Early Recognition and Stratification of the Septic Patient
Vital signs, Scores and Biomarkers

Ricard Ferrer
Critical Care Center
Sabadell Hospital
Autonomous University of Barcelona
Spain
## Table 1  Diagnostic criteria for sepsis

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>Documented or suspected and some of the following;</td>
</tr>
<tr>
<td></td>
<td>General parameters</td>
</tr>
<tr>
<td></td>
<td>Fever (core temperature &gt;38.5°C)</td>
</tr>
<tr>
<td></td>
<td>Hypothermia (core temperature &lt;36°C)</td>
</tr>
<tr>
<td></td>
<td>Heart rate &gt;90 bpm or &gt;2 SD above the normal value for age</td>
</tr>
<tr>
<td></td>
<td>Tachypnea &gt;30 bpm</td>
</tr>
<tr>
<td></td>
<td>Altered mental status</td>
</tr>
<tr>
<td></td>
<td>Significant edema or positive fluid balance (&gt;20 ml/kg over 24 h)</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia (plasma glucose &gt;110 mg/dl or 7.7 mM/l) in the absence of diabetes</td>
</tr>
<tr>
<td><strong>Inflammatory parameters</strong></td>
<td>Leukocytosis (white blood cell count &gt;12,000/µl)</td>
</tr>
<tr>
<td></td>
<td>Leukopenia (white blood cell count &lt;4,000/µl)</td>
</tr>
<tr>
<td></td>
<td>Normal white blood cell count with &gt;10% immature forms</td>
</tr>
<tr>
<td></td>
<td>Plasma C reactive protein &gt;2 SD above the normal value</td>
</tr>
<tr>
<td></td>
<td>Plasma procalcitonin &gt;2 SD above the normal value</td>
</tr>
<tr>
<td><strong>Hemodynamic parameters</strong></td>
<td>Arterial hypotension (systolic blood pressure &lt;90 mmHg, mean arterial pressure &lt;70, or a systolic blood pressure decrease &gt;40 mmHg in adults or &lt;2 SD below normal for age)</td>
</tr>
<tr>
<td></td>
<td>Mixed venous oxygen saturation &gt;70%</td>
</tr>
<tr>
<td></td>
<td>Cardiac index &gt;3.5 l/min-m²</td>
</tr>
<tr>
<td><strong>Organ dysfunction parameters</strong></td>
<td>Arterial hypoxemia (PaO₂/FIIO₂ &lt;200)</td>
</tr>
<tr>
<td></td>
<td>Acute oliguria (urine output &lt;0.5 ml kg⁻¹ h⁻¹ or 45 mmH/d for at least 2 h)</td>
</tr>
<tr>
<td></td>
<td>Creatinine increase &gt;0.5 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Coagulation abnormalities (international normalized ratio &gt;1.5 or activated partial thromboplastin time &gt;60 s)</td>
</tr>
<tr>
<td></td>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia (platelet count &lt;100,000/µl)</td>
</tr>
<tr>
<td></td>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dl or 70 mmol/l)</td>
</tr>
<tr>
<td><strong>Tissue perfusion parameters</strong></td>
<td>Hyperlactemia (&gt;3 mmol/l)</td>
</tr>
<tr>
<td></td>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>
The Natural History of the Systemic Inflammatory Response Syndrome (SIRS)

A Prospective Study

M. Sigfrido Rangel-Frausto, MD, MSc; Didier Pittet, MD; Michele Costigan, RN, BSN; Taekyu Hwang, MS; Charles S. Davis, PhD; Richard P. Wenzel, MD, MSc

3768 pts
3 ICU, 3 wards

SIRS
2527 (68%)

Sepsis
649 (26%)
Previously classified as SIRS
285 (44%)

Severe Sepsis
467 (18%)
Previously classified as SIRS or sepsis
271 (58%)

Septic Shock
110 (4%)
Previously classified as SIRS, sepsis or Severe sepsis
78 (71%)

Continuum from SIRS to sepsis to severe sepsis to septic shock

Rangel-Frausto JAMA 1995;273:117
Early Recognition and Stratification

- Start treatment in early stages of sepsis.
- Reduce time to treatment. Sepsis golden hours.
- Identify patients at high risk of death
- Homogenize inclusion criteria in clinical trials.

Requires complete clinical evaluation + biomarkers
Time to Treatment

A delay in diagnosis and administration of the proper antibiotic may result in an increase in mortality.

