Biomarkers: Do They Help EM Physician for Diagnosis in Sepsis?

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Objectives

- Definition of sepsis and biomarkers
- Why do we need biomarkers for sepsis?
- Marker of Acute Inflammatory Response
  - **C-Reactive Protein**
- Potential Marker of Infection
  - **Procalcitonin**
- **Other Markers** of Acute Inflammatory Response
  - IL-6, IL-8, Lipopolysaccharide-binding protein
- **Lactate and lactate clearance**
- **Conclusion**

Really,
Do you think that we need biomarkers for diagnosis of sepsis?

Terminology

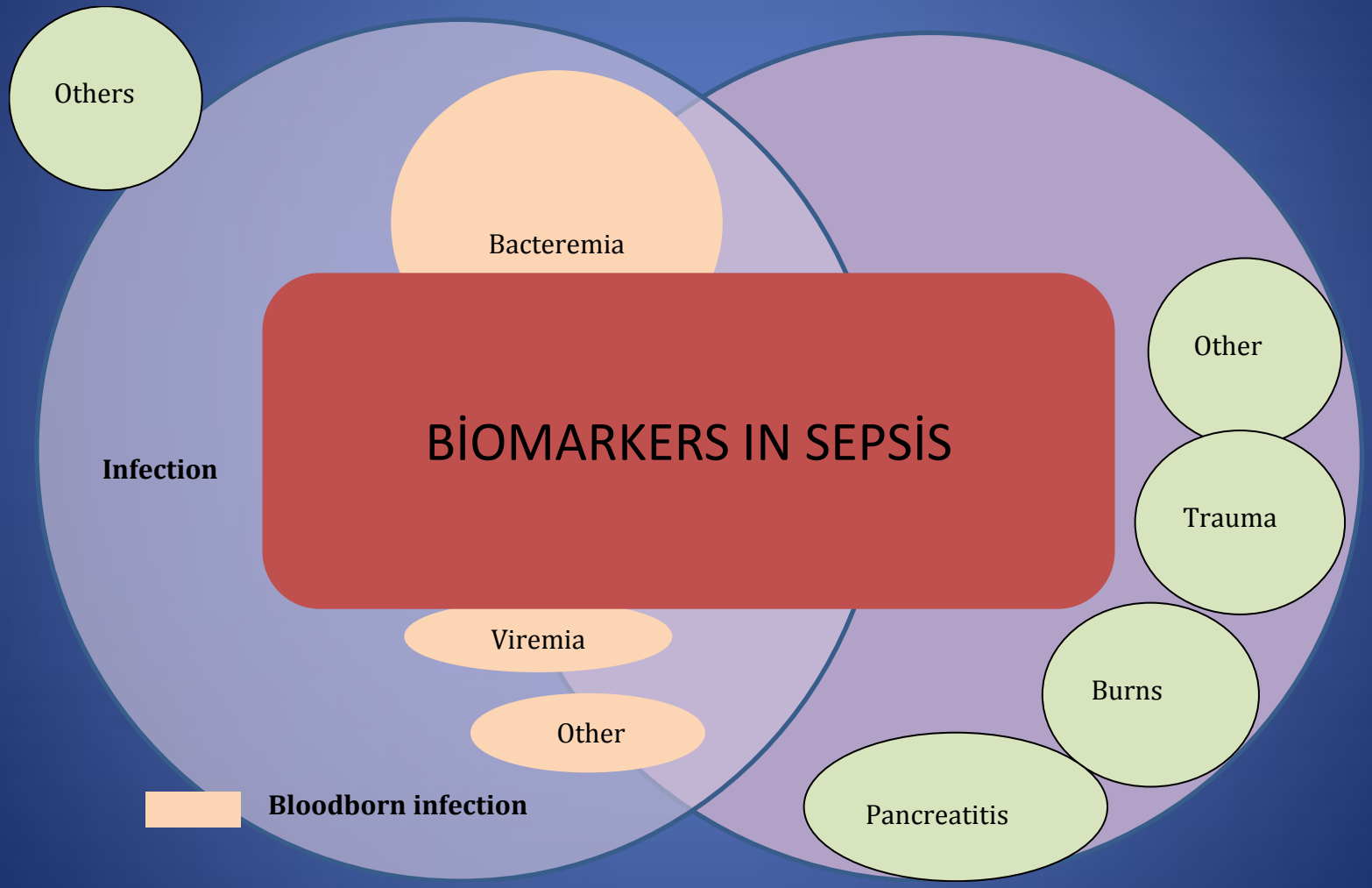
- Systemic Inflammatory Response Syndrome (SIRS)
  - ✓ Temp > 38.3°C or < 36°C
  - ✓ HR > 90/min
  - ✓ RR > 20 or PaCO2 < 32
  - ✓ WBC > 12 or < 4 or Bands > 10%

