergency room for the management of UTI. In our study blood samples were tested with both methods, and results showed an excellent correlation. No determination above 0.5 ng/ml with the quantitative test was below the threshold of detection (0.5 ng/ml) of the rapid test. By contrast three samples were just below 0.5 ng/ml with the quantitative assay but slightly positive with the rapid test for both observers, suggesting that the rapid test does not lead to more false negative results than the immunoluminometric test.

Among 34 children with renal parenchymal involvement, 25 (73.5%) had elevated PCT values and 9 had normal values. This could be the result of the lag between PCT determination and CS examination in children who came early to medical attention after the onset of symptoms. During this interval and despite antibiotic treatment, the inflammation induced by the infection can progress and lead to proximal tubular dysfunction, resulting in CS abnormality. This hypothesis is supported by the fact that 7 of the 9 children with normal PCT values had symptoms lasting for 12 h or less before consultation. Another clue comes from the results of a previous study showing that when the renal lesions were graded, normal or low PCT values were associated with very mild or mild lesions,12 suggesting the possibility that diagnosis and treatment were prompt.

For clinicians the usefulness of a diagnostic test is largely determined by the accuracy with which it identifies its target disorders. This is best approached by the calculation of the likelihood ratio,15,19 which depends on the sensitivity and the specificity of the test for specified ranges of values. With PCT-Q any positive results predicted pyelonephritis in 87 to 92% of children with febrile UTI. The higher the PCT value the better was the positive predictive value. By contrast CRP gave a different pattern. For example children with a CRP value ranging from 20 to 40 mg/dl had a probability of renal involvement of 71%, whereas those with CRP values between 40 and 80 mg/dl had a probability of only 44%. Although these findings may be the result of the small number of patients in each range of values, the absence of a good correlation between increased CRP values and increased risk of pyelonephritis makes this test difficult to interpret in children with febrile UTI. Also the prediction of these tests may differ in other situations in which the prevalence of pyelonephritis is different.

In conclusion although larger studies may be needed, these data demonstrate that the new semiquantitative rapid test for the measurement of blood procalcitonin values could be useful for the management of children with febrile UTI.

REFERENCES

2. Hoherman A, Chao HP, Keller DM, Hickey R, Davis EW,


IV) Conclusion and future development:

Fever without source:

*Resolution of the clinical case:*

Which laboratory test would be a good screening test to exclude SBI in a 4 month old baby with high fever without focus?

We have chosen to perform PCT and CRP dosage combined with a urinary dipstick. The PCT level was 1.2 ng/ml and the CRP dosage was 80 mg/L.

There was no leucocyturia on the urinary dipstick. We then decided to complete our work-up and we performed blood culture, urinary culture and CSF culture and we decided to administer intravenous cefuroxime until the culture results became available. After 24 hours, the blood culture was positive for Streptococcus pneumoniae. The baby became afebrile after three days of treatment and recovered with no further complications.

It was decided to use PCT and CRP as screening tests to evaluate the risk of SBI in this baby because review of the literature, including our studies, conclude that inflammatory markers such as PCT and CRP perform constantly better than the traditional markers (WBC). It is perhaps time to consider abandoning the use of WBC as a screening test for SBI.

We showed that the association of PCT and CRP dosage with urinary dipstick, combined in the Lab-score, had the best accuracy compared to all other single markers. We have demonstrated the superiority of this risk index score in two different independent populations with post-test probabilities close to 2 % with a negative score and of more than 60 % for a positive score\(^{70, 71}\).
However, we have to remind that these laboratory tests will never replace the clinical assessment, first of all to identify the ill appearing child who requires immediately a septic work-up with antibiotic treatment. Besides, the physical examination may reveal the source of infection and may decrease the need for additional testing. Moreover, no test or combination of tests have 100 % sensitivity; for this reason a close follow-up of the febrile children is required, in order to identify children with SBI not initially detected by a positive score.

Furthermore, caution must be drawn to the generalization of the good performance of the Lab-score to all population of children. The studies analyzing the performance of the Lab-score have been performed in populations recruited in the emergency departments of reference tertiary care hospitals. Therefore, the incidence of SBI was high (close to 25%). This bias could influence the positive and negative predictive values of the Lab-score, but not its sensitivity and specificity. As the majority of children with FWS are seen primarily by private practitioners, who refer sicker children to reference hospitals, the incidence of SBI is supposed to be lower in the general population. Thus, to extrapolate the predictive values of the Lab-score to a standard population of children with a 10% incidence of SBI, we calculated the post-test probabilities using likelihood ratios. The post-test probability in this standard population would be less than two percents for a negative score and approximately 40 % for a positive score.

