Making the diagnosis of Sepsis in the Emergency Department

Sohil Pothiawala
FAMS(EM), MRCSEd(A&E), M.Med(EM), MBBS
Consultant
Department of Emergency Medicine
Singapore General Hospital
Sepsis - known since the ancient times of human history

In the Egyptian legends the "u-khed-u" was mentioned as a disease: "originating from the intestine spreading via the circulatory system, the disease finally results in death, when seizing the heart"

The word "sepsis" derives from the ancient Greeks. It means a dysequilibrum (foulness and digestion) of body fluids.
CHANGING THE WORLD

US sepsis expert says
Rory’s case will change the world
Emergency Department Critical Care Volume Increases

> 50% of Severe Sepsis cases initially present to the ED

Figure 1.
Estimated annual burden of critical care and emergency department (ED) capacity in the United States, 2001–2009.

Severe Sepsis: A Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - Leading cause of death in non-coronary ICU
- Mortality rates associated with sepsis
  - 30-50% for severe sepsis
  - 50-60% for septic shock
- Sepsis kills approximately 1,400 people worldwide every day

Future

Incidence projected to increase by 1.5% per year
Comparison With Other Major Diseases

Incidence of Severe Sepsis

- AIDS*
- Colon Cancer§
- Breast Cancer
- CHF†
- Severe Sepsis‡

Mortality of Severe Sepsis

- AIDS*
- Breast Cancer§
- AMI†
- Severe Sepsis‡

Why do you think that severe sepsis has not received the same focus as these other common diseases?
An Unseen Enemy
The Sepsis Cascade

Unbalanced Immune Reaction

Coagulation and complement system

Procoagulant State

Microvascular Thrombosis

Endothelial damage

Mediators of Inflammation

Free Radical Damage

Vasodilatation

Capillary Leak

Tissue injury and Organ dysfunction
Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

Sir William Osler – 1904
The Evolution of Modern Medicine
Surviving Sepsis Campaign

Adult and Pediatric Evidence-based Studies

1. Early Detection
2. Early Treatment
   • Sepsis Resuscitation Bundle
3. Monitor reliability and outcomes
The Importance of Early Detection

- Efforts to **just treat recognized sepsis** alone are incomplete.

- A critical aspect of mortality reduction in the Surviving Sepsis Campaign has been pushing practitioners to identify sepsis early.

- It may well be that earlier recognition accounts for much of the signal in mortality reduction and partially explains sharply increasing incidence.
Where is the Gain?

Lead Time to Diagnosis

Delivery of Proper Treatment

Lead time to Diagnosis

Delivery of Proper Treatment
Dear SIRS, I don’t like you...

1. New terminology does not help us to understand the underlying problem.
2. There are enough problems with the current terminology “sepsis,” “infection,” “septicemia.”
3. SIRS is too sensitive, but is not specific (like, “critically ill”).
4. SIRS does not reflect the severity of the disease process.
5. SIRS may detract from the search for infection.
Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

However, the need for patients to meet two or more SIRS criteria has been criticized because of a low specificity for infection\textsuperscript{12,13} within 24 hours after admission to the ICU.\textsuperscript{14} Moreover, some patients (the elderly and those taking medications that affect heart rate, respiratory rate, or body temperature) may not have symptoms meeting two or more SIRS criteria, despite having infection and organ failure. Thus, the face validity and sensitivity of two or more SIRS criteria in the diagnosis of severe sepsis remain unclear.\textsuperscript{15}

CONCLUSIONS
The need for two or more SIRS criteria to define severe sepsis excluded one in eight otherwise similar patients with infection, organ failure, and substantial mortality and failed to define a transition point in the risk of death. (Funded by the Australian and New Zealand Intensive Care Research Centre.)
Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

**Respiratory**
- \( \text{PaO}_2/\text{FiO}_2 \leq 200 \) if lung only dysfunction/site of infection
- \( \text{PaO}_2/\text{FiO}_2 \leq 250 \) with other organ dysfunction/lung not site of infection

**Cardiovascular**
- Tachycardia
- SBP < 90 mmHg
- MAP < 70 mmHg (despite fluid)
- Need for Vasopressors

**Renal**
- UO < 0.5 ml/kg per hr (despite fluid)

**Metabolic**
- Unexplained metabolic acidosis
- Lactate > 1.5 times upper normal

**Hematologic**
- Platelets < 80,000/mm³
- Decline in platelet count of 50% over 3 days
Evidence of Lactate

Serum Lactate as a Predictor of Mortality in Emergency Department Patients With Infection

Nathan L. Shapiro, MD, MPH
Michael D. Howell, MD
Daniel Talmor, MD, MPH
Larry A. Nathanson, MD
Alan Lisbon, MD
Richard E. Wolff, MD
J. Woodrow Weiss, MD

From the Department of Emergency Medicine (Shapiro, Wolfe, Nathanson), the Department of Medicine, Division of Pulmonary and Critical Care Medicine (Howell, Weiss), and the Department of Anesthesiology and Critical Care (Talmor, Lisbon), Beth Israel Deaconess Medical Center, Boston, MA.

Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock.

Mark E. Mikkelsen, MD, MS; Andrea N. Mitiades, BA; David F. Gaierski, MD; Munish Goyal, MD; Barry D. Fuchs, MD; Chirag V. Shah, MD, MS; Scarlett L. Bellamy, ScD; Jason D. Christie, MD, MS

Crit Care Med 2009 Vol 37, No. 5

Early Lactate-Guided Therapy in Intensive Care Unit Patients

A Multicenter, Open-Label, Randomized Controlled Trial

Tim C. Jansen1, Jasper van Bommel1, F. Jeanette Schoonderbeek1, Steven J. Sleeswijk Visser1, Johan M. van der Klooster2, Alex P. Lima1, Sten P. Willemsen2, and Jan Bakker1, for the LACTATE study group.

Am J Respir Crit Care Med Vol 182. pp 752–761, 2010

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy
A Randomized Clinical Trial

Alan E. Jones, MD

(Reprinted) JAMA, February 24, 2010—Vol 303, No. 8

Lactate in Sepsis

Hernando Gomez, MD; John A. Kellum, MD

http://www.annalsofindicaret.org/content/3/1/12

Clinical use of lactate monitoring in critically ill patients

Prognosis of emergency department patients with suspected infection and intermediate lactate levels: a systematic review.

Puskarich MA, et al

Lactate Levels and Clearance

- Lactate levels proportional to mortality and MODS
- Lactate $\geq 4$ associated with poorer outcomes
- Clearance of lactate is associated with improved survival
- Lactate clearance non-inferior to ScVO2 monitoring (Jones, JAMA, 2010)
- **Good means to screen for occult severe sepsis**
  - occult sepsis is when the patient’s blood pressure and mental status are good, but the patient is still at high risk of death
  - 1 in 5 patients in the Rivers trial had MAP >100, half of these had high lactate
- Algorithms of care based on lactate clearance appear to work as well or better than other approaches
## Biomarkers in Sepsis

<table>
<thead>
<tr>
<th>Acute Phase Protein Biomarkers</th>
<th>Cytokine Biomarkers</th>
<th>Coagulation Biomarkers</th>
<th>Soluble receptor, cell surface and other markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>IL-6</td>
<td>aPTT</td>
<td>sTREM-1</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>IL-8</td>
<td>Protein C &amp; S</td>
<td>suPAR</td>
</tr>
<tr>
<td>Lipopolysaccharide-binding protein</td>
<td>Macrophage migration inhibitory factor</td>
<td>D-dimer, Fibrin, Thrombomodulin</td>
<td>Midregional proadrenomedullin</td>
</tr>
<tr>
<td>Pentraxin</td>
<td>High-mobility-group box 1</td>
<td>Plasminogen activator inhibitor</td>
<td>Polymorphonuclear CD64 index</td>
</tr>
</tbody>
</table>
C Reactive Protein (CRP)

- Acute phase protein released 4-6hrs after stimulation
- Greater availability
- Performance to discriminate patients with and without sepsis is only moderate
- Inferior compared to PCT, can’t predict prognosis or positivity of blood culture
- Some ability to correctly diagnose pts with severe sepsis in ED, but significantly inferior to PCT and IL-6
- Elevated CRP correlates with increased risk of organ failure and death
- Levels decrease over 48 hrs with successful antimicrobial therapy
- Increases even during minor infection and non-infectious states; unable to assess severity

Serum Procalcitonin and C-Reactive Protein Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis

Liliana Simon, Franco Gauvin, Devendra K. Amro, Patrick Saint-Louis, and Jacques Lacroix

Clinical Infectious Diseases 2004;39:206–17

Additional value of procalcitonin for diagnosis of infection in patients with fever at the emergency department.


Research

Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department

Critical Care Vol 11 No 3 Hausfater et al.

Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

Lancet 2010 Feb 6;375(9713):463-74

High serum procalcitonin concentrations in patients with sepsis and infection.