Ferrer R et al. AJRCCM 2009;180:861–866
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RISSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP

In hospital mortality (all patients) 28-day mortality 60-day mortality

Mortality (%)
Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment*

Steroids

**The NEW ENGLAND JOURNAL of MEDICINE**

Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D.,
Mervyn Singer, M.D., F.R.C.P. Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D, Julie Berbenisty, R.N.,
Avnur Kalinka, M.D., Helmut Forst, M.D., Ph.D., Pierre-Francois Latte, M.D., Konrad Reichart, M.D.,
Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Biegele, M.D., Ph.D., for the CORTICUS Study Group

**Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock**

- **Treatment window: 72h**
- **Treatment window: 8h**
Identification of Severe Patients

Table 1 The 10 signs of vitality

<table>
<thead>
<tr>
<th>Ten signs of vitality</th>
<th>Triggering parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>≤36°C</td>
</tr>
<tr>
<td>Pulse</td>
<td>≤50 or ≥100/min</td>
</tr>
<tr>
<td>Pain</td>
<td>New or significant increase</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>≤6 or ≥20/min</td>
</tr>
<tr>
<td>SaO₂</td>
<td>&lt;90% and increased fiO₂</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>SBP &lt; 90 mmHg, MAP &lt; 60 mmHg</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Anxiety/lethargy</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>≥3 s</td>
</tr>
<tr>
<td>Urinary output</td>
<td>&lt;30 ml/h × 5 h (≤100 ml/4 h – excluding renal failure)</td>
</tr>
<tr>
<td>ScvO₂/base deficit</td>
<td>&lt;65% or B deficit ≥ 5 or lactic acid &gt; 2.0</td>
</tr>
</tbody>
</table>

• A 1-year cohort study in 28 intensive care units in Europe, Canada and Israel.
• 1,531 patients having a first episode of infection on admission or during the ICU stay.
• At 30 days, 11% of patients progress to severe sepsis and 13% to septic shock.

Alberti C and EuroSepsis, AJRCCM 2005;171:461-8
# RISSC: Risk of infection to Severe Sepsis and Shock Score

Alberti C and EuroSepsis, AJRCCM 2005;171:461-8

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\hat{b}$ (SE)</th>
<th>Points From the Model (No.)</th>
<th>Points From Bootstrap (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin &gt; 30 $\mu$mol/L</td>
<td>$0.30 (0.12)$</td>
<td>3</td>
<td>$3.0 (2.2-3.9)$</td>
</tr>
<tr>
<td>Heart rate &gt; 120/minute</td>
<td>$0.29 (0.11)$</td>
<td>3</td>
<td>$3.0 (2.2-3.7)$</td>
</tr>
<tr>
<td>Sodium &gt; 145 mmol/L</td>
<td>$0.41 (0.13)$</td>
<td>4</td>
<td>$4.0 (3.1-5.0)$</td>
</tr>
<tr>
<td>Platelets &lt; $150 \times 10^9$/L</td>
<td>$0.39 (0.11)$</td>
<td>4</td>
<td>$3.9 (3.2-4.6)$</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 110 mm Hg</td>
<td>$0.41 (0.11)$</td>
<td>4</td>
<td>$4.1 (3.4-4.8)$</td>
</tr>
<tr>
<td>Temperature &gt; 38.2°C</td>
<td>$0.49 (0.10)$</td>
<td>5</td>
<td>$4.9 (4.2-5.6)$</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>$0.64 (0.13)$</td>
<td>6.5</td>
<td>$6.4 (5.5-7.4)$</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>$0.38 (0.11)$</td>
<td>4</td>
<td>$3.8 (3.1-4.5)$</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>$0.41 (0.18)$</td>
<td>4</td>
<td>$4.1 (2.9-5.3)$</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>$0.23 (0.11)$</td>
<td>2.5</td>
<td>$2.3 (1.5-3.1)$</td>
</tr>
<tr>
<td>Aerobic gram-negative bacilli</td>
<td>$0.32 (0.14)$</td>
<td>3</td>
<td>$3.2 (2.3-4.2)$</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>$0.59 (0.20)$</td>
<td>6</td>
<td>$5.8 (4.4-7.2)$</td>
</tr>
</tbody>
</table>

![Graph showing percentage of patients with sepsis at initial presentation and percentage progressing to severe sepsis across different RISSC scores.](image)
Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤300</td>
<td>≤200†</td>
<td>≤100†</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>&gt;150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Platelets × 10⁹/µL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>Bilirubin, mg/dL‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Hypotension</td>
<td>No hypotension</td>
<td>Mean arterial pressure &lt;70 mm Hg</td>
<td>DOP ≤5 or dobutamine (any dose)§</td>
<td>DOP &gt;5, epinephrine ≤0.1, or norepinephrine ≤0.1§</td>
<td>DOP &gt;15, epinephrine &gt;0.1, or norepinephrine &gt;0.19</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Score Scale</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>8-0</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9 or &lt;500</td>
<td>&gt;5.0 or &lt;200</td>
</tr>
<tr>
<td>or urine output, mL/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Change in SOFA Score During First 48 Hours**
- Decrease
- Increase or No Change

**Lopes Ferreira et al. JAMA 2001;286:1754-8**
Early changes in organ function predict eventual survival in severe sepsis*

Crit Care Med 2005;33:2194-2201

Mitchell M. Levy, MD, FCCM; William L. Macias, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM; James A. Russell, MD; Eliezer Silva, MD, PhD; Benjamin Trzaskoma, MS; Mark D. Williams, MD

