Biomarkers identifying sepsis phenotypes
A biomarker may serve one or more of five overlapping roles

<table>
<thead>
<tr>
<th>Uses of biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td>To identify patients at increased risk of adverse outcome to inform a prophylactic intervention, or further diagnostic test</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>To establish a diagnosis to inform a treatment decision, and to do so more reliably, more rapidly, or more inexpensively than available methods</td>
</tr>
<tr>
<td><strong>Risk stratification</strong></td>
</tr>
<tr>
<td>To identify subgroups of patients within a particular diagnostic group who may experience greater benefit or harm with therapeutic intervention</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
</tr>
<tr>
<td>To measure response to intervention to permit the titration of dose or duration of treatment</td>
</tr>
<tr>
<td><strong>Surrogate end point</strong></td>
</tr>
<tr>
<td>To provide a more sensitive measure of the consequences of treatment that can substitute for a direct measure of a patient-centered outcome</td>
</tr>
</tbody>
</table>

Marshall J, Reinhart K CCM 2008
Potential of sepsis biomarkers

“Sepsis biomarkers may help to transform sepsis from a physiologic syndrome to a group of distinct biochemical disorders”

Marshall J, Reinhart K CCM 2008
Search results

Items: 1 to 20 of 5320

1. Defining Physiological Predictors of Peripartum Maternal Bacteremia.
   Molina RL, Easter SR, Venkatesh KK, Cantonwine DE, Kaimal AJ, Tuomaala RE, Riley LE.
PMD: 26489062
Similar articles

2. Comparison of genomic DNA methylation pattern among septic and non-septic newborns - An epigenome wide association study.
   Dhars DB, Ashmi AH, Bhat BV, Kalanwani S, Panja SC.
PMD: 26484145
Similar articles

PMD: 26477627
Similar articles

4. Recent knowledge on the pathophysiology of septic acute kidney injury: A narrative review.
   Shum HP, Yan WW, Chan TM.
Potential Sepsis Biomarkers

Insult → Trigger → Sensors and effector cells → Mediators and biomarkers → Impact on organ function → Outcome

- **Uncontrolled infection/major trauma/circulatory shock/tissue necrosis/apoptosis/anaphylaxia**

  - **PAMPs**
    - LPS, LTA, lipoproteins, peptidoglycans, bacterial DNA, etc.
  - **DAMPs**
    - HMGB-1, heat-shock protein, DNA, uric acid, etc.

- **Complex protein systems**
  - Complement system
  - Coagulation system

- **Vascular and tissue cells**
  - Endothelial cells
  - Epithelial cells
  - Adipose tissue

- **Blood and lymphatic cells**
  - Granulocytes
  - Macrophages/monocytes
  - Lymphocytes (T-cells, B-cells)

- **Mediators and biomarkers**
  - C5a, C3a, C5aR, C5b-9, etc.
  - aPPT, PT, AT, Protein C etc.
  - Endothelial stress response: ELAM-1, ICAM-1, Selectins
  - Acute phase reactants: CRP, LBP, PCT, etc.
  - Cytokines/chemokines: IL-6, IL-8, IL-4, IL-10, MIF, HMGB1, sTNF, suPAR, sTREM-1, etc.
  - Cell surface markers: mHLA DR, CD64, CD48, C5aR, etc.

- **Impact on organ function**
  - **Brain**
    - Confusion
  - **Lung**
    - Respiratory distress
  - **Cardiovascular system**
    - Shock
  - **Kidney**
    - Oliguria/Anuria
  - **Liver**
    - Excretory failure
  - **Gut**
    - Loss of barrier function, ileus
  - **Micro-circulation**
    - Capillary leak edema, DiC

- **Outcome**
  - **Effective source control**
    - Normalization of biomarker abnormalities
    - Resolution of organ dysfunction; recovery
  - **Ineffective source control**
    - Persistence of biomarker abnormalities
    - Multiple organ failure; death
Understanding of the host response a decade ago
There is no biphasic or uniform immune response
Potential of an ideal sepsis marker

• Supports the diagnosis – infectious or other causes of systemic inflammation
• Prognosis – risk stratification
• Impacts measures for infection control – antimicrobials
• Contributes to improved patient outcome
• Reflects the course of the immunopathology of sepsis and identifies suitable patient populations for sepsis trials
Sepsis versus SIRS