TWO out of four criteria
acute change from baseline

- Sepsis
  - ✓ The systemic inflammatory **response to infection**.
- Severe Sepsis
  - ✓ Organ dysfunction secondary to sepsis.
  - ✓ e.g. hypoperfusion, hypotension, acute lung injury, encephalopathy, acute kidney injury, coagulopathy.
- Septic Shock
  - ✓ **Hypotension** secondary to sepsis that is resistant to adequate fluid administration and associated with hypoperfusion.

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55.

SIRS and Sepsis



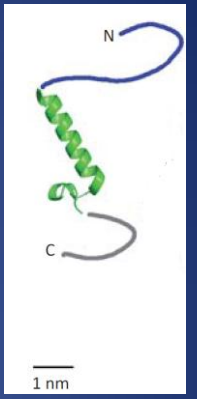
What is expected from such a marker?

- Fast increase---To be present at the onset or even before the appearance of the clinical signs of infections/sepsis.
- To be highly sensitive and specific for infection/sepsis (differentiation between infectious and non-infectious causes of inflammation, organ dysfunction and shock)
- Improve accuracy of clinical diagnosis
- To indicate the effectiveness of therapy

Marker of Acute Inflammatory Response

C-Reactive Protein (CRP)

C-Reaktive Protein (CRP)



- A protein that precipitate the “C” polysaccharide derived from the pneumococcal cell wall in acute phase.*
- Hepatocyte predominant
- IL-6, IL-1Beta, TNF-alfa
- Acting as an opsonin for gram positive bacteria to aid in their phagocytosis, CRP increases late during the onset of sepsis.

* Tillett W, Francis T. Serological reactions in pneumonia with nonprotein somatic fraction of pneumococcus. J **Exp Med 1930**,**52:561**-571

C-Reaktive Protein (CRP)

- CRP is effective
- CRP is non-specific in critically ill patient
- Procalcitonin (PCT) is better and more reliable to prognosis
- CRP: sensitivity---75%
  specificity---67%
- The secretion of CRP begins within 4-6 hours after stimulus
- Doubles every 8 hours
- Peaks at 36-50 h
- Half-life of 19 h
- >30-35 mg in bacterial infections.
- Up to 20 mg in viral infections.

– ↓ levels within first 48 h of therapy ⇒ correlate with an effective response to the initial antimicrobial therapy in septic patients.
– It's specificity in indicating the presence of an infection has been challenged
  - High levels of CRP among patients with burn injury
    complications.

Given its limited diagnostic performance, current guidelines do not recommend CRP as a sepsis biomarker

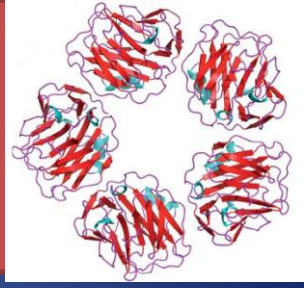
*Role of biomarkers in sepsis care. Shock. 2013;40(5):358-65.

Potential Marker of Infection

Procalcitonin (PCT)

Diagnosis of bacterial infection / sepsis and monitoring of the disease.

Procalcitonin (PCT)



- Muller et all demonstrated that PCT was superior to CRP, IL-6, lactate levels in predicting sepsis, with
  - **Sensitivity —89%**
  - **Specificity — 94%**
- Protein (116 amino-acids peptide precursor of the hormone calcitonin.
- PCT produced for a few hours only, by monocytes adherent to tissues (not produced in circulating monocytes)
- Secreted PCT acts is chemotactic to other monocytic cells.

