TITLE: Early Identification of Sepsis: A Review of the Evidence for Clinical Indicators and Guidelines for Management

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CONTEXT AND POLICY ISSUES:

Sepsis syndrome covers a broad array of illnesses including systemic inflammatory response syndrome (SIRS), sepsis (infection with SIRS), severe sepsis (sepsis with multi-organ dysfunction), and septic shock (severe sepsis with hypotension unresponsive to fluid resuscitation).[1,2] There is no single clinical sign or diagnostic test to confirm diagnosis.[2]

Sepsis may occur at any age, in any patient population, and in response to a multitude of microbial pathogens from different anatomical sites.[2] The mortality rate of sepsis is 25% to 80%, depending on illness severity, the number of failed organs and severity of organ failure.[1] Factors which influence outcomes include the age and health status of the patient, and the nature and source of the infection.[1]

Early identification and treatment of severe sepsis and septic shock may improve outcomes.[3] Patient risk assessment, screening tools, and scoring systems are helpful in determining the severity of sepsis.[3] Early goal-directed therapy (EGDT) has been shown to reduce mortality rates in clinical trials.[3] EGDT includes early initiation of hemodynamic resuscitation with specified treatment end-points and is most effective if implemented within six hours of arrival at the emergency department (ED).[3] However, one prospective study showed that only 15.8% of patients with severe sepsis were diagnosed correctly by the medical team of an ED.[4]

This report reviews the evidence regarding the clinical indicators for the early diagnosis of sepsis and the early treatment of SIRS and sepsis in a pre-hospital setting.

RESEARCH QUESTIONS:

1. What is the evidence regarding the clinical indicators for sepsis to assist in an early diagnosis?

2. What are the guidelines regarding the early treatment management of patients identified to have clinical indicators for sepsis or systemic inflammatory response syndrome?

METHODS:

A focused search (main concept appeared in title or major subject heading) was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and May 4, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews are presented first. These are followed by observational studies, and evidence-based guidelines.

SUMMARY OF FINDINGS:

On the topic of the early diagnosis of sepsis, one systematic review[5] and two observational studies[6,7] were retrieved. Also found were two guidelines that included recommendations on both the diagnosis and the treatment of sepsis in the ED.[8,9] A third set of guidelines included recommendations on the management of sepsis, applicable to both the intensive care unit (ICU) and the non-ICU setting.[10] There were no relevant health technology assessments, meta-analyses, randomized controlled trials, or controlled clinical trials retrieved.

Systematic review

One systematic review on the clinical signs of sepsis in young infants (0 to 2 months old) was identified (Appendix 1, Table 1).[5] The authors conducted a literature search using Medline and found eight studies that met their inclusion criteria. The included studies were community-based, hospital-based, or a mix of both. No additional information was provided on these studies. Clinical predictors of severe illness in infants included: cyanosis, history of feeding difficulty, breathing difficulty (grunting), respiratory rate greater than 60 beats per minute, abnormal behavior, or a temperature above 38º Celsius. The authors concluded that there was no highly sensitive and highly specific clinical screening tool for the identification of seriously sick infants with sepsis.[5]

Observational studies

Two observational studies on the diagnosis of sepsis in the ED and out-of-hospital were found and are described in Appendix 1, Table 2.[6,7]
Dremsizov et al. examined whether the SIRS criteria, measured at the time of presentation to the ED, could predict the development of severe sepsis, septic shock, or death.[6] SIRS criteria included: body temperature >38º Celsius or <36 º Celsius; heart rate >90 beats/ minute; respiratory rate >20 breaths/ minute, minute ventilation >10 litres/ minute, or $Paco_2$ <32 mm Hg; and white blood cell count >12,000/ µL or < 4,000/ µL (with >10% immature forms). Physiologic

data were collected in 686 adult patients with clinical and radiologic evidence of pneumonia within 24 hours of presentation to the ED. The predictive value of SIRS was calculated in patients free of severe sepsis on day one of the study (initial presentation to the ED until midnight). A total of 82% of patients had two of the four SIRS criteria on day one. SIRS at presentation was not associated with increased odds of subsequent development of severe sepsis, septic shock, or death. The receiver operating characteristic curve for the discriminative ability of the SIRS criteria to predict severe sepsis, septic shock, or death was less than 0.5, meaning that these criteria were poor predictors of outcomes. The authors concluded that SIRS criteria, measured in the ED, are poorly predictive of severe sepsis, shock, or death in pneumonia patients.[6]

