Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count

Mark Hatherill, Shane M Tibby, Kim Sykes, Charles Turner, Ian A Murdoch

Abstract

Background—Procalcitonin has been advocated as a marker of bacterial infection. Objective—To evaluate diagnostic markers of infection in critically ill children, comparing procalcitonin with C reactive protein and leucocyte count in a paediatric intensive care unit (PICU).

Methods—Procalcitonin, C reactive protein, and leucocyte count were measured in 175 children, median age 16 months, on admission to the PICU. Patients were classified as: non-infected controls (43); viral infection (14); localised bacterial infection without shock (25); bacterial meningitis/encephalitis (10); or septic shock (77). Six children with “presumed septic shock” (without sufficient evidence of infection) were analysed separately. Optimum sensitivity, specificity, predictive values, and area under the receiver operating characteristic (ROC) curve were evaluated.

Results—Admission procalcitonin was significantly higher in children with septic shock (median 94.6; range 3.3–759.8 ng/ml), compared with localised bacterial infection (2.9; 0–24.3 ng/ml), viral infection (0.8; 0–4.4 ng/ml), and non-infected controls (0; 0–4.9 ng/ml). Children with bacterial meningitis had a median procalcitonin of 25.5 (7.2–118.4 ng/ml). Area under the ROC curve was 0.96 for procalcitonin, 0.83 for C reactive protein, and 0.51 for leucocyte count. Cut off concentrations for optimum prediction of septic shock were: procalcitonin > 20 ng/ml and C reactive protein > 50 mg/litre. A procalcitonin concentration > 2 ng/ml identified all patients with bacterial meningitis or septic shock.

Conclusion—In critically ill children the admission procalcitonin concentration is a better diagnostic marker of infection than C reactive protein or leucocyte count. A procalcitonin concentration of 2 ng/ml might be useful in differentiating severe bacterial disease in infants and children.

Keywords: sepsis; infection; procalcitonin; C reactive protein; leucocyte count

The non-specific nature of signs and symptoms in febrile infants and children makes the clinical differentiation of bacterial and viral infection difficult even for the experienced clinician. It may be even more problematic to identify children with severe bacterial disease, such as septicaemia or meningitis, especially if no localising signs are present.

Because the diagnosis of “possible sepsis” has implications for antibiotic usage and hospital stay, management strategies have evolved based on a combination of clinical and laboratory information. Although laboratory markers of infection might aid in differentiating the type of infection in infants and children, opinions vary on the interpretation of tests such as the leucocyte count, neutrophil count, band cell count, and C reactive protein concentration.

A polypeptide identical to a prohormone of calcitonin, procalcitonin, was initially described as a potential marker of bacterial disease by Assicot et al. Procalcitonin is almost undetectable under physiological conditions (pg/ml range), but rises to very high values in response to bacteraemia or fungaemia, and appears to be related to the severity of infection. This response can be duplicated by in vivo endotoxin administration, which results in a rapid rise in procalcitonin, paralleling that of tumour necrosis factor and interleukin 6. Several measurements in patients with bacteraemia have shown a rapid fall within 48 hours of antibiotic administration. An immunoluminometric procalcitonin assay is now commercially available (BRAHMS Diagnostika, Berlin, Germany) and values can be obtained on a routine basis within two hours of blood sampling.

Several authors have postulated that procalcitonin measurement might be superior to commonly used tests, such as C reactive protein measurement, as an aid to the early diagnosis of childhood bacterial sepsis. Others have cautioned that procalcitonin values should be interpreted with caution in the early neonatal period, because of the transient physiological rise in procalcitonin in apparently well newborns. We present a prospective observational study of markers of infection in children admitted to a paediatric intensive care unit. The diagnostic value of admission procalcitonin measurement is compared with that of C reactive protein and the leucocyte count.