Dynamic Assessment

• Placebo arms of two RCT on severe sepsis (n= 1036): Standard treatment.
• Baseline SOFA score vs Day 1 SOFA score
• Outcome of severe sepsis may largely be determined by organ dysfunction evolution after first day of treatment
PIRO concept

**Predisposition**
- Genetic susceptibility
- Coexisting health complications

**Insult (Infection)**
- Pathogen, toxicity and sensitivity
- Location and compartmentalization

**Response**
- Increased biomarkers or mediators
- Manifested physiologic symptoms

**Organ Dysfunction**
- Number of failing organs

*Carrigan Clin Chem 2004;50:1301*
Mortality in Emergency Department Sepsis (MEDS) score predicts 1-year mortality

Nathan I. Shapiro, MD, MPH; Michael D. Howell, MD; Daniel Talmor, MD, MPH; Michael Donnino, MD; Long Ngo, PhD; David W. Bates, MD, MSc

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposition</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 65 year</td>
<td>3</td>
</tr>
<tr>
<td>Nursing home resident</td>
<td>2</td>
</tr>
<tr>
<td>Rapidly terminal comorbid illness</td>
<td>6</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Lower respiratory infection</td>
<td>2</td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>Bands &gt; 5%</td>
<td>3</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td></td>
</tr>
<tr>
<td>Tachypnea or hypoxemia</td>
<td>3</td>
</tr>
<tr>
<td>Septic shock</td>
<td>3</td>
</tr>
<tr>
<td>Platelet count &lt;150,000/mm³</td>
<td>3</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>2</td>
</tr>
</tbody>
</table>

[Graph showing survival probability vs. survival time]
Why Do We Need Biomarkers For Diagnosing and Staging Sepsis?

- Heart Attack
  - EKG
  - Cardiac Enzymes
    - CPK
    - MB
  - Troponin
  - CRP
  - BNP
  - Echocardiogram
  - Cardiac Catheterization

- Sepsis
  - Signs and symptoms
    - Fever, chills, elevated WBC, difficulty breathing
  - “Look sick”
  - Cultures (30-40% +)
  - Objective measurements
Sepsis definitions in XXI century?

A poll of the SCCM and ESICM showed that 86% of the responding intensivists doubt the validity of existing criteria for sepsis at the bedside!

Poeze Critical Care 2004;8:R409
UTILITY OF BIOMARKER OF SEPSIS

- Screening
- Diagnosis
- Risk Stratification
- Identify responders to therapy.
- Monitoring of the Response to Therapy (Surrogate end point).
Diagnosis of Infection

- Site, type and extent of infection have significant impact on prognosis
- Gram positive and Gram negative could elicit different host response

Biomarkers
- Unable to identify the nature of the underlying infection
- Helpful in the diagnosis of infection
- *Not risk factors*

*Levy ICM 2003;29:530*  
*Marshall CCM 2003;31:1560*
INFECTION
risk factor vs biomarker vs biomediator

- **Risk Factor**
  - clinical or laboratory sign that identifies a group of patients with a specified risk to develop an infection in the future (when?, severity?)

- **Biomarker**
  - absent if the patient is not infected, appear concomitantly and ideally precede the infection, disappear with successful therapy or remain elevated if infection is refractory to treatment

- **Biomediator**
  - causes a disease and that is present during some or all of the clinical expression of the disease (Koch’s postulates)

Marshall JC. CCM 2003;31:1560
What Do We Expect From An Ideal Sepsis Marker?

- To be highly sensitive and specific for sepsis
- To allow the differentiation between infectious and non-infectious causes of inflammation, organ dysfunction and shock
- To be present at the onset or even before the appearance of the clinical signs of sepsis
- To have prognostic value
- To indicate the severity and the course of sepsis
- To be biologically plausible
APPROACHES TO IDENTIFICATION OF BIOMARKERS

• Biological association with a disease or therapeutic intervention (endotoxin, TNF, IL-6).
• Absence of a biological link (PCT).
• Unbiased approaches of large number of molecular species (microarray, proteomics).
• Appropriated control.
MARKER ANALYSIS

Over 150 markers analyzed by immunoassay, including various pro-forms, variants, and fragments.

Markers of:
- **Pro-inflammation** (e.g., CRP, TNFα, IL-1β, IL-8)
- **Anti-inflammation** (e.g., IL-10, IL-6, soluble TNF receptors)
- **Coagulation and fibrinolysis** (e.g., D-dimer, tissue factor, protein C)
- **Apoptosis** (e.g., caspase-3)
- **Vasoregulation** (e.g., BNP, proBNP, bigET-1, calcitonin)
- **Organ and tissue dysfunction** (e.g., NGAL, myoglobin, I-FABP, pulmonary surfactant proteins)
The Biomarker Response in Sepsis

• Most commonly studied and correlated with outcomes
  – CRP
  – Pro-calcitonin (PCT)
  – IL-6
  – HMGB1
  – STREM1
  – Coagulation parameters: Protein C
  – Panels of Biomarkers
Time course: Endotoxin Challenge

Reinhardt K et al. Crit Care Clin 22 2006 503-19
C-Reactive Protein (CRP)

- CRP measurement is a rapid, reproducible and inexpensive.

