Comparing Biomarkers in Used in Infection, Sepsis, and Septic Shock: What is the Role of Procalcitonin

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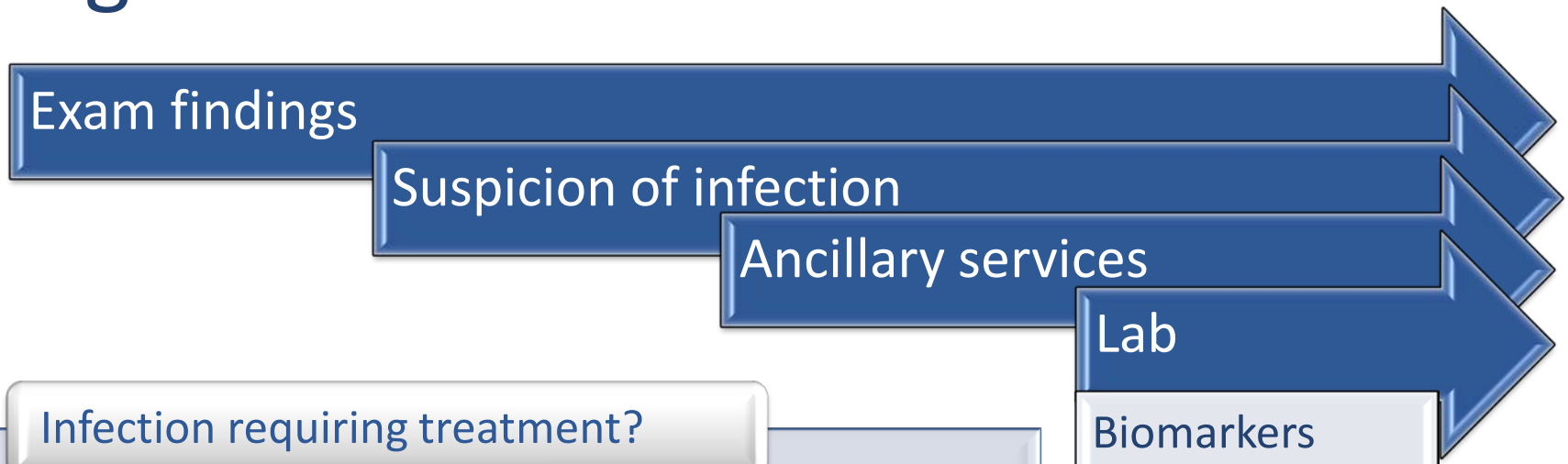
Disclosure

- No financial disclosures
  - No financial gain from pharmaceutical companies
  - No stock ownership
- Historically, I have partnered with the healthcare companies bioMerieux (Vitek), Carefusion, Cardinal Health, TheraDoc, and ICNet to help them with special projects at their requests
- Information presented is based on my interpretation of the evidence and clinical experience

Objectives

- Provide a synopsis of currently available biomarkers used in infectious disease
- Compare and contrast common biomarkers to determine which marker or group of markers can provide the clinician with effective diagnostic information and risk stratification
- Attendees will be able to assess if their current biomarker choices provide their clinicians with optimal clinical effectiveness

Diagnoses of the Patient



- Infection requiring treatment?
- Infectious Agent
  - Bacteria
  - Virus
  - Fungus….
- Severity
- Treatment plan

