Biomarkers in Sepsis

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Rasht, IRAN, 18.08.1402

TABLE 65-1 Summary of Sepsis-1 and Sepsis-2 Definitions

Disease State	Definition	Mortality
Sepsis	Infection + at least two SIRS criteria	Determined by the underlying condition
Severe sepsis	Sepsis with acute organ dysfunction	25%-40%
Septic shock	Sepsis with refractory hypotension despite adequate fluid loading (vasoplegia)	40%-80%

- ACCP/SCCM: 1992 >>> Sepsis-1: **focused on the presence of SIRS**
- ACCP/SCCM/ESICM/ATS/SIS: 2001 >>> Sepsis-2

  expanding the SIRS criteria , PIRO model: Predisposition, Insult/Infection, Response, Organ dysfunction

SCCM/ESICM: 2016 >>> "sepsis-3": Impetus for update

(1)Increase the validity of the sepsis definition in the absence of a "gold standard" diagnostic tool;

(2)Incorporate a greater understanding of underlying pathophysiology and the spectrum of clinical manifestations;

(3)Improve earlier recognition and management of patients with sepsis;

(4)Increase consistency in criteria for clinical trials and epidemiologic studies

A dysregulated host response to infection with life-threatening organ dysfunction

The biggest differences between sepsis-3 and the prior definitions

1-Sepsis as a dysregulated host response and notably, the deletion of the SIRS criteria,

2-Organ dysfunction is a core element of all sepsis cases, thus removing "severe sepsis" as a category of disease,

