SEPSIS BIO-MARKERS AFTER CARDIAC SURGERY

Dr/ Sameh R Ismail
Consultant Pediatric Cardiac Intensive Care
King Abdulaziz Medical City for National Guard
Introduction

• “SEPSIS AT ITS INCEPTION IS DIFFICULT TO RECOGNIZE BUT EASY TO TREAT; AND IF LEFT UNATTENDED IT BECOMES EASY TO RECOGNIZE BUT DIFFICULT TO TREAT”

Machiavelli
The Sepsis Continuum

SIRS  | Sepsis  | Severe Sepsis  | Septic Shock

- A clinical response arising from a nonspecific insult, with ≥2 of the following:
  - T >38°C or <36°C
  - HR >90 beats/min
  - RR >20/min
  - WBC >12,000/mm³ or <4,000/mm³ or >10% bands

SIRS with a presumed or confirmed infectious process

Sepsis with organ failure

MOD & Refractory Hypotension

SIRS = systemic inflammatory response syndrome

Slide modified from Eloise Harman ppt
Introduction
Mortality In Septic Patients

Incidence

Sepsis
400,000

Severe Sepsis
300,000

Septic Shock

Mortality

7-17%

20-53%

53-63%

Approximately 200,000 patients including 70,000 Medicare patients have septic shock annually

Balk, R.A. Crit Care Clin 2000; 337:52
CHALLENGES:

- Sepsis: Major cause of morbidity and mortality
- Clinical presentation is often similar as with viral or noninfectious causes
- Anti-biotic treatment of viral infections/noninfectious causes is not only ineffective, but:
  - Costs
  - Risk of toxicity
  - Resistance
Problem: Time to and accuracy of diagnosis

- **SIRS criteria**
  - Heart rate
  - Respiration rate
  - Blood temperature
  - Leucocyte count

- **Blood culture**

Gold standard of diagnosis
- Sensitivity is low
- Takes more than 24 hours
Current practice
Treating Sepsis

**Current practice**

- Clinical diagnosis supported by non-specific & tests eg: WBC, CRP, radiology
- **Guess** what is the likely infecting organism
- **Guess** what antibiotic to use
- **Wait** to see if it works....?
- If it doesn't ....have another guess
- add/upgrade/change abx
- If it still doesn’t work ask micro/ID/pharma
- to **guess** as well
- The treating physician sometimes cannot decide which direction to go
NEED: something that help

- Early correct diagnosis ????
- Infection vs non-inf????
- Bacterial vs non-bact??????
- Use of antibiotics only when needed??
- De-escalate??
- Use short course of therapy ??
- Risk stratification??
What is the SOLUTION?

What is The ideal biomarker?
The ideal biomarker

1. Does not increase in the absence of the disease (high specificity)
2. Increases pathologically in the presence of disease (high sensitivity)
3. Relates to the disease burden and extent
4. Changes in accordance with the clinical evolution, reflecting the current status of disease
5. Anticipates clinical changes before it happens
6. Shows no major fluctuation in serum levels
7. Adds independent information about the risk or prognosis
8. Reproducible
9. Easy and cheap
<table>
<thead>
<tr>
<th></th>
<th>Specific response to infection</th>
<th>Sensitive for inflammation</th>
<th>Clinical use</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>++++</td>
<td>+</td>
<td>Rapid induction (2 h)</td>
<td>Low sensitivity for local infections</td>
<td>High specificity for severe sepsis and septic shock release in severe SIRS settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High biostability half time 24 h</td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>wide biologic range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slow induction time (peak &gt; 24 h)</td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low biologic range</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No correlation with severity of inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokines</td>
<td>+</td>
<td>+++</td>
<td>High sensitivity</td>
<td>Short half time in plasma (minutes)</td>
<td>High variability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rapid induction (minutes)</td>
<td></td>
<td>Low biostability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low correlation with severity of inflammation</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>+</td>
<td>+++</td>
<td>Simple method</td>
<td>Expensive</td>
<td>Very low specificity</td>
</tr>
<tr>
<td>Temperature</td>
<td>+</td>
<td>++++</td>
<td>Simple method</td>
<td></td>
<td>Very low specificity</td>
</tr>
</tbody>
</table>
C Reactive Protein (CRP)
CRP