Biomarkers

WBC

CRP

Lactate

Procalcitonin

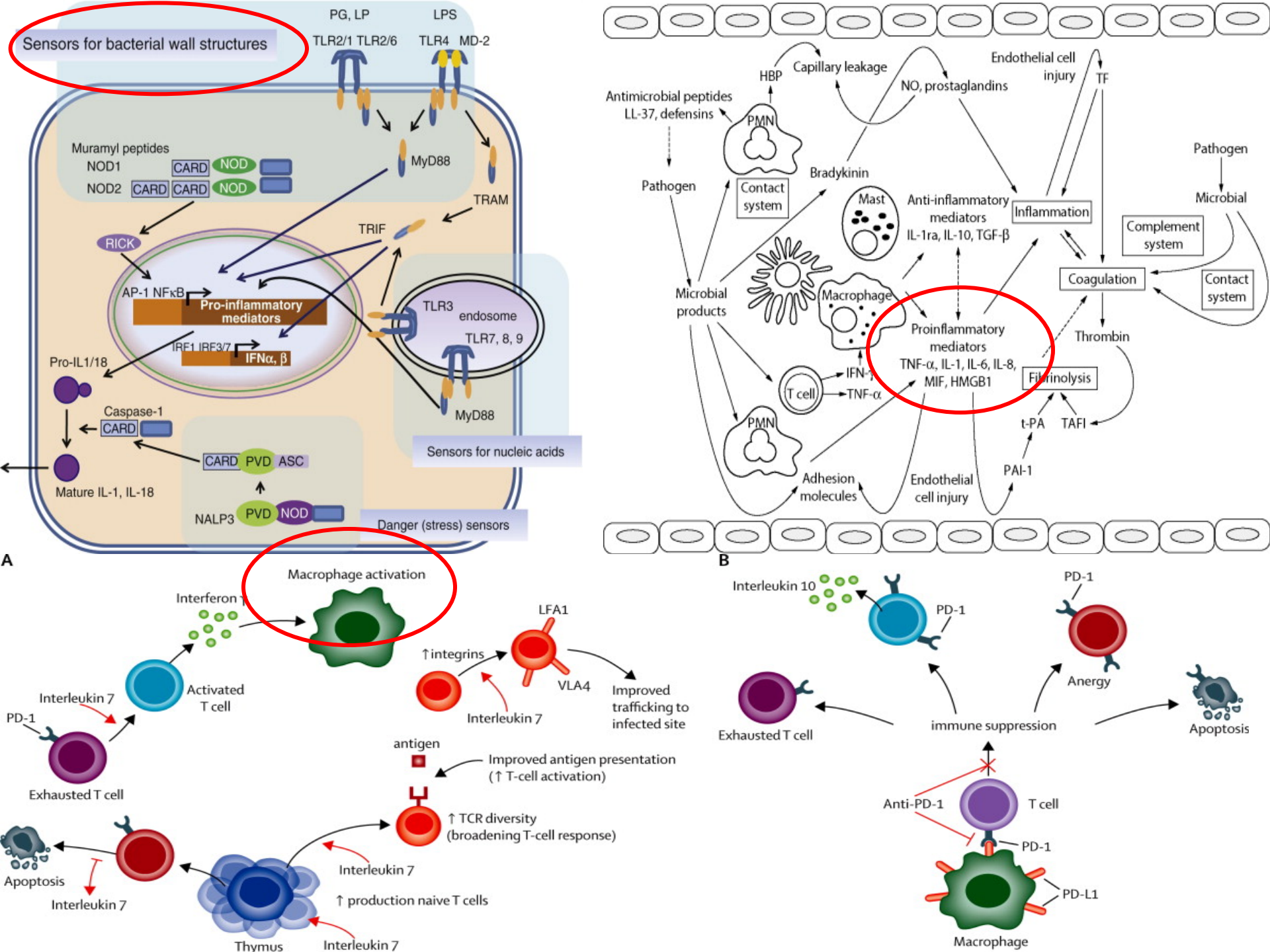
Others

Biomarker

- Anything that can be used as an indicator of the physiological state of an organism, even temperature is considered a biomarker.
- NIH: Any characteristic that is objectively measured and evaluated as an indicator of normal biologic process, pathogenic process, or pharmacologic response to a therapeutic intervention
- Over one hundred seventy six (176) biomarkers studied for the diagnosis or management of infection and sepsis
- Biomarkers
  - Infection
  - Cancer
  - Cardiac

The Biomarker Catch

- The clinical phenotype of a patient with significant infection/sepsis generally is similar to that of a patient with systemic inflammatory response caused by non-infectious" inflammation
- Difficult to differentiate bacterial, viral, and fungal
- Affected by immunosuppressed patients
- Autoimmune diseases
- Anti-inflammatory, disease modifying, steroids


