Procalcitonin in 2018

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Disclosures

- Consultant for Biofire, Biomerieux, Medicine Co., Melinta, Leonard-Meron Biosciences
- Independent speaker for Biomerieux
- Research grant from Biofire
Absolute Truths

- There is nothing faster than the speed of light
- Physicians will overuse empiric antibiotics unless confident that there is no chance of an invading bacterial infection
How to lessen physician anxieties?

- Rapid detection of the presence of viral and/or bacterial pathogens AND
- Rapid adjudication as to whether the detected pathogens are colonizing or invading
Thyroid follicle

Follicular cells secrete thyroxine

C-cells secrete calcitonin

Blood capillaries
Serum/Plasma Assay for Procalcitoning

- Immunoassay
- Sensitive and specific over broad range
- No interference by icterus, hemolysis, hyperlipidemia

**RESULTS IN UNDER ONE HOUR !!**
Procalcitonin Immunologic Assay

Immunoassay: developed by Brahms; marketed by bioMerieux; performed on Vidas system; Analytically validated. Results in 20 minutes.

Figure 1: PCT increase reflects the continuous development from a healthy condition to the most severe states of disease (severe sepsis and septic shock).
Which tissues and organs carry the PCT gene?

- Thyroid
- White Blood Cell
- Perit. Macrophage
- Spleen
- Lung
- Liver
- Kidney
- Adrenal
- Brain
- Spine
- Pancreas
- Stomach
- Small Intestine
- Colon
- Heart
- Muscle
- Skin
- Fat
- Testes

*E. coli* peritonitis in hamsters (JCEM 2001;86:396)
Endotoxin-induced PCT Increase in Human “Volunteers”

Figure 1. Peak (fold) increase of interleukin (IL)-8, tumor necrosis factor (TNF)-α, and procalcitonin (ProCT) in four healthy volunteers after increasing doses of endotoxin (lipopolysaccharide [LPS]); 1, 2, and 4 ng/kg). IL-8 reached peak levels at 4 hrs; TNF-α peaked at 1.5 hrs, and ProCT peaked at 24 hrs (unpublished data from Suffredini et al (164)).
Onset of Fever
Gamma Interferon Blocks PCT IL-1- Induced Release from Adipocytes*

Major Microbial Stimulus for Production of Gamma Interferon ?? Viruses

IL-1 is pro-inflammatory cytokine stimulated by bacteria.

*ENDO. 2003;144:5584
What Stimulates Production of Procalcitonin?

Bacteria

Indirect → +

Direct +

Macrophage

Cytokines

Fat Cell

Know nothing about PCT Cell Receptors.
PCT Gene Expression in Adipose Tissue. Endocrin. 2009;144:5578
Drug-Induced PCT Increases

- Due to drug-induced stimulation of pro-inflammatory cytokines: e.g., TNF, IL-1
- Cytokines in turn stimulate production of PCT
- Elevated levels are transient
- EXAMPLES:
  - OKT3: Antibody vs T-lymphocytes with CD3 receptors
  - Alemtuzumab: Antibody vs. CD52 lymphocytes
  - IL-2
  - Anti-thymocyte globulin (ATG)
  - Rituximab (anti-CD20)
  - Check point inhibitors causing “cytokine storm”
### Comparison: CRP vs PCT*

<table>
<thead>
<tr>
<th></th>
<th>C-reactive protein</th>
<th>Procalcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to detection, hrs</strong></td>
<td>12-24</td>
<td>4-6</td>
</tr>
<tr>
<td><strong>T ½, hrs</strong></td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td><strong>Production sites, stimuli</strong></td>
<td>Liver; IL-6</td>
<td>All tissues; EC Bacteria; Proinflammatory cytokines</td>
</tr>
<tr>
<td><strong>Increases with viral infection</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Elevated coll.-vasc. diseases</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Ann Lab Medicine 2014;34:263
Is Procalcitonin Good or Bad ?