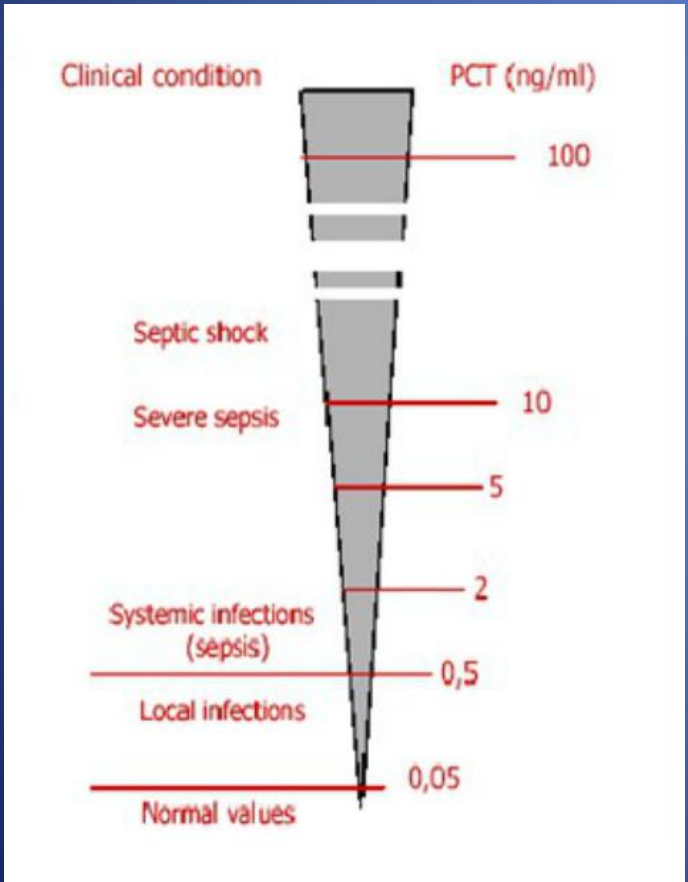
- **Elevations of both CRP and PCT were added to the updated definition of sepsis in 2003**
  - Levels are significantly high in bacteremia and moderately elevated in fungemia.*
  - Levels fall rapidly when infection gets controlled **

Müller B, et al. **Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit.** Crit Care Med. 2000;28(4):977-83.

*Shock. 2009;31(6):586-91.
J Clin Endocrinol Metab. 2004;89(4):1512-25.

Procalcitonin (PCT)

Plasma concentration s increase with extension of infection and severity of disease.



Low serum PCT level accurately predicts the absence of bacteremia in adult patients with acute fever.

- At admission, a **PCT 0.4 ng** (ml enables the exclusion of a positive blood culture with a **NPV of 98.8%.**