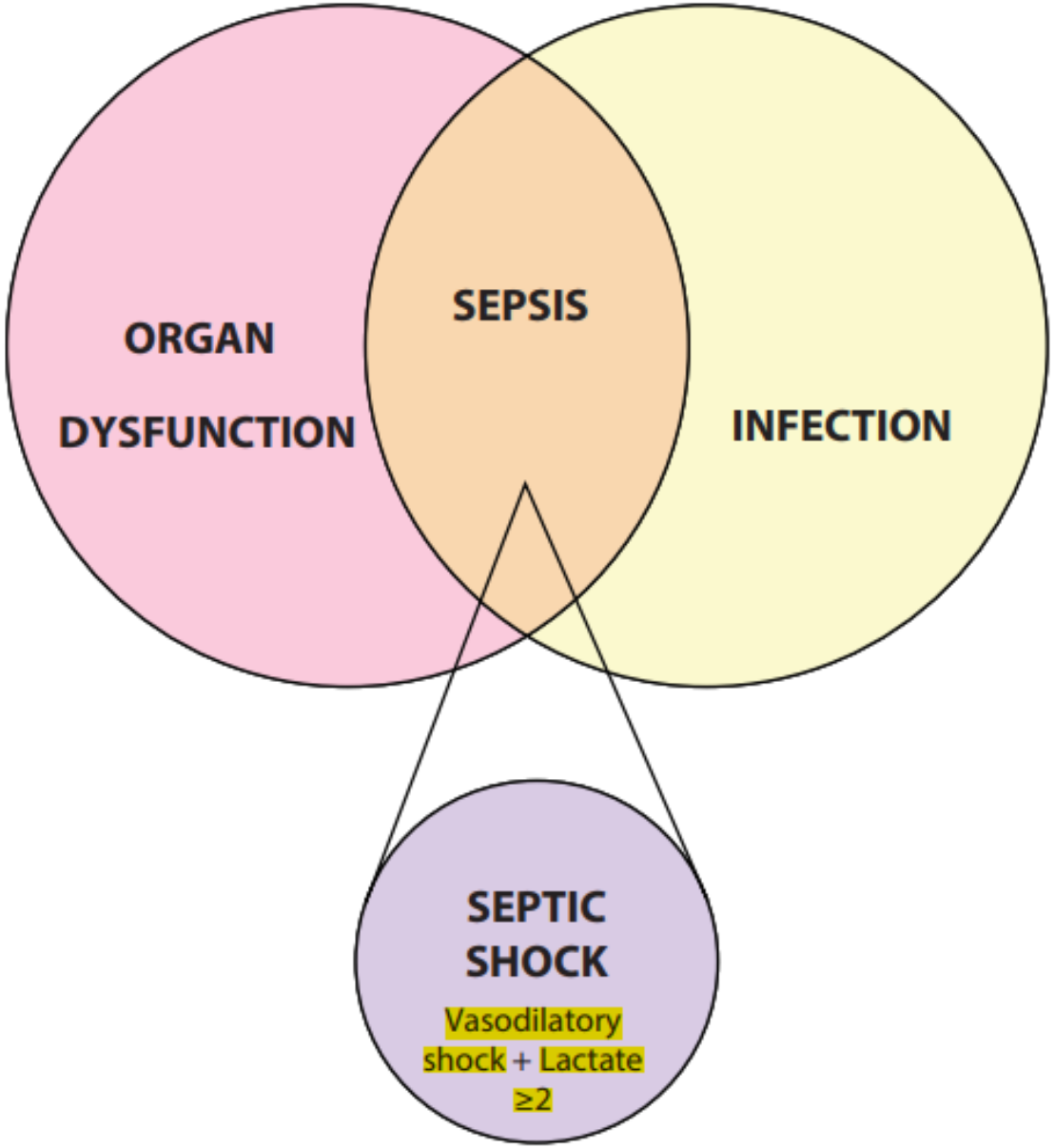
3-The definition of septic shock

TABLE 65-2 Summary of Sepsis-3

Disease State	Definition	Clinical Construct
Sepsis	Life-threatening organ dysfunction due to dysregulated host response to infection	Documented/suspected infection with related organ dysfunction
Septic shock	Increased circulatory and cellular abnormalities that substantial increase mortality	Serum lactate >2 mmol/L with vasopressor requirement to maintain a mean arterial pressure >65 mm Hg despite fluid resuscitation
Organ dysfunction	Single or multiple organ function derangement in the setting of sepsis and not attributed