Potential of an ideal sepsis marker

- Support the diagnosis – infectious or other causes of systemic inflammation
- Prognosis – risk stratification
- Impacts measures for infection control – antimicrobials
- Contributes to improved patient outcome
- Reflect the course of the immunopathology of sepsis and identifies suitable patient populations for sepsis trials
PCT as Prognostic Biomarker

Nonalert values = PCT < 1.0 ng/ml or < 1.0 ng/mL that were not succeeded by values > 1.0 ng/mL

Group 1 = decrease of PCT on day 3 by more than 30% or PCT on day 3 below 0.25 ng/mL

Group 2 = increase of PCT or decrease of PCT on day 3 by less than 30%.

Alert values = PCT > 1.0 ng/mL with an increase daily, counting from the day after exceeding 1.0 ng/mL.

- Jensen JU et al. Crit Care Med 2006; 34: online

- Georgopoulou AP et al J Crit Care, 2010: online
Midregional proadrenomedullin for prognosis in community-acquired pneumonia: A systematic review

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruger</td>
<td>2010</td>
<td>11.29 (3.67, 34.77)</td>
<td>9.38</td>
</tr>
<tr>
<td>Bello</td>
<td>2012</td>
<td>24.70 (3.15, 193.79)</td>
<td>3.30</td>
</tr>
<tr>
<td>Albrich</td>
<td>2011</td>
<td>5.06 (2.68, 9.52)</td>
<td>20.10</td>
</tr>
<tr>
<td>Lacoma</td>
<td>2013</td>
<td>1.75 (0.41, 7.55)</td>
<td>6.10</td>
</tr>
<tr>
<td>Christ-Crain</td>
<td>2006</td>
<td>9.81 (4.30, 22.39)</td>
<td>14.66</td>
</tr>
<tr>
<td>Huang</td>
<td>2009</td>
<td>5.27 (3.50, 7.92)</td>
<td>29.12</td>
</tr>
<tr>
<td>Courtais</td>
<td>2013</td>
<td>10.50 (2.05, 53.88)</td>
<td>5.02</td>
</tr>
<tr>
<td>Julian-Jimenez</td>
<td>2013</td>
<td>24.10 (4.97, 116.92)</td>
<td>5.33</td>
</tr>
<tr>
<td>Suberviola</td>
<td>2012</td>
<td>6.07 (1.58, 23.39)</td>
<td>6.99</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>6.86 (4.64, 10.13)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Figure 2  Forest plot displaying meta-analysis of the odds ratio of short-term mortality in patients with increased level of midregional proadrenomedullin.

Rodrigo Cavallazzi Crit Care 2014
Plasma adrenomedullin is associated with short-term mortality and vasopressor requirement in patients admitted with sepsis

Rossella Marino, Joachim Struck, Alan S Maisel, Laura Magrini, Andreas Bergmann and Salvatore Di Somma

ADM is associated with:
- severity of disease
- mortality

ADM strongly discriminates patients requiring vasopressor therapy from the others

**ADM is associated with severity of disease**

- Correlation with APACHE II score: \( r = 0.46 \)
- \( P < 0.0001 \)

**ADM is associated with mortality**

- ADM median (IQR): survivors: 50 (31 to 77) pg/mL
- non-survivors: 84 (48 to 232) pg/mL
- \( P < 0.001 \)

ADM median (IQR): no vaspressors 48 (32 to 75) pg/mL; with vaspressors 129 (83 to 264) pg/mL
- \( P < 0.0001 \)
Diagnostic and short-term prognostic utility of plasma pro-enkephalin (pro-ENK) for acute kidney injury in patients admitted with sepsis in the emergency department

Rossella Marino · Joachim Struck · Oliver Hartmann · Alan S. Maisel · Miriam Rehfeldt · Laura Magrini · Olle Melander · Andreas Bergmann · Salvatore Di Somma

pro-ENK outperforms creatinine clearance in predicting 7-day mortality

pro-ENK increases with severity of AKI as determined by RIFLE stage

Despite the high correlation between pro-ENK and creatinine clearance, pro-ENK was a better predictor of mortality within 7 days (pro-ENK: $\chi^2$ 13.4, $p < 0.001$, AUC 0.69 vs. creatinine clearance: $\chi^2$ 4, $p = 0.045$, AUC 0.61)
Potential of an ideal sepsis marker

• Support the diagnosis – infectious or other causes of systemic inflammation
• Prognosis – risk stratification
• Impacts measures for infection control – antimicrobials
• Contributes to improved patient outcome
• Reflect the course of the immunopathology of sepsis identifies suitable patient populations for sepsis trials
Meta-analysis 14 RCTs comparing PCT guided antibiotic use v.s. standard care Impact of PCT guided antibiotic therapy.