Therefore, to confirm the security and the usability of the Lab-score, we have to perform an impact analysis. This final development step of a prediction rule: the impact analysis, requires that the risk index score is applied to an interventional study where patients are randomized to the application or not of the predictive rule and that follow-up of all relevant outcomes is documented. We randomize children with FWS
into two groups. In the first group, we perform the traditional work up, ie. WBC with differential, CRP and urinary dipstick. In the second group only the Lab-score (PCT, CRP and urinary dipstick) is performed. We will then compare the prediction of SBI in these two groups (sensitivity, specificity and LR) and the rate of antibiotic prescription. The aim of this study is to prove the advantage of the use of a risk index score in clinical practice. Initially, we must evaluate if the sensitivity of the score is sufficient to securely identify those children at risk of SBI. Secondly, we would evaluate if, in the case of good score specificity, the prescription of antibiotics could be lowered. In our previous study, if children had received antibiotics based on a positive Lab-score, only 33% would have been treated, compared to 67% who actually received antibiotics, according to the clinician’s final decision\textsuperscript{70, 71}. This interventional study started in August 2010. We hope this study will confirm the usefulness of the Lab-score in reducing antibiotic prescription and therefore achieve economic savings without compromising patient’s care. At last, it would be necessary to further validate the Lab-score in a population of children seen in general practice to also assess its feasibility and its performance in this population.

**Urinary tract infections:**

The PCT and CRP have proved to be reliable markers of renal involvement in UTI. About 30 % of children with UTI will be diagnosed with VUR which could result in recurring UTI and renal scarring. Pediatric societies have thus recommended that all young children undergo a cystography after their first febrile UTI. This systemic
strategy is responsible for many unnecessary cystography examinations, which is a painful and not without risk procedure with non-negligible irradiation to the child. In opposition to this strategy, some guidelines have currently recommended not to perform cystography after a first febrile UTI \(^{138}\). These new guidelines have raised concerns and therefore an intermediate evidence-based strategy would be useful for the prediction of high grade VUR. It would limit unnecessary cystography without missing patients with VUR. We have confirmed a positive correlation between PCT levels and the presence and grade of VUR in a European multicentric study \(^{100}\). We are now aiming to validate the use of PCT as a predictor of high grade reflux independently of early renal lesion \(^{139}\) (Submitted). We are also expecting to derive a clinical decision rule in order to predict high-grade VUR using a prediction rule which would associate PCT and the presence of ureteral dilatation on ultrasonography \(^{140}\) (Submitted).

**Meningitis:**

Distinguishing between bacterial and aseptic meningitis is challenging in the pediatric ED. In order to predict accurately those children at risk of BM will be helpful to safely avoid unnecessary hospitalisations and reduce antibiotic treatment when not required. Studies reporting physician attitudes have shown that at least 20% of children with meningitis are not treated with antibiotics \(^{141}\). This means that implicit criteria are used to decide when not to treat. But it is essential to validate those predictors of BM to help in the decision of withholding antibiotics in the case of aseptic meningitis. PCT has been shown to be the best single biological predictor to distinguish between bacterial and aseptic meningitis \(^{105, 109}\). A clinical decision rule including PCT: the Meningitest has been developed and internally validated \(^{117}\). We have recently
externally validated this rule using a large cohort of children\textsuperscript{118, 142}. As a final step in the validation process of a clinical decision rule, we need to plan a large prospective multicenter clinical trial. In this study, children with meningitis will be randomized into two groups. For the first group the decision to treat children with antibiotics will be based on the Meningitest and for the second group, the decision will be based on traditional management strategies of meningitis. Using the Meningitest, we hope to reduce antibiotic prescription and the rate of hospitalization, none the less without missing those children with BM.

**Pneumonia**

To evaluate the predictive values of a marker, the etiologic agent of the pneumonia must be determined accurately. This remains a difficult challenge in children. We have prospectively enrolled 99 children with pneumonia, in whom, we performed an extensive work-up to determine the etiological diagnosis: viral and bacterial culture (blood, pleural fluid, naso-pharyngeal aspirate), multiple viral and pneumolysin PCR (blood and naso-pharyngeal aspirate) and serology to numerous antigens\textsuperscript{143, 144}. After having established a clear diagnosis for these children, we intend to analyse the predictive value of inflammatory markers in differentiating between bacterial and viral etiology. If inflammatory markers do prove to be good predictors in the etiology of pneumonia, we could thus plan, as a next step, an interventional study. It would be designed as a prospective study, with randomization of children into two groups. In the first group, the antibiotic prescription would be based on inflammatory markers and in the second, the prescription would be based on traditional clinical decision strategies. The security and the rate of antibiotic prescription will again be compared between the two groups.
Conclusion

It is crucial to establish actual clinical practice on evidence based medicine. However, the current management of febrile children is not always established using this foundation. For example, in children with FWS, the current guidelines recommend to prescribe antibiotics when leucocytosis is superior to 15 G/L despite the fact that leucocytosis is not considered a good predictor of SBI. Moreover, for children with a first UTI, clinical practice differs in pediatric centers ranging from performing cystography in all children to no children. In the case of meningitis, the decision to withhold antibiotics is often based on implicit variables. Finally, for children with radiological pneumonia, the decision not to treat a pneumonia is often based on a “clinical impression” of viral pneumonia, without consideration that CRP may or may not be a good predictor of bacterial pneumonia.

