Title:  Sepsis Management in Pediatric Patients: A Review of the Guidelines

Date:  31 July 2008

Context and policy issues:

Sepsis is defined as infection plus systemic manifestations of infection, such as fever, hypothermia, hypotension, tachycardia, tachypnea, leukocyte abnormalities, and mental status change (i.e. lethargy, difficulty in consoling the child). Young children are vulnerable to sepsis because the immune system is not fully developed. Severe sepsis (defined as sepsis plus sepsis-induced cardiovascular dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions, or tissue hypoperfusion) and septic shock (defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation) form a leading cause of death in children and have an overall associated pediatric mortality rate of 8-10%. In addition, bacterial sepsis is a major problem in the newborn unit. Approximately 10% of all neonates admitted to neonatal intensive care unit are treated with antibiotics for suspected sepsis.

In this report, evidence of sepsis management, including diagnosis, monitoring and treatment, are examined in pediatric patients.

Research question:

What are the guidelines or protocols for the detection, treatment and management of sepsis in pediatric patients?

Methods:

A limited literature search was conducted on key health technology assessment resources, including Medline and Embase through the Ovid platform, The Cochrane Library (Issue 2, 2008, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and the present, and are limited to English language publications only. Filters were applied to limit the retrieval to guidelines and systematic reviews.
In this report, evidence from systematic reviews and clinical practice guidelines were requested. In total, there were three clinical practice guidelines and seven systematic reviews identified.

**Summary of findings:**

Three evidence-based guidelines were identified. Among them, the 2008 guideline by Dellinger and coworkers is an update of the 2004 version. Details of the identified clinical practice guidelines are presented in Table 1.

In the Canadian Paediatric Society guideline, evidence of management of infants at increased risk for sepsis was retrieved through a systematic literature search and evaluated. Risk factors for sepsis in infants included maternal fever or signs of chorio-amnionitis, ruptured membranes >18hrs, previous child with *Group B Streptococcus* (GBS) sepsis, or preterm labour. All the recommendations were graded as B, except for “no further evaluations for well-appearing infant of GBS (+) mother received IAP with penicillin >4hr before delivery”, which was a grade A recommendation. The levels of evidence were determined based on the criteria introduced by the Centre for Evidence-Based Medicine: Grade A recommendation means that the guideline was developed with consistent level 1 studies (systematic reviews of randomized controlled trials or individual randomized controlled trials); grade B recommendation means that the guideline was based on consistent level 2 or 3 studies (systematic reviews of cohort/case-control studies or individual cohort/case-controlled studies, or extrapolations from level 1 studies).

Dellinger and coworkers developed evidence-based guidelines for children with severe sepsis and septic shock. In his guideline in 2004, quality of the evidence and grading of recommendations were based on a system proposed by Sackett in 1989, while in the 2008 guideline, they were judged by pre-defined Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. In the GRADE system, quality of evidence was classified as high (Grade A), moderate (Grade B), low (Grade C) or very low (Grade D); recommendations were classified as strong (Grade 1) or weak (Grade 2). The 2008 version was based on an updated systematic literature search up to 2007. During its preparation, there were no members of the committee from industry, no industry funding or input was involved, also industry awareness or comment on the recommendations was not allowed. However, some industry funding was received in the preparation of the 2004 guideline. Recommendations between the two guidelines were similar but not identical, partly as a result of the inclusion of more clinical trials in the 2008 guideline. The important differences were: 1) antibiotics were recommended be administered within 1hr of the identification of severe sepsis, after appropriate cultures have been obtained; and 2) activated protein C was not recommended for children. These were not stated in the 2004 guideline. Quality of the evidence in the 2008 guideline was relatively poor; most recommendations were rated as level C or D, except for the recommendation related to the use of activated protein C, which was rated as level B. The recommendations regarding the use of antibiotics and activated protein C were strong, while the rest of recommendations were weak.
Table 1. Evidence-based clinical practice guidelines for management of sepsis in pediatric patients

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<th>Guidelines</th>
<th>Patient group</th>
<th>Recommendations</th>
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| Canadian Paediatric Society guideline, 2007²         | Infant at increased risk for sepsis               | *Full diagnostic evaluation and empirical AB therapy* are required for: Any newborn infant with clinical signs suggestive of sepsis (temperature instability, tachycardia, poor peripheral perfusion and respiratory distress), or those WBC count <5.0×10⁹/L.  

*Limited diagnostic evaluation* is required for: Well-appearing infant whose GBS(+) mother received IAP with penicillin <4h before delivery; infant of mother with unknown GBS status and with risk factors and received IAP <4h before delivery; well-appearing infant born <36wks with unknown maternal GBS status; well-appearing infant of a mother with possible chorioamnionitis.  

*No evaluation or further intervention* is required for: Well-appearing infant of GBS(+) mother received IAP with penicillin >4h before delivery, or GBS(-) mother with risk factors, or unknown GBS status and with risk factors and with IAP >4h before delivery.  

