Heparin Binding Protein
a new biomarker in sepsis management

Lunch Symposium, ISICEM 2016
Presentations

• *Heparin-Binding Protein - an early marker of sepsis-induced organ dysfunction*
  Dr Adam Linder, Lund, Sweden

• *Elevated plasma Heparin Binding Protein predicts early death after cardiac arrest*
  Dr. Markus B. Skrifvars, Helsinki, Finland

• *Impact of disease severity assessment on performance of Heparin-Binding Protein for the prediction of septic shock*
  Dr. Ryan Arnold, Newark, USA
Heparin Binding Protein (HBP)

AN EARLY MARKER OF ORGAN DYSFUNCTION IN SEPSIS

Adam Linder M.D., Ph. D.
ISICEM March 18th 2016
Disclosures

- Hansa Medical has filed a patent on the application of HBP as a sepsis biomarker and A.L. is listed as one of the inventors.
Sepsis is a complex syndrome

- Infecting pathogen
- Site of infection
- Disease spectrum
- Sample timing

.. making it hard to identify for the clinician
Appr 30 million sepsis cases/year

Fleischmann C. et al CCM 2015
Early Antibiotic treatment is important

• Every hour in delay of appropriate atbx = 7.6% lower survival

20-30% of sepsis patients progress to organ dysfunction within the first 24 hours in hospital.

Glickman et al 2010
Shapiro et al 2009
Linder et al 2009
Why is a biomarker for sepsis of importance?

- Because identifying patients at risk is often tricky.. especially in the ED.

- Clinical signs of severe sepsis are unspecific. Even with severe symptoms patients are sometimes missed.

- 20-30% of patients with severe sepsis present without clinical signs of organ dysfunction.

- Current biomarkers used such as lactate are "late markers" of organ dysfunction or unspecific.
Heparin Binding Protein (HBP)

- Also known as Azurocidin or CAP 37.
- Stored in neutrophils, within secretory and azurophilic granules
- A multifunctional inactive serine protease – potent inducer of vascular leakage
- Bacterial structures can induce HBP release from neutrophils
HBP is a strong inducer of vascular leakage

Bacterial structures induce the release of HBP — leading to plasma leakage

*S. pyogenes*

HBP antagonist

Heparin-binding protein (HBP/CAP37): A missing link in neutrophil-evoked alteration of vascular permeability

**M Protein, a Classical Bacterial Virulence Determinant, Forms Complexes with Fibrinogen that Induce Vascular Leakage**

Heiko Herrwald,¹* Henning Cramer,¹* Matthias Mergel,¹ Wayne Russell,¹
Bacterial structures induce HBP release with subsequent vascular leakage - A key mechanism in sepsis?

Bacterial structures induce HBP release with subsequent vascular leakage - A key mechanism in sepsis?

Biological plausibility of HBP as an (early) sepsis marker

• Stored in neutrophils which are the first line of defense.
• Pre-fabricated (not produced after stimuli)
• The only neutrophil protein stored in secretory vesicles which are the first to exocytose.
• Induces vascular leakage
• Bacterial structures can induce the release of HBP
Previous findings: plasma-HBP is elevated early in sepsis with organ dysfunction
IMPRESSED study

IMPROVED PREDICTION of SEVERE SEPSIS in the EMERGENCY DEPARTMENT

• A prospective multi-center study evaluating HBP as a marker of severe infection with organ dysfunction in the ED

• 806 patients from 5 Swedish sites and 1 US site (Clin Gov Trial nr:NCT01392508)

• A newly developed commercial HBP-assay.

• Primary endpoint: development of organ dysfunction within 72 hours.