In conclusion, we expect that these promising projects will promote the application and the correct utilization of these inflammatory markers in the clinical practice using an evidence based approach. The objective is to identify children at risk of bacterial infection with the utmost security and to avoid unnecessary antibiotic prescription and reduce the number of hospitalisation of children with viral infection. These new guidelines could not only save financial resources but also limit the antibiotic resistance of bacteria. We hope that these future studies will clarify these statements. And finally, we must not forget that the ultimate goal of these multiple studies is to improve the health of children.
Figure 1: Algorithm for the management of a previously healthy child (3 to 36 months) with fever without source

# Table 1: Predictive values of WBC, CRP and PCT for identifying severe bacterial infections in children < 36 months with fever without source

<table>
<thead>
<tr>
<th>Study</th>
<th>N°</th>
<th>%SBI</th>
<th>Cut-off WBC (G/L)</th>
<th>Cut-off CRP (mg/L)</th>
<th>Cut-off PCT (µg/L)</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>ROC</th>
<th>WBC</th>
<th>CRP</th>
<th>PCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreola (1) 2007</td>
<td>408</td>
<td>23</td>
<td>15</td>
<td>40</td>
<td>0.5</td>
<td>52</td>
<td>71</td>
<td>73</td>
<td>76</td>
<td>81</td>
<td>76</td>
</tr>
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<td>Thayyil (3) 2005</td>
<td>72</td>
<td>11</td>
<td>15</td>
<td>50</td>
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<td>75</td>
<td>88</td>
<td>53</td>
<td>69</td>
<td>50</td>
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<td>Fernandez (21) 2003</td>
<td>445</td>
<td>34</td>
<td>17</td>
<td>28</td>
<td>0.59</td>
<td>54</td>
<td>78</td>
<td>91</td>
<td>76</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>Pulliam (22) 2001</td>
<td>77</td>
<td>18</td>
<td>15</td>
<td>70</td>
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<td>64</td>
<td>79</td>
<td></td>
<td>67</td>
<td>91</td>
<td></td>
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<tr>
<td>Pratt* (4) 2001</td>
<td>119</td>
<td>14</td>
<td>15</td>
<td>30</td>
<td></td>
<td>17/82</td>
<td>67/100</td>
<td>67/69</td>
<td>74/63</td>
<td>0.37/0.85</td>
<td>0.68/0.92</td>
</tr>
<tr>
<td>Isaacman (6) 2002</td>
<td>256</td>
<td>11</td>
<td>15</td>
<td>44</td>
<td></td>
<td>69</td>
<td>63</td>
<td>80</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger (7) 1996</td>
<td>138</td>
<td>24</td>
<td>15</td>
<td>20</td>
<td></td>
<td>52</td>
<td>83</td>
<td>69</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galetto-Lacour (70) 2001</td>
<td>124</td>
<td>23</td>
<td>15</td>
<td>40</td>
<td>0.9</td>
<td>68</td>
<td>89</td>
<td>93</td>
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<td>78</td>
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<td>Galetto-Lacour (71) 2003</td>
<td>99</td>
<td>29</td>
<td>15</td>
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<td>0.5</td>
<td>52</td>
<td>79</td>
<td>93</td>
<td>74</td>
<td>79</td>
<td>74</td>
</tr>
</tbody>
</table>

*results are for <12 hours fever/ > 12 hours fever, *N: number patients

WBC: white blood cell count, ROC: area under the receiver operation characteristic curve , CRP: protein-C reactive, PCT: procalcitonin
**Figure 2: Likelihood Ratio for the prediction of severe bacterial infection in children with fever without source**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreola (1)</td>
<td>2007</td>
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<td>Thayyil (3)</td>
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<td>Pratt (4)</td>
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<td>Isaacman (6)</td>
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<td>Berger (7)</td>
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<td>138</td>
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<td>Galetto Lacour (70)</td>
<td>2001</td>
<td>124</td>
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<tr>
<td>Galetto Lacour (71)</td>
<td>2003</td>
<td>99</td>
</tr>
</tbody>
</table>

**Legend:**
- **WBC:** white blood cell count
- **CRP:** protein-C reactive
- **PCT:** procalcitonin

**Value of LR:** 0


A. Galetto-Lacour, A Gervaix
Expert review of anti-infective therapy
2010;8:1231-7
Table 2: Predictive values of WBC, CRP and PCT for identifying severe bacterial infections in infants < 3 months with fever without source