Sensors for bacterial wall structures
PG, LP
LPS
TLR2/1 TLR2/6
TLR4 MD-2
Muramyl peptides
NOD1
NOD2
CARD
NOD
MyD88
TRAM
TRIF
RICK
AP-1 NFκB
Pro-inflammatory mediators
IRF1 IRF3/7
IFNα, β
TLR3
endosome
TLR7, 8, 9
MyD88
Pro-IL1/18
Caspase-1
CARD
Mature IL-1, IL-18
CARD PYD ASC
NALP3 PYD NOD
Sensors for nucleic acids
Danger (stress) sensors
A
HBP
Capillary leakage
NO, prostaglandins
Endothelial cell injury
TF
Antimicrobial peptides
LL-37, defensins
PMN
Bradykinin
Pathogen
Contact system
Mast
Anti-inflammatory mediators
IL-1ra, IL-10, TGF-β
Inflammation
Pathogen
Microbial
Complement system
Coagulation
Contact system
Microbial products
Macrophage
Proinflammatory mediators
TNF-α, IL-1, IL-6, IL-8, MIF, HMGB1
Thrombin
T cell
IFN-γ
TNF-α
Fibrinolysis
t-PA
TAFI
PMN
Adhesion molecules
Endothelial cell injury
PAI-1
B
Macrophage activation
Interferon γ
Activated T cell
Interleukin 7
PD-1
Exhausted T cell
LFA1
↑integrins
VLA4
Interleukin 7
Improved trafficking to infected site
antigen
Improved antigen presentation
(↑ T-cell activation)
↑ TCR diversity
(broadening T-cell response)
Interleukin 7
↑ production naive T cells
Thymus
Interleukin 7
Apoptosis
Interleukin 7
Interleukin 10
PD-1
PD-1
Anergy
Exhausted T cell
immune suppression
Apoptosis
Anti-PD-1
T cell
PD-1
PD-L1
Macrophage

Marker Categories

- Proinflammatory markers of the immune system
- Proteins produced in response to infection and/or inflammation
- Markers of abnormal coagulation
- Markers of end organ function

Proinflammatory cytokines of the immune system

- Tumor Necrosis Factor (TNF)
- Interleukin-1 (IL-1)
- Interleukin-6 (IL-6)

Faix JD, Established and Novel Biomarkers of Sepsis, Biomrkers Med., 2011 (5)2, 117-130
Reinhart K, New Approaches to Sepsis : Molecular Diagnostics and Biomarkers, Clin Microbiol Rev, 2012, 25(4):609
Pierrakos C, Sepsis Biomarkers: A Review, Critical Care, 2010:14(1):R15

TNF, IL-1, & IL-6

- Primary cytokines that mediate the initial response of the immune system to injury or infection
- Major source is the activated macrophage
- All have been studied extensively
- IL-6 has the most attention; more reliably measured in the plasma (original proof of concept)
- IL-6 is useful in autoimmune rheumatic disorders and malignancies
- Neither is specific enough to be useful clinically, especially alone

Faix JD, Established and Novel Biomarkers of Sepsis, Biomrkers Med., 2011 (5)2, 117-130
Reinhart K, New Approaches to Sepsis : Molecular Diagnostics and Biomarkers, Clin Microbiol Rev, 2012, 25(4):609
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Proteins produced in response to infection &/or inflammation

- Produced in response to proinflammatory cytokines TNF and IL-1
  - Interleukin-8 (IL-8)
  - Monocyte chemo-attractant Protein-1
  - C-reactive protein (CRP)
  - Pentraxin-3
  - Lipopolysaccharide-binding protein
  - Complement C3b and C5a
  - Procalcitonin (PCT)

Markers of abnormal coagulation

- D-dimer
- Protein C
- Plasminogen activator inhibitor-1

Markers of abnormal coagulation

- Consumption of coagulation factors and platelets along with inhibition of the fibrinolytic system results in microvascular fibrin deposits resulting in interruption of blood flow and end organ damage
- D-Dimer is the most common fibrin related marker and is used in DIC scoring
- D-Dimer in conjunction with PCT may be useful in other diagnoses
- Protein C was used with drotrecogin-alfa (Xigris) as a surrogate marker in therapy
- Problem with markers of coagulation is that late sepsis or septic shock has already occurred

Markers of end organ dysfunction

- Lactate
- Membrane microparticles

Lactate

Lactate (lactic acid) is produced when body experiences inadequate tissue perfusion – a defining parameter of late sepsis

- Distinguishes infection from sepsis and septic shock
- Useful in prognosis of septic shock

Blomkalns 2007 www.emcreg.org pg 44 col 1 para 2, table 1]
Smith et al. The Open Inflam J. 2011 (4)23-30