to other causes	Can be identified with an acute change in the SOFA score of ≥ 2 points from baseline SOFA

"Sepsis-3,"

Organ failure *during an infectious episode,* which is operationalized by an increase in the SOFA score



Venn diagram

What Are Biomarkers?

A measurable characteristic that can provide insight into biological or pathological processes

- diagnostic, monitoring, prognostic and stratification biomarkers

Objectives of Biomarker Measurement:

1-Establish diagnosis

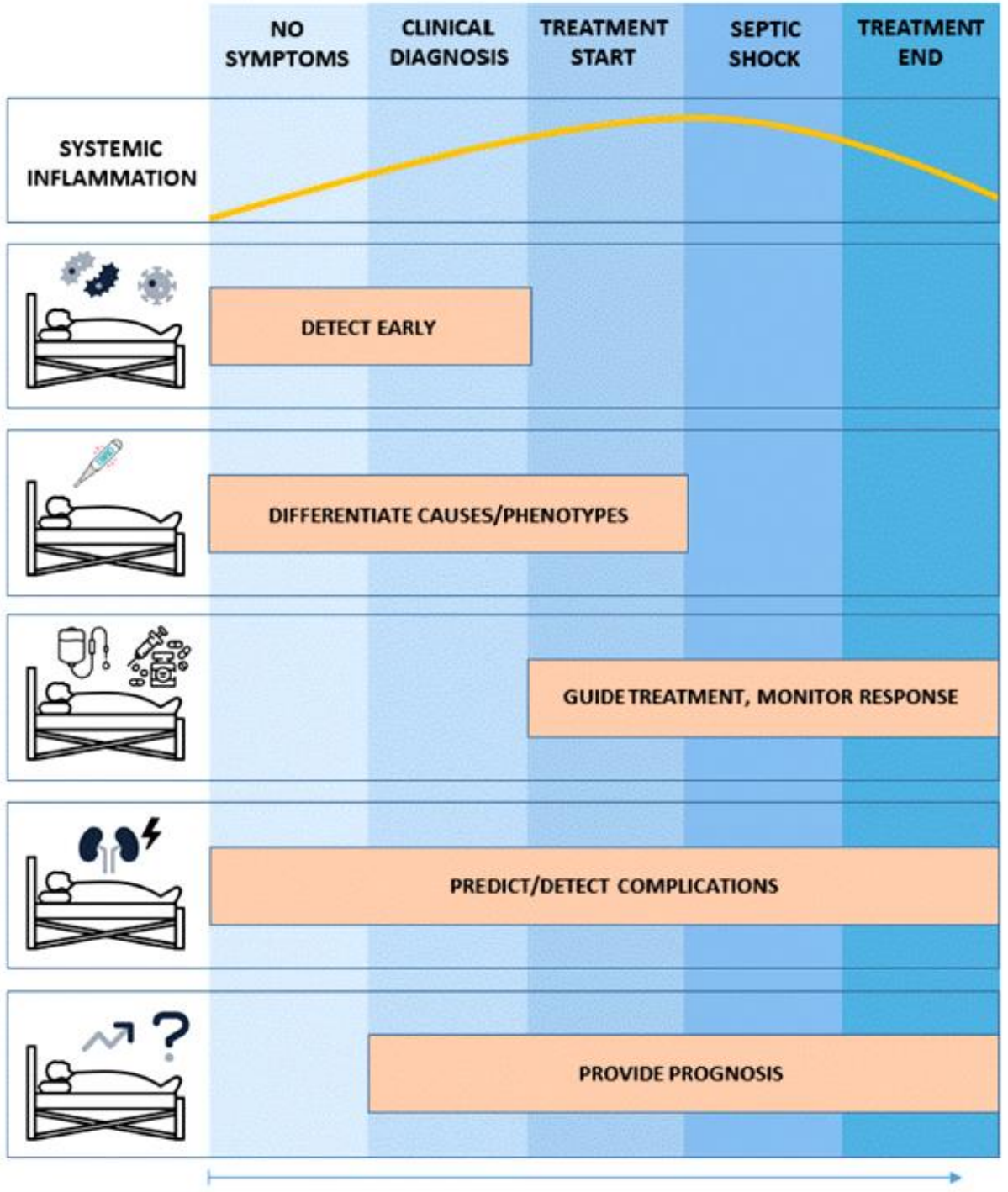
2- Identification of underlying pathophysiology (endotype, between infectious and noninfectious processes