• Compare HBP to Procalcitonin (PCT), CRP, Lactate and WBC as a marker of severe infection with organ dysfunction in the ED.
IMPRESSED study

• Inclusion criteria: 1 SIRS (excluding WBC) and suspicion of infection, >18 years of age
• 759 patients, 58% male, mean age 55.4 years, Pneumonia most common focus.
• 333 infection with organ dysfunction
• Most common organ dysfunctions were: cardiovascular (75%), respiratory (32%), and renal (20%).
Previous findings: plasma-HBP is elevated in sepsis with organ dysfunction

Validation in a multicenter setting (IMPRESSED)

HBP was the best predictor of progression to organ dysfunction

HBP levels are elevated before clinical signs of organ dysfunction in >80% of patients with suspected sepsis

Linder et al CID 2009

Linder et al CCM 2015
HBP predicts progression to organ dysfunction in over 80% of ED patients presenting with infections.
HBP fulfills the criteria for the "Demands on a biomarker"

- Demonstrate biological plausibility. ✔
- Demonstrate high sensitivity, specificity and positive and negative predictive value for the predicted outcome. ✔
- Be reproducible outside the institution or laboratory in which it was developed. ✔
- Be validated in a cohort of patients independent from the original cohort. ✔

Wasson J NEJM 1985 Clinical prediction rules
The evaluation of a patient with sepsis can be difficult...

**A patient case:**

- 65 y old midwife, 6 weeks in Ghana without malaria prophylaxis.
- Presents at the ID clinic at 2 pm with a couple of days with fever and chills.
- Admitted to the ID ward with 1 L Ringer’s lactate - Clinically stable: BP 135/70, pulse 115, Temp 39.1, RR 24.
- Malaria diagnosed, received Artemisinin
- Plasma-HBP 246 ng/ml (very high!)
Malaria patient -12 hours later
HBP predicted circulatory shock in Falciparum Malaria (by 6 hours)

Clinically stable at admission

Circulatory shock after 6 hours

No mechanical ventilation

Admission
Conclusions HBP ED-study

- HBP is a promising marker for early identification of patients in the emergency department at risk of developing sepsis-induced organ dysfunction

- HBP is elevated in plasma several hours before clinical manifestations of organ dysfunction is evident.

- HBP was a more reliable marker of sepsis with organ dysfunction than procalcitonin, IL-6, lactate, CRP and WBC.
Collaborators:

- Lund University
  Per Åkesson
  Bertil Christensson
  Lars Björck
  Heiko Herwald

- IMPRESSED collaborators
  Ryan Arnold – Camden, NJ, USA
  Jim Russell- Vancouver, Canada
  Igor Zindovic – Lund, Sweden
  Marko Zindovic – Lund, Sweden
  Anna Lange- Örebro, Sweden
  Magnus Paulsson – Malmö, Sweden
  Patrik Nyberg – Linköping, Sweden

- Axis-Shield, UK

- Hansa Medical AB, Lund, Sweden
HBP induces capillary leakage and inflammation and these effects are abrogated by Heparin derivatives.

**Heparin**

- **Endothelium**
  - HBP
  - Proteoglycans
  - Vascular Leakage

- **Renal Tubular Epithelium**
  - HBP
  - Proteoglycans
  - IL-6
  - Inflammation

*Linder et al submitted 2015*
HERO study
Help predicting organ dysfunction in the emergency room

• An international multicenter ED study in order to evaluate the specificity of HBP and other biomarkers in predicting organ dysfunction with or without infection.
• Patients admitted to the ED with suspicion of acute critical illness
• Patients are enrolled daytime in Lund, Helsingborg, Bern and Vancouver Feb – April 2015.
• >700 patients enrolled March 1st 2016.
TABLE 3. Quartile Ranges and Odds Ratios for Progression to Organ Dysfunction Among Patients With Infection Who Presented Without Organ Failure \((n = 487)\) in the Emergency Department