<table>
<thead>
<tr>
<th>Source</th>
<th>Diagnoses</th>
<th>Total No.</th>
<th>Mortality, Control vs PCT Groups, No. Dead/Total (%)</th>
<th>Abx Use, Control vs PCT</th>
<th>Relative Reduction, %</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briel et al, 2008^4</td>
<td>Upper and lower RTI</td>
<td>458</td>
<td>1/226 (0.4) vs 232 (0)</td>
<td>Prescription: 97% vs 25%</td>
<td>Duration: 7.1 vs 6.2 d</td>
<td>Reduction of Abx without additional days of restricted activity</td>
</tr>
<tr>
<td>Burkhardt et al, 2010</td>
<td>Upper and lower RTI</td>
<td>550</td>
<td>2/276 (0) vs 276 (0)</td>
<td>Prescription: 36.7% vs 21.5%</td>
<td>Duration: 7.7 vs 7.8 d</td>
<td>Reduction of Abx without causing health impairment</td>
</tr>
<tr>
<td>Christ-Crain et al, 2004</td>
<td>CAP, AECOPD, bronchitis</td>
<td>243</td>
<td>4/119 (3.4) vs 4/124 (3.7)</td>
<td>Prescription: 83% vs 44%</td>
<td>Duration: 12.8 vs 10.9 d</td>
<td>Reduction of Abx prescriptions</td>
</tr>
<tr>
<td>Christ-Crain et al, 2006</td>
<td>CAP</td>
<td>302</td>
<td>20/151 (13.2) vs 19/151 (11.9)</td>
<td>Prescription: 99% vs 85%</td>
<td>Duration: 12.9 vs 5.8 d</td>
<td>Reduction of Abx without adverse outcomes</td>
</tr>
<tr>
<td>Stolz et al, 2007</td>
<td>AECOPD</td>
<td>208</td>
<td>9/106 (8.5) vs 5/102 (4.9)</td>
<td>Prescription: 72% vs 40%</td>
<td>Duration: 11</td>
<td>Reduction of Abx exposure without adverse outcome</td>
</tr>
<tr>
<td>Long et al, 2009</td>
<td>CAP</td>
<td>127</td>
<td>0/64 (0) vs 0/68 (0)</td>
<td>Prescription: 97% vs 86%</td>
<td>Duration: median 10 vs 6 d</td>
<td>Reduction of Abx and shorter Abx duration</td>
</tr>
<tr>
<td>Kristoffersen et al, 2009</td>
<td>Lower RTI</td>
<td>210</td>
<td>1/107 (0.9) vs 2/103 (1.9)</td>
<td>Prescription: 79% vs 85%</td>
<td>Duration: 6.8 vs 5.1 d</td>
<td>Reduction of duration of Abx use</td>
</tr>
<tr>
<td>Schuetz et al, 2009</td>
<td>CAP, AECOPD, bronchitis</td>
<td>1359</td>
<td>33/668 (4.8) vs 34/671 (5.1)</td>
<td>Prescription: 87.7% vs 75.4%</td>
<td>Duration: 8.7 vs 5.7 d</td>
<td>Noninferiority for clinical outcomes and decreased Abx use</td>
</tr>
<tr>
<td>Svobera et al, 2007</td>
<td>Postop septic shock</td>
<td>72</td>
<td>10/36 (28.3) vs 10/36 (28.3)</td>
<td>Duration: median 9.5 vs 8.0 d</td>
<td>Duration: 37</td>
<td>Trend to decrease in SOFA and ventilator/ICU days</td>
</tr>
<tr>
<td>Nobre et al, 2008</td>
<td>Sepsis</td>
<td>79</td>
<td>12/40 (30.0) vs 8/36 (23.5)</td>
<td>Abx-free days alive: 15 vs 15</td>
<td>Duration: 25</td>
<td>Reduction in Abx and ICU LOS without adverse events</td>
</tr>
<tr>
<td>Stolz et al, 2009</td>
<td>VAP</td>
<td>101</td>
<td>12/60 (20.0) vs 8/51 (15.7)</td>
<td>Abx-free days alive: 15 vs 10</td>
<td>Duration: 25</td>
<td>Decrease in Abx use without increasing mortality rate</td>
</tr>
<tr>
<td>Hochreiter et al, 2009</td>
<td>Postop patients with infection</td>
<td>110</td>
<td>15/57 (26.3) vs 15/57 (26.3)</td>
<td>Duration: 7.9 vs 5.9 d</td>
<td>Duration: 20</td>
<td>Reduction in Abx duration and ICU LOS without adverse events</td>
</tr>
<tr>
<td>Schroeder et al, 2009</td>
<td>Postop severe sepsis</td>
<td>27</td>
<td>3/13 (23.1) vs 3/14 (21.4)</td>
<td>Duration: 6.3 vs 6.6 d</td>
<td>Duration: 33</td>
<td>Shorter Abx duration</td>
</tr>
<tr>
<td>Boudzma et al, 2010^6</td>
<td>Sepsis</td>
<td>621</td>
<td>64/314 (20.4) vs 65/307 (21.2)</td>
<td>Abx-free days alive: 11.6 vs 14.3</td>
<td>Duration: 9.9 vs 6.8 d</td>
<td>Reduction in Abx use without increase in mortality rate</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available. Other abbreviations: See Table 2.