- **GOOD ?**
  - High conservation in evolution suggests benefit
  - Stimulates pro-inflammatory cytokines; augments release of nitric oxide
  - Neutralizes bacterial endotoxin in vitro
  - No host response to exogenous PCT alone (no bacteria)

- **BAD ?**
  - Hamster and Pig peritonitis: exogenous PCT increased mortality; antisera reduced mortality

- **Conclusion:** PCT does not initiate inflammation; amplifies host inflammatory response

*Becker, KL. British Journal of Pharmacology 2010;159:253*
So, what have we learned so far?

- Endotoxin stimulates virtually all body cells, tissues, and organs to turn on the procalcitonin (PCT) gene.
- Concomitant increase in other pro-inflammatory cytokines: i.e., TNF, IL-6, IL-8, and C-reactive protein.
- A rise in gamma-interferon during viral infections blocks the production of PCT.
- However, with dual viral and bacterial infection, the bacterial response predominates and the PCT level rises. Needs more study of various virus-bacterial combined infections.
Differences Between PCT and other Markers of Bacterial Infection

- Robust transcription by all tissues and organs tested to date; not just PMNs and Macrophages
- Rapid increase and rapid fall in PCT serum levels: 24 hour half-life if normal renal function. Can use decrease as evidence of “source control”
- No, or minimal, increases in pure viral infections
- Synthesis not influenced by concomitant steroids or non-steroidal anti-inflammatory drugs
- Levels do not increase in patients with giant cell arteritis, SLE, RA, or gout.
Retrospective Analysis of PCT Levels in Children with Acute RTIs*

- Part of PID-ARI Net program in Germany
- 8/04-10/06: Children in ER
- Nasopharynggeal aspirates in 1,154 patients
- Polymerase Chain Reaction probe for 13 viruses and 4 atypical pathogens
- Serum available for PCT level on 327 pts. Aged 1 month to 17 years old
PCT Level < 0.1 ng/ml in 132 of 327 patients

<table>
<thead>
<tr>
<th>Atypical pathogen or Bordetella in 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma in 5; C.pneu. in 1</td>
</tr>
<tr>
<td>Bordetella in 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1 or more viruses in 86#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhino, RSV, and Adeno most common</td>
</tr>
<tr>
<td>Other: hMPV, entero, flu, paraflu, corona</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 of 132 patients</td>
</tr>
<tr>
<td>Lobar in 15 patients</td>
</tr>
</tbody>
</table>

*EJP 2009;168,1117  # Excludes prior or continuing Antibiotic Therapy
PCT Level >0.1 but \( \leq 0.25 \): In 225 Patients (132 + 93)

- **Atypical pathogen or Bordetella**
  - Atypical in 6 patients
  - Bordetella in 4 patients

- **1 or more viruses in 149 patients**
  - Rhino, RSV, and Adeno. Most common
  - Other: hMPV, paraflu, flu, corona, entero.

- **Abnormal CXR**
  - 74 of 225 patients
  - Lobar in 30 patients

**NOTE ABSENCE OF** *S.pneumoniae*, *S.aureus*, etc.
Serum PCT Levels in Viral Meningitis: CCM 2000;28:1828

- 30 consecutive patients with meningitis
- Sequential PCT levels plus standard of care
- Result: 16 with bacterial meningitis and 14 with viral meningitis—HSV 2, enterovirus, EBV and Central European encephalitis virus.
- PCT if viral: 0.12-0.29 ng/ml
- PCT if bacterial: 0.16-60 ng/ml
Serum PCT: Bacterial vs. Viral Meningitis*

PCT Guidance of Antibiotic Therapy of CAP*

- Randomized, controlled, blinded trial in Swiss University Hospital
- Patients admitted from ED with CAP
- Controls: Treating MDs not given PCT results (Sensitive Kryptor assay)
- PCT group: Treating MDs given PCT results with antibiotic treatment suggestion
**Procalcitonin (PCT) algorithm for stewardship of antibiotic therapy in patients with LRTI**