Seymour et al. conducted a secondary analysis of a retrospective cohort study to describe the out-of-hospital characteristics of adult patients hospitalized for severe sepsis after being transported to the ED by emergency medical services (EMS) and to determine out-of-hospital factors associated with an increased in serum lactate and sequential organ failure assessment (SOFA) score in the ED.[7] The following definitions were used. Sepsis: a suspected infection in the presence of two or more SIRS criteria. Severe sepsis: sepsis associated with hypoperfusion, hypotension, or organ dysfunction. Septic shock: hypotension despite adequate fluid resuscitation or use of vasoactive agents. The primary and secondary outcomes were the initial serum lactate and the maximum SOFA score measured during the ED stay, respectively. They also studied the association between out-of-hospital factors and the SOFA score. A total of 216 patients were transported to the ED by city EMS. Vital sign abnormalities were common in the out-of-hospital environment, and hypotension occurred in less than 25% of participants. Forty-one percent of subjects presented with serum lactate levels of 4.0 mmol/ L or higher. Lower out-of-hospital oxygen saturation, systolic blood pressure, and Glasgow Coma Scale (GCS) score (a score of neurological assessment) were associated with an increase in serum lactate ($p<0.03$). Maximum SOFA score was greater in patients with out-of-hospital tachypnea, lower blood pressure, lower GCS, and lower oxygen saturation ($p<0.05$). The authors concluded that out-of-hospital hypotension, hypoxemia, and altered mental status were uncommon in patients who were hospitalized with severe sepsis. Further, routinely measured, out-of-hospital clinical variables were associated with greater serum lactate levels and SOFA scores upon arrival to the ED.[7]

Guidelines and recommendations

Nguyen et al.: Published in 2006, a group of American physicians representing various medical specialties created guidelines for the management of severe sepsis and septic shock in the ED.[8] Their objective was to provide an independent clinical review on contemporary management strategies for ED patients with severe sepsis and septic shock. Although they did not specify the literature search methods used, they did state that the recommendations were developed through consensus and that these were graded according to previously published criteria by D.L. Sackett (Appendix 2). The authors stated that studies on the diagnostic value of laboratory tests, and clinical findings among a broad-based ED population do not exist; that the hallmark finding of infection is fever; and that SIRS criteria, ill appearance, or hypotension should trigger an expedited ED evaluation for presence of sepsis. (Grade E)

Several recommendations were made for the ED treatment of adult patients with severe sepsis or septic shock:

1) institute early goal directed therapy within six hours of presentation; includes fluid resuscitation, vasoactive agents, blood transfusion, inotrope therapy with sedation, paralysis, and intubation (Grade B)
2) give appropriate (Grade D) and timely (Grade E) antimicrobial therapy
3) eradicate the source of the infection (Grade E)
4) consider activated protein C (Grade B)
5) consider low-dose corticosteroids (Grade C)
6) give low tidal volume mechanical ventilation (Grade B).[8]

Green et al.: The Canadian Association of Emergency Physicians formulated guidelines (2008) for the optimal management of severe sepsis applicable to Canadian emergency departments.[9] Their objective was to review key management principles of severe sepsis for Canadian emergency physicians. Their literature search methods included a PubMed search and additional searches by individual members. The evidence was graded according to the Oxford Centre for Evidence-based Medicine (Appendix 2).

With respect to diagnosis, this was identified as an area where a lack of objective data exists and hence, no recommendations were provided.

For the treatment of severe sepsis, several recommendations were made:

1) endotracheal intubation should be instituted when required for airway protection, support of oxygenation or assisted ventilation (Grade D); patients unresponsive to fluid resuscitation should have central venous access (Grade D); the internal jugular or subclavian veins are preferred (Grade D)
2) fluid resuscitation should be initiated immediately (Grade B) using Ringer's lactate, normal saline or albumin (Grade D)
3) vasopressors (norepinephrine and dopamine, Grade C) should be administered through a central line (not graded) after adequate volume resuscitation to maintain blood pressure and organ perfusion (Grade B)
4) inotropes (dobutamine, Grade D) should be used to maintain central venous oxygen saturation over 70% (Grade D) and adequate cardiac output (Grade D) in volume-replete septic patients who have adequate blood pressure
5) patients should receive antibiotics against all likely pathogens (Grade B) as soon as possible (Grade C)
6) sources of infection should be controlled or eliminated (Grade D)
7) limited data is available on the use of activated protein C in the ED; activated protein C infusions may be considered in adult patients with severe sepsis (Grade B)
8) low dose corticosteroids may be considered in hemodynamically unstable patients who do not respond to volume resuscitation and vasopressor infusion (Grade D)
9) blood transfusions may be considered in patients with early septic shock (Grade B)
10) ventilation may be used (Grade D).[9]

Dellinger et al.: The Surviving Sepsis Campaign guidelines 2008[10] were updated from guidelines originally published in 2001 and updated in 2004. The objectives of the guidelines were to provide guidance for the clinician caring for a patient with severe sepsis or septic shock. The recommendations were appropriate to patients across the spectrum of acute care, including the non-ICU setting. A separate Medline search was used for each defined research question,

spanning the years 1991 to 2007. Representatives of associations and societies from various countries formed subgroups charged with providing an update to specific areas. The process included a modified Delphi method, a consensus conference, and other meetings. The quality of the evidence was judged by Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria (Appendix 2).