3-Monitor response to treatment & residual disease activity

4-Prognostic & stratifying

Applications of biomarkers in the clinical pathway of sepsis

Using biomarkers to adjudicate severity is best done in conjunction *with clinical, microbiologic, and pathologic data*.

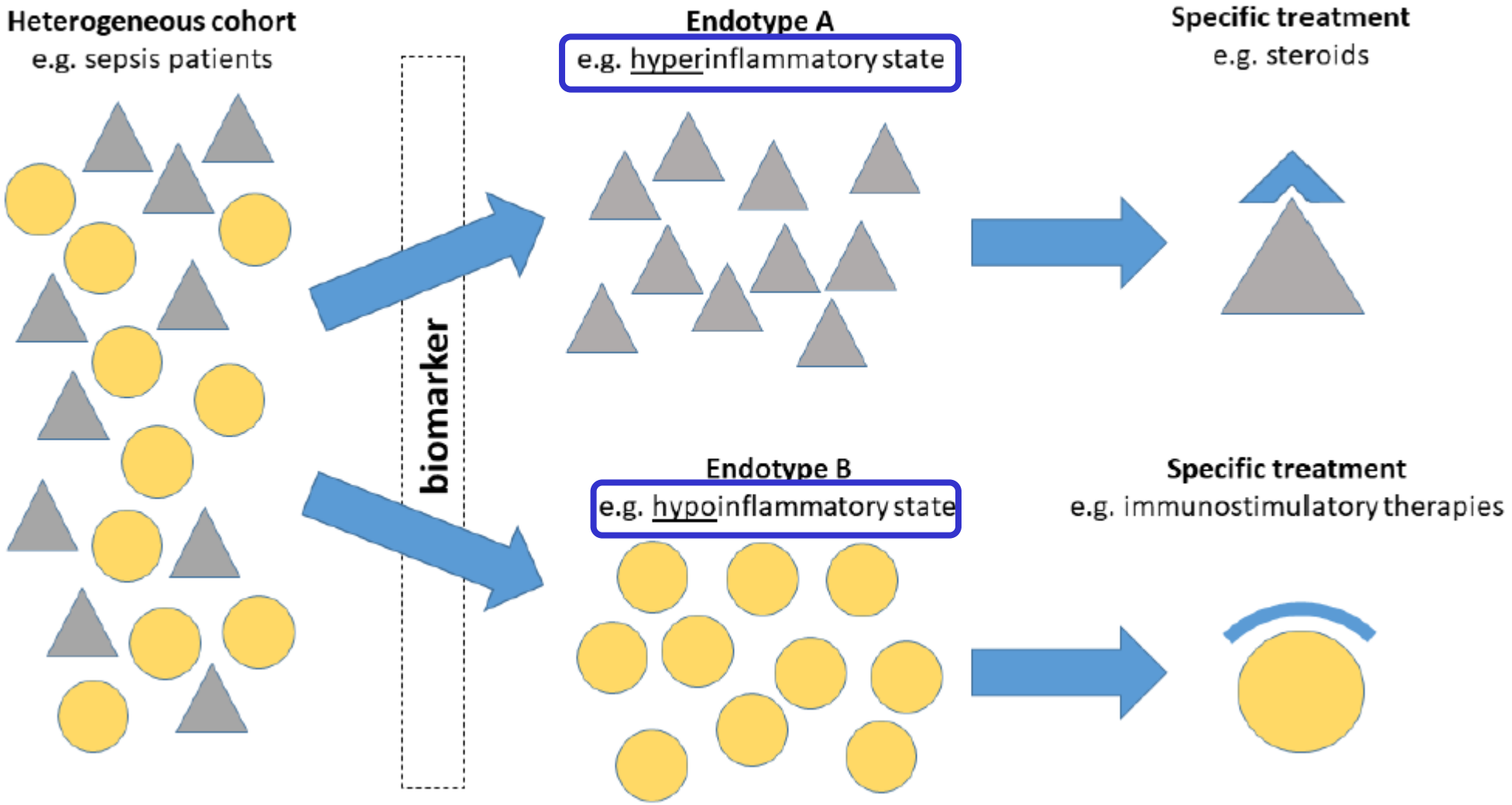


In ICU patients:

- the decision to start antibiotics should never be guided by biomarkers,

- but biomarkers can be used along with other data to decide to stop or shorten the duration of antibiotic therapy

Biomarker-enrichment (Personalized) approach



Biomarkers are used that identify "treatable traits" such as pathophysiologic derangements, for which specific therapies exist

1-Biomarker-Guided Evaluation and Therapy of Patients with Dysregulated Systemic Inflammation and Sepsis

Immunological Biomarkers	
C-reactive protein (CRP)	Indicates acute systemic inflammation [38] Screening for early onset neonatal sepsis [39] (Predict survival in patients with sepsis) [40]
Procalcitonin (PCT)	Diagnosis of sepsis [41,42] Suggest bacterial infection [43] Monitor treatment response to antibiotics and guide cessation of antibiotic treatment [44–47]
Presepsin (soluble CD14)	Early detection of sepsis (earlier increase than PCT and CRP) [48] Monitor host response [49] Higher in patients with bacterial infection [50] May be combined with other biomarkers in a panel [51] No validity in patients with acute kidney injury [52]
Interleukin-6 (IL-6)	Early detection of sepsis [53,54] Early detection of SIRS [55] Differentiate infectious from sterile SIRS [56]

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ELSEVIER

Prevalence and characteristics of nonlactate and lactate expressors in septic shock

Andrea Freyer Dugas MD[a], Julie Mackenhauer BMSc[a,b], Justin D. Salciccioli MA[a], Michael N. Cocchi MD[a,c], Shiva Gautam PhD[d], Michael W. Donnino MD[a,e,*]

