Biomarkers in Infectious Disease: Procalcitonin and Beyond

Trevor Van Schooneveld, MD
Associate Professor, Infectious Disease
9/14/16
Disclosures

• Honoraria – Thermo-Fischer
• Research Support – Merck
Objectives

• Describe the physiologic factors which leading to production of procalcitonin
• Recognize factors which may impair the utility of procalcitonin as a marker of infection
• Utilize procalcitonin and other biomarkers in clinical practice to direct antimicrobial use in lower respiratory tract infections and sepsis
Antimicrobial Use Isn’t Optimal

- From 30-50% of inpatient antimicrobial use is inappropriate
- Antimicrobial use and misuse is the key driver of drug resistance
- Antimicrobials can be toxic
- Antimicrobial is the key risk factor for *C. difficile* infection
Diagnosis of Bacterial Infection is Difficult

• Sepsis
  – Etiology determined 30-60%
  – Cultures often negative

• Pneumonia
  – Etiology determined in only 39-54%
  – Yield of blood cultures low
  – Sputum culture and gram stain
    • 40% can’t produce
    • Yield rapidly drops with antibiotic administration
What We Would Like

Infected

Not Infected
Biomarkers of Infection

- Biomarker = measurable characteristic that reflects the severity or presence of some disease state
- The ideal biomarker of infection
  - Sensitive and specific
  - Higher the level = more likely infected
  - Higher the level = increased severity of illness
  - Goes down when patient getting better
  - Not confounded by immunosuppression or other conditions
  - Rapid
  - Cheap
## Comparison of Clinical Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Specific for Infection</th>
<th>Sensitive to Inflammation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+</td>
<td>+++</td>
<td>Simple Sensitive</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>+</td>
<td>+++</td>
<td>Simple Sensitive</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Cytokines</td>
<td>+</td>
<td>+++</td>
<td>Sensitive Rapid Induction</td>
<td>Highly variable Short half life (minutes) Expensive</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>++</td>
<td>++</td>
<td>Inexpensive Moderately specific</td>
<td>Moderately specific Slow induction (peak &gt;24h) No correlation with severity</td>
</tr>
<tr>
<td>Procalcitonin (PCT)</td>
<td>++++</td>
<td>+</td>
<td>Quite specific Rapid Induction (peak 6-12h) Correlates with severity of illness</td>
<td>Expensive Low sensitivity for localized infection</td>
</tr>
</tbody>
</table>

Procalcitonin Under Normal Conditions

**Physiologic PCT Levels:** 46.7 pg/ml (97.5 percentile); median = 12.7 pg/ml*

Bacterial Infection Stimulates PCT Production

- Bacterial infection and cytokines **stimulate production** of PCT in all parenchymal tissues
- PCT is **immediately released** into bloodstream
- This process can be **blocked** during viral infections
Calcitonin: Sources of production in healthy people

Production is Ubiquitous

- Ubiquitous 10-100 fold increase in production
- More widespread than other common cytokines (TNF-α, IL-6)

Müller B. et al., *JCEM* 2001
PCT is Modulated by Cytokines

- PCT levels rise within 3-6 hours after infectious challenge
  - Peak 6-12 hrs.
  - Half-life ~24hrs

It’s All About the Dynamics

Follow-up of procalcitonin (PCT) over time in patients with bacteremia and with severe sepsis and their response to administration of antimicrobials.


Procalcitonin: Advantages

- Specific for bacterial infection
- Correlates with severity of disease and mortality
- Rapidly rises (~6 hr after insult) and has a half life of 24 hours
  - 50% daily decrease associated with control of infection by host immune system/antimicrobials
- PCT is not impaired by neutropenia or other immunosuppressive states

Schuetz P. *BMC Medicine*. 2011;9:107
Time-course of procalcitonin plasma concentrations (mean, SEM) in 16 patients without postoperative complications after liver transplantation. Tx = day of transplantation.

