Diagnostic accuracy of G-CSF, IL-8, and IL-1ra in critically ill children with suspected infection

Abstract Objective: To elucidate the diagnostic accuracy of granulocyte colony-stimulating factor (G-CSF), interleukin-8 (IL-8), and interleukin-1 receptor antagonist (IL-1ra) in identifying patients with sepsis among critically ill pediatric patients with suspected infection.

Design and setting: Nested case-control study in a multidisciplinary neonatal and pediatric intensive care unit (PICU). Patients: PICU patients during a 12-month period with suspected infection, and plasma available from the time of clinical suspicion (254 episodes, 190 patients).

Measurements and results: Plasma levels of G-CSF, IL-8, and IL-1ra. Episodes classified on the basis of clinical and bacteriological findings into: culture-confirmed sepsis, probable sepsis, localized infection, viral infection, and no infection. Plasma levels were significantly higher in episodes of culture-confirmed sepsis than in episodes with ruled-out infection. The area under the receiver operating characteristic curve was higher for IL-8 and G-CSF than for IL-1ra. Combining IL-8 and G-CSF improved the diagnostic performance, particularly as to the detection of Gram-negative sepsis. Sensitivity was low (<50%) in detecting Staphylococcus epidermidis bacteremia or localized infections.

Conclusions: In this heterogeneous population of critically ill children with suspected infection, a model combining plasma levels of IL-8 and G-CSF identified patients with sepsis. Negative results do not rule out S. epidermidis bacteremia or locally confined infectious processes. The model requires validation in an independent data-set.

Keywords Intensive care, newborns · Granulocyte colony-stimulating factor · Interleukin-8 · Interleukin-1 receptor antagonist · Logistic regression models

Introduction

Premature infants, term newborns, and critically ill children are at increased risk of sepsis [1, 2, 3]. Early diagnosis is impeded because noninfectious processes, such as low cardiac output syndrome, trauma, major surgery, and neonatal respiratory distress can mimic the onset of sepsis [4, 5, 6]. Microbiological results are usually not available at the time of initial assessment. Extensive use of empirical antimicrobial therapy is common [7].

Several biological markers with variable sensitivity and specificity have been evaluated to improve the early diagnosis of sepsis [8, 9, 10]. Among the most promising parameters for increasing diagnostic accuracy are granu-
locyte colony-stimulating factor (G-CSF), interleukin-8 (IL-8), and interleukin-1 receptor antagonist (IL-1ra) [11, 12, 13]. It has been claimed that measurement of IL-1ra even allows diagnosis to be advanced by up to 48 h [11]. However, many of the encouraging data have been obtained from selected populations of infants [11] or after excluding surgical cases [12].

It remains unknown whether these favorable findings can be extended to the more heterogeneous population encountered in pediatric intensive care, which includes surgical and trauma patients. Therefore we compared the diagnostic properties of IL-8, G-CSF, and IL-1ra determinations in identifying patients with sepsis among a heterogeneous group of pediatric intensive care patients who were clinically suspected to have infection.

**Methods**

**Patient population and setting**

The population comprised all infants and children admitted during a 12-month period to the level III multidisciplinary neonatal and pediatric intensive care unit of a tertiary referral center. The unit serves a population base of approximately 3 million and provides postoperative care after major pediatric or neonatal surgery including cardiac surgery, treatment for children with severe trauma or medical conditions, and for outborn neonates with critical illness.

**Study design**

We prospectively followed a cohort of critically ill patients to enroll all episodes of illness in which clinicians suspected infection. During these episodes we performed nested case-control analyses using a stringent and a broadened definition of sepsis. For the primary analysis we used plasma samples obtained simultaneously with a diagnostic sepsis-workup. In a secondary analysis we evaluated plasma samples collected 1 day prior to clinical suspicion of sepsis to test whether cytokine measurement allows advancement of diagnosis, as suggested by Kuster and coworkers [11]. The study was approved by the institutional review board, who permitted the additional diagnostic assays on plasma obtained for routine laboratory tests.