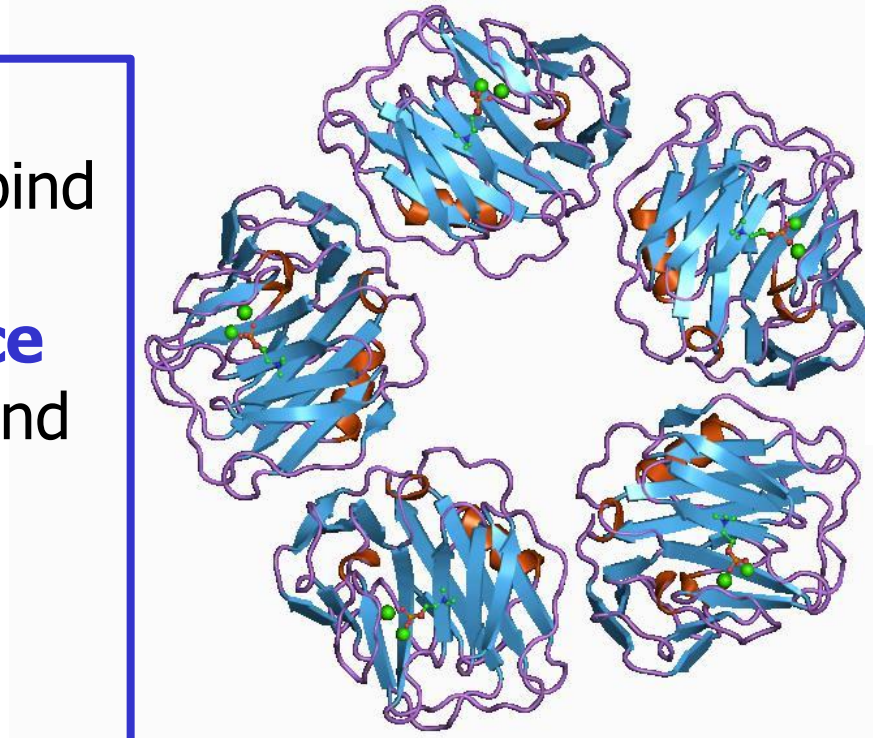
Journal of Critical Care

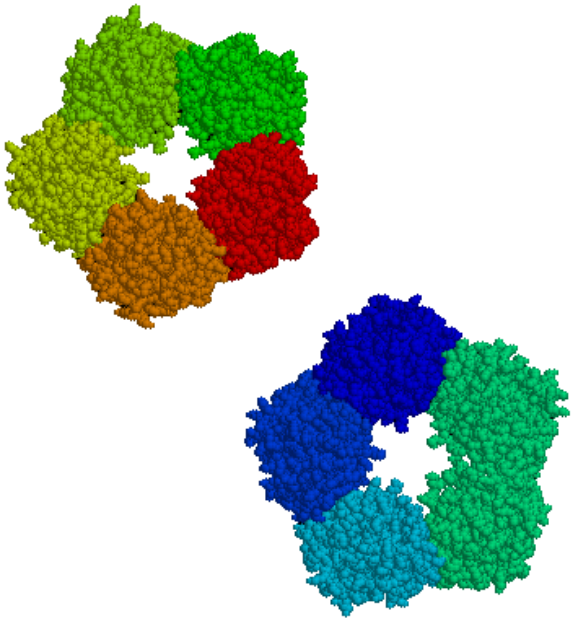
Among patients with vasopressor dependent septic shock, 45% of patients had a lactate level ≤2.4 mmol/L

A normal lactate level is not always an indicator of less severe disease or good prognosis in sepsis patients

CRP: A pentameric protein primarily induced by IL-6

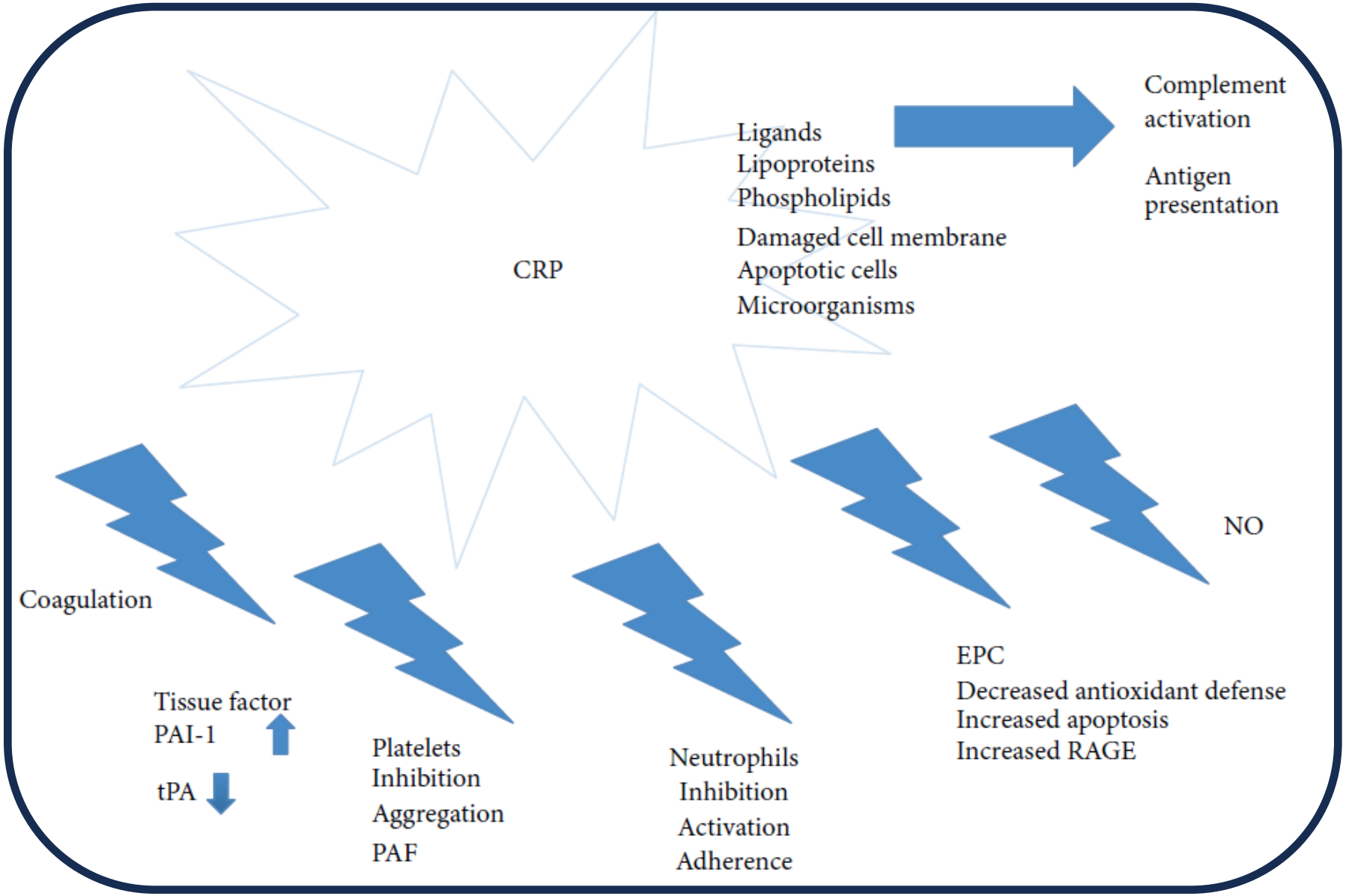
Its physiological role is to bind to lysophosphatidylcholine **expressed on the surface of dead or dying cells** (and some types of bacteria) in order to activate the complement system