* Indicates intention-to-treat analysis.

† Indicates 28-day mortality.

Schuetz P et al  Schuetz et al Arch Intern Med. 2011
Meta-analysis 14 RCTs comparing PCT guided antibiotic use v.s. standard care Impact of PCT guided antibiotic therapy.

PCT-guided AB-Therapy in Sepsis on the ICU

Baseline evaluation and inclusion procedure
- Patient eligible? Informed consent?

Broad-spectrum antimicrobial treatment for 72 hours
- Routine infectious disease work-up with microbiologic cultures
- Daily PCT-measurements

Assessment at day 3

PCT-values on day 1 & 2:
- < 1.0 µg/L

PCT-values on day 3:
- < 0.1 µg/L

Bacterial infection highly unlikely?
(Thorough clinical evaluation)

Stop antibiotic therapy

PCT-values on day 1 or 2:
- > 1.0 µg/L

Continue antibiotic therapy for at least 2 days
- On day 3: apply either 1 of the 2 following possible stop rules after careful clinical evaluation and overall assessment

Stop rule, Option 1:
1) Patient stable and
2) PCT has decreased to an absolute value < 0.25 µg/L (AB stop encouraged)
3) PCT has decreased to an absolute value < 0.1 µg/L (AB stop strongly encouraged)

Stop rule, Option 2:
1) Patient stable and
2) PCT has decreased by at least 90% from the baseline peak value

Stop antibiotic therapy

Shorter Antibiotic Duration

% patients without antibiotics

PCT-guided group (n=31)
Control group (n=37)

6d
10d

HR: 1.9 (1.2-3.1)
p = 0.009

Time to antibiotic discontinuation (days)

HR: 1.9 (95% CI 1.1-2.4)
p = 0.02

Shorter ICU stay

% in ICU

Days

Control group (n=37)
PCT-guided group (n=31)

Nobre V, AJRCCM 07
Potential of an ideal sepsis marker

• Support the diagnosis – infectious or other causes of systemic inflammation
• Prognosis – risk stratification
• Impacts measures for infection control – antimicrobials
• Contributes to improved patient outcome
• Reflect the course of the immunopathology of sepsis and identifies suitable patient populations for sepsis trials
PCT to Increase Early Appropriate Antibiotics and Improve Survival - the PASS Trial

PCT-Guided Algorithm

“alert PCT value” = 1.0 ng/mL and not decreasing by at least 10% from the previous day

Deescalation only when PCT <1.0 ng/ml for at least 3 days
PCT to Increase Early Appropriate Antibiotics and Improve Survival - the PASS Trial
PCT to Increase Early Appropriate Antibiotics and Improve Survival - the PASS Trial