Methods
Over an 18 month period, 175 children, median age 16 months (range, 0.03–193), were enrolled in the study on admission to the

Paediatric Intensive Care Unit, Guy's Hospital, St Thomas's Street, London SE1 9RT, UK
M Hatherill
S M Tibby
K Sykes
I A Murdoch

Children Nationwide Kidney Research Laboratory, Guy's Hospital
C Turner

Correspondence to:
Dr Murdoch

Accepted 23 June 1999
Table 1  The aetiology in 77 patients with septic shock

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative</td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>37</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>1</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>2</td>
</tr>
<tr>
<td>Pasteurella spp</td>
<td>1</td>
</tr>
<tr>
<td>Gram positive</td>
<td></td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>6</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>1</td>
</tr>
<tr>
<td>u Haemolytic streptococcus</td>
<td>1</td>
</tr>
<tr>
<td>Streplococcus viridans</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>1</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>2</td>
</tr>
<tr>
<td>Coagulase negative staphylococcus</td>
<td>5</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
</tr>
<tr>
<td>Fungal</td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatic abscess</td>
<td>1</td>
</tr>
<tr>
<td>Toxic shock syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1</td>
</tr>
</tbody>
</table>

paediatric intensive care unit (PICU). Forty six patients (26%) were aged less than 3 months, and 64 (37%) between 3 and 36 months. Most children (n = 156; 89%) were admitted by a PICU retrieval team, within 24 hours of hospital presentation. Patients were excluded if they had received parenteral antibiotics in the past seven days (except within the preceding 24 hours) or if they had undergone surgery.

Children were classified according to their clinical and laboratory data into one of five categories: non-infected controls—for example, toxin ingestion, trauma or seizures (n = 43; 25%); viral infection (n = 14; 8%); localised bacterial infection without shock—for example, pneumonia, tracheitis, or urinary tract infection (n = 25; 14%); bacterial meningitis/encephalitis (two patients with mycoplasma encephalitis were included in this group) (n = 10; 6%); and septic shock (n = 77; 44%). Table 1 shows the underlying aetiology in patients with septic shock.

Septic shock was defined as hypotension or poor capillary refill responding to fluid or pharmacological intervention, in the presence of hyperthermia or hypothermia, tachycardia, and tachypnoea, in addition to at least one of the following: acute mental changes, hypoxaemia, hyperlactataemia, or oliguria. In addition to these features, evidence of infection was required for final inclusion in the category of septic shock—for example, bacteriological isolate (not necessarily positive blood culture); characteristic meningococcal or staphylococcal rash; or cerebrospinal, bronchoalveolar, or peritoneal fluid profile consistent with bacterial infection. Six children (3%) who were enrolled with diagnoses of presumed septic shock, but who subsequently had no documented focus of infection, were excluded from the group analysis and evaluated separately.

On admission to the PICU, blood was sampled for routine laboratory investigations including blood culture, C reactive protein, and leucocyte count, in addition to 2 ml clotted blood for procalcitonin measurement. The procalcitonin sample was centrifuged, the serum separated, frozen at −70°C, and measured in batches by immunoluminometric assay (BRAHMS Diagnostika). Samples with procalcitonin concentrations at or above the 500 ng/ml upper limit of the assay were diluted 1/4 and repeated. Laboratory results were not available to investigators until after patient classification had taken place, although investigators were not blinded for patient outcome.

Leucocyte counts were measured by the hospital haematology laboratory, and C reactive protein was measured by enzymatic heterogeneous sandwich immunoassay (Vitros 950 analyser; Johnson and Johnson, Rochester, New York, USA) by the hospital biochemistry laboratory.

Data were analysed by sensitivity and specificity derived from the receiver operating characteristic (ROC) curve, and area under the ROC curve. Comparison between groups was made by the Mann-Whitney test, Kruskal-Wallis non-parametric analysis of variance (ANOVA), and Dunn’s test for multiple comparisons. Statistical analysis was performed using GraphPad Instat (GraphPad Software, San Diego, California, USA) and Analyse-It (Analyse-It Software, Leeds, UK). The study was approved by the hospital ethics committee and verbal consent was obtained from parents for the additional blood sampling.