Procalcitonin plasma concentrations in infection and rejection (n = 11, mean and SEM; \( *p < .05 \)). Day 0 = day the diagnosis was made.

Keep In Mind the Confounders

• Physiologic Stress
  – Newborns (<48-72 hours; after 72 interpret levels as usual)
  – Massive stress (severe trauma, surgery, cardiac shock, burns)
    • In absence of infection levels trend down
  – Prolonged, severe cardiogenic shock or organ perfusion abnormalities

• Non-bacterial cytokine activation
  – Some forms of vasculitis and acute graft vs. host disease
  – Malaria and some fungal infections
  – Chronic renal disease (mild increase in baseline)

• Dysregulated PCT production
  – Treatment with agents which stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, granulocyte transfusion)
  – Paraneoplastic syndromes due to medullary thyroid and small cell lung cancer
Clinical Application

What I Don’t Have Time to Discuss

• Lots of observational studies of PCT utility at diagnosing bacterial infection
• The data from the meta-analyses of these observational studies
  – Conflicting findings
• Any sort of sensitivity, specificity, PPV, or NPV for diagnosis of bacterial infection

Randomized Controlled Trials with Treatment Based on Procalcitonin
Why Not Look at All the Diagnostic Studies?

Meta-Analysis

Randomized Controlled Studies

Meta-Analysis

Observational Studies

Quality of Evidence

Reasons for conflicting results:
- Gold Standard
- PCT Cut-off
- Assay Used
- Clinical Setting
- Selection Bias
What are clinical situations where PCT has the most evidence?

Key: + moderate evidence; ++ good evidence; +++ strong evidence; ? Evidence still undefined
PCT in LRTI

• Single center, randomized, single-blinded trial of PCT in LRTI presenting to the ED
  – PCT guided antibiotic initiation vs. standard care
    - PCT <0.1 μg/L – Abx Strongly discouraged
    - PCT 0.1-0.25 μg/L – Abx discouraged
    - PCT >0.25 μg/L – Abx encouraged
    - PCT >0.5 μg/L – Abx strongly encouraged
  – Antibiotics not started repeat PCT in 6-24 hours
  – Physician over-ruling was allowed
    • Occurred in 17.7%

Antibiotic Prescriptions in LRTI

- Significant decrease in antibiotic initiation
- No increase in mortality or adverse events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Care (n=119)</th>
<th>PCT (n=124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3%</td>
<td>3%</td>
<td>0.95</td>
</tr>
<tr>
<td>Days Admitted (mean)</td>
<td>11.2</td>
<td>10.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Antibiotics Prescribed</td>
<td>83%</td>
<td>44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antibiotic Use /1000 days</td>
<td>661</td>
<td>332</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
ProHOSP Trial

- Multicenter, non-inferiority, randomized trial of adults with LRTI presenting to ED
  - PCT levels at admission and if antibiotics started on day 3, 5, 7

Antibiotic Use Outcomes

- Compliance 90.8%
- Antibiotic exposure reduced 35% (range 32-65%)
- Antibiotic prescription rate decreased 12% (range 8-27%)
- Largest difference seen in COPD and bronchitis

### ProHOSP: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=688)</th>
<th>PCT (n=671)</th>
<th>Statistical Analysis [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic Prescription Rate</strong></td>
<td>603 (87.7%)</td>
<td>506 (75.4%)</td>
<td><strong>-12.2% (-16.3% to -8.1%)</strong></td>
</tr>
<tr>
<td><strong>Mean Antibiotic Exposure (days)</strong></td>
<td><strong>8.7</strong></td>
<td><strong>5.7</strong></td>
<td><strong>-34.8% (-40.3% to -28.7%)</strong></td>
</tr>
<tr>
<td><strong>30 day Adverse Outcomes</strong></td>
<td>130 (18.9%)</td>
<td>103 (15.4%)</td>
<td><strong>-3.5% (-7.6% to 0.4%)</strong></td>
</tr>
<tr>
<td><strong>Antibiotic Adverse Event Rate</strong></td>
<td>193 (28.1%)</td>
<td>133 (19.9%)</td>
<td><strong>-8.2% (-12.7% to -3.7%)</strong></td>
</tr>
<tr>
<td><strong>Mortality - ITT</strong></td>
<td>34 (5.1%)</td>
<td>33 (4.8%)</td>
<td>Absolute difference: 0.3% (-2.1 to 2.5)</td>
</tr>
<tr>
<td><strong>Mortality - PP</strong></td>
<td>29 (4.6%)</td>
<td>31 (4.8%)</td>
<td>Absolute difference: -0.2% (-2.6 to 2)</td>
</tr>
</tbody>
</table>

