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PEARLS OF LABORATORY MEDICINE

Sepsis and the Clinical Laboratory

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DOI: 10.15428/CCTC.2013.211383

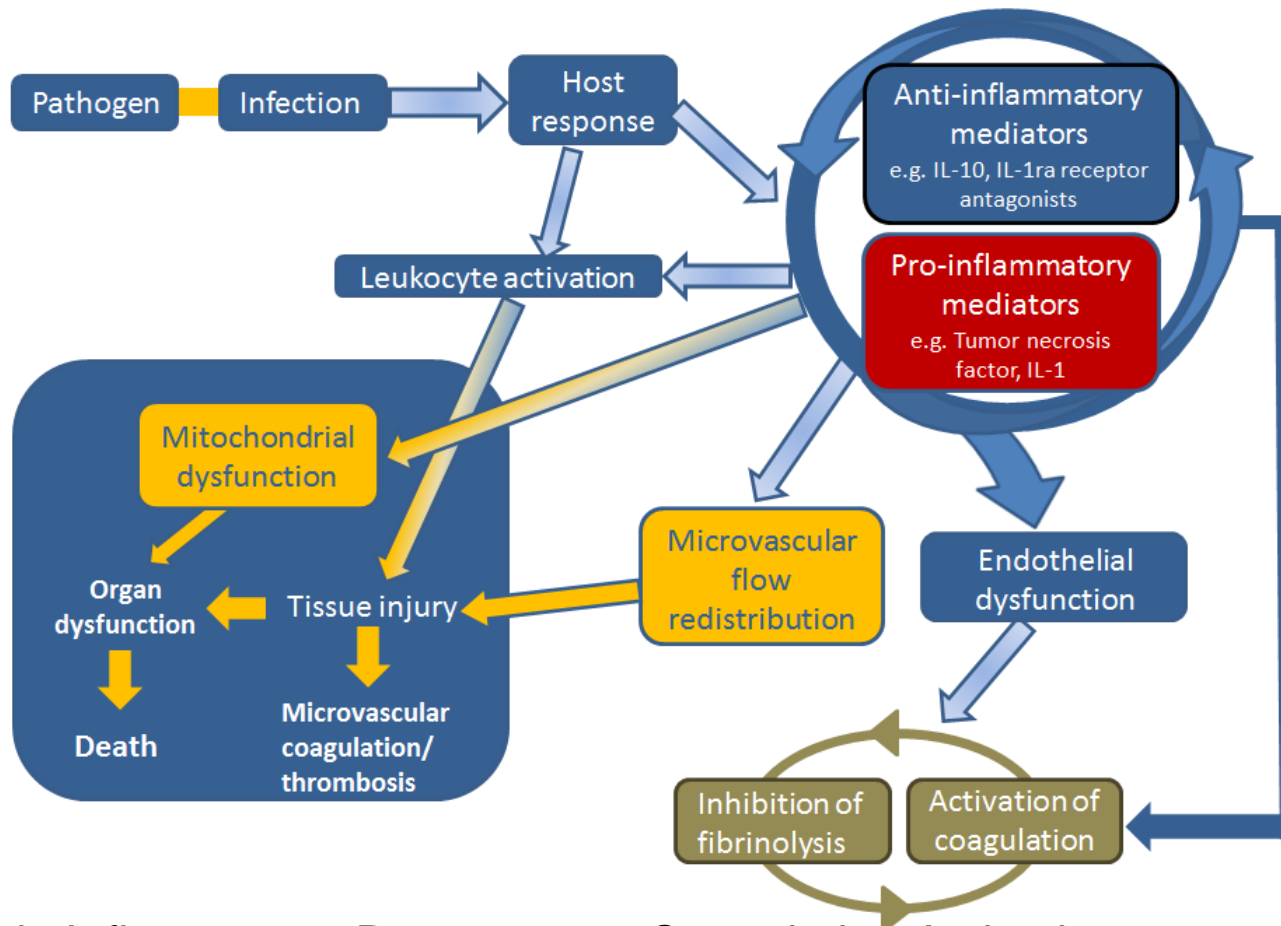


Sepsis Background and Significance

- Per year sepsis affects >750,000 American and >1.8 million patients worldwide per year.
- >200,000 septic patients die in the US/year.
- US hospital costs for sepsis are >\$17 billion, with an uptrend of ~12%/year
- Severe forms of sepsis require ICU care – sepsis prevalence in medical ICUs is >40%
- Leading cause of death in non-cardiac ICUs

