Clinical Utility of Sepsis Biomarkers

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a
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a

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Objectives

– Describe the role of the clinical laboratories in the diagnosis and management of sepsis and bacterial infections

– Describe the biology & kinetics of key biomarkers used in the diagnosis management of sepsis

– Describe the role of biomarkers and other rapid tests in the management of sepsis and their ability to predict clinical outcome

– Describe the limitations of biomarkers as single tests for the diagnosis of sepsis
Sepsis

From Global Burden – To Global Health Priority

- Incidence is rising rapidly
- High mortality rate
  - 14% (community-onset BSI) - 34% to 60% (nosocomial BSI)
- Risk of death from septic shock increases by 7.6% with every hour until start of appropriate therapy
- 10th leading cause of death in U.S

- True global burden of sepsis is difficult to assess
- Estimated 30 million cases of sepsis per year, worldwide
- Estimated 6 million deaths per year, worldwide, due to sepsis
Sepsis – Healthcare Cost

Aggregate hospital cost (2011, USA) ; $ 20.3 billion
5.2% of total aggregate cost; most expensive condition treated

1. Septicemia $ 20,298 million
2. Osteoarthritis $ 14,810 million
3. Complication of device (graft, implant) $ 12,881 million
4. Liveborn $ 12,390 million
5. Acute Myocardial Infarction $ 11,504 million

Rank of Expense and number of discharge codes* in thousands
- Most expensive to Medicare (722)
- 2nd most expensive to Medicaid (113) and Uninsured (44)
- 4th most expensive to private insurance (189)

Tiru B et al. Pharmaco Economics 2015; 33 (9): 925-937
Earlier is Better!

Time in the Context of Acute Illness

Funk DJ, Kumar A. Crit Care Clin 2011; 27: 53-76

Laboratory interventions that decrease TAT can be effective

The “Golden Hour”

R. Adams Cowley, M.D. – University of Maryland Medical Center, Baltimore

From his personal experiences and observations in post-World War II Europe, and then in Baltimore (1960s), he recognized that the sooner trauma patients reached definitive care, the better their chance of survival.

- 1970s/1980s importance of early antimicrobial therapy for pediatric meningitis
- 1990s rapid initiation of antimicrobial therapy for community-acquired pneumonia
- 2000s effective antimicrobial therapy for severe sepsis / septic shock

Sepsis & Septic Shock

Initiate Antimicrobial Therapy within 1 hour of recognition of sepsis

Early Sepsis Recognition – Early Pathogen Detection

SSC: Focus on improving outcomes in sepsis

- hemodynamic resuscitation
- development of novel & adjunctive therapies
- development of novel antimicrobials

Early recognition & appropriate antimicrobial therapy
Improves sepsis survival

Dellinger RP. et al. 2013; Crit Care Med 41 (2): 580-630
Funk DI, Kumar A. Crit Care Clin 2011; 27: 53-76


“Time is Tissue”
Revascularization of arteries in acute MI and Stroke

Clinical signs of sepsis have been used for hundreds of years!
(hyperthermia; hypothermia; tachycardia; tachypnea; elevated WBC counts – SIRS)

Hyperthermia / fever is a poor predictor of sepsis and yield of positive blood cultures

Early Sepsis Recognition – Early Pathogen Detection

**SSC : Focus on improving outcomes in sepsis**

- hemodynamic resuscitation
- development of novel & adjunctive therapies
- development of novel antimicrobials

**Early recognition & appropriate antimicrobial therapy**
**Improves sepsis survival**


Sepsis & Septic Shock

**“Speed is Life”**

Continued & growing interest in biomarkers as predictors of sepsis!

Riedel S, Carroll KC. *Clin Lab Med* 2013; 33: 413-437

Time of Diagnostic Uncertainty & Empiric Therapy

Patient presenting to Healthcare Provider

Recognition of Sepsis

1st dose of Antibiotic

Blood Cultures

Rapid Molecular Diagnostic Tests

Antimicrobial Stewardship

Early Sepsis Recognition

1 hour

6 – 8 hours

24 – 72 hours

2nd dose of Antibiotic

Definitive Diagnosis (traditional microbial ID & AST)
A “simplistic view” of sepsis and infection

SIRS: Systemic Inflammatory Response Syndrome

SEPSIS

Bacteremia
Fungemia
Parasitemia
Viremia
other

INFECTION

SIRS

Other
Trauma
Burns
Pancreatitis

Severe Sepsis
Septic Shock
Sepsis may be divided into two phases

Systemic Inflammatory Response Syndrome (SIRS)

Compensatory Anti-Inflammatory Response Syndrome (CARS)

**SIRS criteria:** two or more of the following:

- body temperature > 38°C or < 36°C
- heart rate > 90 beats/min
- respiratory rate > 20 breaths/min (or arterial pCO₂ < 32 mmHg)
- WBC > 12.0 x 10⁹/L or < 4.0 x 10⁹/L (or >10% immature forms)

**Alternative model:**

- CARS begins while pro-inflammatory SIRS is still present
Sepsis is NOT a “single / definitive” Diagnosis

Difficulty to define sepsis based on its pathophysiology from localized infection to “Cytokine Storm”

Revised Sepsis Definition (2016)

…. a life-threatening organ dysfunction caused by a dysregulated host response to infection.

[ Sepsis is a life-threatening condition that arises when the body’s response to an infection injures its own tissues and organs. ]
The Inflammatory Response to Sepsis

Uncontrolled infection and/or major trauma (shock, tissue damage, etc.)

**PAMPs**
(pathogen-associated molecular patterns)
LPS; LTA; bacterial DNA; etc.

**DAMPs**
(danger-associated molecular patterns)
heat-shock protein; DNA; uric acid; etc.

**Insult**

**Trigger**

**Sensor & Effector cells**

**Mediators & Biomarkers**

**Impact on Organ Function**

**Outcome**

**Complement System**

**Endothelial Stress Response**

**Coagulation System**

**Acute Phase Reactants**

**Cell Surface Markers**

**Chemokines / Cytokines**

**MODS**: brain; lung; cardiovascular; kidney; liver; intestines
respiratory distress; shock; oliguria/anuria; capillary leakage, edema; DIC; etc.

**Effective source control**
(normalization of biomarkers & resolution of organ dysfunction)

**Ineffective source control**
(persistent biomarker abnormalities; multi-organ failure; death)

Adapted from: *Clin Microbiol Rev* 2012; 25 (4): 609-634
Biomarkers: Definition & Utility

Biomarker: “...a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention.” (NIH, 2001)

Clin Pharmacol Ther 2001; 69 (3): 89-95

1) Screening patients at risk for sepsis
2) Establish early diagnosis in order to assist initial management of sepsis
3) Risk stratification to identify patients at risk for poor/adverse outcome
4) Predict (overall) outcome
5) Monitoring the response to therapeutic intervention(s)
Biomarkers & Sepsis

Myocardial infarction – 14 biomarkers; Alzheimer’s disease – 8 markers
Sepsis – 34 biomarkers (178 markers in 3370 studies, 160 clinical studies)

Complex pathophysiology of sepsis
Coagulation, complement, inflammation, apoptosis
Many mediators of inflammation
Most biomarkers are evaluated clinically but not experimentally

Is there a single, best biomarker to establish the diagnosis of sepsis?
Examples of Potential / Actual Biomarkers

FDA-approved tests for Sepsis
- Procalcitonin (PCT)

FDA-approved tests, but not specifically approved for Sepsis
- Lactate; CRP; IL-6; IL-8; IL-10

Other biomarkers / tests
- Proadrenomedullin (pro-ADM); CD-14 (presepsin); CD-64

Experimental biomarkers
- sTREM-1; Pentraxin-3
Procalcitonin
(clinical utility first discovered in the 1990s)

Prohormone (PCT) for calcitonin (CT) → but different biologic activities

- produced in C-cells of thyroid and K-cells of the lung
- elevated serum Ca^{++} concentrations and neoplastic changes result in transcription & increased production of PCT
  - Calcitonin lowers serum Ca^{++} concentrations

- PCT can also be induced by
  - Bacterial endotoxins
  - Pro-inflammatory cytokines
  - Trauma and cardiogenic shock

- No response to viral etiologies of infection

\[ \text{increase within 2-4 hours after onset of inflammation} \]

Kinetics of Procalcitonin

- Rapid and sustained response to bacterially induced systemic inflammation
- Half-life: 24 hours
- If the pathogen is not contained, infection spreads and the body up-regulates pro-inflammatory mediators
The Progression of Procalcitonin Levels
From Healthy State to Sepsis – Utility of a Biomarker

Clinical Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCT (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic Shock / MODS</td>
<td>100</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>10</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
</tr>
<tr>
<td>Local Infections / Bacteremia (?)</td>
<td>2</td>
</tr>
<tr>
<td>Normal Values</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>≤ 0.05</td>
</tr>
</tbody>
</table>

**less than 0.5 ng/mL**
Low risk for progression to severe sepsis / septic shock

**0.5 and 2.0 ng/mL**
Sepsis should be considered

**greater than 2.0 ng/mL**
High risk for progression to severe sepsis / septic shock
PCT – Sepsis – SIRS: “how useful is it?”

- Meta-analysis of 30 studies (initial search looked at 3487 reports)
- Meta-analysis included reports for a total of 3244 patients
- PCT may accurately differentiate sepsis from SIRS
- Mean Sensitivity: 77%
- Mean Specificity: 79%
- Area under ROC curve (AUC): 0.85

Limitations
- Substantial heterogeneity among studies
- Reliable, “gold standard” test is absent
- Differences in study implementations
- Publication bias may have been present
- Differences in cut-off values among studies

PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients.
The Power of the Negative Predictive Value

Normal PCT values in a hypotensive/febrile patient virtually exclude bacteremia/sepsis as an etiology!

- Serum PCT levels take 4-5 hours to increase
- With an acute illness: consider a second PCT level (after 4-6 hours)
Multicenter Procalcitonin Monitoring Sepsis (MOSES) Study

- Blinded, prospective multicenter, observational clinical trial, following a Food and Drug Administration (FDA) approved protocol
- Thirteen U.S.-based emergency departments and ICUs
- Consecutive patients meeting criteria for severe sepsis or septic shock, who are admitted to the ICU from the emergency department, other wards, or directly from out-of-hospital
- Procalcitonin was measured daily over the first 5 days of admission

**OBJECTIVE**

To prospectively validate that the inability to decrease PCT levels by more than 80% between baseline and day 4 is associated with increased 28-day all-cause mortality.
# Prognostic Performance of PCT Decrease (baseline to day 4)

<table>
<thead>
<tr>
<th>Intention-to-diagnose population</th>
<th>Dead</th>
<th>Alive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{PCT decrease} \leq 80% )</td>
<td>83</td>
<td>330</td>
<td>413</td>
</tr>
<tr>
<td>( \Delta \text{PCT decrease} &gt; 80% )</td>
<td>24</td>
<td>209</td>
<td>233</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td>539</td>
<td>646</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subpopulation with ICU care on day 4</th>
<th>Dead</th>
<th>Alive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{PCT decrease} \leq 80% )</td>
<td>58</td>
<td>138</td>
<td>196</td>
</tr>
<tr>
<td>( \Delta \text{PCT decrease} &gt; 80% )</td>
<td>15</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>203</td>
<td>276</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subpopulation without ICU care on day 4</th>
<th>Dead</th>
<th>Alive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{PCT decrease} \leq 80% )</td>
<td>25</td>
<td>192</td>
<td>217</td>
</tr>
<tr>
<td>( \Delta \text{PCT decrease} &gt; 80% )</td>
<td>9</td>
<td>144</td>
<td>153</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>336</td>
<td>370</td>
</tr>
</tbody>
</table>

Mortality:
- \( \Delta \text{PCT decrease} \leq 80\% \): 20.0\% (16.2–23.9\%)
- \( \Delta \text{PCT decrease} > 80\% \): 10.4\% (6.5–14.4\%)

Sensitivity:
- \( \Delta \text{PCT decrease} \leq 80\% \): 77.3\% (69.3–85.3\%)
- \( \Delta \text{PCT decrease} > 80\% \): 38.8\% (34.6–43.0\%)

Specificity:
- \( \Delta \text{PCT decrease} \leq 80\% \): 20.0\% (16.2–23.9\%)
- \( \Delta \text{PCT decrease} > 80\% \): 20.0\% (16.2–23.9\%)

Positive predictive value:
- \( \Delta \text{PCT decrease} \leq 80\% \): 89.6\% (85.6–93.5\%)
- \( \Delta \text{PCT decrease} > 80\% \): 89.6\% (85.6–93.5\%)

Negative predictive value:
- \( \Delta \text{PCT decrease} \leq 80\% \): 89.6\% (85.6–93.5\%)
- \( \Delta \text{PCT decrease} > 80\% \): 89.6\% (85.6–93.5\%)

Multicenter Procalcitonin Monitoring Sepsis (MOSES) Study

Kaplan-Meier survival curves, comparing survival of patients with PCT decrease of at least 80% (red, high-risk group) and patients with PCT decrease > 80% (green, low risk group)
A. overall population
B. in patients in the ICU on day 4

The 80% PCT decrease cutoff from baseline to day 4 significantly separated survivors from non-survivors

- 2-fold higher risk of death for patients with a decrease in PCT ≤ 80%, as compared to those with > 80% decrease in the first 4 days following ICU admission
- baseline PCT > 2.0 ng/mL has three-fold greater mortality, if PCT did not drop by > 80%
Limitations of Procalcitonin as a Sepsis Biomarker

\[ \text{J Leukoc Biol 2002; 72: 643-649} \quad \text{BMC Medicine 2011; 9: 107} \]
\[ \text{Clin Chim Acta 2016; 460: 203-210} \quad \text{Infect Dis Clin N Am 2017; 31: 435-453} \]

**Good news:** kinetics of PCT are less influenced by corticosteroids!

<table>
<thead>
<tr>
<th>DO Increase Serum PCT to $\geq 0.25$ ng/mL</th>
<th>DO NOT Increase Serum PCT to $&gt; 0.25$ ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microorganisms</strong></td>
<td><strong>Bacteria:</strong></td>
</tr>
<tr>
<td>Bacteria:</td>
<td>- Chlamydia species(^{26})</td>
</tr>
<tr>
<td>- Alone or with viral coinfection(^{9,15,16})</td>
<td>- Mycoplasma pneumoniae(^{26})</td>
</tr>
<tr>
<td>- Gram-positive and gram-negative pathogens</td>
<td>- Mycobacteria species(^{6,97,98})</td>
</tr>
<tr>
<td>- Legionella species(^{118,119})</td>
<td>- Lyme borreliosis(^{131})</td>
</tr>
<tr>
<td>- Mycobacteria species(^{8,97,98})</td>
<td>- Fungi(^{122-124}):</td>
</tr>
<tr>
<td>- Scrub typhus(^{96})</td>
<td>- Aspergillosis</td>
</tr>
<tr>
<td>Bacterial toxin-mediated inflammation:</td>
<td>- Coccidioidomycosis(^{123})</td>
</tr>
<tr>
<td>- Clostridium difficile toxin(^{120})</td>
<td>- Mucormycosis(^{124})</td>
</tr>
<tr>
<td>- Toxic shock syndrome toxins(^{62})</td>
<td>Viruses: Virtually all, so far</td>
</tr>
<tr>
<td>Fungi: Candida species(^{122})</td>
<td></td>
</tr>
<tr>
<td>Parasites: Plasmodium species (malaria)(^{121})</td>
<td></td>
</tr>
<tr>
<td>Viruses: None, so far</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Syndromes**

| Bacterial:                                | Viral: respiratory tract infections\(^{9,15,17}\) |
|   - Aspiration pneumonia\(^{125-127}\)   |   - Meningitis\(^{10-32}\)                      |
|   - Bacterial meningitis\(^{10-32}\)     |   - Abscess, chronic: for example, empyema\(^{36}\) |
|   - Bacterial pancreatitis\(^{69,109}\)  |   - Gout, pseudogout\(^{108}\)                  |
|   - Bacterial peritonitis\(^{132}\)      |   - Inflammatory bowel disease\(^{101-103}\)  |
|   - Bacterial pneumonia\(^{7,9,15,17}\)  |   - Rheumatic diseases\(^{104-108}\):          |
|   - Bacterial septic shock\(^{135}\)     |     - Behcet syndrome                          |
|   - Febrile neutropenia\(^{74,128}\)     |     - Polyarteritis nodosa                     |
|   - Mushroom poisoning\(^{130}\)         |     - Rheumatoid arthritis                    |
|   - Pyelonephritis\(^{129}\)             |     - Systemic lupus erythematosus             |
|   - Renal insufficiency\(^{45,46}\)      |     - Still disease                            |
|   - Septic arthritis\(^{108,109}\)       |     - Temporal arteritis                       |
|   - Shock\(^{54-62,117,133}\):           |     - Wegener granulomatosis                   |
|     - anaphylactic, bacteremic,           |                                               |
|     - cardiogenic, toxic shock syndrome,  |                                               |
|     - adrenal insufficiency, hemorrhagic, |                                               |
|     - obstructive                         |                                               |
|   - Thermal injury, burns\(^{133}\)      |                                               |
|   - Trauma: crush injury (case reports)\(^{134}\)|                                               |