- **< 0.1 µg/l**
  - Bacterial etiology very unlikely
  - **NO antibiotics!**

- **0.1 - 0.25 µg/l**
  - Bacterial etiology unlikely
  - **no antibiotics**

- **>0.25 - 0.5 µg/l**
  - Bacterial etiology likely
  - **Antibiotics yes**

- **>0.5 µg/l**
  - Bacterial etiology Very likely
  - **Antibiotics YES!**

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**Remeasure PCT after 6-24 hours**

**Initial antibiotics can be considered in case of:**
- Respiratory or hemodynamic instability
- Life-threatening comorbidity
- Need for ICU admission
- **PCT < 0.1 µg/l:** CAP with PSI IV or CURB = ≥ 4, COPD with GOLD IV
- **PCT < 0.25 µg/l:** CAP with PSI ≥IV or CURB ≥3, COPD with GOLD ≥III
- Localised infection (abscess, empyema)
- Compromised host defense (e.g. immunosuppression other than corticosteroids)
- Concomitant infection in need of antibiotics

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**Consider the course of PCT**

**If antibiotics are initiated:**
- Repeated measurement of PCT on days 3, 5, 7
- Stop antibiotics using the same cut offs above
- If initial PCT levels are >10 µg/l, then stop when 80-90% decrease of peak PCT
- If initial PCT remains high, consider treatment failure (e.g. resistant strain, empyema, ARDS)
- **Outpatients:** duration of antibiotics according to the last PCT result:
  - **>0.25 - 0.5 µg/l:** 3 days
  - **>0.5 - 1.0 µg/l:** 5 days
  - **>1.0 µg/l:** 7 days
Figure 2. (A) Percentage of patients receiving antibiotic therapy in the control group and the procalcitonin group on admission and during the course of the disease. AB = antibiotics. (B) Cumulative frequency distribution curve for the time to discontinuation in patients for whom antibiotic therapy was prescribed. Patients in the procalcitonin group were compared with those in the control group.
Effect of PCT-Guided Antibiotic Treatment on Mortality and Safety in Acute Respiratory Infections*

- Meta-analysis of 6708 patients in 26 trials in 12 countries (2 in USA) from 2004-2016
- Pre-specified Cochrane Protocol
- Individual patient data:
  - Acute bronchitis
  - AECB
  - CAP
  - HAP, VAP

*Lancet Infect. Dis 2018;18:95; JAMA 2018;319:925
### Clinical Outcomes and Antibiotic Use

<table>
<thead>
<tr>
<th></th>
<th>PCT Guided</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3336</td>
<td>3372</td>
<td></td>
</tr>
<tr>
<td>30-day Mortal., %</td>
<td>8.6</td>
<td>10.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Treatment Failure, %</td>
<td>23</td>
<td>25</td>
<td>0.07</td>
</tr>
<tr>
<td>Initiation of Antibiotics, %</td>
<td>71.5</td>
<td>86.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration (days) of Antibiotics</td>
<td>6.0</td>
<td>8.0</td>
<td>0.001</td>
</tr>
<tr>
<td>median AB adverse effects, %</td>
<td>16.3</td>
<td>22.1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Adherence To Protocol Varied from 44 to 100 %

**PROBLEM:** Virtually no diagnostic microbiology
Huang, DT et al, PCT Use for Lower RTI. NEJM 2018; 379:236

- “PCT results…..did not result in less use of antibiotics”
- Striking in that 92% of the patients had PCT levels < 0.25 ng/ml.
- 466 MDs were asked why they continued antibacterial therapy despite low PCT levels?
  - Belief: “Bacterial infection is present”
  - Belief: “AECOPD requires antibiotic regardless”
  - “Antibiotic started before PCT result available”
## PROBLEM: No diagnostic microbiology