Biomarker Summary

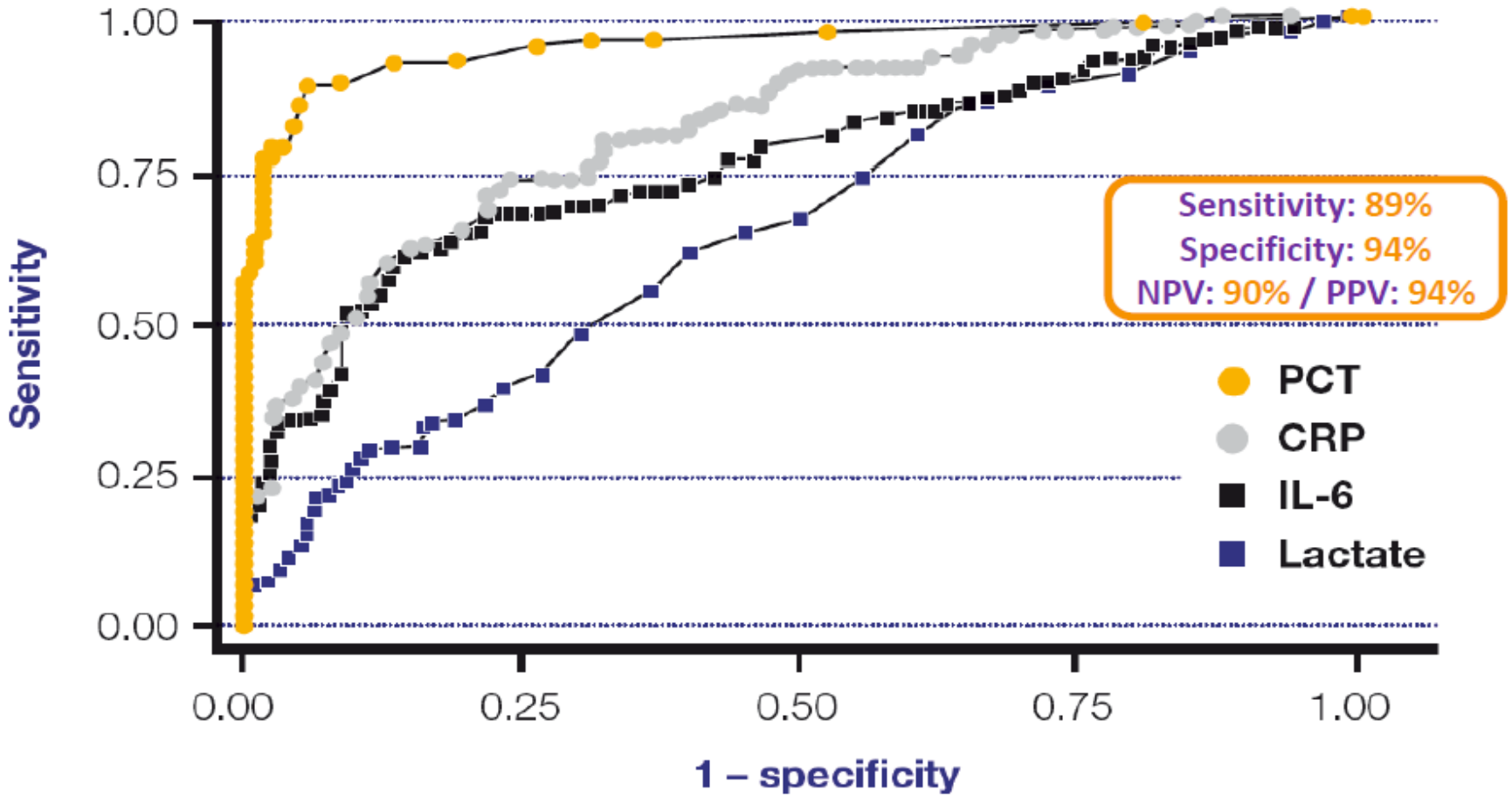
Marker	Differentiate Bacteria	Clinical Usefulness	Availability	Cost
TNF, IL-1, Il-6	No	+	+	++++
Il-8	No	++	+	++++
Pentraxin-3	No	++	+	+++
LPS Binding	?	+	+	+++++
C3b & C5a	No	+	+	+++++
CRP	No	+	+++++	+
CD64	No	++	+	+++++
TREM-1	No	+	+	+++++
PCT	Yes	+++++	+++++	+
Lactate	No	+++	+++++	+
D-Dimer	No	+	+++++	+
Protein-C	No	+	+++	++++