- acute phase protein; synthesised in liver
- IL-6 (and IL-1 and TNFα) stimulate synthesis via action on promoter

- binds bacterial polysaccharide, chromatin

- activates the classical complement pathway

- increased in the immune inflammatory response; especially in bacterial (vs viral) infection
Diseases associated with only minor elevations of C-reactive protein

- Systemic lupus erythematosus
- Systemic sclerosis
- Dermatomyositis
- Sjögren’s disease
- Ulcerative colitis
- Leukaemia
- Graft-versus-host disease
PRO-CALCITONIN PCT
Publications about Procalcitonin since 1980

**Pro-calcitonin**

- PCT is the 116-amino acid prohormone of calcitonin
- In healthy individuals, PCT is produced by C cells of thyroid gland
- Increased markedly in septic states
  - Stimulation by sepsis-related cytokines and has bactericidal effect.
- Approved by FDA as a diagnostic tool
- Easy to measure in serum and plasma by immunoassay
- Its level not only correlates with the severity of infection but also acts as a prognostic marker
<table>
<thead>
<tr>
<th>Procalcitonin Reference Ranges ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
</tr>
<tr>
<td>Chronic inflammatory processes and autoimmune diseases</td>
</tr>
<tr>
<td>Viral infections</td>
</tr>
<tr>
<td>Mild to moderate localized bacterial infections</td>
</tr>
<tr>
<td>SIRS, multiple trauma, burns</td>
</tr>
<tr>
<td><strong>Severe bacterial infections, sepsis, multiple organ failure</strong></td>
</tr>
</tbody>
</table>
Principal cause of hyperprocalcitonemia

A. Neuroendocrine tumors
   Medullary thyroid cancer
   Small cell lung cancer
   Carcinoid syndrome

B. Noninfectious systemic inflammation
   Inhalational injury
   Pulmonary aspiration
   Pancreatitis
   Heat stroke
   Mesenteric infarction

C. Severe infection
   Bacterial
   Viral
   Parasitic

D. Sepsis

E. Trauma
   Mechanical injury
   Burns
   Surgery
Nonbacterial infection: Viruses, Fungi, Parasites

- **PCT tend to be low in viral infection**
  - However, in systemic viral infection, PCT value can be as high as 16 ng/ml

- A low serum PCT cannot be used to exclude bacterial from viral infections but that a combination of PCT, CRP, white blood cell count, and clinical illness scoring might be more useful

- In patients with **fungal infections**, results have been variable

- Infection with the **malaria** parasite often leads to very high levels of serum, as high as 662 ng/mL
**Procalcitomin**

- Rapid increase usually around 3-4 hours after stimulation
- Plasma concentrations between 0.02 ng/ml und 1000 ng/ml
- Short half-life time (~24 h) not dependent on renal function
- Easy to measure in serum and plasma
Kinetics of Biomarkers in Sepsis

• PCT distinguishes between bacterial and viral infections or other distress states in children; more discriminatory than CRP and IL-6 (Gendrel et al, 1996; J Pediatr 128:570. Gendrel et al, 1999; Pediatr Inf Dis J 18:875)

![ROC curves for PCT, CRP and IL-6 for discrimination between bacterial and viral infections.](image-url)
Efficiency diagnostic and advantages of procalcitonin and C-reactive protein in the early diagnosis of sepsis