<table>
<thead>
<tr>
<th>Category — no./total no. (%)</th>
<th>PET</th>
<th>NO</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1 µg/liter</td>
<td>588/808 (72.8)</td>
<td>648/788 (82.2)</td>
<td></td>
</tr>
<tr>
<td>0.1—0.25 µg/liter</td>
<td>158/808 (19.6)</td>
<td>72/788 (9.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.25—0.5 µg/liter</td>
<td>27/808 (3.3)</td>
<td>23/788 (2.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5 µg/liter</td>
<td>35/808 (4.3)</td>
<td>45/788 (5.7)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Final diagnosis — no./total no. (%)††</th>
<th>PET</th>
<th>NO</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>310/822 (37.7)</td>
<td>336/823 (40.8)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>265/822 (32.2)</td>
<td>259/823 (31.5)</td>
<td></td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>208/822 (25.3)</td>
<td>190/823 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>167/822 (20.3)</td>
<td>161/823 (19.6)</td>
<td></td>
</tr>
<tr>
<td>PSI class I</td>
<td>48/167 (28.7)</td>
<td>34/161 (21.1)</td>
<td></td>
</tr>
<tr>
<td>PSI class II</td>
<td>52/167 (31.1)</td>
<td>52/161 (32.3)</td>
<td></td>
</tr>
<tr>
<td>PSI class III</td>
<td>30/167 (18.0)</td>
<td>33/161 (20.5)</td>
<td></td>
</tr>
<tr>
<td>PSI class IV</td>
<td>29/167 (17.4)</td>
<td>38/161 (23.6)</td>
<td></td>
</tr>
<tr>
<td>PSI class V</td>
<td>7/167 (4.2)</td>
<td>3/161 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Other lower respiratory tract infection</td>
<td>42/822 (5.1)</td>
<td>42/823 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Non-lower respiratory tract infection</td>
<td>20/822 (2.4)</td>
<td>21/823 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Hospitalized — no. (%)‡‡</td>
<td>378 (45.8)</td>
<td>404 (48.7)</td>
<td></td>
</tr>
</tbody>
</table>
Blaschke, AJ et al, PCT in Hospitalized Children with CAP. JPIDSOC. 2018;7:46

- Multicenter, Pop.-based, prospective study of children with radiographic pneumonia

- Micro. Diagnostic “Bundle”:
  - Airway specimen for Biofire multiplex PCR panel for 17 viruses and 2 atypical bacteria
  - Sputum and blood cultures for *S. pneumo*, *S. pyogenes*, *Haemophilus sp*, *S. aureus*
  - Serum PCT
Negative predictive value for PCT <0.25 was 96% for invasive bacterial infection

Limitation: limited diagnostics for bacterial pathogens
The Import of Microbial Etiology of CAP/AECOPD

- With diagnostic bundles can now rapidly detect presence of potential viral and/or bacterial respiratory pathogens in roughly 80% of patients

- Diagnostic Bundle at Providence Portland:
  - Sputum for C & S
  - Urine for Antigen detection: *S. pneumo*; *Legionella pneumophila*
  - *Nasal NAATs: S.pneumo.* & *S.aureus*
  - 20 target NP multiplex PCR panel (17 viruses, 3 bacteria)
  - Serum PCT X 2

- Detection: 1/3 viral, 1/3 bacterial, 1/3 mixture (Gilbert, DN et al; Walsh, E et al)
PCT Levels for Antimicrobial Stewardship (AMS) of RTIs

- PCT Negative predictive value for invasive bacterial disease is excellent. HENCE, can decrease empiric use of antimicrobials for viral infections.
- PCT levels can help distinguish colonization vs. invasion by potentially pathogenic bacteria.
- Sequential PCT levels are useful to determine the duration of antimicrobial therapy.
Powerful Duo for Antibiotic Stewardship: Microbial Etiology plus PCT Level