<table>
<thead>
<tr>
<th>Variable</th>
<th>Reference Group</th>
<th>Level</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin-binding protein (ng/mL)</td>
<td>0.0–12.2</td>
<td>12.3–23.1</td>
<td>1.30</td>
<td>0.56–2.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.2–48.0</td>
<td>3.86</td>
<td>1.85–8.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48.1–807.3</td>
<td>20.5</td>
<td>9.92–42.37</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>0.0–0.16</td>
<td>0.17–0.32</td>
<td>1.56</td>
<td>0.80–3.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.33–0.75</td>
<td>2.07</td>
<td>1.08–3.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.76–69.2</td>
<td>6.25</td>
<td>3.33–11.74</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>0.0–7.7</td>
<td>7.8–10.1</td>
<td>2.95</td>
<td>1.35–6.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.2–13.8</td>
<td>5.53</td>
<td>2.62–11.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.9–57.9</td>
<td>13.0</td>
<td>6.21–27.22</td>
</tr>
<tr>
<td>C-reactive protein ((\mu)g/mL)</td>
<td>0.0–42</td>
<td>43–96</td>
<td>2.56</td>
<td>1.18–5.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>97–175</td>
<td>4.01</td>
<td>1.9–8.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>176–474</td>
<td>7.85</td>
<td>3.77–16.3</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.0–1</td>
<td>1.1–1.3</td>
<td>2.31</td>
<td>1.16–4.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4–1.8</td>
<td>3.25</td>
<td>1.73–6.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.9–5.3</td>
<td>4.17</td>
<td>2.21–7.89</td>
</tr>
</tbody>
</table>
HBP is the best marker for predicting progression to organ failure.

Linder et al. CCM 2015
Elevated plasma Heparin Binding Protein predicts early death after cardiac arrest

ISICEM 2016

MD, PhD, EDIC, FCICM Markus Skrifvars
Cardiac arrest is a major health problem

700,000 patients die of sudden cardiac arrest annually in Europe.
Successful Cardiopulmonary Resuscitation After Cardiac Arrest as a “Sepsis-Like” Syndrome

TABLE 2. Plasma Cytokine and sTNFRII Concentrations on Hospital Admission in OHCA Patients, in Patients With Sepsis (Positive Control Group), and in Healthy Volunteers (Negative Control Group)

<table>
<thead>
<tr>
<th>Cytokines and Receptors, pg/mL</th>
<th>OHCA Patients (n=61)</th>
<th>Patients With Sepsis (n=5)</th>
<th>Healthy Volunteers (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>16 (0–30)</td>
<td>16 (0–46)</td>
<td>0 (0–0)*</td>
</tr>
<tr>
<td>sTNFRII</td>
<td>5714 (3629–8350)</td>
<td>4000 (7021–12 656)</td>
<td>1458 (1589–3617)**</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>13 972 (1947–40 319)</td>
<td>72 897 (657–94 884)</td>
<td>46 (0–111)**</td>
</tr>
<tr>
<td>IL-6</td>
<td>177 (53–355)</td>
<td>406 (390–4901)*</td>
<td>0 (0–0)**</td>
</tr>
<tr>
<td>IL-8</td>
<td>67 (22–183)</td>
<td>399 (76–529)</td>
<td>0 (0–0)**</td>
</tr>
<tr>
<td>IL-10</td>
<td>122 (41–250)</td>
<td>199 (160–1003)</td>
<td>0 (0–0)**</td>
</tr>
<tr>
<td>RANTES</td>
<td>7035 (3892–20 369)</td>
<td>2021 (583–2184)**</td>
<td>11 957 (9527–12 817)</td>
</tr>
</tbody>
</table>

Data are median (25% to 75% quartile). OHCA patients had a plasma cytokine pattern similar to that observed in patients with sepsis.

*P<0.05, †P<0.01, and ‡P<0.001 for patients with sepsis and healthy volunteers vs OHCA patients.

Adrie et al. Circulation 2002
A more profound inflammation is related to shock.