**Table 1**

Output curve results: PCT/CRP, sensitivity, specificity

<table>
<thead>
<tr>
<th></th>
<th>PCT</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>24 ng/ml</td>
<td>227 mg/day</td>
</tr>
<tr>
<td>AUC</td>
<td>0.983</td>
<td>0.965</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.93 to 0.99</td>
<td>0.91 to 0.99</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92.6%</td>
<td>91.1%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.1%</td>
<td>100%</td>
</tr>
</tbody>
</table>


**Conclusions**
PCT and CRP have the same efficiency in early sepsis diagnosis. The PCT and CRP efficiency diagnostic together is significant but small. **We suggest using both with the doubt of sepsis.**
The likelihood for bacterial infections increases with PCT levels.
Prospective Comparison of Eubacterial PCR and Measurement of Procalcitonin Levels with Blood Culture for Diagnosing Septicemia in Intensive Care Unit Patients

Farjana B. Rowther,1 Camilla S. Rodrigues,2* Minal S. Deshmukh,1,2 Farhad N. Kapadia,3 Ashit Hegde,3 Ajita P. Mehta,2 and Vinay R. Joshi4


RESULTS
Compared with blood culture as the gold standard, sensitivity, specificity, ppv, npv

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>100%</td>
<td>43.33%</td>
<td>46.87%</td>
<td>100%</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>100%</td>
<td>61.66%</td>
<td>56.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>

The average times required to produce a final result were as follows:
- PCR, 10 h;
- Blood culture, 33 h;
- Procalcitonin, 45 min

Concordance between PCR and procalcitonin was 88.88%.

CONCLUSION:
Both PCR and procalcitonin may be useful as rapid tests for detecting septicemia but compared with blood cultures lacked specificity.
Non-ICU

ICU

Survivors

Non-survivors

PCT concentration (ng/mL)

P = 0.004

P = 0.001

Survivors

Non-survivors

PCT concentration (ng/mL)

P = 0.004

P = 0.001

Available online at www.sciencedirect.com

Journal of Hospital Infection

2nd Department of Surgery, University of Thessaloniki, Medical School, Thessaloniki, Greece
2nd Department of Urology, 'Sismanoglion' Athens Hospital, Athens, Greece
Intensive Care Unit, 'Korgialeneion-Benakiton' Hospital of Athens, Athens, Greece
1st Department Propedeutic Surgery, University of Athens, Medical School, Athens, Greece
Department of Internal Medicine, Chios General Hospital, Chios, Greece
2nd Department of Surgery, 'Evangelismos' Athens General Hospital, Athens, Greece
1st Department Prop. Surgery, University of Thessaloniki, Medical School Thessaloniki, Greece
Intensive Care Unit, 'Tzanion' Hospital of Piraeus, Piraeus, Greece
Intensive Care Unit, 'Hippokrateion' Athens General Hospital, Athens, Greece
2nd Department of Internal Medicine, 'Sismanoglion' Athens Hospital, Athens, Greece
Department of Critical Care, University of Ioannina Medical School, Ioannina, Greece
Intensive Care Unit, 'Thriasio' Elefsina General Hospital, Elefsina, Greece
1st Department of Internal Medicine, 'Thriasio' Elefsina General Hospital, Elefsina, Greece
This is the first large multicentre study clearly showing that PCT may be useful in the early discrimination of the septic patient at risk of unfavourable outcome and providing specific concentration cut-offs to aid this prognostication. Although previous studies have shown that PCT early in the septic process is greater among non-survivors than among survivors, they did not identify practical cut-off concentrations nor did they define survival curves.\textsuperscript{17,18} Our results strongly support the use of PCT in the routine management of the septic patient.
PCT GUIDES ANTIBIOTICS USE
Effect of PCT-guided treatment on antibiotic use and outcome in lower respiratory tract infections

Respiratory tract infection?

Non-PCT group
(without PCT-result)

Randomization

PCT group

Treatment is up to the discretion of the treating physician

Follow-up after 10-14 days

PCT (ng/ml)

<0.1

NO!