- Allows meaningful direct communication with providers; Empowers providers with data. Analogy: Rapid Strept tests in the evaluation of pharyngitis
- With the Diagnostic Bundle and direct provider discussions, PPMC achieved statistically significant decrease in:
  - Days of antibiotic use
  - Length of antibiotic use
  - Cost of antimicrobials
  - Reference: Diagnostic Microbiology and Infectious Disease 2016;86:102
## Interpretation of PCT Levels and RTIs: Virus

<table>
<thead>
<tr>
<th>Bacteria Detected</th>
<th>Virus Detected</th>
<th>PCT Level</th>
<th>Shock</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>(\leq 0.10)</td>
<td>No</td>
<td>No infection</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>0.5 - 1000</td>
<td>Yes</td>
<td>GI Translocation, aspiration, &amp;/or failure to detect airway bacterial pathogen</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>(\leq 0.10)</td>
<td>No</td>
<td>Viral infection</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>0.25—1000</td>
<td>No</td>
<td>Dual infection; Failure to detect bacterial path or translocation</td>
</tr>
</tbody>
</table>

*From Minireview: JCM 2010; 48: 2325*
## Interpretation of PCT Levels & RTIs: Bacterial

<table>
<thead>
<tr>
<th>Bact. Detect.</th>
<th>Virus Detect.</th>
<th>PCT level</th>
<th>Shock</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>0.25-1000</td>
<td>No</td>
<td>Bact. Infection</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>0.25—1000</td>
<td>No</td>
<td>Dual Infection</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>$\leq 0.10$</td>
<td>No</td>
<td>Bact. Colonization</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>$\leq 0.10$</td>
<td>No</td>
<td>Bact. Colon. &amp; Viral Infection</td>
</tr>
</tbody>
</table>

*From Minireview: JCM 2010; 48: 2325*
THE Future: Patient #1

- 70 y.o. male admitted with hemoptysis/hematemesis and acute respiratory failure
- H/O:
  - Schizophrenia
  - IDDM
  - Hypertension
  - COPD (home inhalers)
- PX: T 37.2, P 82, R 24, BP 130/60
  - Old blood in mouth
  - Dyspneic on 2 L / min; O2 sat. 95%
Initial Studies

- CT of chest: RLL “aspiration pneumonia”
- Empiric therapy with levofloxacin
- Pneumonia diagnostic bundle ordered
- Patient admitted
Results of “Standard” CAP Diagnostic Tests

- T max, first 24 hrs: 37.1 C
- WBC 7400 with 74% polys
- Urine antigens for S.pneumo. And L.pneumophila: Negative
- Sputum submitted for culture
- Blood cultures ordered
Microbial etiology of the Pneumonia?

- Aspirated blood
- Aspirated gastric content
- Respiratory virus
- Bacterial infection
- Some combination of the above
Rest of the current diagnostic bundle

- Biofire Film array respiratory multiplex PCR panel for 17 viral strains and 3 bacteria on nasopharyngeal swab specimen: Coronavirus
- Nasal swabs for:
  - *S. aureus* NAAT: Negative
  - *S. pneumoniae* PCR: Negative
- Sputum gram-stain: gm-neg diplococci and small gram-neg. rods
- Serum procalcitonin: < 0.05 ng/ml
FilmArray LRTI Panel (IUO)

**Bacteria (quantitative):**
- Acinetobacter calcoaceticus-baumannii complex
- Enterobacter aerogenes/cloacae complex
- Escherichia coli
- Haemophilus influenzae
- Klebsiella oxytoca
- Klebsiella pneumoniae group
- Moraxella catarrhalis
- Proteus spp.
- Pseudomonas aeruginosa
- Serratia marcescens
- Staphylococcus aureus
- Stenotrophomonas maltophilia
- Streptococcus agalactiae
- Streptococcus pneumoniae
- Streptococcus pyogenes