- Acute Phase Protein
  - The acute phase response accompanies inflammation.
  - Acute phase proteins are defined as those proteins whose plasma concentrations increase by at least 25 percent during inflammatory states.
  - Changes in levels of acute phase proteins result from cytokines: IL-6, IL-8 effect on hepatocytes.
CPR Diagnostic Marker of Infection

CRP > 8.7 mg/dl  Cut-off

Sensitivity 93.4%
Specificity 86.1%
AUC 0.93
Positive LR 6.71
Negative LR 0.008

Povoa Clin Microbial Infect 2005;11:101-108
Sierra Intensive Care Med 2004;30:2038-2045
Biomarkers of infection

- **Single determination**
  - value in the diagnosis of infection

- **Serial determinations**
  - as predictor of infection
  - monitoring clinical course and response to antibiotic therapy

*Póvoa ICM 2002;28:235*
CRP as a marker of infection prediction day -5 to day 0

N=63 pts (28 controls; 35 infected – documentation)

p<0.001
CRP as a marker of infection prediction
day -5 to day 0

N=63 pts (28 controls; 35 infected – documentation)

Max daily ∆ CPR

AUC (day -5 to day 0)
0.86 (95% CI: 0.75–0.93)

maximum daily ∆ CRP > 4.1 mg/dL → ICU-acquired infection
sensitivity 0.92, specificity 0.71, LR+ 3.22, LR- 0.11
Differentiation between Sepsis and SIRS

**PCT**

Data from 12 published papers

*Carrigan Clin Chem 2004;50:1301*

**CRP**

N=76 infected pts

P=0.024; $r^2=0.12$

*Póvoa Clin Microbiol Infect 2005;11:101*
PCR as a Marker of Severity of Sepsis

N=313 ICU pts

\[
\text{PCR} = 7.00 + 1.05 \times \text{SOFA}
\]

R-Square = 0.12

\[ r = 0.34, r^2 = 0.12 \]

p=0.004

N=76 infected pts

Lobo Chest 2003;123:2043

Póvoa Clin Microbiol Infect 2005;11:101
**PCR as a Marker of Severity of Sepsis**

Joana Silvestre  
P. Pávoa  
L. Coelho  
E. Almeida  
P. Moreira  
A. Fernandes  
R. Mealha  
H. Sabino  

Is C-reactive protein a good prognostic marker in septic patients?

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>Documented Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dL)</td>
<td>0.55 (0.45–0.65)</td>
<td>0.66 (0.53–0.79)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>0.48 (0.38–0.58)</td>
<td>0.44 (0.29–0.59)</td>
</tr>
<tr>
<td>WCC (×1,000) mL⁻¹</td>
<td>0.46 (0.35–0.56)</td>
<td>0.6 (0.46–0.73)</td>
</tr>
<tr>
<td>APACHE II</td>
<td>0.75 (0.67–0.83)</td>
<td>0.65 (0.51–0.78)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>0.82 (0.75–0.89)</td>
<td>0.75 (0.63–0.86)</td>
</tr>
<tr>
<td>SOFA</td>
<td>0.80 (0.72–0.88)</td>
<td>0.77 (0.66–0.88)</td>
</tr>
</tbody>
</table>

area under the receiver operating characteristics curves

The Time Course of Blood C-reactive Protein Concentrations in Relation to the Response to Initial Antimicrobial Therapy in Patients with Sepsis

X. Schmit, J.L. Vincent
PCR. Conclusion

• Single determination could be useful in the diagnosis of infection.

• Daily measurement of CRP is easy and inexpensive to perform, and can aid in the diagnosis of sepsis and in assessing response to antibiotic therapy.

• Limited value in determining prognosis.
Procalcitonin (PCT)

- PCT is a 13-kd propeptide of calcitonin. In healthy individuals, levels of PCT are below 0.1 ng/mL.

- In patients with sepsis, PCT levels may increase up to 5000 to 10,000 times with calcitonin still in the normal range.

- In contrast to the short half-life of calcitonin (10 minutes), the half-life of PCT is approximately 24 hours.
Procalcitonin: a ‘hormokine’

- In sepsis and inflammation
  - Proinflammatory mediators (IL-1β, TNFa, LPS) induce CT-mRNA
  - Unprocessed PCT is released

- Classical neuroendocrine paradigm
  - Expression of CT-mRNA is restricted to neuroendocrine cells (C-cells of the thyroid)
  - PCT is processed to Calcitonin

Linscheid P et al., Endocrinology, 2003
Procalcitonin Triggers & Response

- Bacterial endotoxins are a major stimulus for PCT induction, but gram-positive infections may also induce a PCT release.

- Major surgery, severe trauma, or burns may induce an increase of PCT levels.

- Plasma levels observed under these conditions are not as high, however, as in patients with severe sepsis or septic shock.