<table>
<thead>
<tr>
<th>Cytokines and Receptors, pg/mL</th>
<th>Survivors Without Catecholamines (n=8)</th>
<th>Survivors With Catecholamines (n=10)</th>
<th>Nonsurvivors Without Catecholamines (n=18)</th>
<th>Nonsurvivors With Catecholamines (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>0 (0–7.5)</td>
<td>12 (0–30)</td>
<td>12 (0–30)</td>
<td>17.5 (0–27)</td>
</tr>
<tr>
<td>sTNFRII</td>
<td>3790 (2927–5153)</td>
<td>5485 (2209–7400)</td>
<td>3325 (2801–7516)</td>
<td>8550 (5207–14 133)</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>1172 (263–8021)</td>
<td>2656 (811–5890)</td>
<td>1603 (625–4144)</td>
<td>36 997 (1949–75 146)*</td>
</tr>
<tr>
<td>IL-6</td>
<td>114 (73–270)</td>
<td>88.5 (66–127)</td>
<td>148 (61–717)</td>
<td>2233 (247–4113)†</td>
</tr>
<tr>
<td>IL-8</td>
<td>15 (0–50)</td>
<td>26 (13–58)</td>
<td>27 (6–42)</td>
<td>322 (61–767)*</td>
</tr>
<tr>
<td>IL-10</td>
<td>32 (13–49)</td>
<td>27.5 (16–34)</td>
<td>48 (23–106)</td>
<td>193 (64–361)†</td>
</tr>
<tr>
<td>RANTES</td>
<td>3847 (2019–14 035)</td>
<td>10 924 (5508–14 621)</td>
<td>8588 (5023–17 264)</td>
<td>9194 (4929–15 625)</td>
</tr>
</tbody>
</table>

Data are median (25% to 75% quartile). On day 1, nonsurvivors receiving catecholamines had significantly higher levels of some plasma cytokines compared with levels in those not requiring vasopressor agents. Two patients receiving catecholamines were deceased before collection of blood samples at day 1.

*P<0.01 and †P<0.001 vs nonsurvivor group.

Adrie et al. Circulation 2002
C-reactive protein levels after cardiac arrest in patients treated with therapeutic hypothermia

Fig. 1. CRP time course in the entire studied population. Data are expressed as median and interquartile range.
CRP and ICU and long-term outcome

Dell´anna Resuscitation 2013
• 84 patients treated with therapeutic hypothermia
• HBP measured at 7 time points with ELISA
• Outcome assessed at 6 months and divided into Good (CPC 1 or 2) and Poor (CPC 3 to 5)
• Studied HBP associations with organ dysfunction (SOFA), delay to return of spontaneous circulation
HBP over time and outcome

Dankiewicz Resuscitation 2013
HBP and delay to ROSC

Fig. 3. Correlation between levels of heparin-binding protein (HBP) on admission to hospital and time to return of spontaneous circulation (ROSC). Correlation coefficient 0.61 (n = 43, p < 0.001).
The FINNRESUSCI study

- Blood samples obtained in the observational prospective national cohort trial **FINNRESUSCI** conducted in 2010-2011
- 21 Finnish intensive care units
- OHCA patients admitted to the ICU
- Prospective data collection of resuscitation and intensive care unit data
- Outcome was measured with cerebral performance categories assessed by a neurologist (phone interview) at 12 months from the event
- Blood samples obtained in 278 patients in all
Measurement of HBP

- Samples obtained on ICU admission and at 48 hours
- Samples were stored at -70°C
- Laboratory analysis at the Mario Negri Institute in Milan, Italy
- Thawed and divided into aliquots
- HBP was measured using an enzyme immuno assay from Axis Shield
- Inter assay variation was assessed in 11 samples
## Study sample