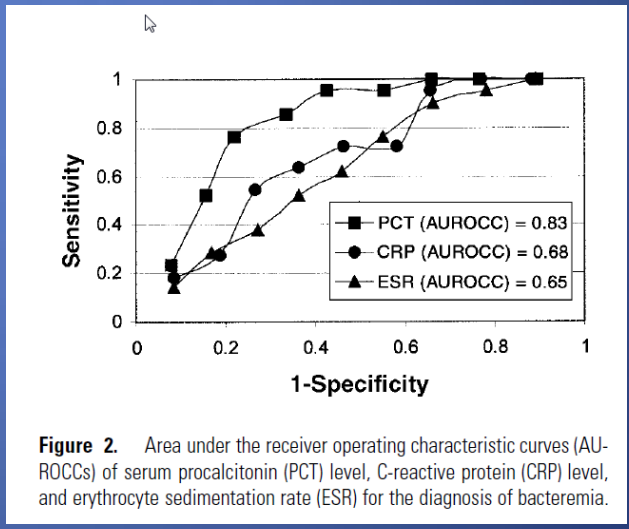
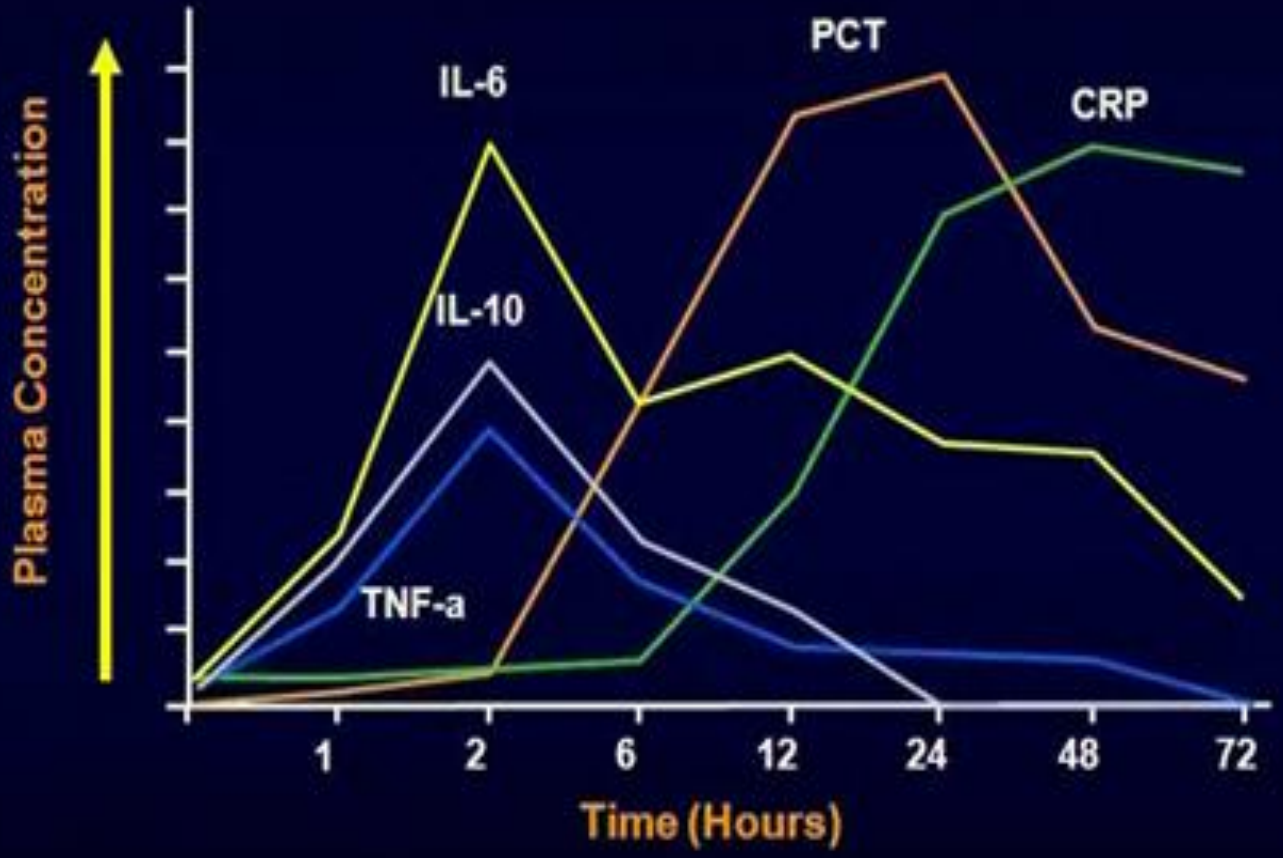


Figure 2. Area under the receiver operating characteristic curves (AUROCCs) of serum procalcitonin (PCT) level, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR) for the diagnosis of bacteremia.

*Chirouze C et al.Low serum procalcitonin level accurately predicts the absence of bacteremia in adult patients with acute fever. Clin Infect Dis. 2002;35(2):156-61.