<table>
<thead>
<tr>
<th>Consumption of Antimicrobials</th>
<th>Procalcitonin-Guided (n = 604)</th>
<th>Standard-of-Care-Only (n = 596)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam used within 28 days (DDD)</td>
<td>2925</td>
<td>1893</td>
<td>—</td>
</tr>
<tr>
<td>Proportion of days(^a) followed when piperacillin/tazobactam was used</td>
<td>0.11 (0.00–0.56)</td>
<td>0.00 (0.00–0.33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Meropenem used within 28 days (DDD)</td>
<td>2480</td>
<td>2174</td>
<td>—</td>
</tr>
<tr>
<td>Proportion of days(^a) followed when meropenem was used</td>
<td>0.00 (0.00–0.07)</td>
<td>0.00 (0.00–0.00)</td>
<td>.23</td>
</tr>
<tr>
<td>Cefuroxime used within 28 days (DDD)</td>
<td>3390</td>
<td>4369</td>
<td>—</td>
</tr>
<tr>
<td>Proportion of days(^a) followed when cefuroxime was used</td>
<td>0.04 (0.00–0.29)</td>
<td>0.11 (0.00–0.39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ciprofloxacin used within 28 days (DDD)</td>
<td>8382</td>
<td>6210</td>
<td>—</td>
</tr>
<tr>
<td>Proportion of days(^a) followed when ciprofloxacin was used</td>
<td>0.33 (0.04–0.88)</td>
<td>0.21 (0.00–0.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number (%) intensive care unit days spent with at least three antimicrobials</td>
<td>3570 (65.5%)</td>
<td>2721 (57.7%)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Need for organ support, no. (%)

<table>
<thead>
<tr>
<th>ICU days(^a) with mechanical ventilation</th>
<th>Procalcitonin-Guided (n = 604)</th>
<th>Standard-of-Care-Only (n = 596)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3569 (65.5%)</td>
<td>2861 (60.7%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
The SISPCT-study, a multicenter, randomized, controlled, bifactorial trial patient n= 1089

• Primary hypothesis: High dose selenium and PCT guided sepsis therapy result in reduction in 28 day all cause mortality

• Secondary hypothesis: PCT monitoring results in a reduction in antibiotic exposure and more effective detection of the source of sepsis
PCT-Algorithm SepNet SISPCT Trial

Baseline PCT
max. value of day 0 and day 1 after randomization

Assessment day 4

Decrease PCT <50% from baseline? yes no

- No change in therapy
- Diagnostic work-up/ change in antibiotics recommended

Assessments day 7, 10, 14

PCT <1 ng/ml or decrease ≥50% from last measurement? yes

- Stopping of antibiotics recommended

Bloos et al submitted
Overall Survival – PCT

Overall Survival

Day after randomisation

log rank test  p = 0.6273

PCT guided
not PCT guided

Patients at risk
not PCT guided  537  427  381  355  338  334  321
PCT guided  552  454  413  368  354  342  336
Secondary outcomes

- PCT-guidance did not affect resource allocation measured by frequency of diagnostic or therapeutic procedures.
- PCT-guidance did result in a reduction of antibiotic exposure per 1000 patient-days by 4.5% (p=0.021).
Subgroup Analysis – PCT
28 day all cause mortality

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat</td>
<td>0.9 (0.7; 1.2)</td>
<td>0.625</td>
</tr>
<tr>
<td>PPS Selen</td>
<td>1.0 (0.7; 1.3)</td>
<td>0.880</td>
</tr>
<tr>
<td>IMP for at least 48 hours</td>
<td>0.9 (0.6; 1.2)</td>
<td>0.406</td>
</tr>
<tr>
<td>Medical Patients</td>
<td>0.8 (0.5; 1.2)</td>
<td>0.264</td>
</tr>
<tr>
<td>Surgical Patients</td>
<td>1.1 (0.7; 1.6)</td>
<td>0.722</td>
</tr>
<tr>
<td>APACHE II Score &lt; 25 points</td>
<td>1.0 (0.6; 1.6)</td>
<td>0.959</td>
</tr>
<tr>
<td>APACHE II Score &gt;= 25 points</td>
<td>0.9 (0.6; 1.3)</td>
<td>0.526</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>2.2 (0.9; 5.6)</td>
<td>0.086</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>0.8 (0.6; 1.1)</td>
<td>0.246</td>
</tr>
<tr>
<td>Less then 3 OD at inclusion</td>
<td>1.1 (0.5; 2.1)</td>
<td>0.839</td>
</tr>
<tr>
<td>At least 3 OD at inclusion</td>
<td>0.9 (0.7; 1.3)</td>
<td>0.626</td>
</tr>
<tr>
<td>Primary Focus pulmonal</td>
<td>1.0 (0.6; 1.5)</td>
<td>0.961</td>
</tr>
<tr>
<td>Primary Focus Abdominal</td>
<td>1.0 (0.6; 1.6)</td>
<td>0.914</td>
</tr>
</tbody>
</table>
Compliance with PCT algorithm