<table>
<thead>
<tr>
<th></th>
<th>Whole population</th>
<th>ICU survival</th>
<th>12-month neurological outcome&lt;sup&gt;°&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=278)</td>
<td>Yes (n=229)</td>
<td>No (n=49)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>63 ± 13</td>
<td>63 ± 12</td>
<td>64 ± 14</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>229 (82)</td>
<td>189 (83)</td>
<td>40 (82)</td>
</tr>
<tr>
<td>Shockable rhythm, n (%)</td>
<td>180 (65)</td>
<td>163 (71)**</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Witnessed cardiac arrest, n (%)</td>
<td>254 (91)</td>
<td>212 (93)</td>
<td>42 (86)</td>
</tr>
<tr>
<td>Bystander initiated BLS, n (%)</td>
<td>158 (57)</td>
<td>133 (58)</td>
<td>25 (51)</td>
</tr>
<tr>
<td>Adrenaline used, n (%)</td>
<td>186 (67)</td>
<td>141 (62)**</td>
<td>45 (92)</td>
</tr>
<tr>
<td>Time to ROSC in min, mean (SD)</td>
<td>21 ± 11</td>
<td>20 ± 11**</td>
<td>25 ± 10</td>
</tr>
<tr>
<td>Therapeutic hypothermia, n (%)</td>
<td>202 (73)</td>
<td>173 (76)*</td>
<td>29 (59)</td>
</tr>
</tbody>
</table>

SD, standard deviation; BLS, basic life support;

<sup>°</sup> data on 12-month survival/outcome were missed for two patients;

* p < 0.05 and ** p < 0.01 vs. ICU death; § p < 0.01 vs. poor outcome at 12 months.

Ristagno et al. Submitted 2016
Levels at admission and 48 hours
HBP on ICU admission

- No age difference
- Higher in non-shockable rhythm
- Higher with prolonged ROSC

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>HBP ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 59</td>
<td>79</td>
<td>15.5 (9.1-33.7)</td>
</tr>
<tr>
<td>59-68</td>
<td>86</td>
<td>15.7 (9.9-30.2)</td>
</tr>
<tr>
<td>&gt; 68</td>
<td>80</td>
<td>14.5 (9.9-31.5)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td>0.967</td>
</tr>
<tr>
<td><strong>CA presenting rhythm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shockable</td>
<td>154</td>
<td>13.1 (8.9-21.5)</td>
</tr>
<tr>
<td>Non-shockable</td>
<td>90</td>
<td>21.5 (11.4-46.1)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Time to ROSC, min</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-15</td>
<td>83</td>
<td>11.9 (7.9-21.2)</td>
</tr>
<tr>
<td>16-24</td>
<td>83</td>
<td>17.4 (9.9-33.2)</td>
</tr>
<tr>
<td>25-57</td>
<td>79</td>
<td>18.4 (10.8-41.7)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td></td>
<td>0.004</td>
</tr>
</tbody>
</table>
HBP at 48 hours

- No age difference
- Higher in non-shockable rhythm
- Higher with prolonged ROSC
- No difference with hypothermia
Admission HBP predicts pending shock

Ristagno et al. Submitted 2016
HBP and multi-organ failure

HBP and development of multiple organ dysfunction syndrome

HBP, ng/mL

24h SOFA score

MODS (-)
(n=228)

MODS (+)
(n=50)

p < 0.0001

Sensitivity

1.0

0.8

0.6

0.4

0.2

0.0

1-Specificity

AUC 0.70±0.04

p=0.0001

17.6 ng/mL
HBP and ICU outcome

ICU Outcome

- **Alive (n=229)**
- **Dead (n=49)**

- HBP, ng/mL

- ICU admission, 0 h

- 48 h

Ristagno et al. Submitted 2016
HBP and 12 month outcome

12-month Outcome

- Favourable (n=133)
- Unfavourable (n=143)

HBP, ng/mL

AUC 0.65±0.03
p<0.0001

AUC 0.62±0.04
p=0.0026

ICU admission, 0 h

48 h

Ristagno et al. Submitted 2016
Multivariate analysis

Table 3. Univariate and multivariate logistic models for the prediction of multiple organ dysfunction syndrome (MODS), ICU death, and 12-month poor outcome.