Kinetics After Bacterial Challenge



- Relatively to measure in serum and plasma - stable *in vivo* and *in vitro*

Procalcitonin (PCT)

- More sensitive marker in predicting late mortality at 30 days compared with CRP*
- Monitoring biomarker for antibiotic stewardship.
  - A recent meta-analysis of randomized controlled trials PCT-based algorithm may reduce antibiotic exposure in adult septic patients without compromising clinical outcomes. **
- Dynamic changes of PCT have predictive value for hospital stay.
  - A decrease in PCT level by 25% over a 5-day period ⇒ useful indicator of survival in septic shock patients ***

** Shock. 2008;29(3):322-7.
**Crit Care Med. 2010;38(11):2229-41.
*** Shock. 2011;36(6):570-4.

Procalcitonin (PCT)

Positivity

Procalcitonin (PCT):

- Circulating levels
  - Superior diagnostic accuracy compared with other established biomarkers and indicators of sepsis*
  - Unaffected by the administration of anti-inflammatory therapy (glucocorticoids)**
  - In pediatric patients differentiating viral and bacterial infection (better than CRP, WBC count, IL-6 levels)

*Infect. 2010;60(6):409-16.
**J Leukoc Biol. 2002;72(4):643-9.

Negativity

Procalcitonin (PCT):

- Significant heterogeneity among studies and selection criteria*
- Meta-analyses have not confirmed the superior diagnostic performance of PCT over other sepsis biomarkers. *
- Nonspecific elevations of PCT levels can occur in situations of massive stress, such as after severe trauma and surgery or in patients after cardiac shock**

*Systematic review and meta-analysis.Lancet Infect Dis. 2007 Mar;7(3):210-7.
**Clin Microbiol Rev. 2012; 25(4): 609–634.

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Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: A prospective, observational, cohort study ☆

Dimple Anand, MSc [a], Sabari Das, PhD [a], Seema Bhargava, MD, PhD [a], Lalit Mohan Srivastava, PhD [a], Ashish Garg, MD [b], Niraj Tyagi, MD [b], Saurabh Taneja, MD [b], Sumit Ray, MD [b,*]

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ARTICLE INFO

Keywords:
Culture negative
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Systemic inflammatory response syndrome (SIRS)
Negative predictive value (NPV)

ABSTRACT

Purpose: Differentiation between culture-negative sepsis and noninfectious systemic inflammatory response syndrome (SIRS) remains a diagnostic challenge for clinicians, both conditions having similar clinical presentations. Therefore, a swift accurate diagnostic tool, which helps differentiate these 2 conditions would immensely aid appropriate therapeutic continuum. This prospective study was conducted to evaluate the potential diagnostic role of biomarkers, procalcitonin (PCT) and interleukin 6 (IL-6), in culture-negative sepsis patients.
Methods: Enrolled patients (208) included 46 noninfectious SIRS, 90 culture-negative sepsis, and 72 culture-positive sepsis. Culture, PCT, and IL-6 estimations were performed on day 1 of intensive care unit admission.
Results: Procalcitonin and IL-6 levels were significantly higher ($P < .001$) in both culture-negative and culture-positive groups as compared with SIRS group. Procalcitonin was a better predictor of sepsis in both culture-negative (area under curves 0.892 vs 0.636) and culture-positive (area under curves 0.959 vs 0.784) groups as compared with IL-6. In culture-negative group, the best cutoff point for PCT was at 1.43 ng/mL (92% sensitivity; 83% negative predictive value), best cutoff point for IL-6 was at 219.85 pg/mL (47% sensitivity and 42% negative predictive value).
Conclusions: Procalcitonin can accurately differentiate culture-negative sepsis from noninfectious SIRS and thereby contribute to early diagnosis and effective management of these conditions.