Community-acquired Pneumonia

COPD Exacerbation

• Single-center, randomized trial PCT guided Tx of patients with COPD exacerbation in ED
  – Enrolled 208 with >70% GOLD stage III-IV
  – PCT <0.1 μg/L – Abx discouraged
  – PCT 0.1-0.25 μg/L – Base abx on stability
  – PCT >0.25 μg/L – Abx encouraged

• Abx use 40% PCT vs. 72% control ($p<0.0001$)

• No difference clinical success, mortality, LOS, ICU stay, exacerbation rate or hospitalization rate at 6 months

## Results of Two Meta-Analyses

### Meta-Analysis and Systematic Review of Procalcitonin-Guided Therapy in Respiratory Tract Infections

N= 3431

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR [95% CI]</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>I-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>0.998 (0.977 - 1.018)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>ICU admissions</td>
<td>0.785 (0.57 - 1.076)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Abx Prescriptions</td>
<td>0.69 (0.55 - 0.88)</td>
<td>-</td>
<td>96.9%</td>
</tr>
<tr>
<td>Length of Stay</td>
<td></td>
<td>-0.35 (-0.077 – 0.06)</td>
<td>95.0%</td>
</tr>
<tr>
<td>Duration of Abx Use</td>
<td></td>
<td>-1.27 (-1.86 - 0.68)</td>
<td>98.2%</td>
</tr>
</tbody>
</table>

### Adjusted OR [95% CI]

N=4211

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted OR [95% CI]</th>
<th>Standardized Mean Difference (95% CI)</th>
<th>I-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d mortality</td>
<td>0.94 (0.71 - 1.23)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>0.83 (0.71 - 0.97)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Initiation of Abx</td>
<td>0.24 (0.20 - 0.29)</td>
<td>-</td>
<td>NR</td>
</tr>
<tr>
<td>Total Abx Days</td>
<td>-</td>
<td>-3.47 (3.78 - 3.17)</td>
<td>NR</td>
</tr>
</tbody>
</table>

---


Does PCT Work Outside the Research Setting?

- Prospective, observation trial of LRTIs presenting to ED
- Physicians educated in PCT use and algorithm (1hr)
- 1520 LRTIs
  - More comorbidity immune compromise, and overruling (68% compliance)
- Antibiotic duration shorter if algorithm followed – 5.9 vs. 7.4 days, $P < .001$
- No increase adverse outcomes with initial withholding or stopping
  - Complications, mortality (hospital or 30-d), ICU admission, mechanical ventilation, empyema, recurrence, or rehospitalization
- Antibiotic adverse events significantly decreased

### Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Days Therapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProREAL</td>
<td>6.2 (5.8-6.7)</td>
</tr>
<tr>
<td>ProHOSP PCT Group</td>
<td>5.0 (4.4-5.6)</td>
</tr>
<tr>
<td>ProHOSP Control Group</td>
<td>7.9 (7.3-8.4)</td>
</tr>
</tbody>
</table>

$P = .001$, $P < .001$
Conclusions: Respiratory Tract Infection

- PCT based antimicrobial use decreases antimicrobial use without any adverse clinical outcomes
  - May have clinical benefits?
- PCT effect on antimicrobial use varies based on underlying patient population (ICU vs. outpatient) and disease (CAP vs. COPD exacerbation)
The Sepsis Dilemma

• Early treatment decreases mortality
• Non-specific criteria
• Cultures take time
• Overuse of antibiotics leads to toxicity, super infection, and resistance
• A rapid and accurate marker of infection is needed
Is PCT That Marker?