**Antibiotic Resistance Markers:**
- $bla_{CTX-M}$ (Extended spectrum beta-lactamase)
- $bla_{IMP}$ (Carbapenem resistance)
- $bla_{KPC}$ (Carbapenem resistance)
- $bla_{NDM}$ (Carbapenem resistance)
- $bla_{Oxyb-lke}$ (Carbapenem resistance)
- $bla_{VIM}$ (Carbapenem resistance)
- $mecA/mecC$ and MREJ (Methicillin resistance)

**Viruses:**
- Adenovirus
- Coronavirus
- Human Metapneumovirus
- Human Rhinovirus/Enterovirus
- Influenza A
- Influenza B
- MERS-CoV
- Parainfluenza virus
- Respiratory Syncytial virus

**Fungi:**
- Aspergillus spp.
- Cryptococcus neoformans/gattii
- Pneumocystis jirovecii

**Atypical Bacteria:**
- Chlamydia pneumoniae
- Legionella pneumophila
- Mycoplasma pneumoniae
Results of SPUTUM Lower Respiratory Tract Investigational Multiplex PCR panel from Biofire;

- Treating physicians unaware of the results of the investigative panel
- *Haemophilus influenzae*, $10^6$/ml
- *Moraxella catarrhalis*, $10^6$/ml
- MRSA, $10^6$/ml
- *Streptococcus agalactiae*, $10^6$/ml
- Coronavirus
Adjudication

- Does patient have clinical syndrome of pneumonia?
- How to interpret presence of both viral and bacterial pathogens? Colonization or Invasive Infection?
- Clinical picture and normal CBC and PCT support bacterial colonization in COPD patient with Chronic Bronchitis
- Clinical illness compatible with infection due to a coronavirus?
PCT Levels and the Septic Patient

- PCT is an Indicator of prognosis
- PCT Roles in care of patients with septic shock:
  - Fluid resuscitation: no role for PCT
  - Need for pressors: no role for PCT
  - Need for the Rapid initiation of appropriate Antibiotics: Yes
  - Sequential levels should fall with Source Control: Yes
  - Can guide duration of antibacterial therapy: Yes
Role of PCT in Decision to Initiate Empiric Antibacterial Therapy

- Clinical syndrome of septic shock with:
  - Elevated PCT (>0.50).
    - Sensitive but not specific due to frequent increases in all categories of shock: e.g., cardiogenic, hypovolemic, septic
  - Normal PCT (<0.25)
    - Excludes invasive bacterial etiology of the patient's hypotension
    - Negative predictive value of 95% or higher
103 patients with Acute Appendicitis*

Fig. 1. Percentage of patients with elevated PCT levels (>0.5 μg/ml) among groups 1–5.

## Examples of the Power of the NPV of Procalcitonin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Clinical Setting</th>
<th>Endpoint</th>
<th>PCT “cut-off”</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest 2012;141:1537</td>
<td>CAP Inpatients</td>
<td>Bacteremia</td>
<td>( \leq 0.36 )</td>
<td>98</td>
</tr>
<tr>
<td>Dis.Colon Rectum 2013;56:475</td>
<td>GI Surgery pts.</td>
<td>Anastomotic Leak</td>
<td>(&lt;0.31)</td>
<td>100</td>
</tr>
<tr>
<td>Lupus 2012;21:1172</td>
<td>Flare vs. Infection</td>
<td>Positive culture</td>
<td>(&lt;0.17)</td>
<td>94</td>
</tr>
<tr>
<td>Surgery 2011;149:394</td>
<td>Bowel Obstruction</td>
<td>Ischemia/perfor-ation.</td>
<td>(&lt;0.25)</td>
<td>95</td>
</tr>
<tr>
<td>AJCP 2011;135:182</td>
<td>Emerg.Dept.</td>
<td>Bacteremia</td>
<td>(&lt;0.1)</td>
<td>96</td>
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<tr>
<td>PloS One 7(12):e53279, 2012</td>
<td>Med-Surg Inpts.</td>
<td>Bacteremia</td>
<td>( \leq 0.25 )</td>
<td>99</td>
</tr>
<tr>
<td>Clin.Ped. 2012;51:1175</td>
<td>Febrile neutropenia</td>
<td>Bacteremia</td>
<td>( \leq 0.5 )</td>
<td>93</td>
</tr>
</tbody>
</table>
PCT Levels, Source Control and Mortality

