BIOMARKERS IN SEPSIS

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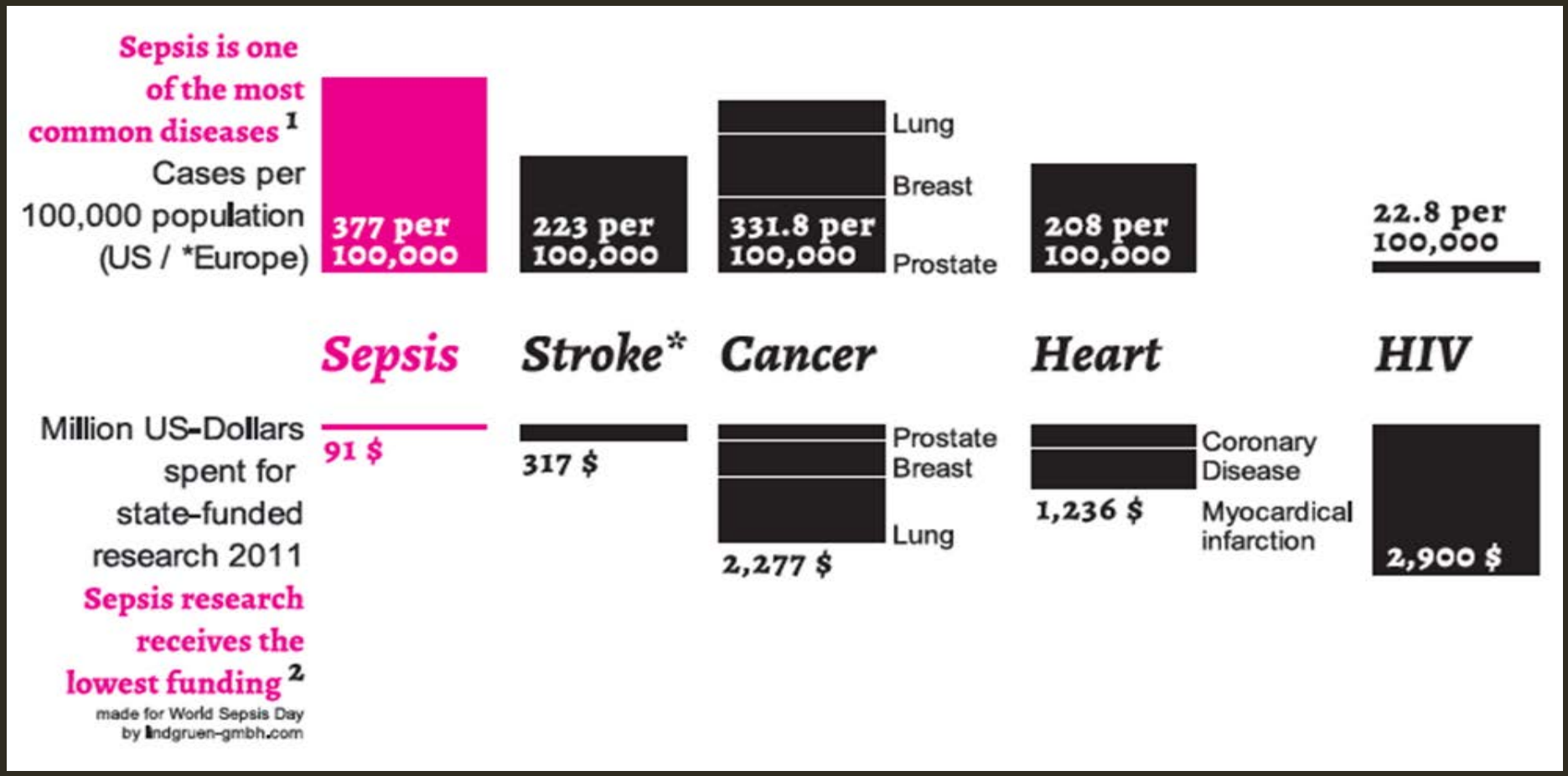
BSMCON 17