Procalcitonin and Sepsis Guideline

Special Articles

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

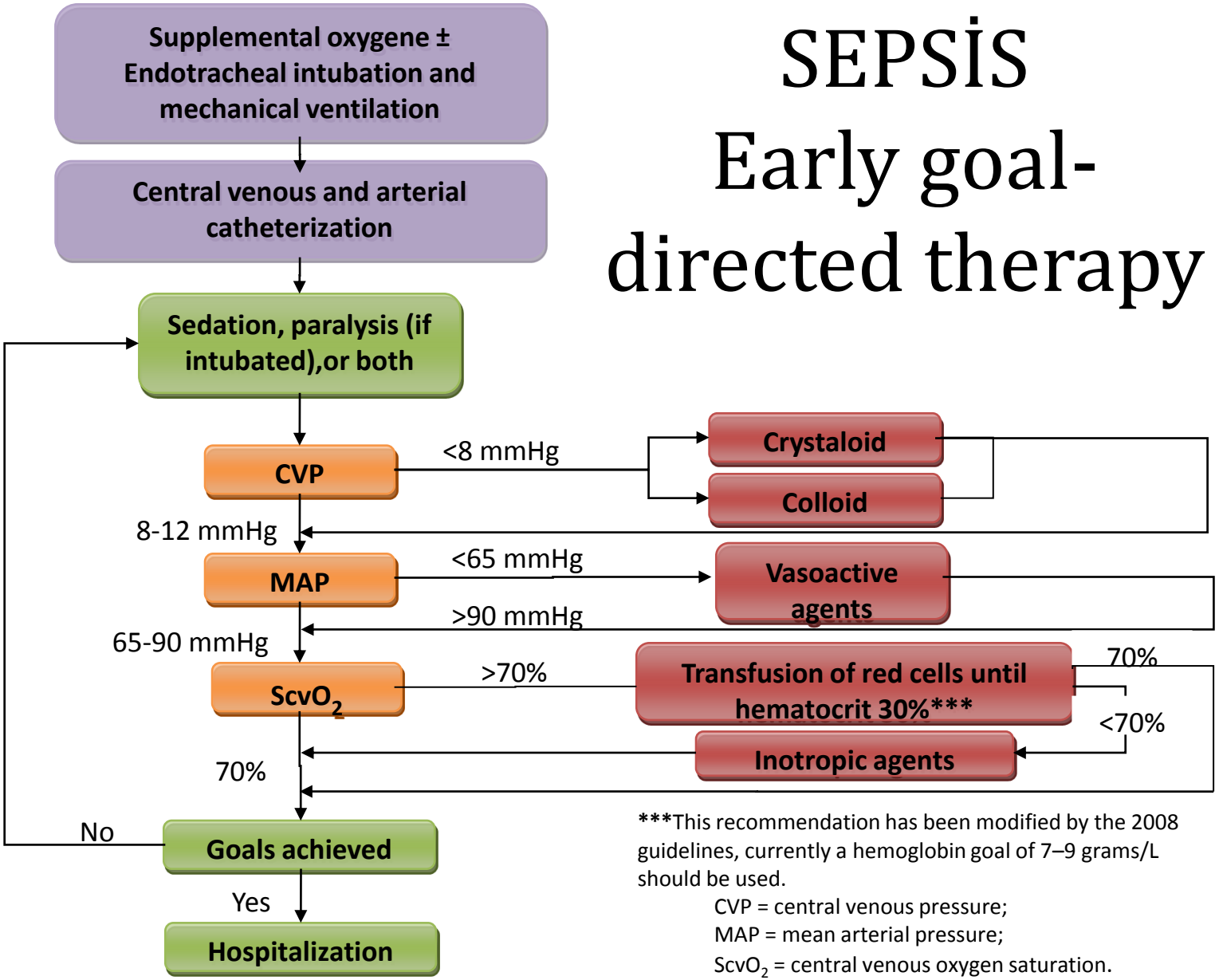
R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew
Herwig Gerlach, MD, PhD[5]; Steven M. Opal,
Ivor S. Douglas, MD[9]; Roman Jaeschke, M
Sean R. Townsend, MD[13]; Konrad Rei
Derek C. Angus, MD, MPH[16]; Cliffo
Gordon D. Rubenfeld, MD[19]; Steven A
Jean-Louis Vincent, MD, PhD[22]; Rui Mor
Guidelines Committee including the Pediatr

The surviving sepsis guidelines included procalcitonin as a biomarker for sepsis diagnostic criteria.

Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Critical Care Medicine 2013;41(2):580–637.

Biomarkers during sepsis management

SEPSİS
Early goal-directed therapy



***This recommendation has been modified by the 2008 guidelines, currently a hemoglobin goal of 7–9 grams/L should be used.

CVP = central venous pressure;
MAP = mean arterial pressure;
$ScvO_2$ = central venous oxygen saturation.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, *345*(19), 1368–1377

Markers of Impaired Metabolism

- The most commonly used parameters are the
  - Mixed venous O_2saturation (SvO_2)
  - Central venous O_2 saturation ($ScvO_2$), and
  - Serum lactate levels
  - Lactate clearence

Markers of Impaired Metabolism

$ScvO_2$ and SvO_2 :

- Central venous oxygen saturation can replace mixed venous saturation???*
- Time, expertise, and specialized equipment

*Am J Respir Crit Care Med. 2011 Sep 1;184(5):514-20.
**Results of a national survey. Crit Care Med. 2007 Nov;35(11):2525-32.
**Crit Care Med. 2005 Aug;33(8):1888-9.