C-reactive protein was the first pattern recognition receptor (PRR) to be identified

Principal physiological roles of C-reactive protein



PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator, PAF: platelet activator factor; RAGE: receptor for advanced glycation endproducts; NO: Nitric oxide.

C-reactive protein (CRP):

- One limitation is that rises in CRP are delayed and **peak late (about 36-50 hours into illness) making it** less useful as a biomarker to screen for sepsis
- The CRP ratio, already at day 2 but certainly at day 4, is more predictive of infection and/or adequate antibiotic therapy than individual values.
- A CRP value is not sufficient to discriminate between infected and uninfected patients
- Only the late concentration of CRP can help identify patients who are at risk of death
- High-sensitivity C-reactive protein (hs-CRP) test can find smaller increases in CRP

Advantages of CRP measurement

- ❑ Relatively low pricing in routine labs,
- ❑ Widespread availability as point-of-care tests
- ❑ High sensitivity even for low grade and chronic systemic inflammation.

Disadvantages

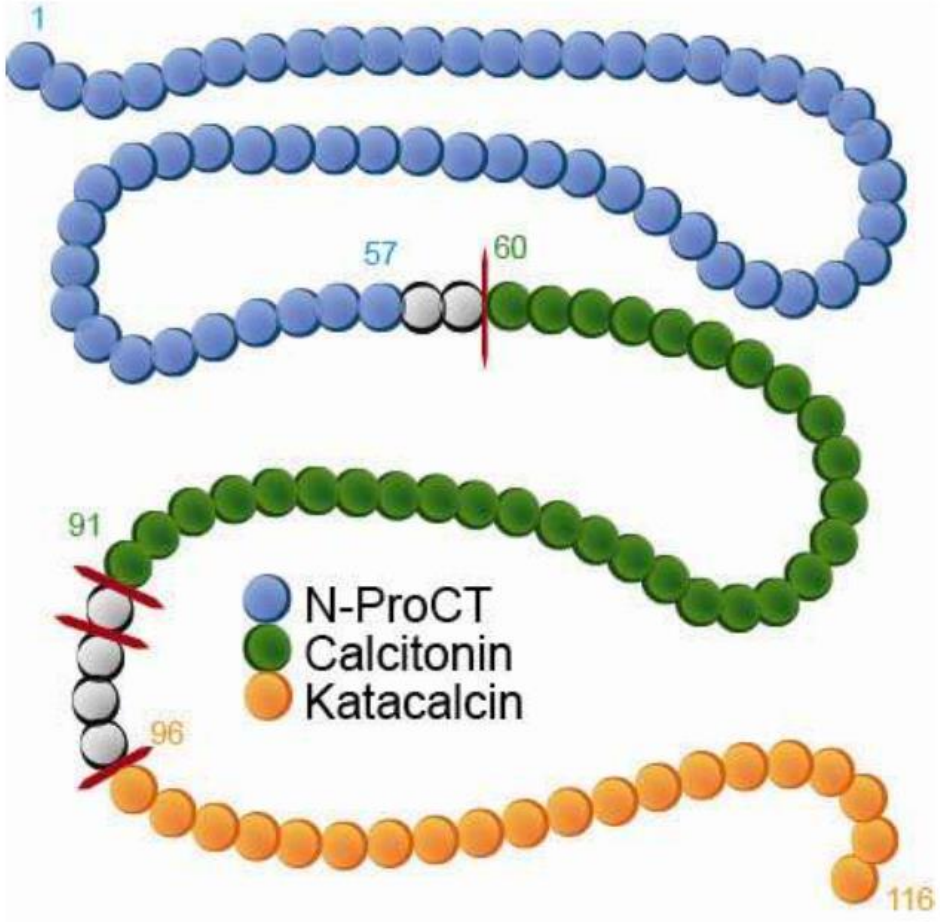
- ❑ A low specificity,
- ❑ Delayed dynamics,
- ❑ Attenuated rise by concomitant steroid