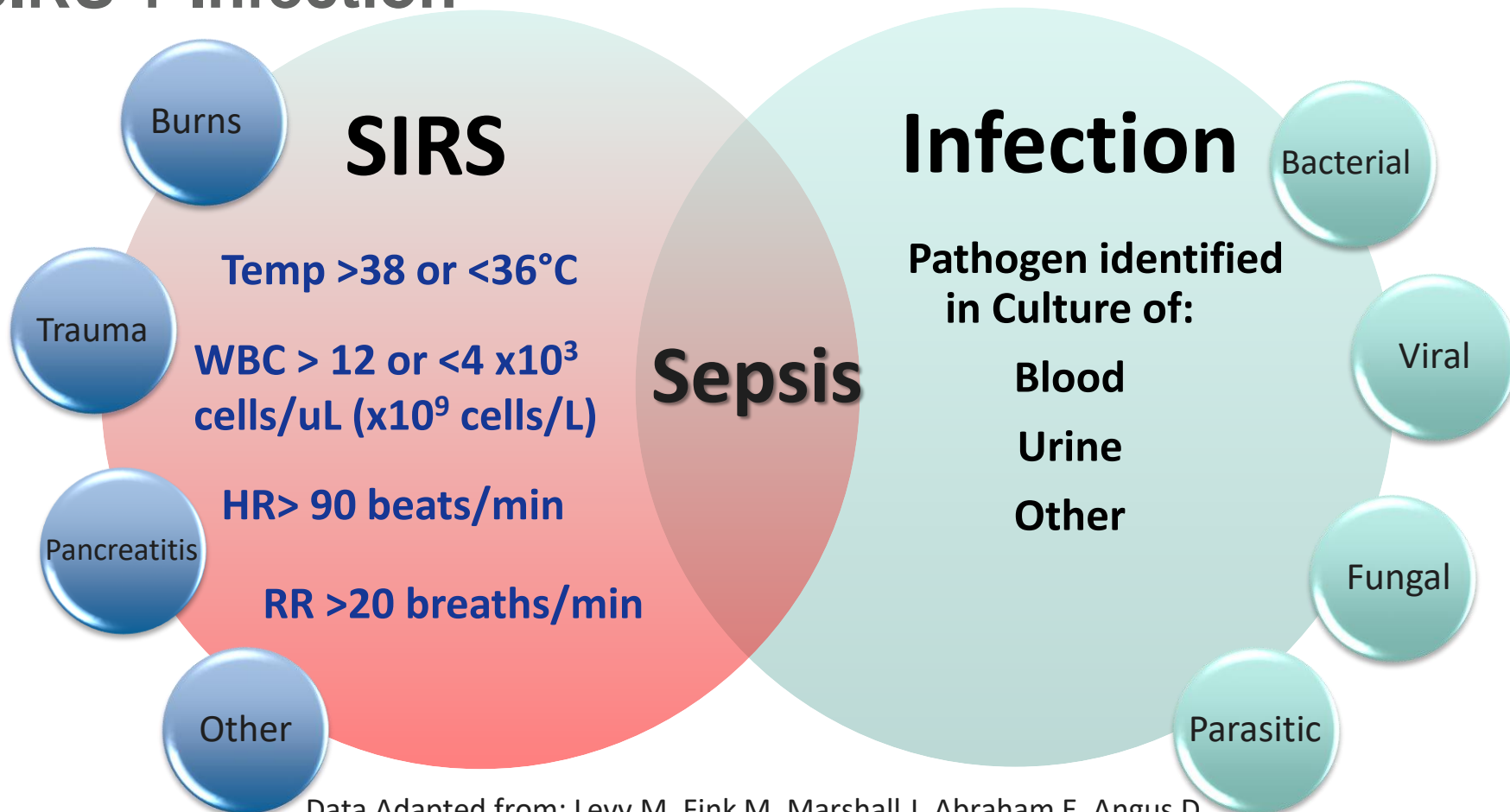


Pathophysiology of Sepsis



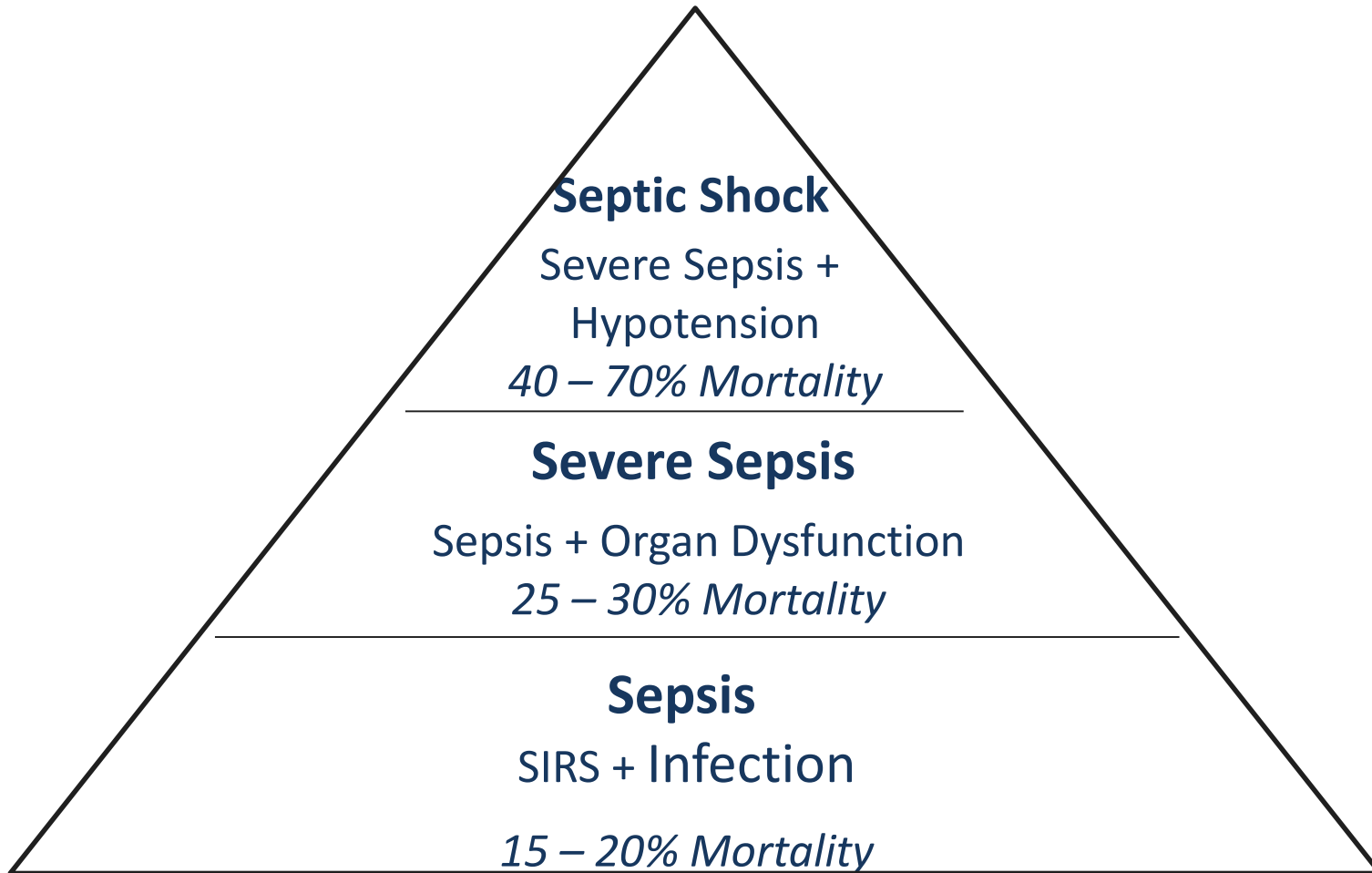
Systemic Inflammatory Response → Coagulation Activation → Impaired Fibrinolysis → End organ dysfunction → Hypotension