Markers of Impaired Metabolism

Lactate

Lactate

- Hyperlactataemia has many causes, so lactate has no role in the diagnosis of sepsis.

- However, lactate can be used as an indicator of tissue hypoxia in patients with sepsis.*

**Park JH, Lee JWl, Park YS, Lee C-H, Lee S-M, Yim J-J, et al. Prognostic value of central venous oxygen saturation and blood actate levels measured simultaneously in the same patients with severe systemic inflammatory response syndrome and severe sepsis. *Lung* 2014;192:435-40.
*Nguyen HB, Loomba M, Yang JJ, Jacobsen G. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apopotosis, organ dysfunction and mortality in severe sepsis and septic shock. *J Inflamm* 2010;7:6.

Consequently, current sepsis guidelines recommend reduction of serum lactate by timely fluid resuscitation as a therapeutic endpoint.

Lactate

Evidence is clear that lactate levels are predictive of death and MODS

Clearance of lactate is associated with improved survival

Algorithms of care based on lactate clearance appear to work as well or better than other approaches.

Jones AE, Shapiro NI, Trzeciak S, et al. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial. JAMA: The Journal of the American Medical Association 2010;303(8):739–46.

Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. American Journal of Respiratory and Critical Care Medicine 2010;182(6):752–61.

Are there any other clinically useful sepsis biomarkers?

Other clinically useful sepsis biomarkers

- **INTERLEUKINS (IL-6 and IL-8)**
- **LIPOPOLYSACCHARIDE BINDING PROTEIN**
- **ADRENOMEDULLIN**
- **ENDOTOKSIN ACTIVITY ASSAY**
- **PENTRAXIN**
- **S-TREM-1 (Soluble form of triggering receptor expressed on myeloid cells-1)**
- **PRESEPSİN**

Not suitable for regular clinical use

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J Crit Care. 2015 Apr 1. pii: S0883-9441(15)00132-X. doi: 10.1016/j.jcrc.2015.03.023. [Epub ahead of print]

Serum melatonin levels are associated with mortality in severe septic patients.

Lorente L[1], Martín MM[2], Abreu-González P[3], de la Cruz T[4], Ferreres J[5], Solé-Violán J[6], Labarta L[7], Díaz C[8], Jiménez A[9], Borreguero-León JM[10].

Author information

Abstract

OBJECTIVE: Melatonin in septic patients has been scarcely explored and only in studies of small sample size (maximum 20 patients). Thus, the objective of this study was to determine whether serum melatonin levels are associated with severity, oxidant and inflammatory state, and mortality in a large series of septic patients.

METHODS: A prospective, observational, multicenter study was performed in 6 Spanish intensive care units with 201 severe septic patients. Serum levels of melatonin were measured at moment of severe sepsis diagnosis. The end point was 30-day mortality.

RESULTS: Non-surviving patients (n = 71) showed higher serum melatonin levels (P < .001) than survivors (n = 130). Multiple logistic regression analysis showed that serum melatonin levels were associated with 30-day mortality (odds ratio, 1.022; 95% confidence interval, 1.001-1.043; P = .04), controlling for serum tumor necrosis factor-α levels, serum interleukin 6 levels and age. Serum melatonin levels were positively associated with serum levels of malondialdehyde as biomarker of oxidative stress, interleukin-6 and lactate, and with SOFA score.

CONCLUSIONS: The novel finding of our study was that serum melatonin levels are associated with mortality in septic patients.

KEYWORDS: Melatonin; Mortality; Outcome; Sepsis

PMID: 25869726 [PubMed - as supplied by publisher]

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Adv Clin Chem. 2015;68:71-86. doi: 10.1016/bs.acc.2014.11.005. Epub 2015 Jan 7.

Procalcitonin: potential role in diagnosis and management of sepsis.