Procalcitonin (PCT):

A protein of *116 amino acids* produced in the C cells of the thyroid gland

This molecule contains:

- An amino terminus (N-ProCT) composed of 57 amino acids,
- An immature calcitonin (CT) portion &
- A 21 amino acid C-terminus, also known as katacalcin moiety

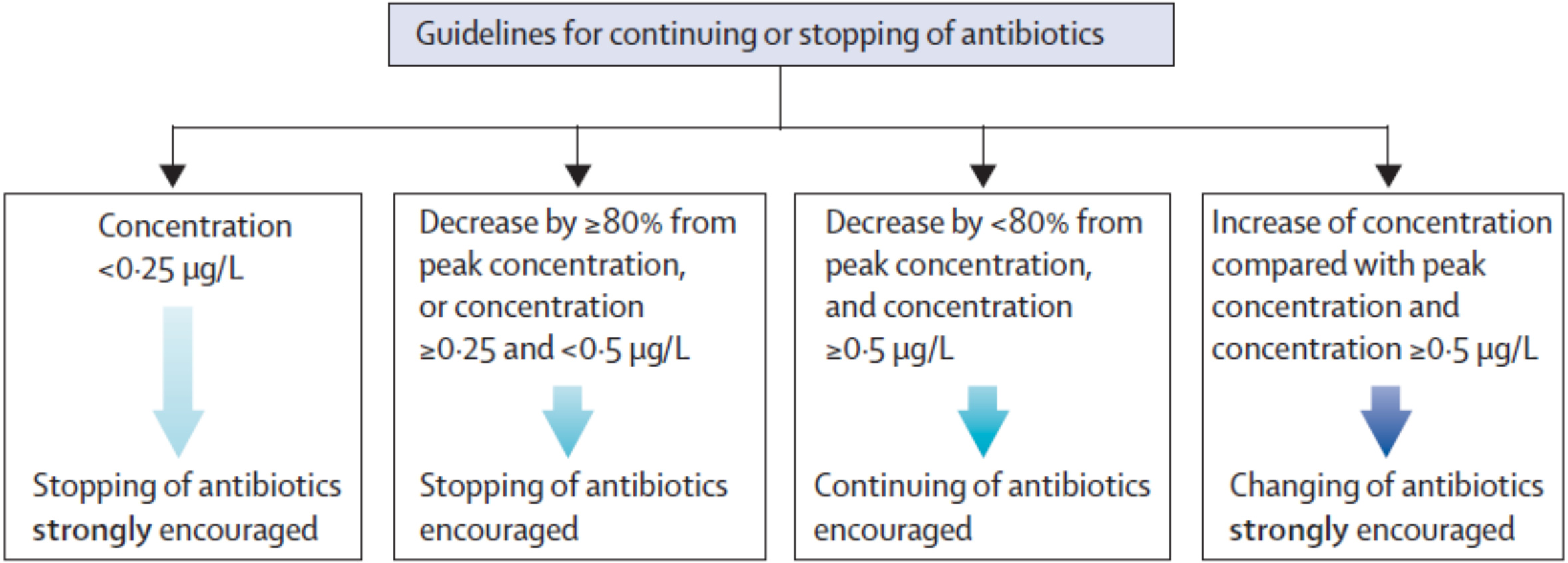


Procalcitonin (PCT):