The guidelines did not address the early diagnosis of sepsis. Treatment recommendations for adults included:

1) initiate resuscitation immediately (within first six hours) in patients with hypotension or elevated serum lactate >4 mmol/ L (Grade C)
2) begin intravenous antibiotics within the first hour of recognizing severe sepsis (Grade D) or septic shock (Grade B)
3) use on or more agents active against likely bacterial/ fungal pathogens and with good penetration in presumed source (Grade B)
4) site of infection should be established as early as possible (Grade C) and within first six hours of presentation (Grade D)
5) implement source control measures (Grade C)
6) fluid-resuscitate using crystalloids or colloids (Grade B)
7) give norepinephrine or dopamine centrally administered as the initial vasopressor of choice (Grade C)
8) use dobutamine in patients with myocardial dysfunction (Grade C)
9) consider intravenous hydrocortisone for septic shock when hypotension remains poorly responsive to adequate fluid resuscitation (Grade C)
10) consider activated protein C in patients with sepsis-induced organ dysfunction (Grade B).[10]

Limitations

The included systematic review is limited by the fact that the search methods for identifying studies were not comprehensive; the authors did not clearly describe the criteria used for selecting the included studies; and they did not describe the study designs and their quality. Although both observational studies described themselves as cohort studies, the authors re-analyzed the data of a group of patients that were part of a larger study. Because all patients recruited into the studies had SRIS or sepsis, these sub-studies appeared to be more like large case series. Case series should be seen as hypothesis generating rather than studies from which to derive firm conclusions. The guidelines were generally well prepared, although one guideline did not specify the literature search methods used.[8]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

One systematic review, two observational studies, and three guidelines that met our selection criteria were identified.

Early diagnosis of sepsis: One systematic review[5] of eight studies conducted in infants 0 to 2 months reported that signs of cyanosis, feeding difficulty, grunting, respiratory rate greater than 60 beats per minute, abnormal behavior, or fever may predict sepsis in this population.

Two observational studies gave conflicting results. In one, the presence of SIRS in adult patients with community-acquired pneumonia presenting to the ED was a poor predictor of whether or not severe sepsis or septic shock would develop.[6] In another observational study, adult patients who developed severe sepsis while in the ED had vital signs abnormalities and SIRS before arriving to the hospital.[7]

Two of the three sets of guidelines addressed the diagnosis of sepsis in the ED. Whereas one guideline could not make a recommendation due to a lack of evidence,[9] the other guideline based its recommendation on expert opinion. It stated that clinicians should suspect sepsis in patients with SIRS, ill appearance, or hypotension.[8]

Based on the findings above, we cannot make a definitive conclusion about the clinical signs that may best assist in the early diagnosis of sepsis.

Early treatment of sepsis: The treatment of sepsis in a non-ICU setting or in the ED was addressed in three sets of guidelines. All had similar sets of recommendations. These included initiating fluid resuscitation immediately, administering medications such antibiotics, vasopressors, inotropes, low-dose corticosteroids, and activated protein C, and controlling the source of the infection. These recommendations were based on evidence ranging from large randomized controlled trials to expert opinions.

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REFERENCES:

1. Nee PA. Critical care in the emergency department: severe sepsis and septic shock. Emerg Med J [Internet]. 2006 Sep [cited 2010 May 6];23(9):713-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2564220

2. Opal SM. Severe sepsis and septic shock: defining the clinical problem. Scand J Infect Dis. 2003;35(9):529-34.

3. Rivers EP, Ahrens T. Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation. Crit Care Clin. 2008 Jul;24(3 Suppl):S1-47.

4. Rezende E, Silva JM Jr, Isola AM, Campos EV, Amendola CP, Almeida SL. Epidemiology of severe sepsis in the emergency department and difficulties in the initial assistance. Clinics [Internet]. 2008 Aug [cited 2010 May 6];63(4):457-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664120

5. Newton O, English M. Young infant sepsis: aetiology, antibiotic susceptibility and clinical signs. Trans R Soc Trop Med Hyg [Internet]. 2007 Oct [cited 2010 May 6];101(10):959-66. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2673057

6. Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest [Internet]. 2006 Apr [cited 2010 May 7];129(4):968-78. Available from: http://chestjournal.chestpubs.org/content/129/4/968.full.pdf+html

7. Seymour CW, Band RA, Cooke CR, Mikkelsen ME, Hylton J, Rea TD, et al. Out-of-hospital characteristics and care of patients with severe sepsis: a cohort study. J Crit Care. 2010 Apr 7.