Comparison of Clinical Biomarkers

Biomarker	Specificity Bacterial Infection	Sensitivity Inflammation	Advantages	Disadvantages
WBC	+	+++	Simple Inexpensive	Sensitivity for bacteria Non-specific for bacterial infection All inflammation & infections Disease states/drug - 596
C-reactive protein (CRP)	++	++	Inexpensive Moderately specific	All inflammation & Infections Slow induction (peak >24h) No correlation with severity
Lactate	+	+	Inexpensive Reliable marker of perfusion Prognosis > Sepsis	Must be in sepsis to be elevated Very poor specificity for bacterial infection
Procalcitonin (PCT)	++++	+	Specificity for bacteria Favorable kinetics Rise/half-life Correlates with severity of illness Antibiotic use	Education Instrument for Lab More expensive than WBC, CRP, and lactate

Reinhart K, et al. *Crit Care Clin*. 2006;22:503-19

Diagnostic accuracy of PCT compared to other biomarkers used in sepsis for bacteria



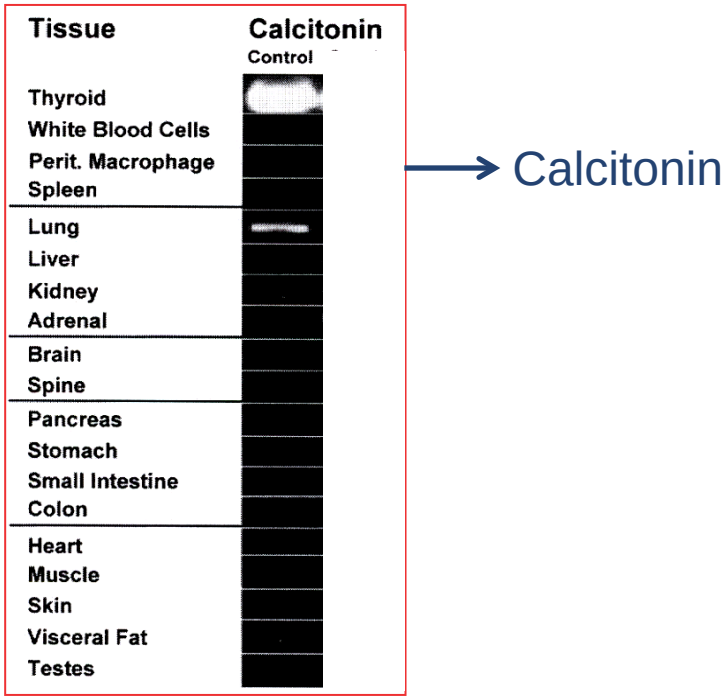
- **PCT levels accurately differentiate** sepsis from noninfectious inflammation*
- **PCT has been demonstrated** to be the best marker for **differentiating** patients with **sepsis** from those with systemic inflammatory reaction not related to infectious cause

Simon L. et al. Clin Infect Dis. 2004; 39:206-217.

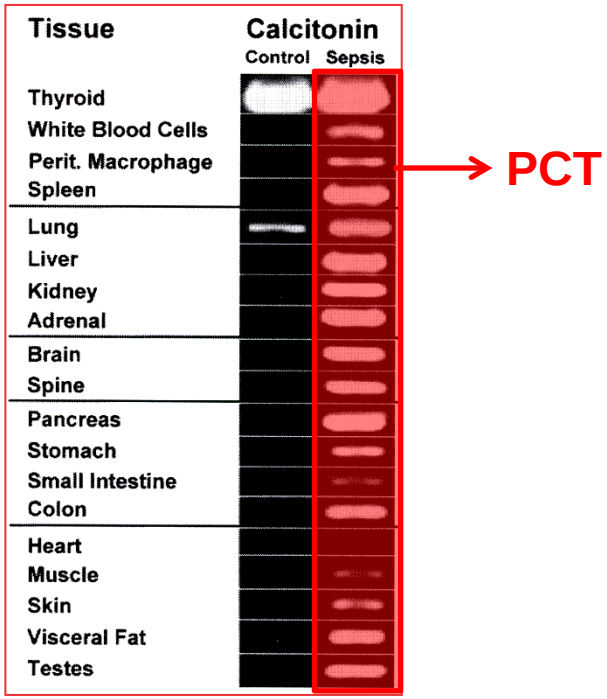
What is Procalcitonin and its role in sepsis management?