WHY WE NEED TO KNOW



SEPSIS

Sepsis…..ever evolving phenomenon

1992

- Systemic inflammatory response (SIRS) caused by documented infection

2001

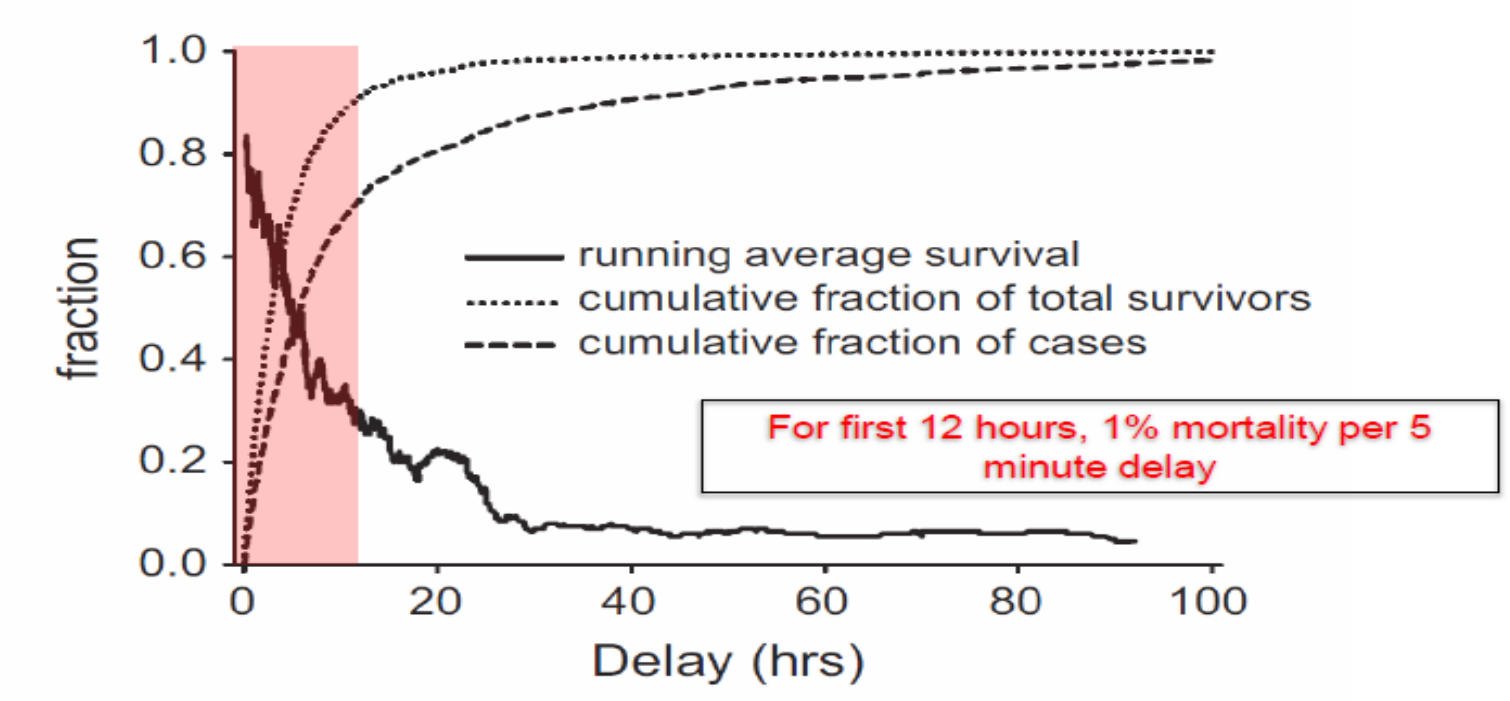
- Infection documented or suspected *and* some of the parameters

2016

- Life-threatening organ dysfunction caused by a dysregulated host response to infection

SEPSIS..

The clock is ticking - the first 12 hours...



Funk and Kumar, *Crit Care Clinics* 2011; 53-76.

SEPSIS..

Early Detection is Paramount…**BUT**

SEPSIS..

- Fever, tachycardia, hypotension, and other vital sign abnormalities found in SIRS are not specific for infection
- Overlap with noninfectious etiologies presenting with systemic inflammation
- There is no gold standard for diagnosing infection, and blood cultures, even if processed with standard microbiologic techniques, are often futile

THE PARADIGM SHIFT

- Sepsis is not only direct pathogen effects but also an exuberant inflammatory host response
- Hundreds of mediators are released that could be potentially measured for diagnosis and prognosis
- A number of pathogen and host responses have been in focus, including
  - cytokines, cell markers, receptor biomarkers, coagulation, vascular endothelial damage, vasodilation, organ dysfunction, acute phase protein markers, and other systems.