Rowland T[1], Hilliard H[2], Barlow G[3].

⊕ Author information

Abstract

Sepsis is an important cause of worldwide morbidity and mortality. Early recognition and diagnosis are keys to achieving improved outcomes. Procalcitonin has been widely investigated as a potential biomarker for sepsis. Furthermore, management of sepsis and other infectious disease is becoming increasingly complicated by the emergence of antibiotic resistant strains of pathogens. Good antibiotic governance is important in reducing the risk of the development of further antibiotic resistance. We reviewed the current literature on the use of procalcitonin in sepsis to determine whether it should be recommended for use in either of these roles. Procalcitonin should not be used as a stand-alone diagnostic test to rule-in or rule-out sepsis or bacterial infection, or for prognostication, in the absence of clinical judgment. Used as part of a clinical algorithm, however, it has been shown to reduce antibiotic prescribing in critical care environments and for respiratory tract infections.

KEYWORDS: Antibiotic stewardship; Biomarkers; Procalcitonin; Sepsis

PMID: 25858869 [PubMed - in process]

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Indian J Crit Care Med. 2015 Mar;19(3):140-6. doi: 10.4103/0972-5229.152755.

Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock.

Poddar B[1], Gurjar M[1], Singh S[2], Aggarwal A[2], Singh R[1], Azim A[1], Baronia A[1].

⊕ Author information

Abstract

BACKGROUND AND AIMS: To evaluate the prognostic value of change (fall) in serum procalcitonin level (PCT) in critically ill adults with severe sepsis/septic shock.

METHODS: This was a prospective observational study in a general purpose Intensive Care Unit of a teaching Institute. PCT was measured at admission (D0) and after 72-96 h (D4) by electrochemi-luminescence immunoassay (BRAHMS PCT kit) in adults (>18 years) admitted with severe sepsis or septic shock. Change in procalcitonin values from D0 to D4 was correlated with the primary outcome, that is, 28 days mortality. All results are reported as median (interquartile range).

RESULTS: A total of 171 (100 males) of 181 patients were included. The median age was 46 years (range 19-79). 137 patients were in septic shock and 34 in severe sepsis. The sequential organ failure assessment (SOFA) score in all patients was 11 (9-14).91 (53.2%) patients survived at 28 days (survivors). The baseline procalcitonin was similar in two groups (3.48 [1.04-15.85] vs. 5.27 [1.81-23.57] ng/ml in survivors and nonsurvivors [NS] respectively). The procalcitonin change was 1.58 (0.20-8.52) in survivors and 0.28 (-1.38-6.17) in NS (P = 0.01). The C-statistic of percentage change in procalcitonin from D0 to D4 to predict survival was 0.73 (95% confidence interval [CI]: 0.65-0.82) when compared to 0.78 (95% CI: 0.71-0.86) for change of SOFA score. For an absolute fall in procalcitonin of >1 ng/ml, a 70% fall predicted survival with 75% sensitivity and 64% specificity.

CONCLUSIONS: In critically ill-patients with severe sepsis/septic shock, change (fall) in procalcitonin is associated with good outcome.

KEYWORDS: Biomarker; critical illness; organ dysfunction score; prognosis; septic; shock

PMID: 25810608 [PubMed] PMCID: PMC4366911 Free PMC Article

DNA Fingerprinting

- Current genetic studies indicate that detection of specific DNA sequences common to all bacteria is another possible means of diagnosis
- 16S rRNA
- mecA gene was highly specific for the detection of methicillin-resistant strains of staphylococci.
- Specific targets in an 5-6 h time frame.

New Parameters and Methods For Diagnosis of Sepsis

- Signet ABP 26 (CD 26)
- Endotoxin activity determination (EAA)
- PCR-DNA fingerprinting (determination of 16S r RNA)

CONCLUSIONS

- **Clinical assessment** remains the **mainstay of** diagnosis of sepsis.
- **Current biomarkers** have **only moderate** diagnostic performance and have a limited role.
- International sepsis guidelines therefore recommend their use only as an adjunct to clinical assessment, which remains the mainstay of sepsis diagnosis.

Do you think that we need biomarkers for diagnosis of sepsis?

THANK YOU FOR YOUR ATTENTION