- PCT elevation is recognized already 2 hours after endotoxemia bacteriemia.
Patients with PCT levels below or equal to 0.5 ng/mL are unlikely to have severe sepsis or septic shock (de Werra 1997).

Levels above a threshold of 2 ng/mL identify patients at high risk (Muller 2000).

PCT concentrations exceeding 10 ng/mL usually occur in patients with organ failure remote to the site of infection (Monneret 1997, Meisner 1999).
### Comparison of Procalcitonin Assays

<table>
<thead>
<tr>
<th>Assay</th>
<th>Source</th>
<th>Type of Test</th>
<th>Status</th>
<th>Peptides Identified</th>
<th>Low Assay Standard pg/mL</th>
<th>Functional Sensitivity pg/mL</th>
<th>Healthy Control pg/mL</th>
<th>Assay Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMITest²</td>
<td>BRAHMS</td>
<td>ILMA</td>
<td>Commercial</td>
<td>ProCT and CT:CCP1</td>
<td>80</td>
<td>500</td>
<td>235</td>
<td>2 hrs 45 mins</td>
</tr>
<tr>
<td>ProCa-S</td>
<td>BRAHMS</td>
<td>ILMA</td>
<td>Research</td>
<td>ProCT and CT:CCP1</td>
<td>5</td>
<td>20</td>
<td>31</td>
<td>3 hrs</td>
</tr>
<tr>
<td>PCT sensitive</td>
<td>BRAHMS</td>
<td>ILMA</td>
<td>Research</td>
<td>ProCT and CT:CCP1</td>
<td>5</td>
<td>50</td>
<td>13</td>
<td>3 hrs</td>
</tr>
<tr>
<td>Kryptor</td>
<td>BRAHMS</td>
<td>TRACE</td>
<td>Commercial</td>
<td>ProCT and CT:CCP1</td>
<td>20</td>
<td>60</td>
<td>53</td>
<td>50, 25–45 mins⁴</td>
</tr>
<tr>
<td>QPCT</td>
<td>BRAHMS</td>
<td>Solid-phase</td>
<td>Commercial</td>
<td>ProCT and CT:CCP1</td>
<td>(500)</td>
<td>(500)</td>
<td>(500)</td>
<td>Bedside</td>
</tr>
<tr>
<td>NProCT</td>
<td>Becker</td>
<td>ELISA</td>
<td>Research</td>
<td>ProCT and NProCT</td>
<td>10</td>
<td>20</td>
<td>33⁵</td>
<td>16–18 hrs</td>
</tr>
</tbody>
</table>
**Procalcitonin Thresholds**

- **Suspicion of sepsis**
  - $< 0.5 \mu g/L$
  - $\geq 0.5$ but $< 2 \mu g/L$

- **Measure PCT**
  - $\geq 2 \mu g/L$ → **Confirmed sepsis**
  - $< 2 \mu g/L$

- **Strong suspicion**
  - $\geq 2 \mu g/L$
  - $< 0.5$ but $< 2 \mu g/L$ → **Uncertain Dx**

- **Re-measure PCT (12-24h)**
  - $< 0.5 \mu g/L$
  - $\geq 2 \mu g/L$
PCT improves the reliability of the clinical diagnosis of sepsis

Patients with SIRS and suspicion of infection (n=78)

Pattern calculation for ICU patients with SIRS with / without PCT on a clinical model

S. Harbarth et al. Am J Respir Crit Care Med 2001;164:396-402
Differentiation between Sepsis and SIRS

Plasma levels of PCT, IL-6 und IL-8

Medical and surgical ICU pat. (n=78), with SIRS and suspicion of infection

S. Harbarth et al. Am J Respir Crit Care Med 2001;164:396-402
Meta-Analyses
Meta-Analysis: PCT differentiates between bacterial and non-infectious causes of inflammation

10 Studies, 905 Patients

PCT is significantly better than CRP for the differential diagnosis of bacterial vs. non-infectious cause of inflammation.

PCT: 88 % Sensitivity / 81 % Specificity
CRP: 75 % Sensitivity/ 67 % Specificity

Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis.

- Global diagnostic OR for PCT
  - 2966 pts
  - 25 studies
  - 15.7 (9.1-27.1)
  - Risk for positive PCT test in infected pts was 16-fold higher than in non-infected pts.

- Global diagnostic OR for CRP
  - 1322 Pts
  - 15 studies
  - 5.4 (3.2-9.2)
  - $Q^* 0.78$ vs. $0.71 \ p = .02$

Uzzan et al.

*Crit Care Med 2006; 34:1996–2003*
Meta-analysis: Limitations

- Heterogeneity (Uzzan)
  - Age
  - Medical vs. Surgical
    - Uzzan: No medical pts
  - Co-morbidities
  - Underlying illness
    - Cardiac surgery, peritonitis, meningitis, burns
- Single sample (Uzzan)
  - Timing of sample

- Consecutive patients
- Publication bias
  - Negative studies
  - Sample size
- Level of sepsis
  - Critically ill or not
- Diagnostic Accuracy of OR
  - 0-25: Test of little use
  - 25-100: intermediate value
  - >100: excellent performance

Tang B. Crit Care Med 2007
Accuracy of Procalcitonin for Sepsis Diagnosis in Critically Ill Patients: Systemic Review and Meta-Analysis

Sensitivity and specificity: 71% (95% CI 67–76)
AUC 0.78 (95% CI 0.73–0.83).