Ampicillin and gentamicin are usually appropriate based on the usual susceptibilities of the predominant organisms causing early-onset sepsis. |
| Dellinger et al., 2008³ (This is an update of the 2004 guideline) | Severe sepsis and septic shock patients (there is a section specific for pediatric patients) | ABs were recommended be administered within 1h of the identification of severe sepsis, after appropriate cultures have been obtained.  

Young infants and neonates with severe sepsis may require early intubation.  

Initial resuscitation begins with infusion of crystalloids with boluses of 20mL/kg over 5-10mins, titrated to clinical monitors of cardiac output (i.e. heart rate, urine output, capillary refill and level of consciousness); initial volume for resuscitation usually requires 40-60mL/kg but can be much higher.  

Vasopressors should only be used in volume loaded patients with fluid resuscitation. Dopamine is the first choice of support for patients with hypotension refractory to fluid resuscitation. Dopamine-refractory shock may reverse with epinephrine or norepinephrine infusion.  

Hydrocortisone therapy should be restricted to children with catecholamine resistance and suspected or proven adrenal insufficiency.  

Use of APC in children was NOT recommended.  

Use of DVT prophylaxis was suggested.  

IVIG was suggested being considered in severe sepsis. |

AB – antibiotic; APC – activated protein C; DVT – deep vein thrombosis; GBS – group B streptococcus; h – hour; IAP – intrapartum antibiotic prophylaxis; WBC – white blood cell; wk – week; full diagnostic evaluation: consists of complete blood count, blood culture and lumbar puncture, a chest X-ray is required if respiratory difficulties are present; limited diagnostic evaluation: consists of complete blood count and observation of vital signs every 4h for a period of 24h.
Six Cochrane reviews that assessed various treatments in neonates with suspected or proven sepsis were identified.\textsuperscript{8-13} Another systematic review by Malik et al. related to the diagnosis of sepsis was identified as well.\textsuperscript{14} All Cochrane reviews were rigorously conducted, evidence from the included randomized controlled trials were evaluated and synthesized when appropriate. However, these reviews were not able to provide definite conclusions regarding the clinical benefit of the interested interventions. This is partly because of the poor quality of the included individual studies, and also the small number of participants in such studies. All these reviews indicated that additional well designed and adequately powered trials are needed to solve this issue. This is also true in the systematic review by Malik and coworkers.

Details of the included systematic reviews are presented in Table 2.