**Inclusion and exclusion criteria**

Patients with suspected bacterial infection were eligible. Clinically suspected bacterial infection was defined as the presence of an explicit statement to that effect in the patient’s records plus the initiation of a standard diagnostic workup to rule out infection (including two sets of blood cultures), and/or the initiation of empirical antibiotic therapy. Patients with long-term hospitalization could contribute more than one episode, provided each occasion of clinical suspicion (onset of episode) was at least 10 days apart and antibiotic treatment was discontinued for at least 72 h before the onset of the next episode. Episodes were excluded from the analysis when waste plasma obtained at diagnostic workup for suspected infection yielded less than 85 µl. For the primary analysis only results from plasma samples obtained in parallel to blood cultures drawn at the time of clinical suspicion of infection or within 2 h were used. We also excluded episodes of patients admitted with a proven localized viral infection (e.g., Respiratory syncitial virus).

**Specimen collection and cytokine determination**

All plasma samples were refrigerated at -80°C within 6 h of collection. Samples were thawed once for cytokine determination and all cytokines were determined within 8 h after thawing (parallel assays). Cytokines were measured using commercially available enzyme-linked immunosorbent assays (ELISA, R&D Systems, Abingdon, UK). Blood cultures were processed on automated analyzers (Bactec: 9240, Becton Dickenson, Fullerton, Calif., USA). C-reactive protein was determined using a turbidimetric assay analyzer (Beckman Synchron CX5, Beckman Instruments, Fullerton, Calif., USA).

**Table 1** Patient characteristics of 254 episodes of suspected infection

<table>
<thead>
<tr>
<th>Category</th>
<th>Episodes/patients</th>
<th>Female gender: episodes</th>
<th>Age: mean (years)</th>
<th>Age: median/interquartile range (years)</th>
<th>Length of stay: median/interquartile range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes/patients</td>
<td>254/190</td>
<td>91 (36%)</td>
<td>2.8±4.3</td>
<td>0.69/0.03–3.6</td>
<td>7/4–16</td>
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<tr>
<td>Admission diagnosis</td>
<td></td>
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<tr>
<td>Postoperative care after cardiac surgery</td>
<td>68 (27%)</td>
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<tr>
<td>Postoperative care after other major surgery</td>
<td>37 (15%)</td>
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<td>Trauma</td>
<td>18 (7%)</td>
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<td>Suspected infection</td>
<td>30 (12%)</td>
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<td>Respiratory failure</td>
<td>48 (19%)</td>
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<td>Circulatory failure</td>
<td>28 (11%)</td>
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<td>Neurological disorders</td>
<td>13 (5%)</td>
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<td>Monitoringa</td>
<td>10 (4%)</td>
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<tr>
<td>Others</td>
<td>2 (1%)</td>
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<tr>
<td>Outcomes</td>
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<tr>
<td>Discharged alive: episodes/patients</td>
<td>232/170</td>
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<tr>
<td>Death: episodes/patients</td>
<td>22/20</td>
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</tr>
</tbody>
</table>

a Patients admitted for cardiac catheterization, decannulation from tracheostomy, or adjustment of home ventilation

**Patient population**

During the study period 775 patients were admitted to the unit. In 347 patients (46%) clinicians suspected 461 episodes of bacterial infection. Sufficient plasma from the sample obtained at suspicion of infection was available in 254 episodes (56%), which were contributed by 190 patients. An average of 2.9±1.1 samples were measured per patient. Twenty-seven episodes (11%) were classified as sepsis with positive blood culture and served as cases when the stringent case definition was applied. A further 27 episodes were classified as probable sepsis (negative blood cultures). Of the 25 episodes considered as localized infection without major systemic manifestation 15 were due to ventilator-associated pneumonia. The 130 episodes classified as no infection (50%) included 58 (45% of 130) episodes in which patients developed fever of unknown origin after surgery. Among the 45 episodes deemed to be unclassifiable, there were 8 episodes with a Gram-positive isolate for Staphylococcus epidermidis, S. sanguis, or S. hominis in which only one set of blood cultures was drawn from indwelling lines. Table 1 summarized the characteristics of the study population. Systemic antibiotic therapy was initiated at suspicion of infection in 215 episodes (85%) and within 24 h thereafter in a further 29 episodes (11%).