<table>
<thead>
<tr>
<th>Study</th>
<th>age (months)</th>
<th>type of studies</th>
<th>N°</th>
<th>sensitivity (%)</th>
<th>specificity (%)</th>
<th>ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bressan (77) 2010</td>
<td>&lt; 1</td>
<td>pro</td>
<td>99*</td>
<td>15 20</td>
<td>28 48</td>
<td>88 93</td>
</tr>
<tr>
<td>Maniaci (2) 2008</td>
<td>&lt; 3</td>
<td>pro</td>
<td>234</td>
<td>15 0.12</td>
<td>38 64 63</td>
<td>84 84 87</td>
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<td>Olaciregui (78) 2009</td>
<td>&lt; 3</td>
<td>retro</td>
<td>347</td>
<td>15 0.5</td>
<td>52 100</td>
<td>79 29</td>
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<tr>
<td>Hsiao (5) 2006</td>
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<td>pro</td>
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<td>15 20</td>
<td>38</td>
<td>82</td>
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<td>449</td>
<td>15</td>
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</table>

*°N: number patients, *children with fever < 12 hours

WBC: white blood cell count, ROC: area under the receiver operation characteristic curve, CRP: protein-C reactive, PCT: procalcitonin
pro: prospective, retro: retrospective
Table 3: Inflammatory markers predicting renal lesions in febrile urinary tract infections as assessed by DMSA

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>study</th>
<th>°Nr</th>
<th>WBC G/L</th>
<th>CRP mg/L</th>
<th>PCT ng/mL</th>
<th>cut off sensitivity (%)</th>
<th>specificity (%)</th>
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<td>100</td>
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<td>2002</td>
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<td>0.5</td>
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<tr>
<td>Pecile (86)</td>
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<td>*</td>
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<td>0.5</td>
<td>94</td>
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<tr>
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<td>63</td>
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<td>94</td>
<td>39  23</td>
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pro: prospective, retro: retrospective VUR: vesico-ureteral reflux, °Nr:number patients, p.a.: positive association, WBC: white blood cell count, CRP: C-reactive protein, PCT: procalcitonin, *: no difference between children with and without renal lesions
Figure 3: Likelihood Ratios for the prediction of pyelonephritis in children with urinary tract infection

- **LR**: likelihood ratio
- **WBC**: white blood cell count
- **CRP**: protein-C reactive
- **PCT**: procalcitonin

* Value of LR: 0
Table 4: Predictors of bacterial meningitis

<table>
<thead>
<tr>
<th>Author</th>
<th>Ye</th>
<th>Study</th>
<th>N</th>
<th>%bac</th>
<th>cut off</th>
<th>Sensitivity(%)</th>
<th>Specificity(%)</th>
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Gram neg CFS

<table>
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<td>20 2</td>
<td>89 0</td>
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</table>

pro: prospective, retro: retrospective, Nr: number of patients, %bac: % bacterial meningitis, AUC: area under the receiver operating characteristic curve

WBC: white blood cell count, CRP: C-reactive protein, PCT: procalcitonin, C: cerebrospinal fluid, W: white blood cell count, P: protein, G: glucose

*ICU: intensive care unit, outcome: bacterial meningitis and sepsis, **meningitis with Gram stain-negative cerebrospinal fluid

*selection of patients, **mg%, □ % neutrophils

%
Figure 4: Likelihood Ratios for bacterial meningitis

LR: likelihood ratio, WBC: white blood cell count, CRP: protein-C reactive, PCT: procalcitonin, C-Prot: cerebrospinal fluid protein, C-WBC: cerebrospinal fluid WBC, * Value of LR: 0, ** Value of LR: ∞
Table 5: Description of the Bacterial Meningitis Score (BMS) and the Meningitest

<table>
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<tr>
<th>Criteria</th>
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<th>Meningitest</th>
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<td>CFS positive Gram staining</td>
<td>CFS positive Gram staining</td>
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<td>seizure</td>
<td>seizure</td>
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<tr>
<td>blood neutrophil count &gt; 10 G/L</td>
<td>purpura</td>
<td>toxic appearance</td>
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<tr>
<td>CFS neutrophil count &gt; 1000/ml</td>
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<td>CFS protein &gt; 0.8 g/L</td>
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<td>PCT &gt; 0.5 ng/ml</td>
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</tr>
</tbody>
</table>

CFS: cerebrospinal fluid, PCT: procalcitonin
VI) References


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89. Sheu JN, Chen MC, Lue KH, et al. Serum and urine levels of interleukin-6 and interleukin-8 in children with acute pyelonephritis. Cytokine 2006;36:276-82.