Tang BM et al Lancet Infect Dis 2007;7:210-17
Static vs. Dynamic Measurements
Study Goal
- PCT and CRP in multitrauma
- Clinical value of the markers in complications due to: SIRS, Sepsis, Organ dysfunction

Design
- Prospective,
- no burn patients
- PCT LIA

Patients
- 90 ICU patients

Results
- Mechanical trauma induces only low PCT level; maximum, PCT-conc. on day 1-2 after trauma and fast return to normal values.
- Initial PCT > 1ng/ml more common in trauma patients who will develop complications
- PCT allows an early and reliable diagnosis of sepsis also in trauma patients
- CRP has a slow kinetic and the concentrations have no prognostic value!

Crit Care 2006;10:R1
Survival & Concentration Changes over time for PCT and CRP after Multiple Trauma

Correlation of procalcitonin and C-reactive protein to inflammation, complications, and outcome during the intensive care unit course of multiple-trauma patients
Michael Meisner¹, Heide Adina² and Joachim Schmidt²

PCT<0.8 ng/ml:
- 94 % Probability of survival (NPV)
- 24 % Probability of non-survival (PPV)

Crit Care 2006;10:R1
Procalcitonin increase in early identification of critically ill patients at high risk of mortality.

Antibiotic therapy: when to stop?

- After 7–10 days of antibiotic therapy guided by clinical response (1D) ???
- When SIRS or shock is not due to a bacterial infection (1D)
- Stop vancomycin when negative MRSA cultures (48 hrs)
- According to an algorithm based on procalcitonin
Why should we care about duration of antibiotic therapy?

- Bacterial resistance
- Toxicity - interactions
- €€€
Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients
A Randomized Trial

Vandack Nobré¹, Stephan Harbarth², Jean-Daniel Graf³, Peter Rohner⁴, and Jérôme Pugin¹

PCT group

Daily plasma PCT measurement, given to the clinician
Stop antibiotics when PCT has decreased > 90% from initial value if patient stable (not before D5)

Control group

Daily plasma PCT measurement, hidden from the clinician
Stop antibiotics according to empiric rules
PCT guidance allows to shorten antibiotic therapy

Median time 6 vs. 10 days
Median reduction: **4 days**
HR: 1.9 (1.2-3.1)
\( p=0.009 \)

Nobre et al. Am J Respir Crit Care Med 2008
Algorithm to guide the duration of antibiotic therapy

Clinical suspicion of severe sepsis or septic shock*

Antibiotic therapy

PCT D1

Cultures

PCT D5

PCT decreased < 90% on D5

PCT decreased > 90% on D5**

Daily PCT measurements

PCT decreased > 90% on Dx **

STOP antibiotics

PCT Dx

PCT decreased < 90% on D5

STOP antibiotics

• non-complicated infections
** and patient stable
Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial


---

**Guidelines for starting of antibiotics**

- **Concentration <0.25 μg/L**
  - Antibiotics strongly discouraged
- **Concentration ≥0.25 and <0.5 μg/L**
  - Antibiotics discouraged
- **Concentration ≥0.5 and <1 μg/L**
  - Antibiotics encouraged
- **Concentration ≥1 μg/L**
  - Antibiotics strongly encouraged

If blood sample taken for calculation of procalcitonin concentration at early stage of episode, obtain a second procalcitonin concentration 6-12 h later

---

**Guidelines for continuing or stopping of antibiotics**

- **Concentration <0.25 μg/L**
  - Stopping of antibiotics strongly encouraged
- **Decrease by ≥80% from peak concentration, or concentration ≥0.25 and <0.5 μg/L**
  - Stopping of antibiotics encouraged
- **Decrease by <80% from peak concentration, and concentration ≥0.5 μg/L**
  - Continuing of antibiotics encouraged
- **Increase of concentration compared with peak concentration and concentration ≥0.5 μg/L**
  - Changing of antibiotics strongly encouraged
Use of procalcitonin to reduce patients’ exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

Procalcitonin. Conclusion

- Measurement of procalcitonin can aid in the diagnosis and stratification of sepsis.
- Serial determinations could help in determining prognosis.
- Serial determinations could be useful in guiding antibiotic therapy.
Cytokines such as IL-6 and IL-8 of limited use clinically because of short half life and rapid receptor binding/antagonism.

IL-6 and IL-8 levels are closely related to the severity of the physiologic response to infection and systemic inflammation.