- The higher the initial PCT the greater the risk of death
- A fall in PCT with therapy indicates control of the source of the active infection
- “Source control” correlates with a reduction in mortality attributable to resolution of the infectious etiology of the sepsis
Sepsis Survival Based PCT decrease between days 2 and 3: “Source Control”.

*Charles et al. Critical Care 2009; 13: R38

First few days are Key. 24 hour half life.
PCT-Guidance Shortens Antibiotic Therapy of Septic Patients

- Treat until PCT < 0.25 or 80-90 % decrease from peak level.
- Lam, W et al: Duration decreased by 1.3 to 3.1 days with lower mortality. CCM 2018;46:684
- Iankova, I et al: Duration decreased from 8.85 days to 7.35 days, p<0.001. CCM 2018;46: 691
- Kalil, AC . Supportive editorial. CCM 2018;46:811
From Iankova, I et al. CCM 2018; 46: 691

### Table

<table>
<thead>
<tr>
<th>First author, year</th>
<th>AB duration (days), mean (SD)</th>
<th>AB duration (days), mean (SD)</th>
<th>WMD (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCT</td>
<td>Standard care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anname, 2013(24)</td>
<td>4.67 (0.7)</td>
<td>4.00 (2.2)</td>
<td>0.67 (-0.16, 1.49)</td>
<td>16.50</td>
</tr>
<tr>
<td>Bouadma, 2010(25)</td>
<td>10.30 (7.7)</td>
<td>13.30 (7.6)</td>
<td>-3.00 (-4.20, -1.80)</td>
<td>13.65</td>
</tr>
<tr>
<td>de Jong, 2016(26)</td>
<td>5.67 (4.4)</td>
<td>7.33 (5.2)</td>
<td>-1.67 (-2.15, -1.19)</td>
<td>18.79</td>
</tr>
<tr>
<td>Deliberato, 2013(27)</td>
<td>15.50 (9.0)</td>
<td>17.25 (10.8)</td>
<td>-1.75 (-6.08, 2.58)</td>
<td>2.79</td>
</tr>
<tr>
<td>Hochreiter, 2009(28)</td>
<td>5.90 (1.7)</td>
<td>7.90 (0.5)</td>
<td>-2.00 (-2.46, -1.54)</td>
<td>18.90</td>
</tr>
<tr>
<td>Nobre, 2008(31)</td>
<td>12.25 (7.8)</td>
<td>13.50 (7.8)</td>
<td>-1.25 (-4.67, 2.17)</td>
<td>4.14</td>
</tr>
<tr>
<td>Schroeder, 2009(32)</td>
<td>6.60 (1.1)</td>
<td>8.30 (0.7)</td>
<td>-1.70 (-2.39, -1.01)</td>
<td>17.47</td>
</tr>
<tr>
<td>Shehabi, 2014(33)</td>
<td>11.67 (10.4)</td>
<td>13.00 (11.9)</td>
<td>-1.33 (-3.53, 0.87)</td>
<td>7.76</td>
</tr>
<tr>
<td>Layios, 2012(29)</td>
<td>(Excluded)</td>
<td>(Excluded)</td>
<td>-1.49 (-2.27, -0.71)</td>
<td>100.00</td>
</tr>
<tr>
<td>Najafi, 2015(30)</td>
<td>(Excluded)</td>
<td>(Excluded)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (Heterogeneity: $I^2=81.3%$, p&lt;0.001, $T^2=0.782$)</td>
<td></td>
<td>(Excluded)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Antibiotic (AB) duration. Layios et al (29) was excluded because it reported the proportion of days with ABs during patients' stay in the ICU. Najafi et al (30) was excluded because it reported the sum of AB exposure days for each study arm, with no information on variance. Diamonds are point estimates. PCT = procalcitonin, WMD = weighted mean difference.
Why are PCT Levels Increased in Patients With Hypotension?