0.1 - 0.25

No

0.25 - 0.5

Yes

>0.5

YES!

Clinical and PCT control after 6-12 hrs

Christ-Crain M et al Lancet 2004; 363: 600–07

*Kryptor assay*
Effect of PCT-guided treatment on antibiotic use and outcome in lower respiratory tract infections

<table>
<thead>
<tr>
<th></th>
<th>Standard group (n=119)</th>
<th>Procalcitonin group (n=124)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for stay in ICU</td>
<td>6 (5%)</td>
<td>5 (4%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Died</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Antibiotics prescribed</td>
<td>99 (83%)</td>
<td>55 (44%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of antibiotic treatment (days)</td>
<td>12.8 ± 5.5</td>
<td>10.9 ± 3.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Antibiotic costs per patient (US $)</td>
<td>202.5 ± 250.6</td>
<td>96.3 ±172.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PCT PREDECT OUTCOME
PCT as Prognostic Marker of Therapeutic Failure in VAP Patients

**Kinetics of serum procalcitonin** in patients who died (●), had pulmonary and/or extrapulmonary infection recurrence (●) or had favorable outcome (∗) from day 1 to day 7.

* p < 0.05
** p < 0.001

**PCT values > 0.5 ng/ml on day 7 predict treatment failure**
(AUC 0.9; sensitivity 90%, specificity 88%; odds ratio 64.2)

Luyt et al., AJRCCM 2004
Prognosis in Patients with High and Low PCT Values on Admission

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Procalcitonin &lt; 0.25 ng/ml</th>
<th>Procalcitonin ≥ 0.25 ng/ml</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay &lt;24 hours %</td>
<td>27.2%</td>
<td>3.2%</td>
<td>0.004</td>
</tr>
<tr>
<td>Length of hospital stay in days</td>
<td>15 (9.5-20)</td>
<td>17.5 (9.5-24)</td>
<td>0.002</td>
</tr>
<tr>
<td>Need for ICU stay %</td>
<td>5.9 %</td>
<td>25.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>Death during hospitalization %</td>
<td>2.2%</td>
<td>6.5%</td>
<td>0.211</td>
</tr>
<tr>
<td>Death within 6 months %</td>
<td>6.6%</td>
<td>16.1%</td>
<td>0.058</td>
</tr>
</tbody>
</table>
Mortality and PCT (n=2,320)

PCT and severity of illness scoring

Moderate to fairly strong statistical correlation

- Acute Physiology and Chronic Health Evaluation (APACHE III) scores
- Simplified Acute Physiology Score (SAPS II)
- Pediatric Risk of Mortality scores
- APACHE II and the Multiple Organ Dysfunction Score (MODS)
- Sequential Organ Failure Assessment (SOFA) scores
- Baltimore Sepsis Scale (BSS)
Conclusion

In septic patients, we found that APACHE II score and mid-regional pro-ANP level on admission to a medical ICU had similar ability to predict outcome. The results of our study are novel and of interest because they may help to improve stratification of septic patients. Our findings are descriptive in nature and warrant validation in future prospective studies, including measurement of cardiac indices or evaluating patients who have undergone surgery. If our findings are confirmed, then mid-regional pro-ANP might become a new and useful additional prognostic marker for individual risk assessment in sepsis, and may represent a helpful tool for patient stratification in future intervention trials.

Results

On admission, 53 patients had sepsis, severe sepsis, or septic shock, and 68 had systemic inflammatory response syndrome. The median pro-ANP value in the survivors was 194 pmol/l (range 20–2000 pmol/l), which was significantly lower than in the nonsurvivors (median 853.0 pmol/l, range 70–36,198 pmol/l).
The future ??