8. Nguyen HB, Rivers EP, Abrahamian FM, Moran GJ, Abraham E, Trzeciak S, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. Ann Emerg Med [Internet]. 2006 Jul [cited 2010 May 7];48(1):28-54. Available from: http://www.ptolemy.ca/members/archives/2006/gyn/Nguyen2006.pdf

9. Green RS, Djogovic D, Gray S, Howes D, Brindley PG, Stenstrom R, et al. Canadian Association of Emergency Physicians Sepsis Guidelines: the optimal management of severe sepsis in Canadian emergency departments. CJEM [Internet]. 2008 Sep [cited 2010 May 7];10(5):443-59. Available from: http://www.cjem-online.ca/sites/default/files/pg443(2).pdf

10. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med [Internet]. 2008 Jan [cited 2010 May 6];34(1):17-60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2249616

APPENDIX 1: Findings

Table 1: Systematic review

First author	Literature search	Inclusion criteria, methods	Outcomes	Results
Newton, 2007[5]	Medline 1990 to March 2006; Cochrane Library Issue 2, 2006; bibliographies of retrieved articles; reference collection of experts; no language restrictions	studies with primary data on clinical signs predicting severe illness in infants less than 2 months; titles and abstracts examined by 2 reviewers; quality of studies assessed using Oxford Centre for Evidence-Based Medicine, but not reported	clinical signs for predicting severe illness in infants	n=8 studies found signs: -cyanosis -history of feeding difficulty -breathing difficulty (grunting) -respiratory rate >60 beats per minute -abnormal behaviour -temperature >38ºC

Table 2: Clinical indicators for the early diagnosis of sepsis

First author	Study design	Population	Outcomes	Results
Dremsizov, 2006[6]	subgroup analysis of a retrospective, multi-site, cohort study	adult patients ≥18 years old, with CAP diagnosed within 24 hours of presentation to ED n= 686 mean age: 54.4 years male gender: 49.1%	predictive value of SIRS (for patients free of severe sepsis on initial presentation at ED)	562/ 686 (82%) patients with 2 of 4 SIRS criteria on day one severe sepsis: -OR 0.65 (95%CI: 0.38, 1.11), p=0.10 -ROC 0.46 (95%CI: 0.40, 0.53) septic shock: -OR 0.80 (95%CI: 0.23, 3.62), p=0.74 -ROC 0.48 (95%CI: 0.33, 0.64) death: -OR 0.65 (95%CI: 0.24, 2.04), p=0.41 -ROC 0.46 (95%CI: 0.33, 0.60)

Seymour, 2010[7]	secondary analysis of a retrospective cohort study January 2005 to December 2006	adult patients with severe sepsis and septic shock as well as being transported to the ED by emergency medical services n=216 mean age, standard deviation: 61±17 male gender: 54%	primary: initial serum lactate	median serum lactate: 3.0 mmol/ L (IQR: 2.0 mmol/ L to 5.0 mmol/ L); 41% of subjects presented with initial lactate levels of 4.0 mmol/ L

CAP=community-acquired pneumonia; CI=confidence interval; ED=emergency department; IQR=interquartile range; OR=odds ratio; ROC=receiver operating characteristic; SIRS=systemic inflammatory response syndrome

APPENDIX 2: Grades of recommendations

Nguyen et al.: graded according to previously published criteria by D.L. Sackett[8]

Grade A: supported by at least two level I investigations (large randomized trials with clear cut results; low risk of false-positive error or false-negative error)
Grade B: supported by one level I investigation (large randomized trial with clear cut results; low risk of false-positive error or false-negative error)
Grade C: supported by level II investigations only (small, randomized trials with uncertain results; moderate to high risk false-positive error or false-negative error)
Grade D: supported by at least one level III investigation (nonrandomized, contemporaneous controls)
Grade E: supported by level IV or V evidence (nonrandomized, historical controls, case series, uncontrolled studies, and expert opinion)[8]

Green et al.: graded according to the Oxford Centre for Evidence-based Medicine[9]

Grade A: level 1 studies (systematic review of randomized controlled trials or individual randomized controlled trial with narrow confidence interval)
Grade B: level 2 studies (systematic review of cohort studies or individual cohort study or low quality randomized controlled trials or outcomes research) or level 3 studies (systematic review of case-control studies or individual case-control study), or extrapolations from level 1 studies
Grade C: level 4 studies (case-series or poor quality cohort and case-control studies), or extrapolation from level 2 or 3 studies
Grade D: level 5 evidence (expert opinion) or troublingly inconsistent or inconclusive studies of any level[9]

Dellinger et al.: graded according to Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria[10]

Grade A: RCT
Grade B: downgraded RCT or upgraded observational studies
Grade C: well-done observational studies
Grade D: case series or expert opinions (p19)[10]