BIOMARKERS

The National Institutes of Health defines a **biomarker** as a characteristic that should objectively measure and evaluate (be an indicator of) normal biological processes or pharmacological response to a therapeutic intervention

IDEAL BIOMARKER

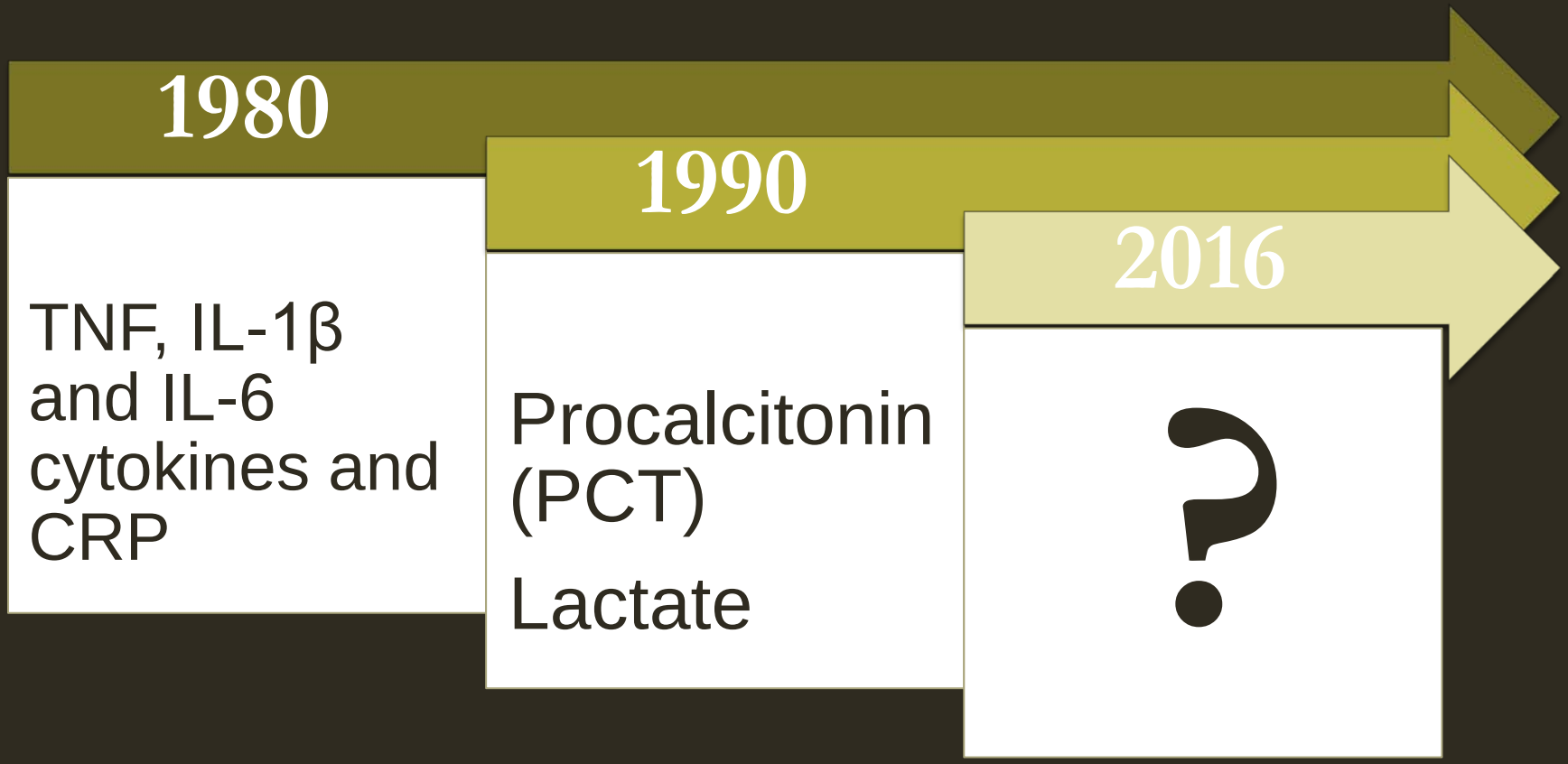
To be clinically useful,

- A sepsis biomarker needs to additional provide information to that already available
- It needs to be able to differentiate accurately bacterial infection from non-infective and viral causes of SIRS
- Be available in a timely and cost-effective manner
- The utility is potentially further enhanced if it can indicate the severity of infection and
- Be a guide to the effectiveness of therapy