- Increased in All categories of Shock:
  - Hypovolemic shock (Hemorrhagic, Burn injury)?
  - Anaphylactic shock?
  - Cardiogenic shock?
  - Distributive shock?
    - Bacteremia: e.g., *S. aureus* in IVDU, Ischemic bowel
    - Drug overdose
    - Cytokine storm: e.g., pancreatitis

- What is causing the increase in the PCT?
Translocation of Gut Bacteria in Humans and Animal Models

- Translocation documented by:
  - Intestinal bacteria in submucosa, mesenteric lymph nodes, and portal vein
  - Changes in biomarkers in absence of positive systemic blood cultures:
    - Increase in serum sCD14 (Preseptin)
    - Presence of LPS in Blood (Limulus lysate test)
    - Decrease in serum LPS Binding protein
    - 16s ribosom al RNA in serum
Evidence for GUT Translocation Driving Increased PCT Levels

- Cardiogenic shock (Expert Rev. Mole. Diag 2018;18:1)
- Hemorrhagic/ Hypovolemic shock
- Pancreatitis
- Transient: Aortocoronary Bypass Surgery
- Prolonged general anesthesia
- Any drug-induced distributive shock
PCT & CRP Levels in Patients with Myocardial Infarction and Cardiogenic Shock.

Fig. 1 Percentage of positive values of procalcitonin (PCT) and C-reactive protein (CRP) (%) in patients with CS, STEMI and UA/NSTEMI.
What are cut-offs for PCT in patients with ESRD? *

- Normal renal function: PCT cleared by kidneys with $T_{\frac{1}{2}}$ of 24-36 hrs
  - $T_{\frac{1}{2}} > 36$ hrs with ESRD
  - Pre-dialysis range of serum PCT levels: 0.75-2.5 ng/ml

- PCT levels with 3X/week hemodialysis:
  - Draw level pre-dialysis
  - PCT cleared by HD; amount cleared varies with high-flux vs low-flux membranes
  - “Normal” levels on HD: 0.25-0.75

* Expert Review of Molecular Diagnostics 2018; 18:1
n=55, mean ±SD, *: P < 0.05, n.s.: no significant difference
FDA-Approved Clinical Use of Serum Levels of PCT*

1. *Prognosticate survival of septic patients (FDA approval).
2. *Help differentiate bacterial from viral infections: e.g., RTIs, Meningitis
3. *Determine “source control” of systemic bacterial infections
4. *Guide duration of antibacterial therapy
5. Help guide efforts to determine the cause of a fever of unknown origin
SUMMARY: Clinical Role of PCT Levels

- CAN serve as a marker of activation of innate immune system by invasive bacteria.
- Can assist Antimicrobial Stewardship of respiratory infections when combined with molecular diagnostics.
- Cannot differentiate the etiology of clinical shock: i.e., elevated in TSS, Septic Shock, Hypovolemic Shock, Drug-Induced Hypotension, severe cardiogenic shock.
- A normal PCT helps eliminate bacteremic shock as a cause of the patients hypotension.
IN SHORT

- **For best results:** Combine modern molecular diagnostics with Serum PCT levels
- **TRUST THE BIOLOGY:**
  - The negative predictive value of a low PCT for invasive bacterial infection is 95% or higher
  - A high PCT equals activation of innate immunity by:
    - Invasion of extracellular bacteria to include translocation of gut bacteria and/or
    - Bacteria/Drug stimulation of a pro-inflammatory cytokine “storm”
Recent Review Article

- Gilbert, David N.
- Role of Procalcitonin in the management of infected patients in the intensive care unit
- Infectious Disease Clinics of North America
- 2017; 31: 435-453