Thus, non-specific: elevated in major surgery, severe trauma, burns, autoimmune disorders, viral infection.
High-mobility group box 1 (HMGB1)

- HMGB1 is released from myeloid cells exposed to lipopolysaccharide.
- HMGB1 has delay kinetics and remains in the circulation for extended periods of time.
- HMGB1 may be an important mediator and therapeutic target in sepsis and related conditions.
Circulating high-mobility group box 1 (HMGB1) concentrations are elevated in both uncomplicated pneumonia and pneumonia with severe sepsis.

Derek C. Angus, MD, MPH; LiHong Yang, PhD; Ian Kong, PhD; John A. Kellum, MD; Russell L. Delude, PhD; Kevin J. Tracey, MD; Lisa Weissfeld, PhD; for the GenIMS Investigators
HMGB1 as a predictor of organ dysfunction and outcome in patients with severe sepsis
Triggering receptor expressed on myeloid cells-1 (TREM-1)

- Immunoglobulin up-regulated in response to infection.
- Soluble TREM-1 is shed from membranes of activated phagocytic cells and can be quantified.

Soluble Triggering Receptor Expressed on Myeloid Cells and the Diagnosis of Pneumonia

Sébastien Gibot, M.D., Aurélie Cravoisy, M.D. Bruno Levy, M.D., Ph.D., Marie-Christine Bene, M.D., Ph.D., Gilbert Faure, M.D., Ph.D., and Pierre-Edouard Bollaert, M.D., Ph.D.

Independent predictors for diagnosing pneumonia

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P Value</th>
<th>Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pulmonary infection score &gt;6</td>
<td>0.002</td>
<td>3.0 (1.5–5.9)</td>
</tr>
<tr>
<td>Tumor necrosis factor α &gt;150 pg/ml of BAL fluid</td>
<td>0.004</td>
<td>2.4 (1.8–5.8)</td>
</tr>
<tr>
<td>Interleukin-1β &gt;75 pg/ml of BAL fluid</td>
<td>0.003</td>
<td>2.7 (2.0–13.2)</td>
</tr>
<tr>
<td>sTREM-1 &gt;5 pg/ml of BAL fluid</td>
<td>&lt;0.001</td>
<td>41.5 (20.9–77.6)</td>
</tr>
</tbody>
</table>

Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis

Sébastien Gibot, MD, PhD; Aurélie Cravoisy, MD; Marie Nathalie Kolopp Sarda, PharmD, PhD; Marie-Christine Bénéc, PharmSci, PhD; Gilbert Faure, MD, PhD; Pierre-Edouard Bollaert, MD, PhD; Bruno Levy, MD, PhD
Severe Protein C Deficiency at Baseline is Associated with Early Death

Kaplan-Meier estimates of mortality within the PROWESS placebo group

- **PC > 80% (N=105)**
- **PC = 41-80% (N=385)**
- **PC <= 40% (N=285)**

Survival Rate (%)

Survival Rate (%) vs. Days

- **p < 0.0001**

- **Survival Rate (%)**
  - 0%
  - 10%
  - 20%
  - 30%
  - 40%
  - 50%
  - 60%
  - 70%
  - 80%
  - 90%
  - 100%

- **Days**
  - 0
  - 4
  - 8
  - 12
  - 16
  - 20
  - 24
  - 28
POINT-OF-CARE ASSAY SYSTEM: The ECG of Sepsis?

- Comprised of a portable instrument and a microfluidics array
- No sample preparation
- Results available in 15 minutes
A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis

Nathan I. Shapiro, MD, MPH; Stephen Trzeciak, MD, MPH; Judd E. Hollander, MD; Robert Birkhahn, MD; Ronny Otero, MD; Tiffany M. Osborn, MD; Eugene Moretti, MD, MHS; H. Bryant Nguyen, MD; Kyle J. Gunnerson, MD; David Milzman, MD; David F. Gajeski, MD; Munish Goyal, MD; Charles B. Cairns, MD; Long Ngo, PhD; Emanuel P. Rivers, MD, MPH

- **Design**: Prospective multicenter observational study.
- **Patients**: 971 patients septic enrolled.
- **Nine biomarkers were assayed.**
- Multivariable logistic regression was used to identify an optimal combination of biomarkers to create a panel.
- Derived formula for weighting biomarker values was used to calculate a “sepsis score”