Bacterial induction and release from all tissues

Healthy Individuals

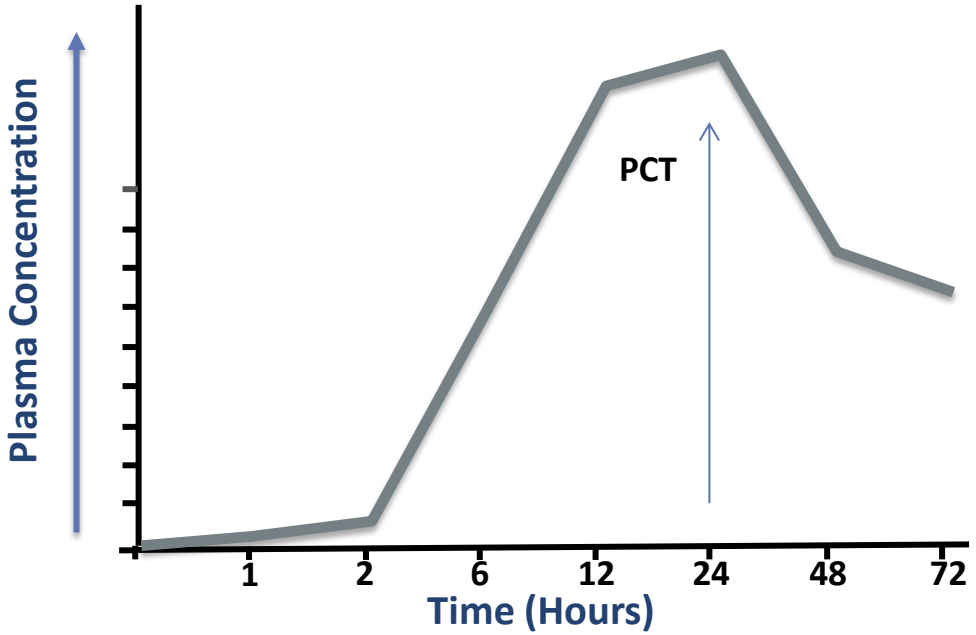


Systemic response to
bacterial infection



Muller B, et al. J Clin Endocrinol Metab 2001 Jan;86(1):396-404.

PCT Kinetics



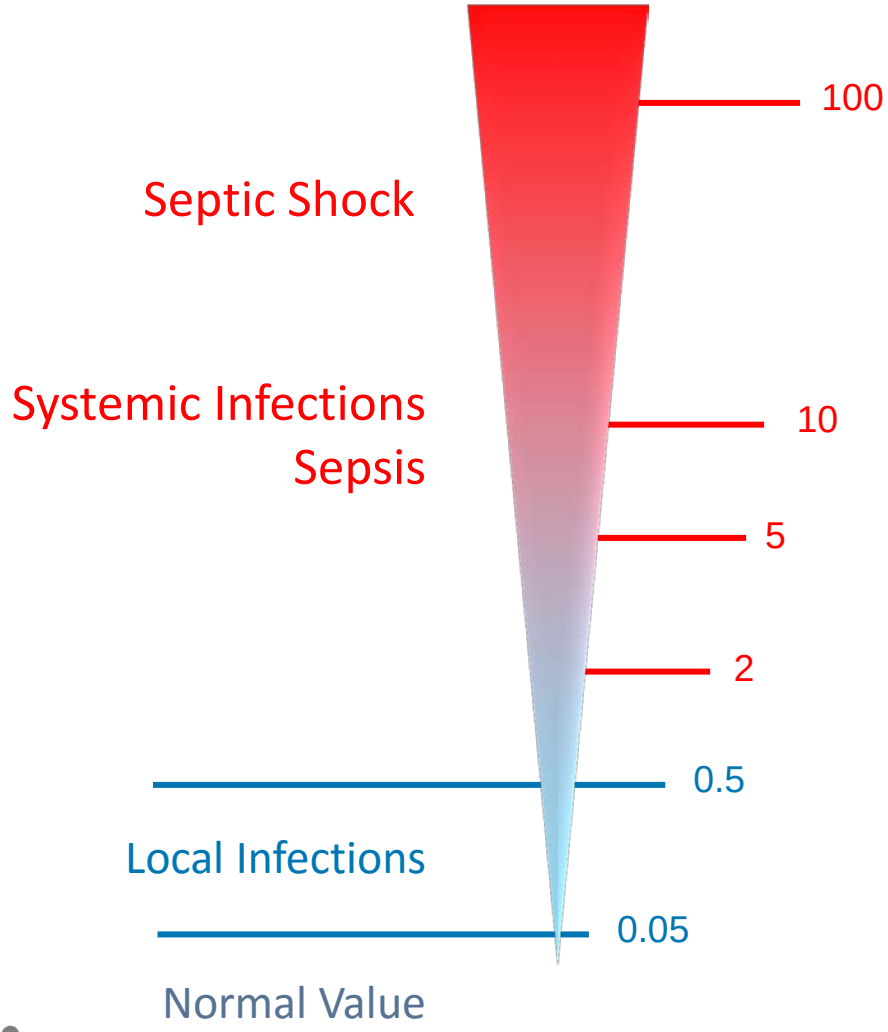
- Rapid kinetics: detectable 3 hours after infection has begun, with a peak after 12 to 24 hours
- Peak values up to 1000 ng/ml
- Half-life: ~ 24 hours