Day 7
N=173 ; 173/279 = 62.0%

course of PCT known 153 (88%)
Recommendation followed 67 (39%)
  AMT stopped 43 (64%)
  imaging diagnostics 30 (45%)
not followed 91 (53%)
  result of microbiological assessment 41 (45%)
  course of WBC 39 (43%)
not answered 15 (9%)
Potential of an ideal sepsis marker

• Support the diagnosis – infectious or other causes of systemic inflammation
• Prognosis – risk stratification
• Impacts measures for infection control – antimicrobials
• Contributes to improved patient outcome
• Reflects the course of the immunopathology of sepsis and identifies suitable patient populations for sepsis trials
Survival by IL-6 Test Result - RAMSES Trial
MONARCS TRIAL:
Probability of Mortality Versus Baseline IL-6 by ELISA

Baseline Medgenix IL-6 (pg/mL)

Probability of Mortality (Adjusted Mortality)

Placebo
Afelimomab
Population: ITT
Approaches to the identification of biomarkers

• Selection on the basis of a biologically compelling association with a disease state or a candidate therapeutic intervention i.e endotoxin, TNF, IL 6

• Serendipitously on the basis of an apparent association with a disease in the absence of a biologically plausible link i.e PCT

• Unbiased approaches using high dimensional “omic” approaches to identify those species that are differentially expressed in the population of interest.
Verification data set

Bauer et al in revision
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>Function</th>
<th>Implicated pathway</th>
<th>Expression in severe inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR 5</td>
<td>Toll-like receptor 5 (flagellin)</td>
<td>Pathogen recognition</td>
<td>Toll-like receptor Signaling</td>
<td>Up-regulation</td>
</tr>
<tr>
<td>CD59</td>
<td>Protectin</td>
<td>Complement regulatory protein</td>
<td>Fcy receptor mediated phagocytosis</td>
<td>Up-regulation</td>
</tr>
<tr>
<td>CLU</td>
<td>Clusterin</td>
<td>Complement lysis inhibitor</td>
<td>Integrin signaling</td>
<td>Up-regulation</td>
</tr>
<tr>
<td>FGL2</td>
<td>Fibrinogen-like 2</td>
<td>Immune regulator, Prothrombinase</td>
<td>Nur77 signaling in T lymphocytes</td>
<td>Down-regulation</td>
</tr>
<tr>
<td>IL7R</td>
<td>Interleukin-7 receptor</td>
<td>Lymphocyte development</td>
<td>CD28 signaling in T Helper Cells</td>
<td>Down-regulation</td>
</tr>
<tr>
<td>HLA-DPA1</td>
<td>Major histocompatibility complex class II, DP alpha1</td>
<td>Antigen presentation</td>
<td>Allograft rejection signaling</td>
<td>Down-regulation</td>
</tr>
<tr>
<td>CPVL</td>
<td>Carboxypeptidase, vitellogenic-like</td>
<td>Macrophages, inflammatory protease cascade, phagocytosis</td>
<td>Calcium-induced T lymphocyte apoptosis</td>
<td>Down-regulation</td>
</tr>
</tbody>
</table>
Verification data set

A)
GES-Score versus conventional biomarkers

Days on the ICU

0                    50                 100                 150

0             20                40             60               80

0,5           1,0           1,5           2,0            2,5

PCT [ng/ml]

CRP [mg/ml]

2                4               6                8              10

Days on the ICU
Confirmation data set
Summary

• Single sepsis biomarkers help identifying sepsis phenotypes: severity, differentiation SIRS/Sepsis, control of infection
• Gene expressions scores and other „omics“ based approaches may help to better understand the immune pathology of sepsis
• May help to guide sepsis specific therapies
• Multiplexed markers hold the promise to improve the evaluation of novel adjunctive sepsis therapies
“Sepsis biomarkers may help to transform sepsis from a physiologic syndrome to a group of distinct biochemical disorders.”
Join
www.world-sepsis-day.org

Register Today

September 13
2014

World Sepsis Day