Crit Care Med 2009;37:96-104
## BIOMARKER PANEL IN SEVERE SEPSIS

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Overall Population</th>
<th>Severe Sepsis</th>
<th>Receiver Operating Characteristic Area under the Curve (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Yes (n = 506)</td>
<td>No (n = 465)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Macrophage inhibitory protein-3, ng/mL</td>
<td>0.76 (0.91)</td>
<td>1.02 (0.89)</td>
<td>0.48 (0.83)</td>
</tr>
<tr>
<td></td>
<td>0.74 (0.12–1.39)</td>
<td>1.06 (0.41–1.62)</td>
<td>0.39 (0.15–1.06)</td>
</tr>
<tr>
<td>D-dimer, ng/mL</td>
<td>2200 (1733)</td>
<td>2736 (1730)</td>
<td>1612 (1535)</td>
</tr>
<tr>
<td></td>
<td>2513 (1156–4552)</td>
<td>1009 (456–2249)</td>
<td>66 (60)</td>
</tr>
<tr>
<td>C-reactive protein, μg/mL</td>
<td>61 (62)</td>
<td>35 (61)</td>
<td>18 (60)</td>
</tr>
<tr>
<td></td>
<td>61 (31–131)</td>
<td>84 (43–146)</td>
<td>48 (10–98)</td>
</tr>
<tr>
<td>Neutrophil gelatinase-associated lipocalin, ng/mL</td>
<td>267 (322)</td>
<td>381 (373)</td>
<td>144 (157)</td>
</tr>
<tr>
<td></td>
<td>128 (50–325)</td>
<td>240 (103–565)</td>
<td>71 (50–151)</td>
</tr>
<tr>
<td>Protein C, μg/mL</td>
<td>2.58 (1.08)</td>
<td>2.26 (1.02)</td>
<td>2.91 (1.04)</td>
</tr>
<tr>
<td></td>
<td>2.51 (1.75–3.32)</td>
<td>2.12 (1.40–2.89)</td>
<td>2.90 (2.25–3.60)</td>
</tr>
<tr>
<td>Interleukin-1 receptor antagonist (interleukin-1ra), ng/mL</td>
<td>2371 (4228)</td>
<td>3625 (596)</td>
<td>1005 (295)</td>
</tr>
<tr>
<td></td>
<td>700 (288–275)</td>
<td>1267 (499–4339)</td>
<td>384 (208–859)</td>
</tr>
<tr>
<td>Tumor necrosis factor receptor 1a (tumor necrosis factor-R1a), ng/mL</td>
<td>17.5 (24.7)</td>
<td>24.3 (29.6)</td>
<td>10.1 (14.9)</td>
</tr>
<tr>
<td></td>
<td>17.5 (48–17.7)</td>
<td>15.1 (7.4–27.3)</td>
<td>5.5 (3.5–10.3)</td>
</tr>
<tr>
<td>Peptidoglycan recognition protein, ng/mL</td>
<td>119 (153)</td>
<td>156 (183)</td>
<td>82 (97)</td>
</tr>
<tr>
<td></td>
<td>61 (40–134)</td>
<td>93 (40–179)</td>
<td>59 (34–168)</td>
</tr>
<tr>
<td>Brain natriuretic peptide, ng/mL</td>
<td>287 (761)</td>
<td>401 (877)</td>
<td>163 (587)</td>
</tr>
<tr>
<td></td>
<td>42 (5–211)</td>
<td>94 (18–375)</td>
<td>15 (5–73)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; CI, confidence interval.

The values used for quartile transformations for each individual marker are defined in the table above as follows: quartile 1: (0, beginning IQR range); quartile 2: (lower IQR, median); quartile 3: (median, upper IQR); quartile 4: (> upper IQR).

Crit Care Med 2009;37:96-104
BIOMARKER PANEL IN SEVERE SEPSIS

Crit Care Med 2009;37:96-104
MULTIVARIATE LOGISTIC REGRESSION AND SEPSIS SCORE

Probability of severe sepsis:

Raw Score = \(-8.7 + 0.63 \times \text{NGAL quartile} + 0.41 \times \text{IL-1ra quartile} + 0.50 \times \text{PC quartile}\)

Crit Care Med 2009;37:96-104
SEPSIS SCORE

A Prevalence of Severe Sepsis by Sepsis Score

B Prevalence of Septic Shock by Sepsis Score

C Mortality Rate by Sepsis Score

Crit Care Med 2009;37:96-104
SEPSIS SCORE

Crit Care Med 2009;37:96-104
Proteomics: Heat Map

- Severe sepsis in acute phase vs stable.
- Quantification of 170 proteins in 8 samples.
- Blue = up-regulated protein in acute phase.
- Red = up-regulated protein in stable phase.
Biomarkers in Sepsis
Can we use them in staging?

Answers in 2010:
- Predisposition – NO
- Infection – YES
- Response – YES
- Organ Dysfunction – YES

1. NEVER to be used solely
2. Always in conjunction with a complete clinical evaluation
3. Perfect knowledge of the biology, strengths and limitations of biomarker
Conclusions

- Early identification and short time to treatment is key in reducing mortality in sepsis.
- Our ability to diagnose and predict severity is limited by the insensitivity and nonspecific clinical and laboratory parameters.
- CRP and IL-6 are sentinels markers of inflammation and infection.
- PCT enhance clinicians’ ability to diagnose the presence of infection and perhaps guide antimicrobial therapy.
- Combinations of several biomarkers may be more effective than single biomarkers, but this requires further evaluation.
FUTURE RECOMMENDATIONS

- To Standardize Assays and Understand the Differences.
- Rigorous Methodologic Approaches to characterize the value.
- Wider Use of Validated Biomarkers in Decision-Making Processes.
- Clinical Trials.
- Pooling Data and Defining Biochemical Natural History of Sepsis.
- Increase Collaboration between Companies, Clinical Investigators and Regulatory Agencies.
THANK YOU!