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>MODS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBP, 0 hr</td>
<td>1.339</td>
<td>1.023-1.753</td>
</tr>
<tr>
<td>ICU death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBP, 0 hr</td>
<td>1.843</td>
<td>1.280-2.654</td>
</tr>
<tr>
<td>HBP, 48 hr</td>
<td>1.066</td>
<td>0.726-1.565</td>
</tr>
<tr>
<td>12-month poor outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBP, 0 hr</td>
<td>1.980</td>
<td>1.170-3.351</td>
</tr>
<tr>
<td>HBP, 48 hr</td>
<td>1.337</td>
<td>0.965-1.851</td>
</tr>
</tbody>
</table>

OR, odds ratio per 1 SD increase.
Elevated Plasma Heparin Binding Protein Predicts Early Death after Resuscitation from Cardiac Arrest

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Conclusions

• Admission HBP is a promising marker for risk stratification very early after cardiac arrest
• Validation in other settings is required
• High levels on admission has a moderate ability to predict early death
• Non-specific for long-term outcome
• May be part of a multimodal prognostocation approach
  – Clinical testing
  – Biomarkers, including those for neurological injury and shock
  – Electrophysiological evaluation, radiology
Thank you!

• Role of Axis Shield:
  – Provided kits for HBP measurement but did not play any part in data analysis or the writing of the manuscript
Impact of disease severity assessment on performance of Heparin-Binding Protein and Procalcitonin for the prediction of septic shock

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DEPT OF CLINICAL SCIENCES, DIV OF INFECTION SKANE UNIVERSITY HOSPITAL, LUND UNIVERSITY, LUND, SWEDEN.
Introduction

- Prognostic biomarkers for sepsis are described irrespective of patient severity or co-morbidity.
- Heparin-binding protein is a predictive biomarker able to identity sepsis patients who will progress to shock.
- The PIRO score is a validated risk stratification for describing the sepsis phenotype relative to mortality risk.
Objective

- To describe and compare the ability of heparin-binding protein (HBP) and Procalcitonin (PCT) to predict the development of septic shock in subgroups classified by the PIRO score as a determinant of sepsis phenotype and disease severity.
Methods

• A secondary analysis of a prospective, multi-centered observational trial (Linder et al CCM 2016).

• **Inclusion Criteria:**
  1) clinical suspicion or confirmation of infection;
  2) hospital admission for infection; and
  3) serial HBP measurements.

• **Exclusion Criteria:**
  1) Hypotension <12 hours from arrival.
• **Primary outcome:**
  
  Delayed septic shock (dShock) = systolic blood pressure < 90 mmHg ≥ 12 hours after arrival in ED.

• **Analysis:**
  
  Subjects were grouped according to PIRO score divided into quintiles using previously defined ranges (0-4, 5-9, 10-14, 14-19, ≥20)
Methods

PIRO Score

P Score
- Age
  - < 65: 0
  - 65-80: 1
  - > 80: 2
- COPD: 1
- Liver Disease: 2
- Nursing Home Resident: 2
- Malignancy
  - Without metastases: 1
  - With metastases: 2
- Total Possible P Points: 9

I Score
- Pneumonia: 4
- Skin/soft tissue infection: 0
- Any other infection: 2
- Total Possible I Points: 4

R Score
- Respiratory rate > 20: 3
- Bands > 5%: 1
- Heart rate > 120: 2
- Total Possible R Points: 6

O Score
- BUN > 20: 2
- Resp failure/hypoxemia: 3
- Lactate > 4.0: 3
- Systolic Blood Pressure
  - < 70: 4
  - 70-90: 2
  - > 90: 0
- Platelet Count <150,000: 2
- Total Possible O Points: 14

P + I + R + O = PIRO

Proof of principle: The predisposition, infection, response, organ failure sepsis staging system*

Michael D. Howell, MD, MPH; Daniel Talmor, MD, MPH; Philipp Schuetz, MD; Sabina Hunziker, MD; Alan E. Jones, MD; Nathan I. Shapiro, MD, MPH