Receiver Operating Characteristic (ROC) Curve
Comparing Procalcitonin and C-reactive Protein for Prediction of Sepsis

Median PCT and CRP Concentration by Diagnostic Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Median PCT</th>
<th>Median CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.1</td>
<td>50.4</td>
</tr>
<tr>
<td>SIRS</td>
<td>0.4</td>
<td>79.9</td>
</tr>
<tr>
<td>Localized Infection</td>
<td>1.3</td>
<td>85.5</td>
</tr>
<tr>
<td>Sepsis Group</td>
<td>3.6</td>
<td>115.9</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3.1</td>
<td>125.6</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>3.2</td>
<td>73.6</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>10.7</td>
<td>108.0</td>
</tr>
</tbody>
</table>

PCT ROC = 0.925
CRP ROC = 0.677

Maybe, Maybe Not

• Multiple meta-analyses
• Most recent and rigorous meta-analysis
  – 30 studies with 3487 patients
  – Sepsis prevalence 34-88% (overall 57%)
• ROC = 0.85
  – Pooled sensitivity 77%, specificity 79%
• Likelihood ratios problematic
  – Not a specific cutoff or dichromatous in nature
    • Higher values more likely to have sepsis

PCT for Sepsis Diagnosis

• Data worth evaluating
  – Can assist in the diagnosis of sepsis (or other bacterial infection)
  – Can help sort out ambiguous cases
  – Very useful for early stopping

• Decisions regarding antimicrobial initiation should NOT be based solely on PCT serum concentrations
  – Put PCT into clinical context of each patient scenario considering the site of possible infection, the likelihood of bacterial infection, severity of illness, and any other clinical data
PRORATA Trial

• Multicenter (7), randomized, open-label
  – Goal: assess safety and effectiveness of PCT guided therapy in sepsis
  – Patients admitted to ICU with suspected bacterial infection on antibiotics <24 hours (N=630)
    • Excluded: Kids, BMTx or neutropenia, infections requiring long duration of abx therapy (e.g. endocarditis), low chance survival
  – Randomized to PCT guided therapy or usual care

PRORATA algorithm

Guidelines for starting of antibiotics:

- Concentration <0.25 µg/L: Antibiotics strongly discouraged
- Concentration ≥0.25 and <0.5 µg/L: Antibiotics discouraged
- Concentration ≥0.5 and <1 µg/L: Antibiotics encouraged
- Concentration ≥1 µg/L: Antibiotics strongly encouraged

If blood sample taken for calculation of procalcitonin concentration at early stage of episode, obtain a second procalcitonin concentration 6-12 h later.

Guidelines for continuing or stopping of antibiotics:

- Concentration <0.25 µg/L: Stopping of antibiotics strongly encouraged
- Decrease by ≥80% from peak concentration, or concentration ≥0.25 and <0.5 µg/L: Stopping of antibiotics encouraged
- Decrease by <80% from peak concentration, and concentration ≥0.5 µg/L: Continuing of antibiotics encouraged
- Increase of concentration compared with peak concentration and concentration ≥0.5 µg/L: Changing of antibiotics strongly encouraged

PRORATA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCT (n=307)</th>
<th>Control (n=314)</th>
<th>Absolute difference, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 day mortality</td>
<td>65 (21.2%)</td>
<td>64 (20.4%)</td>
<td>0.8% (-4.6% to 6.2%)</td>
</tr>
<tr>
<td>60 day mortality</td>
<td>92 (30%)</td>
<td>82 (26.1%)</td>
<td>3.8% (-2.1% to 9.7%)</td>
</tr>
<tr>
<td>#days without abx</td>
<td>14.3 (9.1%)</td>
<td>11.6 (8.2%)</td>
<td>2.7 (1.4 to 4.1)</td>
</tr>
<tr>
<td>DOT/1000 pt days</td>
<td>653</td>
<td>812</td>
<td>-159 (-185 to -131)</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>15.9 (16.1)</td>
<td>14.4 (14.1)</td>
<td>1.5 (-0.9 to 3.9)</td>
</tr>
</tbody>
</table>