**Table 2. Systematic reviews identified on the management of sepsis in pediatrics**

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<th>Interventions</th>
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| Rao et al., 2006\textsuperscript{8} | Newborn infants <28ds of life, with suspected or proven sepsis; 11 studies (N=574) were included, only 1 enrolled infants <32wks gestation. | Once a day gentamicin vs. multiple doses/d gentamicin | Both tx groups showed adequate clearance of proven sepsis.  
*RD 0.00 (95%CI –0.19, 0.19)*  
Fewer pts in “once a day” group failed to attain peak level of gentamicin ≥5μg/ml when compared to “multiple doses”;  
*RR 0.22 (95%CI 0.11, 0.47)*  
*RD –0.13 (95%CI –0.19, -0.08)*  
Pts in “once a day” group attained higher peak levels of gentamicin compared to “multiple doses”;  
*WMD 2.58 (95%CI 2.26, 2.89)*  
Pts in “once a day” group had lower trough levels.  
*WMD –0.57 (95%CI –0.69, -0.44)*  
Ototoxicity and nephrotoxicity were not noted with either regimen. | Insufficient evidence to conclude whether “once a day” or “multiple doses a day” regimen of gentamicin is superior in treating proven neonatal sepsis. However, data suggested that pharmacokinetic properties of “once a day” regimen were superior in that it achieved higher peak levels while avoiding toxic trough levels. No change in nephrotoxicity or auditory toxicity. |
| Gordon et al., 2005\textsuperscript{5} | Newborn infants with suspected late onset sepsis commenced on ABs after 48hs of age; 1 study (N=24) was included. | To compare different initial AB regimens (beta-lactam vs. beta-lactam + aminoglycoside) | No difference in mortality;  
*RR 0.17 (95%CI 0.01, 3.23)*  
No difference in tx failure;  
*RR 0.17 (95%CI 0.01, 3.23)*  
No cases in either group showed AB resistance. | Inadequate evidence in favor of any regimen for tx of suspected late onset neonatal sepsis. |
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| Mitimila et al., 2004<sup>10</sup> | Presumed early neonatal sepsis in newborn babies <48hs of life; 2 studies (N=127) were included. | To compare various AB regimens (monotherapy vs. combination therapy)          | No difference in mortality in the first 28ds of life; RR 0.75 (95% CI 0.19, 2.9)  
No difference in tx failure; RR 1.25 (95% CI 0.19, 8.39)  
No cases of bacteriological resistance were found in either group.                                                                 | No evidence to suggest that any AB regimen may be better than any other in tx of presumed early neonatal sepsis.                                                                                          |
| Carr et al., 2003<sup>11</sup>   | Newborn infants with suspected or proven sepsis in intensive care; 7 tx studies (N=257) and 3 prophylaxis studies (N=359) were included. | Tx studies: G-CSF or GM-CSF + AB vs. AB alone; Prophylaxis studies: G-CSF or GM-CSF vs. no CSF | Tx studies:  
No difference in mortality to d 14; RR 0.71 (95% CI 0.38, 1.33)  
Subgroup analysis of 97 infants with neutropenia showed reduction in mortality by d 14; RR 0.34 (95% CI 0.12, 0.92)  
RD -0.18 (95% CI -0.33, -0.03)  
Prophylaxis studies:  
No difference in mortality in neonates receiving GM-CSF. RR 0.59 (95% CI 0.24, 1.44)  
RD -0.03 (95% CI -0.08, 0.02)  
Both G-CSF and GM-CSF were well tolerated, and no report of adverse events.                                                                 | Insufficient evidence to support the introduction of G-CSF or GM-CSF into neonatal practice, either as tx or prophylaxis.                                                                                   |
| Haque et al., 2003<sup>12</sup>  | Neonates <28ds with suspected or proven sepsis; 2 studies (N=140) were included; outcomes were reported for 107 pts with confirmed sepsis. | Pentoxifylline + AB vs. placebo + AB                                           | A reduction was noted in all cause mortality during hospital stay following pentoxifylline tx; RR 0.14 (95% CI 0.03, 0.76)  
RD -0.16 (95% CI -0.27, -0.04)  
No adverse events due to pentoxifylline were reported.                                                                                       | Pentoxifylline as an adjunct to ABs in neonatal sepsis reduced mortality without any adverse events.                                                                                                       |
| Mohan et al., 2003<sup>13</sup> | Neutropaenic neonates with suspected or confirmed sepsis; 4 studies (N=79) were included. | Granulocyte transfusions vs. placebo/no transfusion  
Granulocyte transfusions vs. IVIG | No difference in all-cause mortality when compared to placebo; RR 0.89 (95% CI 0.43, 1.86)  
RD -0.05 (95% CI -0.31, 0.21)  
Reduction in all-cause mortality in granulocyte transfusion group was noted; RR 0.06 (95% CI 0.00, 1.04)  
RD -0.34 (95% CI -0.60, -0.09)                                                                 | Inconclusive evidence to support or refute the routine use of granulocyte transfusions in neutropaenic, septic neonates.                                                                              |
Studies | Patient groups | Interventions | Results | Conclusions
---|---|---|---|---
Malik et al., 2003\(^{14}\) | Infants younger than 90ds with proven bacterial growth in a sample from a sterile site; 37 studies were included | To compare the accuracy of modern lab tests (cytokine levels, fibronectin levels, neutrophil elastase inhibitor levels, procalcitonin levels, TNF receptor p55 and p75 levels, etc.) for the diagnosis of serious bacterial infection in newborns | Pulmonary complications were the only adverse effect reported in trials used buffy coat transfusions. | Sensitivities ranged from 57%-100%, specificities ranged from 43%-100%, positive LRs ranged from 1.5-∞. Few methodologically rigorous studies of the accuracy of lab tests for the diagnosis of bacterial infection in newborns; there was marked heterogeneity in sample selection and cutoff levels for diagnosis of neonatal sepsis. A few tests showed promising accuracy, but there are insufficient data to support their confident use as clinical tools. |

**Limitations**
- There is a limited number of systematic reviews or evidence-based guidelines evaluating the management of sepsis in the pediatric population in the search time frame;
- Most of the reviews examined management of sepsis in neonates; there is a lack of evidence investigating children in other age groups;
- Most of the reviews included randomized trials with small number of participants, and quality of the evidence from these trials were low;
- Fewer reviews evaluated the diagnosis of sepsis in the targeted population;
- No long-term clinical outcomes were assessed.

**Conclusions and implications for decision or policy making:**

The evidence for management of sepsis in pediatric patients is limited and not comprehensive. The majority of the guidelines and systematic reviews focused on newborn infants. There is insufficient information on the septic management for children in other age groups.

Some antibiotic regimens were not related to better clinical outcomes when compared with the other regimens. There were no adverse events reported during the treatment. Pentoxifylline administered in addition to antibiotics was demonstrated to be superior to placebo in reducing...
all-cause mortality during hospital stay without adverse effects. Granulocyte transfusions did not alter the mortality rates when compared with placebo; a small trial indicated that granulocyte transfusions reduce the mortality when compared with intravenous immunoglobulin; however the difference just reached statistical significance.

In general, it is difficult to draw definite conclusions in the management of sepsis in pediatric patients. The limited data however, suggested that rapid antibiotic therapy plus general supportive measures, including respiratory and hemodynamic management be combined to treat pediatric patients with sepsis, especially in severe disease status. Further well-designed clinical trials are warranted to provide more compelling evidence to estimate the diagnosis, treatment and other management of sepsis in the pediatric population.

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References:


