Conventional biomarkers

- Cytokines
- Endothelial markers
- Receptors
- Other (PCT)
- Cell surface markers
Sepsis biomarkers: a review

Charalampos Pierrakos, Jean-Louis Vincent

Abstract

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 search retrieved 3370 references covering 178 different biomarkers.

Conclusions: Many biomarkers have been evaluated for use in sepsis. Most of the biomarkers had been tested clinically, primarily as prognostic markers in sepsis; relatively few have been used for diagnosis. None has sufficient specificity or sensitivity to be routinely employed in clinical practice. PCT and CRP have been most widely used, but even these have limited ability to distinguish sepsis from other inflammatory conditions or to predict outcome.
Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean

Sensitivity: 71%
Specificity: 71%

AUROC: 0.78

n = 2097 (18 studies)
Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

Christina Wacker, Anna Prkno, Frank M Brunkhorst*, Peter Schlattmann*

Sensitivity: 71%
Specificity: 71%
AUROC: 0.78
n = 2097 (18 studies)

Sensitivity: 77%
Specificity: 79%
AUROC: 0.85
n = 3244 (30 studies)

Lancet Infectious Diseases 2007    Lancet Infectious Diseases 2013
Procalcitonin to guide antibiotic therapy
Reduced antibiotics by 1.83 days (p<0.001)

No worsening in 28-days mortality

ICU patients (n=5486, 15 studies)
Caveats on Procalcitonin

• PCT is a marker of non-specific host response to the presence of infection

• It is not a marker of “sepsis”, according to the new Sepsis III definition

• It is not a specific marker of host response, as there are other causes of high PCT.
Are admission procalcitonin levels universal mortality predictors across different medical emergency patient populations? Results from the multi-national, prospective, observational TRIAGE study

n = 6970, unselected patients to ED
Conventional vs. “Omnics” biomarkers

- Cytokines
- Cell surface markers
- Receptors
- Endothelial markers
- Other (PCT)

- Proteomics
- Metabolomics
- Gene variants

[ CATEGORY NAME ]
The "sepsis" syndrome

Pro-inflammatory  Anti-inflammatory

Anti-inflammatory
Recent advance

Anti-inflammatory → Immune suppression
Dynamics of immune suppression

Previously

Day 1

Week 1

Week 4

Now
Individual variability in immune suppression

Different individuals
Old - same treatment; one syndrome; similar outcome

Day 1

Week 1

Week 4
New - multiple immune deficits; different time-course; variable outcomes
New - multiple immune deficits; different time-course; variable outcomes
The sepsis patients – heterogeneity
Clinically “similar” sepsis patients; but different molecular phenotypes
“Endotypes” – the molecular fingerprints of sepsis
Biomarkers identify “endotypes”

Pathway A – biomarker A

Pathway B – biomarker B
Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

Brendon P Scicluna, Lonneke A van Vught, Aeliko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium*

Summary

Background Host responses during sepsis are highly heterogeneous, which hampers the identification of patients at high risk of mortality and their selection for targeted therapies. In this study, we aimed to identify biologically relevant molecular endotypes in patients with sepsis.

Lancet Respiratory Medicine 2017 (Article in press)
Four endotypes of sepsis

- Mars1
- Mars2
- Mars3
- Mars4

Overexpressed genes (adj. p<0.05, fold expression >1.5)
Underexpressed genes (adj. p<0.05, fold expression <1.5)

Lancet Respiratory Medicine 2017 (Article in press)
Mortality

![Graph showing survival rates over time for different endotypes.]

- **Log-rank p = 0.022**

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Number at Risk</th>
</tr>
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<tbody>
<tr>
<td>Mars1</td>
<td>90</td>
</tr>
<tr>
<td>Mars2</td>
<td>105</td>
</tr>
<tr>
<td>Mars3</td>
<td>71</td>
</tr>
<tr>
<td>Mars4</td>
<td>40</td>
</tr>
</tbody>
</table>

**Survival (%)**

- Time since admission to intensive care unit (days)

*Lancet Respiratory Medicine 2017 (Article in press)*
**Shock**

- **A**
  - Bar chart showing the percentage of patients with septic shock and no shock across different categories.
  - Categories: Mars1, Mars2, Mars3, Mars4.
  - Mars1: 44% septic shock, 56% no shock.
  - Mars2: 41% septic shock, 59% no shock.
  - Mars3: 17% septic shock, 83% no shock.
  - Mars4: 33% septic shock, 67% no shock.
  - Note: \( \chi^2 p = 0.002 \)

**SOFA**

- **B**
  - Box plot comparing SOFA scores across different endotypes.
  - Endotypes: Mars1, Mars2, Mars3, Mars4.
  - Mars1: Lower median SOFA score.
  - Mars2: Higher median SOFA score.
  - Mars3, Mars4: Median SOFA scores are similar.
  - Note: * indicates statistical significance.

*Lancet Respiratory Medicine 2017 (Article in press)*
Key biomarker genes to identify “endotypes”

Lancet Respiratory Medicine 2017 (Article in press)
Therapeutic implications
Biomarker-guided immune therapy in sepsis

Comment

The road to precision medicine in sepsis: blood transcriptome endotypes

Editorial - Lancet Respiratory Medicine 2017 (Article in press)
Application of “omics” science in sepsis
Subtypes of sepsis classified by:
1. Risk of progression
2. Risk of mortality
3. Response to therapy
4. Host factors/genetics

Novel subtype specific therapies
Personalized sepsis treatment
Genes - workers
Gene modules – working units

- Repair
- Pathogen detection
- Inflammation
- Pathogen killing
System – working community
What we hope to see......
The reality......
System biology

Application of artificial intelligence and machine learning algorithms in biology and medicine
Network analysis – hubs
Neutrophils

Cell cycle

Interferon

Immune response
Hypothesis testing: clusters vs. outcome

Healthy controls
Low mortality
High mortality
What is inside each cluster?

Pathway analysis
“Omics”

- Other biomarkers
- PCT
- WCC, lactate

Most

Transcriptomics

Proteomics

Few

Metabolomics

The future