Results

Table 2 shows admission procalcitonin, C reactive protein, and leucocyte count values. Procalcitonin differed significantly across the five categories of infection (p < 0.0001; Kruskal-Wallis). Procalcitonin was higher in children with septic shock compared with all other groups (p < 0.001; Dunn’s) except bacterial meningitis. Procalcitonin was significantly higher in bacterial meningitis compared with viral infection and controls (p < 0.05 and 0.001, respectively). In the subgroup of children with meningococcal disease (n = 37; 21%) admission procalcitonin was no higher (median, 104 ng/ml; range, 7.7–760) than in non-meningococcal septic shock (median, 92 ng/ml; range, 3.3–736; p = 0.32). Separate post hoc analysis of the six patients with presumed septic shock excluded from further comparison showed a median procalcitonin of

Table 2  Admission procalcitonin (PCT), C reactive protein (CRP), and leucocyte count (WCC) values for all children

<table>
<thead>
<tr>
<th></th>
<th>Septic shock (n = 77)</th>
<th>Bacterial meningitis (n = 10)</th>
<th>Localised bacterial infection (n = 25)</th>
<th>Viral infection (n = 14)</th>
<th>Non-infected controls (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (ng/ml)</td>
<td>94.6 (3.3–759.8)</td>
<td>25.5 (7.2–118.4)</td>
<td>2.9 (0–24.3)</td>
<td>0.8 (0–4.4)</td>
<td>0 (0–4.9)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>101 (3–335)</td>
<td>110.5 (32–335)</td>
<td>20 (7–213)</td>
<td>12 (7–76)</td>
<td>8 (2–47)</td>
</tr>
<tr>
<td>WCC (×109/l)</td>
<td>12.1 (0.4–83.8)</td>
<td>18.2 (2–33.5)</td>
<td>9.7 (1.4–30.4)</td>
<td>5.75 (2.5–32)</td>
<td>13.7 (2.4–25.3)</td>
</tr>
</tbody>
</table>

Values are median (range).
Procalcitonin as a diagnostic marker of infection

...across the five categories of infection (p < 0.001; Kruskal-Wallis) and was higher in septic shock compared with localised bacterial, viral infection, and controls (p < 0.01, 0.01, and 0.001, respectively), but not bacterial meningitis. However, C reactive protein did distinguish bacterial meningitis from localised bacterial and viral infection (p < 0.05 and 0.01, respectively).

The leucocyte count did not differ significantly across the five categories of infection (p = 0.39; Kruskal-Wallis).

ROC CURVES

Figure 1 shows ROC curves illustrating the sensitivity and specificity of procalcitonin, C reactive protein, and the leucocyte count for septic shock. The area under the ROC curve was 0.96 for procalcitonin, 0.83 for CRP, and 0.51 for WCC.

182.5 ng/ml (range, 5.1–500), comparable to that of the septic shock group.

C reactive protein also differed significantly across the five categories of infection (p < 0.0001; Kruskal-Wallis) and was higher in septic shock compared with localised bacterial, viral infection, and controls (p < 0.01, 0.01, and 0.001, respectively), but not bacterial meningitis. However, C reactive protein did distinguish bacterial meningitis from localised bacterial and viral infection (p < 0.05 and 0.01, respectively).

The leucocyte count did not differ significantly across the five categories of infection (p = 0.39; Kruskal-Wallis).

AGE GROUPS

Table 3 shows the area under the ROC curve for procalcitonin in all patients, infants aged less than 3 months, children aged 3–36 months, and children older than 36 months, respectively.

Table 3 Area under the ROC curve for procalcitonin in septic shock according to age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Septic shock n (%)</th>
<th>Area under ROC curve</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>77 (44)</td>
<td>0.96</td>
<td>0.93 to 0.99</td>
</tr>
<tr>
<td>&lt; 3 months</td>
<td>16 (35)</td>
<td>0.96</td>
<td>0.91 to 1.0</td>
</tr>
<tr>
<td>3–36 months</td>
<td>22 (34)</td>
<td>0.97</td>
<td>0.94 to 1.0</td>
</tr>
<tr>
<td>&gt; 36 months</td>
<td>39 (64)</td>
<td>0.92</td>
<td>0.86 to 1.0</td>
</tr>
</tbody>
</table>

CI, confidence interval; ROC, receiver operating characteristic.