“Gold Standard” Diagnosis of Sepsis = SIRS + Infection



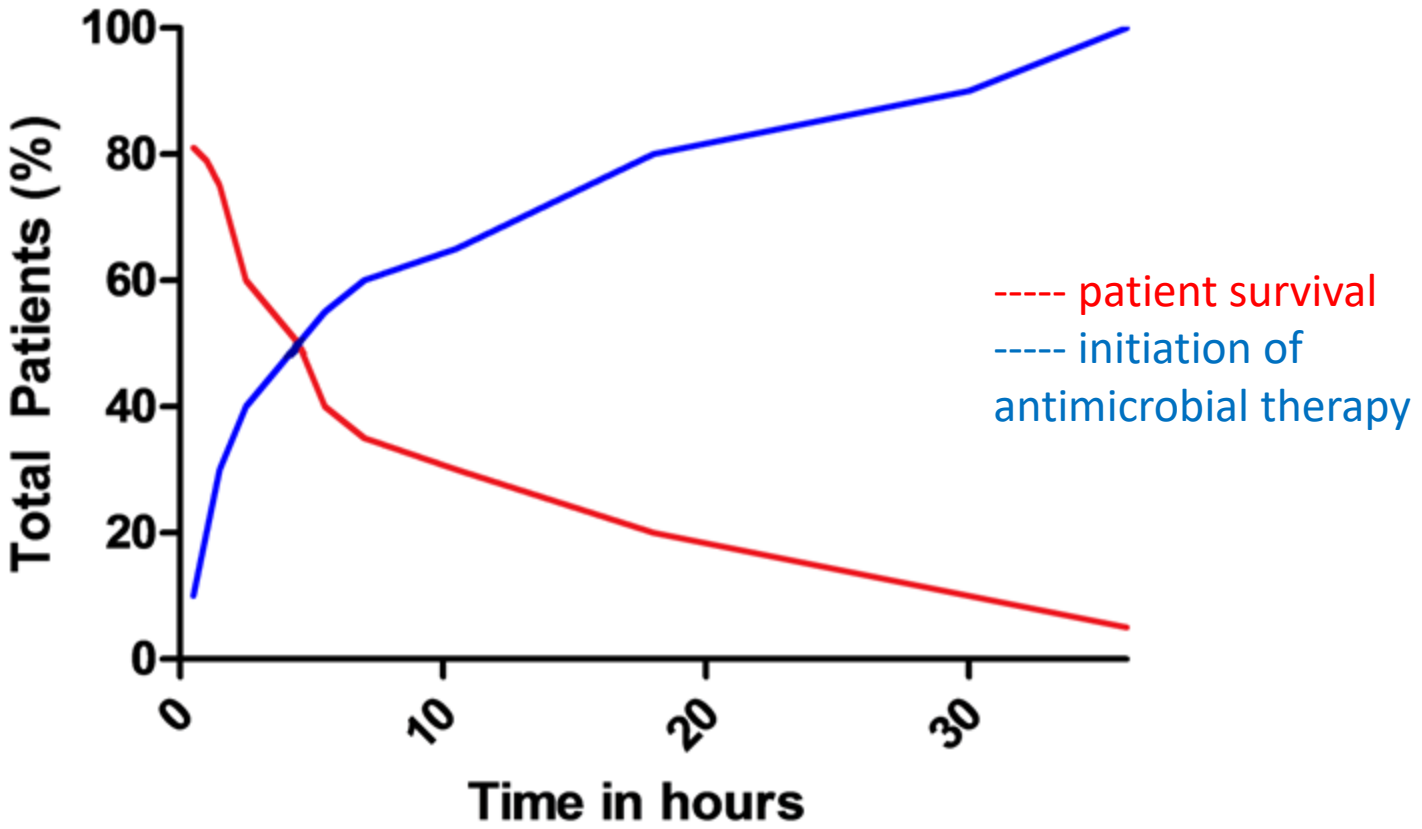
Data Adapted from: Levy M, Fink M, Marshall J, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29(4):530-8.