Procalcitonin (PCT)

- Massive release in blood stream depends on sepsis severity
- Levels increase 4-12 hrs of infection
- Low specificity and sensitivity (<90%) to diagnose sepsis
- Recent ED study found that PCT, IL-6 or CRP only moderately discriminate between infectious and non-infectious inflammation
- Meta-analysis have suggested PCT cut-off 1.1ng/ml in sepsis and 4-45 ng/ml in septic shock
- Recent guidelines of Inf Dis Soc of America and ACCC recommend PCT as adjunctive diagnostic marker

Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction
Gian Paolo Castelli¹, Claudio Pognani¹, Michael Meisner², Antonio Stuani¹, Daniela Bellomi³ and Laura Sgarbi¹

Key messages

• Both CRP and PCT were higher in patients in whom infection was diagnosed at comparable levels of organ dysfunction; CRP was already increased during minor severity of organ dysfunction and sepsis, but did not further increase during more severe stages of the disease.

• PCT on the contrary was low during SIRS and sepsis, but high in patients with severe sepsis/septic shock and higher categories of the SOFA score.

• PCT reacted more quickly than CRP and this kinetic characteristic allows anticipation of a diagnosis of sepsis 24-48 hours before the CRP level would.

• In the trauma patient, when infectious complication occurred, PCT values rose promptly and marked the septic event.
The hospital staff did this to you?

No, the hospital staph.
Cytokines

- IL-6, IL-8
- Reach peak within 2 hrs of infection
- Studies comparing them to PCT and CRP found to be of inadequate discriminative value in sepsis \(^1,^2\)
- IL-6 levels decrease when infection is controlled and is predictive of survival \(^3\)
- Limited value as induced by numerous non-infectious diseases
- Role needs to be established with bigger studies

3. Tschaikowsky K, et al. predictive value of PCT, IL-6 and CRP for survival in postoperative patients with severe sepsis. J Crit care 2011; 26:54-64
sTREM-1

- Soluble Triggering Receptor expressed on myeloid cells-1
- Released by activated phagocytes during sepsis
- Moderate diagnostic accuracy for differentiating sepsis from SIRS
- Non-inferior to TNF-α, IL-6, PCT and CRP 1,2
- Present in other inflammatory diseases without infection
- Requires larger studies

suPAR

- Soluble Urokinase-type Plasminogen Activator
- Expressed on neutrophils, lymphocytes, monocytes/macrophages
- Little value as a single marker to detect CAP in patients with SIRS
- General marker of inflammation and hence diagnostic value is low
- May have some value for outcome predictions and monitoring response to treatment - Higher suPAR levels associated with increased mortality

Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department

Bo Liu, Yun-Xia Chen, Qin Yin, Yun-Zhou Zhao and Chun-Sheng Li

Figure 5 Receiver operating characteristic curves of presepsin and procalcitonin for diagnosis of sepsis. Areas under the receiver operating characteristic (ROC) curve: presepsin (blue line), 0.820 (95% confidence interval: 0.784 to 0.856), P < 0.0001; and procalcitonin (PCT; green line), 0.724 (95% confidence interval: 0.680 to 0.769), P < 0.0001.

Figure 6 Receiver operating characteristic curves of presepsin, procalcitonin, MEDS score and APACHE II score for predicting severe sepsis in septic patients. Areas under the receiver operating characteristic (ROC) curves: presepsin (blue line), 0.840 (95% confidence interval (CI): 0.809 to 0.872), P < 0.0001; procalcitonin (PCT; green line), 0.741 (95% CI: 0.703 to 0.779), P < 0.0001; Mortality in Emergency Department Sepsis (MEDS) score (brown line), 0.818 (95% CI: 0.785 to 0.851), P < 0.0001; Acute Physiology and Chronic Health Evaluation (APACHE) II score (purple line), 0.744 (95% CI: 0.706 to 0.782), P < 0.0001; presepsin in combination with MEDS score (yellow line), 0.875 (95% CI: 0.848 to 0.901), P < 0.0001; and presepsin in combination with APACHE II score (pink line), 0.858 (95% CI: 0.829 to 0.887), P < 0.0001.
### Rapid diagnosis of sepsis

Frank Bloos and Konrad Reinhart

**Table 1. Diagnostic value and limitations of biomarkers to separate infectious from non-infectious causes of inflammation**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Source</th>
<th>Sens.</th>
<th>Spec.</th>
<th>AUC</th>
<th>LR⁺</th>
<th>LR⁻</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>Metaanalysis (n = 1386)</td>
<td>0.75</td>
<td>0.67</td>
<td></td>
<td>2.43</td>
<td>0.42</td>
<td>Slow kinetic, independent of infection severity, increased in many inflammatory diseases</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>Metaanalysis (n = 3244)</td>
<td>0.77</td>
<td>0.79</td>
<td>0.89</td>
<td>4.0</td>
<td>0.29</td>
<td>Increased in various non-infectious causes of SIRS (i.e., cardiac arrest, severe trauma)</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Cohort study (n = 327)</td>
<td>0.82</td>
<td>0.75</td>
<td>0.86</td>
<td>–</td>
<td>–</td>
<td>Limited data, conflicting results</td>
</tr>
<tr>
<td>sTREM-1</td>
<td>Metaanalysis (n = 1795)</td>
<td>0.79</td>
<td>0.80</td>
<td>0.87</td>
<td>4.0</td>
<td>0.26</td>
<td>Present in inflammatory disease without infection</td>
</tr>
<tr>
<td>LBP</td>
<td>Cohort study (n = 327)</td>
<td>0.57</td>
<td>0.85</td>
<td>0.73</td>
<td>–</td>
<td>–</td>
<td>Non-specific marker of inflammation</td>
</tr>
<tr>
<td>suPAR</td>
<td>Cohort study (n = 273)</td>
<td>–</td>
<td>–</td>
<td>0.62</td>
<td>–</td>
<td>–</td>
<td>Limited data; low diagnostic value for sepsis</td>
</tr>
</tbody>
</table>