- specifically treatments that can cause a cytokine storm e.g. OKT3, anti-lymphocyte globulins
- drugs that increase serum PCT levels:
  - Alemtuzumab (CD52 antibody)
  - Granulocyte transfusions
  - Interleukin-2
  - Rituximab (anti-CD20 antibody)
  - T-cell antibodies
- PCT increased in newborns during first 48hrs of life
  - on 3\textsuperscript{rd} day after birth, normal adult reference ranges apply
FDA-approved tests; NOT specifically approved for Sepsis

**Lactate**

Levels are a useful marker for organ dysfunction
- included in the 2016 Sepsis-3 definitions
- may serve as endpoint for resuscitation in patients with severe sepsis / shock
  - > 2 mmol/L - severe sepsis  /  > 4 mmol/L - septic shock
- elevated levels are strongly associated with poor outcome and high mortality

**Limitations:**
- elevated levels are not specific for sepsis and/or predicting mortality

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**CRP**

Is an acute phase reactant synthesized in the liver
- diagnostic and prognostic marker for variety of infections
- widely available and reproducible assay
- elevated levels are strongly associated with poor outcome and high mortality

**Limitations:**
- elevated levels are not specific for sepsis and/or predicting of mortality
Cytokines / Chemokines

- IL-6, IL-8, and IL-10 have been most widely studied to diagnose sepsis
  - IL-6: pro-inflammatory cytokine
  - IL-8: chemokine (neutrophil chemotactic factor)
  - IL-10: anti-inflammatory cytokine

- IL-6, IL-8, and IL-10 serum levels are increased in patients with sepsis
- Increased serum levels correlate with organ dysfunction and mortality
- IL-6 can differentiate sepsis from SIRS
- IL-8 has a good predictive value for severity of sepsis and 28-day mortality

NO greater sensitivity or specificity compared to PCT and/or CRP

May be valuable to monitor intensity of inflammation

*Clin Chim Acta* 2016; 460: 203-210
Other Biomarkers - proADM

Pro-adrenomedullin (proADM)

- first isolated from extracts of pheochromocytoma in 1993
- is ubiquitously expressed in many tissues
- belongs to Calcitonin gene peptide superfamily: PCT, calcitonin gene-related peptide
- primarily vasoactive effects (hypotensive)
- pulmonary circulation is place of ADM clearance (half-life: 22 min)

- 120 ICU patients: 104 with confirmed sepsis and 16 with SIRS without sepsis
- pro-ADM (sepsis) : 4.05 nmol/L
- pro-ADM (SIRS) : 0.309 nmol/L
- $p < 0.001$

- predictive diagnostic power: AUC of 0.95
- cut-off value established at 1.42 nmol/L
- PPV : 99% ; NPV: 42%
Pro-ADM & Sepsis

Diagnostic Value (initial proADM levels)

proADM levels help to identify the infectious origin in patients with systemic inflammatory response syndrome (SIRS) and organ dysfunction

Clin Chim Acta 2016; 460: 203-210

Prognostic Value (ongoing proADM levels)

proADM identifies disease severity and treatment response more accurately than established biomarkers and clinical scores

Crit Care 2018; 22 (1): 79

- 1089 patients with sepsis and a 28-day mortality rate of 26.9%
- proADM, SOFA, APACHE II, PCT, lactate, CRP
- proADM had the strongest association with mortality
Biomarker Panels

• various biomarkers combined (panels) provide **improved sensitivity and specificity** for both **diagnostic AND prognostic** purposes of biomarker testing

• development of “bioscores” based on combination biomarkers

• Examples:
  - PCT, C3a  
    differentiation sepsis vs. SIRS
  - sTREM, PCT, CD64  
    diagnosis of sepsis
  - PCT, presepsin, sTREM-1  
    prediction of mortality of sepsis

Emerging Biomarkers

• microRNAs are a newly identified class of “biomarkers”

• short fragments of endogenous RNA involved in translational gene regulation

• may serve diagnostic & prognostic role for sepsis

Is it really that simple ?
Obviously NOT!