ROC CURVES

Figure 1 Receiver operating characteristic (ROC) curves comparing admission procalcitonin (PCT), C reactive protein (CRP), and leucocyte count (WCC) for prediction of septic shock (all patients). The area under the curve was 0.96 for procalcitonin, 0.83 for CRP, and 0.51 for WCC.

The range of procalcitonin concentrations in children with bacterial meningitis (range, 7.2–118.4 ng/ml) overlapped that of septic shock (range, 3.3–759.8 ng/ml). Because it is clinically important to differentiate those patients from those with less serious bacterial disease, we then combined both bacterial meningitis and septic shock to form an additional category termed “severe bacterial infection”. Further analysis was performed for sensitivity and specificity in identifying children with severe bacterial infection, yielding an area under the ROC curve of 0.98 (95% CI, 0.96 to 1.0) for procalcitonin. Note that procalcitonin > 2 ng/ml also had 100% sensitivity and negative predictive value for septic shock, but with specificity and positive predictive value of only 62% and 69%, respectively.

SEVERE BACTERIAL INFECTION

The range of procalcitonin concentrations in children with bacterial meningitis (range, 2.1–118.4 ng/ml) overlapped that of septic shock (range, 3.3–759.8 ng/ml). Because it is clinically important to differentiate those patients from those with less serious bacterial disease, we then combined both bacterial meningitis and septic shock to form an additional category termed “severe bacterial infection”. Further analysis was performed for sensitivity and specificity in identifying children with severe bacterial infection, yielding an area under the ROC curve of 0.98 (95% CI, 0.96 to 1.0) for procalcitonin. Note that procalcitonin > 2 ng/ml also had 100% sensitivity and negative predictive value for severe bacterial infection, but with specificity and positive predictive value of 70% and 78%, respectively.

Discussion

The issue of differentiating patients with severe bacterial sepsis from infants and children with similar non-specific symptoms and signs has generated interest in identifying useful laboratory markers of infection.11–15 Other authors have described “unconventional” inflammatory markers such as fibronectin, interleukin 6, tumour necrosis factor, and β integrins, which have been used as research tools but not gained widespread acceptance in routine practice.26–27