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Early antimicrobial therapy is critical for survival in septic shock

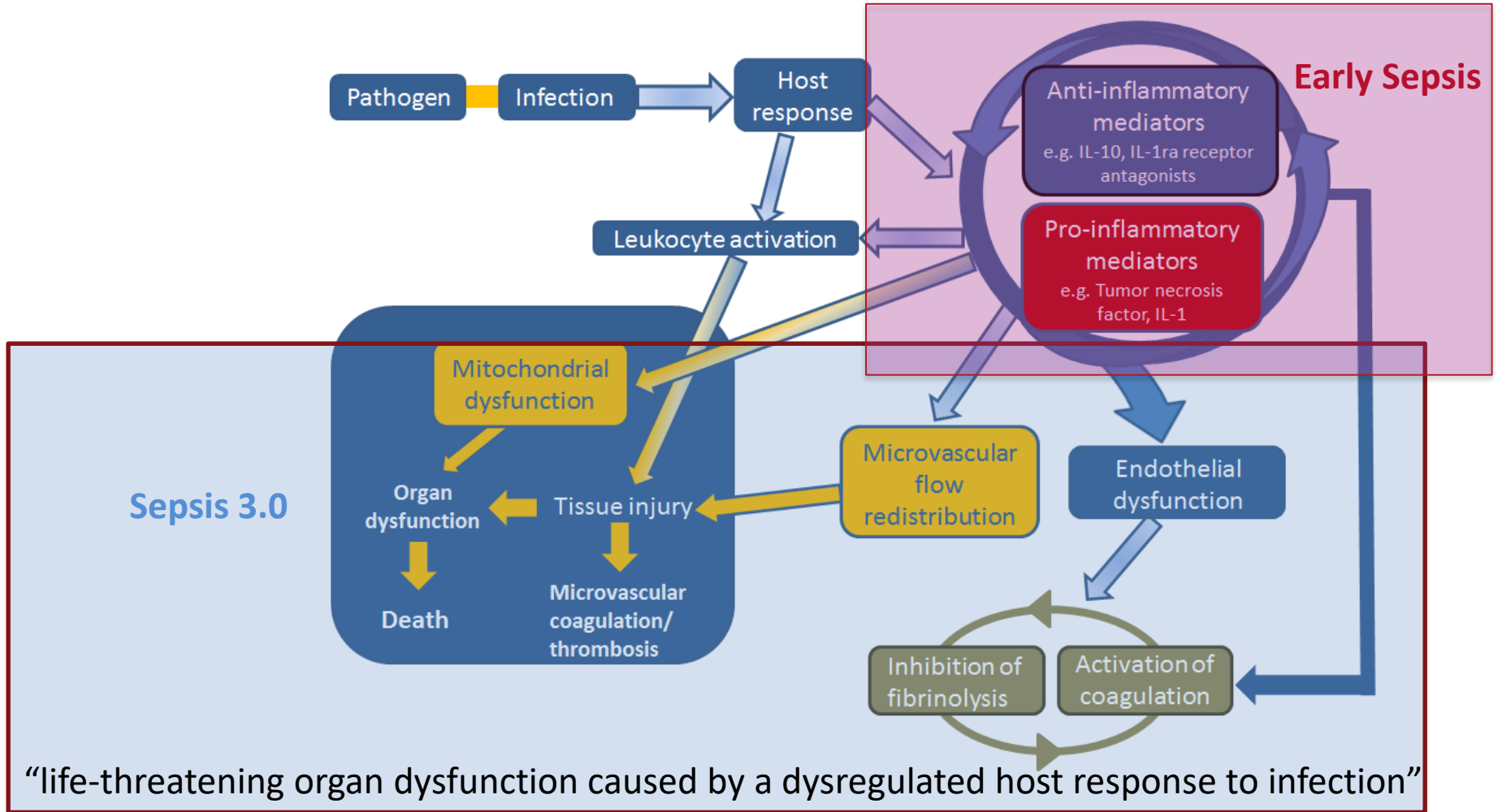


Rapid initiation of treatment reduces mortality

Adapted from: Kumar A, Roberts D, Wood K, Light B, Parrillo J, Sharma S, et al. Critical Care Medicine (2006) 34:1589-1596