 Patients Receiving Antibiotics for Days 1-28

- Duration of first course of antibiotics decreased 3.8 days (10 days vs. 6)
- Adherence lower than respiratory trials (~50%)

SAPS Study
(Stop Antibiotics on Procalcitonin Guidance Study)

• Multicenter, randomized trial comparing PCT-guided antibiotic discontinuation to usual care

• Enrolled ICU patients with presumed infection in country with low baseline abx use (Netherlands)

• PCT guided antibiotic stopping rule
  – PCT <0.5 or decreased >80% from peak
  – Compliance was 44% at 24 hours and 97% at 48 hours

• Groups well matched with high rates of mechanical ventilation, pulmonary infection, and vasopressor use

## SAPS Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCT Group (N=761)</th>
<th>Standard Care (N=785)</th>
<th>Absolute Difference in means (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDD in first 28 days</td>
<td>7.5</td>
<td>9.3</td>
<td>2.69 (1.26 - 4.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration Therapy (days)</td>
<td>5.0</td>
<td>7.0</td>
<td>1.22 (0.65 - 1.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>28-day Mortality</td>
<td>19.6%</td>
<td>25.0%</td>
<td>5.4% (1.2 - 9.5)</td>
<td>0.0122</td>
</tr>
<tr>
<td>1-year Mortality</td>
<td>34.8%</td>
<td>40.9%</td>
<td>6.1% (1.2 - 10.9)</td>
<td>0.0158</td>
</tr>
<tr>
<td>Reinfection</td>
<td>5%</td>
<td>2.9%</td>
<td>-2.1% (-4.1 - -0.1)</td>
<td>0.0492</td>
</tr>
<tr>
<td>Repeat Antibiotic Course</td>
<td>23%</td>
<td>22%</td>
<td>-1.0% (-5.1 - 3.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>8.5</td>
<td>9.0</td>
<td>-0.21 (-0.92 – 1.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>22.0</td>
<td>22.0</td>
<td>0.39 (-2.69 – 3.46)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are median except absolute difference

**Kaplan-Meier Survival Plot**

• Meta-analysis of 5 RCT (N=947)
  – Adult critically ill treated using PCT vs standard care

### Antibiotic Utilization

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (days, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouadma 2010</td>
<td>10.3</td>
<td>7.7</td>
<td>307</td>
<td>13.3</td>
<td>7.6</td>
<td>314</td>
<td>9.0%</td>
<td>-3.00 [-4.20, -1.80]</td>
</tr>
<tr>
<td>Hochreiter 2009</td>
<td>5.9</td>
<td>1.7</td>
<td>57</td>
<td>7.9</td>
<td>0.5</td>
<td>53</td>
<td>61.5%</td>
<td>-2.00 [-2.46, -1.54]</td>
</tr>
<tr>
<td>Nobre 2008</td>
<td>8.6</td>
<td>6</td>
<td>39</td>
<td>10.5</td>
<td>5.7</td>
<td>40</td>
<td>2.0%</td>
<td>-1.90 [-4.48, 0.68]</td>
</tr>
<tr>
<td>Schroeder 2009</td>
<td>6.1</td>
<td>1.1</td>
<td>14</td>
<td>8.3</td>
<td>0.7</td>
<td>13</td>
<td>27.5%</td>
<td>-2.20 [-2.89, -1.51]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>417</strong></td>
<td>100.0%</td>
<td>420</td>
<td><strong>417</strong></td>
<td>100.0%</td>
<td><strong>420</strong></td>
<td><strong>-2.14 [-2.51, -1.78]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.38, df = 3 (P = 0.50); I² = 0%
Test for overall effect: Z = 11.61 (P < 0.00001)