Since Assicot and colleagues first proposed procalcitonin as an early marker of bacteraemia, descriptive reports of procalcitonin measurements in children have been reported.16–18,20 More recently, several authors have reported the quantitative evaluation of procalcitonin as a...
diagnostic marker of bacteraemia and fungae-
ma, quoting sensitivity and specificity ranging
from 57% to 100%, and from 50% to 100%,
respectively.19 21 22 23 24 For example, Chiesa et al
reported that an abnormal procalcitonin con-
centration identified early neonatal sepsis with
a sensitivity of 92.6% and a specificity of
97.5%.25
Interpretation of the literature dealing with
procalcitonin is complicated by variation in the
choice of the “abnormal” cut off value, and by
the diverse age range and nature of the study
populations. Previous studies have suffered
from apparent heterogeneity not only within
the study group, but also within categories
defined as “sepsis”, “distress”, “infected”,
“respiratory distress”, or even “haemodynamic
failure”.18 20 22 Because our own tertiary referral
patient population has a low yield from
pre-admission blood cultures, possibly as a
result of technical factors, it would be imprac-
tical to define septic patients only by a gold
standard of positive blood culture.31 Despite
this limitation, we stress the importance of rig-
idly defined categories of infection. In our
study we have attempted to “capture” children
with bacteraemia under the classification of
septic shock, and excluded six patients without
documented evidence of infection from further
analysis.
Objective assessment of any diagnostic
marker ideally requires a study population with
a high prevalence of disease, and although
critically ill children might not be directly
comparable with the general paediatric popula-
tion, the prevalence of bacterial sepsis is high.
Thus, we are able to compare a range of
procalcitonin cut off values using optimum
sensitivity and specificity derived from the
ROC curve.
We have shown that procalcitonin rises to
very high concentrations early in septic shock,
and that an admission procalcitonin value of
20 ng/ml might be used to distinguish children
with this condition with high sensitivity and
specificity. Because children with bacterial
meningitis appear to have procalcitonin con-
centrations similar to those in septic shock, we
may usefully identify these patients on the basis
of their admission procalcitonin. The ROC
curve illustrates the superior sensitivity and
specificity of procalcitonin compared with C
reactive protein, as a consequence of the wide
range of C reactive protein concentrations in all
categories of infection. Our data support the
view of some authors that the leucocyte count
has little value in differentiating the type of
infection in critically ill children.9 10 These
findings are based on a single admission
measurement, and we acknowledge that se-
quential testing might improve the diagnostic
value of one, or all, of these parameters.
We have shown that procalcitonin has both
greater specificity and positive predictive value
for septic shock than other commonly used
markers, both in the study population as a
whole, and for the subgroups of children aged
less than 3 months, 3–36 months, and older
than 36 months respectively. Critics might
argue that knowledge of the procalcitonin value
is unlikely to change clinical practice, because
these children are likely to receive antibiotic
treatment on the basis of clinical suspicion
alone. However, we suggest that the value of this
investigation lies not in confirming the suspi-
cion of disease, but in helping to exclude severe
bacterial disease from the differential diagnosis.
Although a diagnostic value derived from the
apex of the ROC curve indicates the optimum
combination of sensitivity and specificity, this
value might not be the most useful, because a
clinician might wish to identify all patients with
serious disease at the expense of a high false
positive rate. We point out that a procalcitonin
concentration > 2 ng/ml has 100% sensitivity
and negative predictive value, although only
62% specificity and 69% positive predictive
value, respectively, for both septic shock and
bacterial meningitis in our study population. It
follows that a procalcitonin value of 2 ng/ml
might help distinguish severe life threatening
bacterial infection from localised and viral dis-
ease in febrile children.
This raises the question of whether routine
procalcitonin measurement might be useful in
the paediatric emergency department. We sug-
gest that procalcitonin measurement has the
potential to shorten the duration of both anti-
biotic treatment and hospital stay for
febrile children. However, it remains to be seen
whether data derived from our group of
critically ill children can be applied to an acute
general paediatric population, who might differ
in aetiology, severity of disease, and timing of
presentation. Indeed, we acknowledge the need
for further evaluation of procalcitonin in the
emergency department setting, but point out
that the low prevalence of severe disease in
these children would require a large multicen-
tre study population.
Procalcitonin measurement might provide the
clinician with a useful addition to currently
available investigations, although given the poor
performance of the leucocyte count, and to a
lesser extent C reactive protein, it might even be
argued that the routine use of these tests is moti-
vated more by low cost, easy availability, and
historical practice rather than diagnostic value.
CONCLUSION
The admission procalcitonin concentration has
better sensitivity, specificity, and predictive
value for septic shock than either C reactive
protein or the leucocyte count. The admission
leucocyte count has no value in differentiating
the type of infection in critically ill children.
Procalcitonin measurement might be a useful
additional tool for the diagnosis of severe bac-
terial disease in infants and children.

1 McCarthy PL, Sharpe MR, Spiesel SZ, Dolan TF, Forsyth
BW, DeWitt TG. Observation scales to identify serious ill-
2 Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH,
Powell KR. Practice guideline for the management of infants
and children 0 to 36 months of age with fever without with-
3 Winder KR, Canin KK, Bass JW. A survey about management
of febrile children without source by primary care
4 Lars TA, Schwartz JS, Jaffe DM, Fleisher GR. Strategies for
diagnosis and treatment of children at risk for occult
bacteraemia: clinical effectiveness and cost-effectiveness. J
Procalcitonin as a diagnostic marker of infection

Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leucocyte count

Mark Hatherill, Shane M Tibby, Kim Sykes, Charles Turner and Ian A Murdoch

Arch Dis Child 1999 81: 417-421
doi: 10.1136/adc.81.5.417

Updated information and services can be found at:
http://adc.bmj.com/content/81/5/417

These include:

References
This article cites 31 articles, 4 of which you can access for free at:
http://adc.bmj.com/content/81/5/417#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Meningitis (197)
Infection (neurology) (287)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/