Evolving Sepsis Definitions and Biomarkers



- Sepsis is a “life-threatening organ dysfunction caused by a dysregulated host response to infection”
- Sepsis clinical parameters:
 - Documented or suspected infection
 - SOFA score ≥ 2
- Septic Shock is “a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with greater risk of mortality than sepsis alone”
- Septic Shock Clinical Parameters:
 - Requirement for vasopressors to maintain art pressure >65 mm Hg
 - Serum **lactate** > 2 mmol/L (with no hypovolemia)
- ED and outpatient quickSOFA (qSOFA) ≥ 2 : Resp Rate ≥ 22 /min, Altered mental status or Systolic Blood pressure ≤ 100 mm Hg

Definition adapted from: Singer M, et

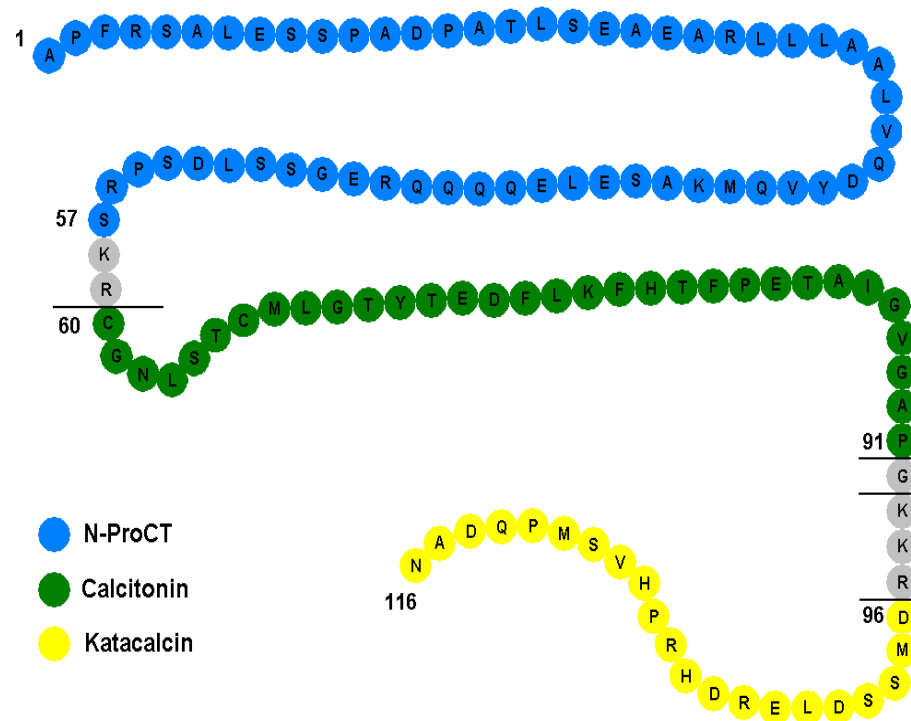
Lactate in Sepsis Management

- **End-product of anaerobic glycolysis and is Increased with:**
 - Excessive energy demands - Tissue hypoperfusion (shock)
 - Low oxygen supply - Impaired cell metabolism
 - Impaired gluconeogenesis
- **Not a useful marker for diagnosis of early disease**
- **The Surviving Sepsis Campaign** advocates measuring lactate within 6 hours of presentation
 - Guide resuscitation to normalize lactate
- **Elevated Lactate > 4 mmol/L is associated with in-hospital mortality**
- **Lactate Clearance** can predict response to therapies and mortality
 - Goal Clearance >10% in first 6 hours



Procalcitonin an Ideal Sepsis Biomarker?