IDEAL BIOMARKER

To find out an ideal biomarker has become one of the holy grails of medicine

THE SEARCH


1980
TNF, IL-1β and IL-6 cytokines and CRP
1990
Procalcitonin (PCT)
Lactate
2016
?

EXAMPLES

- **Acute phase proteins**
  - CRP
  - **Procalcitonin**
  - **Pentraxin 3 (PTX3)**
  - Lipopolysaccharide binding protein (LBP)
- **Cytokines & chemokines**
  - IL-1RA, IL-1β, IL-2, **IL-6, MCP-1**
  - TNF-α, TNFR1/2
  - HMGBP1
- **Cell surface markers**
  - **Soluble CD14 (presepsin)**
  - Neutrophil CD64 index (CD64in)
  - mHLA-DR (monocyte HLA-DR levels)
  - CD-163
- **Receptor markers**
  - VEGF
  - Soluble VEGF-receptor 1 (sFLT)
  - **Soluble urokinase plasminogen activator (suPAR)**
  - **sTREM-1**
  - RAGE (soluble receptor for advanced glycation end products)
- **Coagulation**
  - Activated partial thromboplastin time (aPTT) waveform analysis
  - Protein C receptor
  - Thrombomodulin
- **Endothelial damage**
  - Heparin binding protein
  - E-selectin
  - Neopterin
  - ICAM-1, VCAM-1
  - Angiopoietin-1 and -2
  - Syndecan-1 and -2
- **Vasodilation**
  - **Copeptin (AVP precursor)**
- **Cell damage**
  - MicroRNA
  - Microparticles
- **Cell repair**
  - Procollagen III amino propeptide

THE SEARCH

Crit Care. 2010; 14(1): R15.
Published online 2010 Feb 9. doi: 10.1186/cc8872
PMCID: PMC2875530

Sepsis biomarkers: a review

Charalampos Pierrakos[1] and Jean-Louis Vincent[✉1]

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Abstract

Go to:

Introduction

Biomarkers can be useful for identifying or ruling out sepsis, identifying patients who may benefit from specific therapies or assessing the response to therapy.

Methods

We used an electronic search of the PubMed database using the key words "sepsis" and "biomarker" to identify clinical and experimental studies which evaluated a biomarker in sepsis.

Results

THE BIOMARKERS: REVIEW

- Review of 3370 articles
- 178 Biomarkers evaluated
- 18 had been evaluated in experimental studies only, 58 in both experimental and clinical studies, and 101 in clinical studies only
- Thirty-four biomarkers were assessed for use specifically in the diagnosis of sepsis; just five reported sensitivity and specificity values greater than 90%. Eg. IL-12, IP-10, PLA2-II, CD64, CD11b

PROCALCITONIN (PCT)

- A 116 amino acid polypeptide precursor for the hormone calcitonin, released from many cells,induced by IL-1β, TNF-α, IL-6, and lipopolysaccharides
- **Rise**: 2 hours, **Detectable**:2-4 hours, **peak:** 6 hours, and maintaining a **plateau** through 8 and 24 hours
- Differentiated patients with infectious versus noninfectious, inflammatory conditions and also confirmed bacterial versus viral infections with high sensitivity (95%)
- Positive impact on the reduction of AB treatment

IN BANGLADESH

- Waheeda Nargis, Md Ibrahim and Borhan Uddin Ahmed measured and compared PCT and CRP simultaneously in 73 medico-surgical ICU patients

- PCT is found to be superior to CRP in terms of accuracy in identification and to assess the severity of sepsis even though both markers cannot be used in differentiating infectious from noninfectious clinical syndrome

Nargis W[1], Ibrahim M[2], Ahamed BU[3] **Procalcitonin versus C-reactive protein: Usefulness as biomarker of sepsis in ICU patient.**

Int J Crit Illn Inj Sci. 2014 Jul;4(3):195-9. doi: 10.4103/2229-5151.141356.