### Other Endpoints (# of trials) | Relative Risk (95% CI)
--- | ---
Hospital Mortality (5) | 1.06 (0.86-1.30)
28-day Mortality (5) | 0.98 (0.75-1.29)
Recurrent/Relapsed Infection (2) | 1.26 (0.68-2.35)
Conclusions: Sepsis/ICU

• Issues with studies
  – High rates of overruling
  – Selective populations
  – Renal dysfunction issues
  – Standard care in sepsis treatment should be 7 days of antibiotics – Addressed in SAPS

• PCT based treatment appears safe, particularly for antibiotic discontinuation
  – US trial needed to compared to best care

• PCT may have more utility in early discontinuation of antimicrobials than preventing initiation
Is PCT Use Cost Effective?

- It depends
  - Assay cost
  - Frequency of use
  - Adherence to algorithm
  - Equipment cost
  - Cost and pattern of antimicrobial use
  - Duration of antimicrobial use
  - Impact on *C. difficile* prevention and antibiotic induced renal dysfunction

### Cost analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost/Day</th>
<th>PCT Therapy Cost*</th>
<th>Standard Therapy Cost**</th>
<th>Incremental Costs***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>51.44</td>
<td>605.16</td>
<td>411.52</td>
<td>193.64</td>
</tr>
<tr>
<td>Average</td>
<td>383.57</td>
<td>2597.94</td>
<td>3068.56</td>
<td>-470.62</td>
</tr>
<tr>
<td>Expensive</td>
<td>715.69</td>
<td>4590.66</td>
<td>5725.52</td>
<td>-1134.86</td>
</tr>
</tbody>
</table>

**Note: All costs in Canadian dollars**

Cheap=ceftriaxone  Average=average between cheap & expensive  PCT cost: Can$49.42/test
Expensive=meropenem, ciprofloxacin, linezolid  **Standard therapy based on 8 days abx
*PCT costs = 6 days abx therapy + 6 days PCT
***Incremental=PCT cost-standard therapy cost

PCT in NM ICU

• Retrospective cohort 100 septic ICU patients with at least 2 PCT values drawn
• Adherent vs. non-adherent PCT
  – Didn’t stop abx when PCT low
  – Didn’t change abx when PCT rising
  – Stopped before PCT “normalization”
• Well matched age, admitting service, comorbidities, APACHE II, AKI, infection, ID consult
# Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adherent (n=54)</th>
<th>Non-Adherent (n=46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic days, median (IQR)</td>
<td>8 (4-11.3)</td>
<td>9 (7-13.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Antibiotic DDD (mean ± SD)</td>
<td>12 ± 14.9†</td>
<td>18 ± 7.2†</td>
<td>0.016</td>
</tr>
<tr>
<td>ICU LOS, median (IQR)</td>
<td>2.5 days (1-5.25)</td>
<td>4 days (2-9)</td>
<td>0.0265</td>
</tr>
<tr>
<td>Hospital LOS, median (IQR)</td>
<td>7 days (4-14.3)</td>
<td>10 days (7-17)</td>
<td>0.0298</td>
</tr>
<tr>
<td>ICU Mortality (%)</td>
<td>12.9</td>
<td>17.3</td>
<td>0.53</td>
</tr>
<tr>
<td>Mechanical ventilator days (mean ± SD)</td>
<td>1.6 ± 3.86</td>
<td>3.2 ± 6.4</td>
<td>0.2031</td>
</tr>
<tr>
<td>Relapse (%)</td>
<td>0</td>
<td>19.6</td>
<td>0.007</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> infection (%)</td>
<td>5.5</td>
<td>2.2</td>
<td>0.387</td>
</tr>
<tr>
<td>MDR organisms (%)</td>
<td>5.5</td>
<td>2.2</td>
<td>0.387</td>
</tr>
</tbody>
</table>
Patients with non-pneumonic LRTI randomized to standard care or PCT + respiratory viral testing (N=300)
  – Viral pathogen 42% and 83% PCT values <0.25
  – Compliance with PCT guidance = 64%