- many studies, but variation in design (observational vs. randomized controlled)
- different cut-off values for various biomarkers among different studies
- differences in biomarker expression during various stages of sepsis
- different laboratory assays/methods used to measure various biomarkers
  - PCT: Kryptor compact (TRACE technology);
    VIDAS ELISA; COBAS (ECLIA); Architect
    (chemiluminescent microparticle immunoassay)
  - other methods for other biomarkers: flow-cytometry, immunoluminometric assays; LDTs

Different Performance = Different Clinical Utility
The Traditional & Current Approach to Sepsis Diagnosis

**Traditional BC Culture Methods**
- up to 50% of sepsis patients have negative BCs
- preliminary results within 1-3 days
- definitive results often require more than 3-5 days
- ineffective for modification and/or de-escalation of antimicrobial therapy

**Rapid Diagnostic Test Methods**
- e.g. ePlex; BioFire; Verigene
- provide rapid ID for select organisms
- provide rapid detection of select AR mechanisms (e.g. vanA, KPC)

A two bottle system with blood specimen split evenly between an **AEROBIC** and an **ANAEROBIC** bottle.
The Dilemma of a Diagnostic “Gold Standard”
the example case: Biomarkers & Sepsis

Blood Cultures are considered the Gold Standard for Detection of Bacteremia / Sepsis

- between 30% and 50% of sepsis patients have negative BCs
- problem with contaminant organisms (e.g. CoNS)
- problems with preceding / concomitant antimicrobial therapy

Sepsis is NOT a single diagnosis, but rather a clinical syndrome encompassing highly heterogeneous groups of disorders!

Differences in site and etiology of infection used in various studies.

What is the definition of a true “Gold Standard”?
Early Sepsis Recognition – Ideal Biomarkers?

- Clinically relevant
  - reflects underlying biological process
  - predicts clinical events

- High diagnostic accuracy
  (high sensitivity, specificity, PPV, NPV)
  - Indicator of
    - Normal physiological processes
    - Pathogenic processes
    - Pharmacological response to a therapeutic intervention

- Quickly obtainable & affordable
Common Misconceptions / Diagnostic Challenges

The search for specific marker(s) of sepsis

There is NOT and there will NEVER be one single marker for the diagnosis of sepsis.

Establish the etiology of the illness

- Blood cultures
- Molecular diagnostic tests
- MALDI-TOF/MS
- Direct organism detection in blood
- Biomarkers (e.g. PCT, CRP, sTREM-1, presepsin, IL-6)

Evaluate vital organ function & prognosis

- Hypotension
- Hypoperfusion
- Altered mental status
- Acid-base imbalance / lactate levels
- Hypoxemia
- Renal & liver dysfunction
- Biomarkers (e.g. PCT, IL-6, presepsin)
Conclusions

The clinical utility of biomarkers lies in their ability to …

- support earlier detection of sepsis.
- support earlier detection of high-risk subgroups of patients.
- support antimicrobial stewardship efforts and potential de-escalation of antimicrobial therapy.
- provide prognostic information for outcome.
Future Considerations

Continued development of new technologies for diagnosis of bacterial infections, incl. biomarkers, and other laboratory methods

- PCT and CRP are commonly used in current practice
- Ongoing need for development of additional biomarkers (e.g., microRNAs)

Develop integrated diagnostic & treatment algorithms (include companion diagnostic tests, such as biomarkers, with traditional pathogen detection methods)

Need for comprehensive, prospective, clinical trials for evaluation of (combination) biomarkers to improve sensitivity & specificity (consider the complexity and time-sensitivity of sepsis)

Need for expert groups and engagement of all clinical stakeholders (individual clinicians, healthcare systems, professional societies, funding & regulatory bodies, diagnostics industry, public health agencies)
THANK YOU !