- In the infectious state, PCT is shown to be released from **neuroendocrine cells in the lungs and intestines (Macrophages)**
- Surgery, severe trauma, invasive procedures, and burns can elevate it, though usually at less than 2 ng/mL.
- If the PCT value is less than 0.2 ng/mL, the negative predictive value is greater than 90%.
- In viral infections, there is a minimum elevation of PCT concentration.
- FDA has approved the use of PCT for risk assessment *for day 1 of ICU admission to determine progression of severe sepsis and septic shock*
- If the PCT is <0.25 ng/mL or has decreased >80– 90%, Stopping of Abs encouraged

Limitations of PCT:

- PCT-guided stewardship should not be applied in chronic infections such as osteomyelitis or endocarditis
- PCT is also relatively low in some atypical infections – including mycoplasma
- Some clinical conditions such as kidney failure and dialysis may influence PCT kinetics



Use of PCT in the ICU

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

Lila Bouadma, Charles-Edouard Luyt, Florence Tubach, Christophe Cracco, Antonio Alvarez, Carole Schwebel, Frédérique Schortgen, Sigismond Lasocki, Benoît Veber, Monique Dehoux, Maguy Bernard, Blandine Pasquet, Bernard Régnier, Christian Brun-Buisson, Jean Chastre, Michel Wolff,* for the PRORATA trial group†*

Lancet 2010; 375: 463–74

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Cytokines: IL-6

- Produced by **monocytes**, fibroblasts, endothelial cells, keratinocytes, T lymphocytes, and tumor cells
- Plasma half-life of IL-6 is less than 6 hours (short half-life) & persistent high levels may indicate unfavorable progression of the sepsis.
- An important mediator in *septic shock* and correlate with disease severity (with levels >1000 ng/mL being highly predictive of sepsis-related death) / an early marker formortality
- The normal IL-6 serum concentration is less than 5 pg/mL
- IL-6 levels correlated with AKI
- Acts as a differentiation factor for B lymphocytes & a T lymphocyte activation factor
- **May differentiate infectious from sterile SIRS**

Adrenomedullin (ADM)

- ADM is a key vasoactive peptide (52 amino acids) in sepsis
- It has vasodilatory effects on smooth muscle (Hypotension)
- Helps *maintain endothelial gap junction patency* & reduce vascular leakage
- Anti-inflammatory, anti-apoptotic and proliferative properties
- Adrecizumab, a non-neutralizing anti-ADM monoclonal antibody which causes a long-lasting increase of plasma ADM & longer functional activity to stabilize endothelium, preventing ADM leakage into the extravascular space,

[TIMP-2] & [IGFBP7]:

(Tissue inhibitor of metalloproteinase-2 & Insulin growth factor binding protein 7)

- ❑ Biomarkers of cell cycle arrest that detect subclinical stages of AKI.

- ❑ Combining biomarker-based endotyping with clinical sub-phenotyping: 2 distinct sub-phenotypes of sAKI that were associated with significantly different survival rates and renal recovery were identified

  - ➢ patients in one sub-phenotype had a strong benefit from early addition of vasopressin to norepinephrine

The Coming Era of—Omics Technology

- single-nuclei RNA sequencing technology, could further support these biomarker-driven approaches
- Using whole genome expression profiling for septic shock endo-typing: genomic landscape had significant implications for the individual host response and clinical outcomes

- Using omics technology, Sweeney et al. identified 3 distinct subtypes of sepsis labelled as:

  - "Inflammopathic",
  - "Coagulopathic" and
  - "Adaptive".

Procalcitonin as a Marker for the Detection of Bacteremia and Sepsis in the Emergency Department

295 patients

Stefan Riedel, MD, PhD,[1] Johan H. Melendez, MS,[2] Amanda T. An,[2] Janet E. Rosenbaum, PhD,[3] and Jonathan M. Zenilman, MD[2]

- In 16 patients, there was evidence of BSI by blood culture, and 12 (75%) of 16 patients had a procalcitonin level of more than 0.1 ng/mL.
- Sensitivity and specificity for the PCT assay were 75% and 79%
- positive predictive value was 17% and the **negative predictive value 98% compared with blood cultures.**
- Procalcitonin is a useful marker to rule out sepsis and systemic inflammation in the ED.

No biomarker has sufficient diagnostic accuracy to reliably diagnose or exclude sepsis