Non-significant decrease in antibiotic days
  – Overall (3.0 vs. 4.0; \( P = .70 \)) and in compliant group (N=96; 2.0 vs. 4.0; \( P = .11 \))

Confounded by study effect
  – Control group antibiotic use decreased compared to previous year (6.0 vs. 4.0; \( P < 0.001 \))
Outside the Box PCT Use

PCT Relation to All-cause mortality in 261 Acute Heart Failure Patients Without Infection (N=261)

Excluding Infection with PCT Improves Outcomes in Patients with Heart Failure

Other Biomarkers of Infection

## Biomarkers Not Ready for Prime Time

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarker</strong></td>
<td><strong>Effect</strong></td>
</tr>
<tr>
<td><strong>Endothelial Proteins</strong></td>
<td>Cause vascular permeability under cytokines stimulation</td>
</tr>
<tr>
<td>• Ang-1, Ang-2</td>
<td></td>
</tr>
<tr>
<td>• Endocans</td>
<td></td>
</tr>
<tr>
<td><strong>Cell Surface Receptors</strong></td>
<td>CD64 bind Fc portion of IgG and upregulated in bacterial infection</td>
</tr>
<tr>
<td>• CD64 (neutrophils)</td>
<td></td>
</tr>
<tr>
<td>• sTREM-1 (myelocytes)</td>
<td>TREM-1 upregulated with bacterial infection</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>Multiplex cytokine panels available</td>
</tr>
<tr>
<td>• IL-6, IL-8, TNF-α (pro-inflammatory)</td>
<td></td>
</tr>
<tr>
<td>• IL-10 (anti-inflammatory)</td>
<td></td>
</tr>
<tr>
<td><strong>Immunomodulators</strong></td>
<td>Modulate local inflammatory and cytokine response</td>
</tr>
<tr>
<td>• Tregs (T regularly cells)</td>
<td>Modulate post-sepsis immunosuppression</td>
</tr>
<tr>
<td>• PD-1/PDL-1</td>
<td>Inhibit CD4 T/B cells</td>
</tr>
<tr>
<td>• BTLA and CTLA-4 (B/T cells)</td>
<td></td>
</tr>
</tbody>
</table>
Association of RNA Biosignatures With Bacterial Infections in Febrile Infants Aged 60 Days or Younger

Prashant Mahajan, MD, MPH, MBA; Nathan Kuppermann, MD, MPH; Asuncion Mejias, MD, PhD; Nicolas Suarez, PhD;

Figure 2. RNA Biosignatures of Young Febrile Infants With and Without Bacterial Infections

- Healthy controls and infants with bacterial infections, training set
- Healthy controls and infants with bacterial infections, test set
Diagnostic Test Accuracy of a 2-Transcript Host RNA Signature for Discriminating Bacterial vs Viral Infection in Febrile Children

Jethro A. Herberg, PhD; Myrsini Kaforou, PhD; Victoria J. Wright, PhD; Hannah Shailes, BSc; Hariklia Eleftherohorinou, PhD; Clive J. Hoggart, PhD.

Figure 5. Performance of the 2-Transcript DRS Signature in Indeterminate Infection Group
Final Thoughts

• Interpret in the clinical context of the patient
  – Help with interpretation is important
    • Not as simple as normal vs. abnormal
    • Educate to refine use
    • Some prompting may help
• Serial measurements are preferred and provide more useful information
• If you aren’t going to do anything with it, don’t check it
  – Don’t get daily
  – Don’t get in syndromes where is no data
• Be aware of conditions which may affect PCT levels
• Good clinical judgment should always be applied (Don’t treat or not treat a number)
Questions