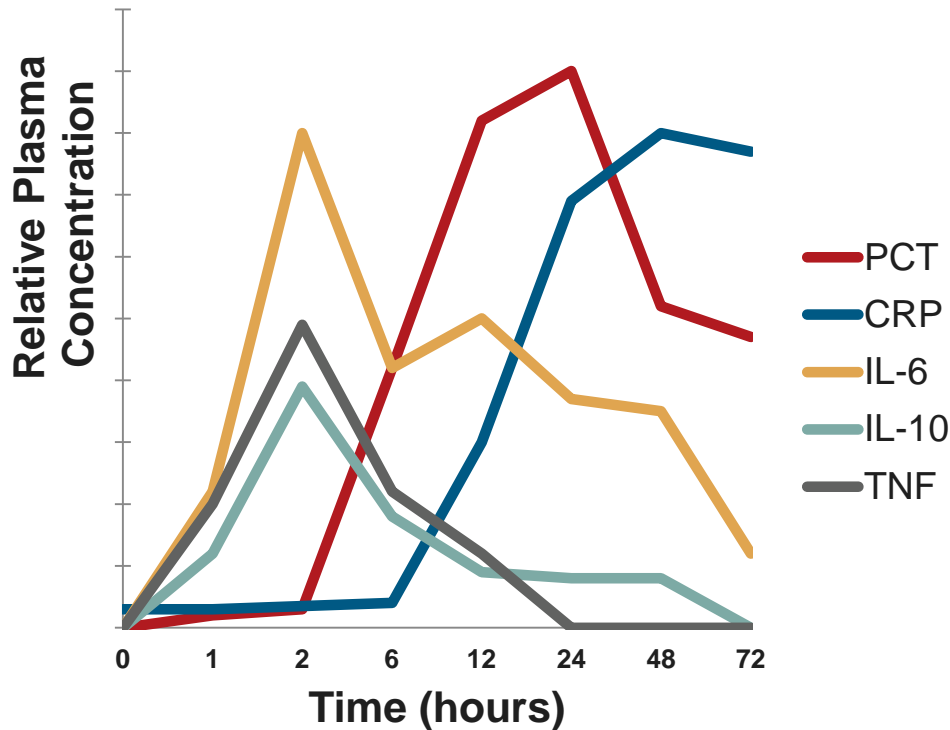
- Precursor to **Calcitonin**-expressed by thyroidal C-cells in healthy patients
- **Inflammation**-Synthesis is upregulated by cytokines in non-thyroidal cells with no cleavage of pro-sequence
- **Sepsis** – Concentrations correlate with disease severity and response to therapy



- **Diagnosis of Early Sepsis**
 - Prediction of infection in SIRS patients – Sens/Spec = 70%
- **Prediction of Prognosis**
 - Decreasing/low PCT – reduced mortality compared to increasing PCT
- **PCT to Monitor Therapy**
 - Evidence based guidelines don't agree
 - Decreasing trend in in adults may be used along with other laboratory and clinical symptoms to direct antibiotic cessation
 - Less is known about pediatric patients
 - No utility in preventing the number of “superbugs”

- Acute phase reactant synthesized in the liver
- Up-regulated in response to inflammation
- Not as good as PCT at predicting early sepsis
- Can be used to Predict Prognosis in patients on antimicrobial therapy
- Cannot be used to Guide Antibiotic Therapy

Diagnostic Utility of Inflammatory Markers to Predict Sepsis



➤ Cytokines

- Rapidly upregulated after infectious insult
- Alone - diagnostic utility similar to PCT
- Panel – superior diagnostic strength to identify sepsis

➤ Prediction of Prognosis

- IL-6 excellent predictor of mortality

➤ Therapy Guidance

- more studies needed

Sepsis Biomarker – Score Card

Which Biomarkers and When?

“Gold Standard” – Bacterial, Viral, or Fungal Cultures - Slow, unreliable, and not always indicated (i.e. patients on antimicrobials)

Biomarker	Sepsis vs SIRS	Prognosis	Therapy	Standard of Care
Lactate	No	Yes	Yes	Yes
Procalcitonin	No	Yes	Yes	No
CRP	No	Yes	No	No
Cytokines	No	Yes	?	No
Multimarker	Yes	Yes	?	No



Conclusions

- Sepsis is a complex disorder associated with significant morbidity and mortality
- Diagnosis of sepsis in early stages is difficult because clinical signs and symptoms and lab tests are not sufficiently sensitive or specific.
- The clinical utility of current sepsis biomarkers is for prediction of disease severity, prognosis and monitoring therapy
- A better understanding of the pathobiology of early sepsis may facilitate identification of better diagnostic markers



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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership:** None declared
- **Consultant or Advisory Role:** None declared
- **Stock Ownership:** None declared
- **Honoraria:** Radiometer, Sysmex
- **Research Funding:** Siemens Healthcare Diagnostics, Sysmex
- **Expert Testimony:** None declared
- **Patents:** 61/757,393



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