PCT…

The most recent meta-analysis evaluating 30 studies with 3244 patients yielded a sensitivity of 77% (95% confidence interval (CI): 72–81%) and specificity of 79% (CI: 74–84%) indicating that

It is a useful biomarker for diagnosis of early sepsis, but could not be used in isolation and must be interpreted in context of patient presentation.

CRP

- An acute-phase reactant produced only by hepatocytes due to inflammation or tissue injury.
- Normal: below 0.8mg/L
- Rise noted by about 6 hours
- Peak around 48 hours
- Plasma half-life: approximately 19 hours
- Elevated CRP levels have been correlated with increased risk of death and organ failure
- But, lacks specificity and remains elevated

ENDOTHELIAL PROTEINS

Marker	Diagnostic Significance	Prognostic Significance
Angiopoeitin 1		– Ang-1 levels at admission were associated with poor outcome and a significant predictor of mortality throughout a 28 day period[44]
Angiopoeitin 2	– Elevated Ang-2 are seen in patients with suspected infection within the first hour of hospitalization[47] – Differentiate between sepsis and severe sepsis[48]	– Ang-2 levels correlated with disease severity along with organ dysfunction and injury[44]
Endocans	– Increased Endocan expression in the serum of patients with sepsis[51]	– Predictive of sepsis severity and organ-specific failure[49–53]

DAMPS/ CELL SURFACE RECEPTORS

Marker	Diagnostic Significance	Prognostic Significance
CD64	– CD64 index can differentiate between sepsis and SIRS patients in various patient populations[54,56–60]	
TREM-1/ sTREM-1	– Plasma sTREM-1 levels higher than 60 ng/mL is indicative of infection[63] – Plasma sTREM-1 level in septic patients was significantly higher than that in SIRS patients[64,67] – Culture-positive or negative septic preterm neonates display significantly higher sTREM-1 levels[66]	– Plasma sTREM-1 level positively correlate with severity score[64] – Non-survivors have increased plasma sTREM-1 level compared to survivors in all SIRS/sepsispatients[64,67] – Plasma sTREM-1 level at admission identify patients with a poor prognosis despite complete initial resuscitation in severe sepsis[65]
Circulating free DNA (c-DNA)		– Useful for early risk stratification and prediction of morbidity and mortality[68,69–70] – Maximum plasma DNA concentration measured during the first 96 h is associated with the degree of organ dysfunction, and disease severity[70]

CYTOKINE/CHEMOKINE SIGNALING

Marker	Diagnostic Significance	Prognostic Significance
Cytokine/ chemokine Signaling	– Cytokine serum levels are raised in patients with sepsis and severe sepsis as compared to non septic patients[76] – Increased levels on IL-6 and IL-8 in neonates used to detect both early and late onset sepsis[80–82]	– Levels of IL-6 and IL-8 are closely related to the severity and outcome of septic patients[78–79] – TNF-α levels are higher in nonsurvivors as compared to survivors[79] – Marked correlation to IL-10 levels and worse outcome and death[78,79,91]

BIOMARKERS: NPV

- Biomarkers can be more useful to rule out sepsis than to rule it in.
- Three biomarkers are identified with high negative predictive value to rule out sepsis:
  - PCT (99% at a cut-off value of 0.2 ng/ml)
  - aPTT waveform (96%) and
  - FDP (100% for Gram-negative sepsis by ELISA assay)

FUTURE MARKERS

Presepsin

- A13-kDa protein that is the truncated N-terminal fragment of cluster of differentiation 14 (CD14), the receptor for lipopolysaccharide (LPS)/LPS binding protein complexes.
- Generated as the body response to bacterial infection Production is induced by phagocytosis of bacteria.
- So, the level of presepsin should reflect the severity of infection rather than the degree of inflammation

TAKE HOME

No biomarker has, therefore, established itself sufficiently to be of great help to clinicians

As each biomarker has limited sensitivity and specificity, it may be interesting to combine several biomarkers However, this hypothesis requires further study. A clinical study showed that the combination of aPTT waveform with PCT increased the specificity of the aPTT waveform in the diagnosis of sepsis.

Studies using panels of sepsis biomarkers have also provided encouraging results

The cost-effectiveness of all these methods must be evaluated.

THANK YOU

- Clinical decision remains paramount
- Use the available biomarkers judiciously as adjunct
- The future is yours