Data give sensitivity (sens.), specificity (spec.), area under the curve (AUC) from receiver operating characteristics, positive (LR⁺) and negative (LR⁻) likelihood ratios of a biomarker for differentiation of infectious vs. non-infectious causes of inflammation. LBP, lipopolysaccharide binding protein; suPAR, soluble urokinase plasminogen activator receptor; sTREM 1, soluble triggering receptor expressed on myeloid cells 1.
Multi-Marker Approach

• Combination of 3-6 pro-inflammatory markers more accurately identified bacterial infection ¹

• Panel of 3 biomarkers best predicted onset of severe sepsis in ED ²
  - No traditional markers
  - Antagonist of IL-1 receptor (IL-1ra): anti-inflammatory
  - Protein C: coagulation
  - Neutrophil Gelatinase associated Lipocalcin (NGAL): organ injury

• Combination increases sensitivity and specificity

• Opportunities for research for the right combination and cost-effectiveness

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Biomarkers in Sepsis

Sepsis biomarkers: a review
Charalampos Pierrakos, Jean-Louis Vincent*

Rapid diagnosis of sepsis
Frank Bloos and Konrad Reinhart*

Key messages
- More than 170 different biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis.
- None has sufficient specificity or sensitivity to be routinely employed in clinical practice.
- Combinations of several biomarkers may be more effective than single biomarkers, but this requires further evaluation.
Multiplex PCR-Based Pathogen Detection

- Practical value of BC is impaired by delay in time to results and its positive in approx 30% patients
- No role in immediate treatment decision
- PCR detects specific sequences of bacterial and fungal rRNA


• Results theoretically available in 6-8 hrs
• Positive PCR is good to rule in infection but sensitivity is too low to rule out
• It has twice as many positive results than BC, but still leaves more than half of septic patients with a negative PCR
• Can detect only those pathogens covered by the target list of assay
• Recommended as an add-on to conventional culture-based methods, but cannot replace BC
Evaluation of an Emergency Department Triage Screening Tool for Suspected Severe Sepsis and Septic Shock

Catherine Patocka, Joel Turner, Xiaqing Xue, Eli Segal

Conclusions
The implementation of a sepsis triage screening tool significantly decreased the mean time to antibiotics in patients presenting to the ED with suspected severe sepsis or septic shock.
Diagnostic accuracy of a screening electronic alert tool for severe sepsis and septic shock in the emergency department

Sami Alsolamy1, Majid Al Salamah2, Majed Al Thagafi2, Hasan M Al-Dorzi3, Abdellatif M Marini4, Nawfal Aljerian2, Farhan Al-Enezi3, Fatimah Al-Hunaidi5, Ahmed M Mahmoud6, Ahmed Alamy7 and Yaseen M Arabi5,8

1. The screening tool automatically scans certain clinical and laboratory parameters, as well as the physician orders for fluid bolus or oxygen therapy (List 1).
2. If certain conditions are met (Sepsis-screening tool alert parameters), the system generates a “severe sepsis and septic shock” alert, and the test is considered to be positive.
3. This alert goes to the “nurse work list”.
4. If the criteria are not met, the test is considered to be negative (Figure 1).
5. The nurse responds to the alert and notifies a physician using a paging system, as instructed in the alert message.
6. To avoid multiple activations on the same patient, the alert is deactivated as follows:
   i. for 48 hours if the patient has suspected severe sepsis and septic shock,
   ii. for 24 hours if the patient does not have severe sepsis or septic shock, and
   iii. indefinitely if the code status precludes intensive care management of sepsis.
7. Alerts do not occur during deactivation time.
Conclusion

- Early diagnosis is the key
- Clinical examination + biomarkers + PCR aid in early detection
- Key ED interventions improve sepsis care
- Potential impact on patient outcomes
- Initiation of early treatment using Sepsis Resuscitation Bundles
THANK YOU