Howell et al. CCM 2011
Methods

Proof of principle: The predisposition, infection, response, organ failure sepsis staging system

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PIRO Score

Howell et al. CCM 2011
Methods

Analysis:

• Evaluated the incidence of dShock relative to PIRO group

• Developed independent models within PIRO-based subgroup
  • Defined the ability of HBP and PCT to predict dShock based on group

• Evaluated for co-linearity of HBP and PCT
Results

- 759 patients were enrolled in the parent study
- Excluded: 57 for hypotension on arrival
- There was a progressive increase in the frequency of the primary outcome of dShock as defined by the PIRO subgroups
RESULTS

Analysis:

Evaluated the incidence of dShock relative to PIRO group

- Logistic regression model using PIRO group relative to outcome of dShock

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Wald Chi-Square</th>
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<tbody>
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</table>

Frequency of Delayed Shock relative to PIRO

- Frequency of delayed shock decreases as PIRO score increases.
  - 37% for PIRO score 0-5
  - 51% for PIRO score 5-9
  - 61% for PIRO score 10-14

Sample sizes:
- n=109 for PIRO score 0-5
- n=191 for PIRO score 5-9
- n=67 for PIRO score 10-14
RESULTS

Analysis:
Developed independent models within PIRO-based subgroup to define HBP and PCT prediction of dShock
RESULTS

Analysis:
Developed independent models within PIRO-based subgroup to define HBP and PCT prediction of dShock

PCT distribution
• Distribution of PCT results by PIRO group

<table>
<thead>
<tr>
<th>Variable</th>
<th>PIROGROUP</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
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<tbody>
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<tr>
<td></td>
<td>High</td>
<td>106</td>
<td>5.03</td>
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</tbody>
</table>
RESULTS

Analysis:

Developed independent models within PIRO-based subgroup to define HBP and PCT prediction of dShock

Low PIRO (0-4)

- Logistic regression model defining prediction of dShock by HBP and PCT

<table>
<thead>
<tr>
<th>Models</th>
<th>Parameter</th>
<th>DF</th>
<th>Estimate</th>
<th>Mean Square</th>
<th>F Value</th>
<th>Pr &gt; F</th>
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HBP Initial Assessment

PCT Initial Assessment
RESULTS

Analysis:
Developed independent models within PIRO-based subgroup to define HBP and PCT prediction of dShock

Medium PIRO (5-9)
- Logistic regression model defining prediction of dShock by HBP and PCT
RESULTS

Analysis:
Developed independent models within PIRO-based subgroup to define HBP and PCT prediction of dShock

High PIRO (≥10)
- Logistic regression model defining prediction of dShock by HBP and PCT

<table>
<thead>
<tr>
<th>Models</th>
<th>Parameter</th>
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<th>Mean Square</th>
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RESULTS

Analysis:
Evaluation of co-linearity between HBP and PCT

- Scatterplot assessment for initial and serial assessment of HBP and PCT
**RESULTS**

*Analysis:*

Evaluation of co-linearity between HBP and PCT

- Scatterplot assessment for initial and serial assessment of HBP and PCT

<table>
<thead>
<tr>
<th></th>
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<th>PCT1</th>
<th>PCT2</th>
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</tbody>
</table>
**RESULTS**

*Analysis:*

Evaluation of co-linearity between HBP and PCT

- Scatterplot assessment for initial and serial assessment of HBP and PCT
Conclusions

• The incidence of dShock increases based on increasing PIRO subgroup
• HBP and PCT performance varies based on
  • HBP predicted dShock across all 3 PIRO subgroups
  • PCT predicted dShock only in medium PIRO score
• HBP and PCT are not co-linear
Illness severity assessment plays an important role in biomarker performance.

HBP thresholds to predict delayed shock can be adjusted based on PIRO subgroup.

PCT interpretation should be made in the context of PIRO score.

- Predictive ability is poor in low and high PIRO subgroups.

HBP and PCT provide unique information and are not interchangeable.