- Proteomics
  - Detect specific bacterial protein signatures
  - Detect biological response markers
- Protein microarrays
Conclusion

• A more rational and explicit incorporation of biomarkers into future research designs may well aid in addressing this challenge.
Thanks

السلام عليكم ورحمة الله وبركاته

SHA22
Mark Your Calendar 29-31 March

10th Echocardiography Workshop on Congenital Heart Disease

TEE Imaging from Knowledge to Clinical Practice

"First Hands-on TEE Workshop"

Your are Invited

main topics
- Live Transmission from Operating room & Cath Laboratory
- "Hands-on" Mannequin Simulator training for TEE procedure
- Wet Lab for Bones Hearts
- Computer Based TEE Training
- 3D TEE During Procedures
- Read with expert sessions
- Emphasis on TEE modality

target audience
This course is designed for pediatric and adult cardiologists, Anesthesiologists, ER Physicians, fellows in training, and Cardiac Sonographers. Participants should have a good working knowledge of echocardiography.

venue
Centers: KACC, King Saud University, KACC Riyadh, King Abdullah Medical City for National Guard Health Affairs, Riyadh, Saudi Arabia

Early Registration: 01 March 2011

29th - 31st March 2011
24th - 26th Rabi II 1432 H

International Guest Speaker:
Dr. Richard Humes, MD, FAAP, FACC
Chief, Cardiology - The Children's Hospital of Michigan
Detroit Medical Center (DMC)
### TABLE 1. Summary of Performance of Some Potential Markers of Sepsis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Functions</th>
<th>Performance for Diagnosis and Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFI</td>
<td>Multiple effects against Gram-negative bacteria; cytotoxicity, opsonization, neutralization of LPS</td>
<td>Fair diagnostic marker; poor predictor of outcome</td>
</tr>
<tr>
<td>CRP</td>
<td>An acute-phase protein; binds bacterial polysaccharide and activates complement</td>
<td>Good marker for diagnosis-sensitive but not very specific; very good for monitoring and outcome prediction</td>
</tr>
<tr>
<td>CD11b, a neutrophil cell-surface marker</td>
<td>An integrin; promotes cell-cell interaction and activation of immune responses; expression up-regulated in sepsis</td>
<td>Fair sensitivity and specificity for prediction of infection/sepsis</td>
</tr>
<tr>
<td>CD64</td>
<td>High-affinity receptor expressed on neutrophils; involved in phagocytosis and intracellular killing of pathogens</td>
<td>Good diagnostic marker</td>
</tr>
<tr>
<td>CGRP</td>
<td>Vasodilation and down-regulation of immune response</td>
<td>Good predictor of outcome; may be an early marker of sepsis</td>
</tr>
<tr>
<td>Cytokines, including TNF-α, IL-6, and IL-8</td>
<td>Stimulation of immune inflammatory response via cellular activation (neutrophils, macrophages, etc); activation of coagulation and inhibition of fibrinolysis; induction of CRP</td>
<td>Good sensitivity for diagnosis (especially IL-6); poor specificity; IL-6 is a good predictor of poor outcome</td>
</tr>
<tr>
<td>HMG-1</td>
<td>Stimulates the release of proinflammatory cytokines from MNCs and macrophages</td>
<td>Fairly good marker of sepsis; high levels indicate poor outcome</td>
</tr>
<tr>
<td>LBP</td>
<td>An acute-phase protein; promotes macrophage activation and cytokine release</td>
<td>Good diagnostic accuracy in pediatrics; a good late marker of sepsis</td>
</tr>
<tr>
<td>MIF</td>
<td>Reduces the immunosuppressive effect of corticosteroids, thus, proinflammatory</td>
<td>Good general marker of inflammation; not discriminatory for severity</td>
</tr>
<tr>
<td>PCT</td>
<td>Function unknown; may be a mediator of the septic inflammatory response</td>
<td>Very good diagnostic marker; good predictor of severity and outcome</td>
</tr>
<tr>
<td>Protein C</td>
<td>Activated protein C; inhibits the coagulation cascade</td>
<td>Good predictor of outcome</td>
</tr>
</tbody>
</table>