Brunkhort FM et al., Intens. Care Med (1998) 24: 888-892

Procalcitonin

- PCT is induced in systemic inflammatory reactions
- Bacterial infections release much greater quantities of PCT compared to non-bacterial etiologies
- PCT induction and release is in direction proportion to the bacterial insult to the body
- Viral infections, autoimmune diseases, transplant rejections, and allergic reactions generally do not induce PCT
- PCT is therefore an “indirect marker” of a bacterial infection: PCT a measurement of the body’s inflammatory response to the bacteria

PCT Interpretation



- PCT thresholds depend on **clinical situation** of the patient
- Correlates with bacterial burden or bacterial load

Harbarth S et al. AJRCC Med. 2001;164:396-402.
*Meisner M et al. **Crit** Care. 1999, 3:45-50.*
Krüger S et al. Eur Respir J. 2008;31: 349–55.

Non-Bacterial Stimuli

- Primary inflammation syndrome following trauma: multiple trauma, extensive burns, major surgery (abdominal and transplant)
- Severe pancreatitis or severe liver damage (1ng/ml)
- Prolonged circulatory failure: IE severe multiple organ dysfunction syndrome (MODS) (1.4ng/ml)
- Medullary or C-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma
- Newborn < 48hr - increased PCT values (physiological peak)

PCT response to bacterial challenge

Elevated or rising PCT values

- Systemic response to bacterial infection
  - Progressing infection
  - Immune system is overwhelmed
- Risk of significant disease progression

Low PCT values in presence of clinical presentation

- Self-limiting infection
- Non-bacterial etiology
- ***Early phase of infection***

Aiding Sepsis Risk Assessment

- PCT levels above 2 ng/ml indicate a higher risk for progression to sepsis or septic shock
- PCT levels below 0.5 ng/ml indicate a low likelihood of progression to sepsis or septic shock
- Suggest a baseline with daily levels for 72 hours resulting in 4 PCT values

Aiding Septic Patient Management

- Multiple PCT measurements over consecutive days aids in assessing the response to empiric antibiotic therapy
- As infection is controlled, PCT will decline daily
- The Procalcitonin Monitoring Sepsis Study (MOSES) showed that sustained PCT elevation is a independent risk factor for mortality
- PCT level decline less than 80% from baseline within four days is associated with increased all cause mortality, especially with initial PCT is greater than 2 ng/ml

BE

CC/Hx

67 Y/O female

CC: Mild mental confusion, c/o pain in neck, shoulders, upper and lower back, and other diffuse arthralgia's

Medical History:

Recurrent Urinary Tract Infections

Hypertension

Migraine headaches

Depression NOS

Generalized Anxiety D/O

Fibromyalgia

Restless leg syndrome

Osteoporosis

Medications

Chlorthalidone 25mg daily

Lisinopril 10mg daily

Verapamil 240mg daily

Sumatriptin 50mg prn

Milnacipran 50mg bid

Sertraline 50mg daily

Pregabalin 150mg bid

Clonazepam 0.5mg prn bid

Pramipexole 1mg HS

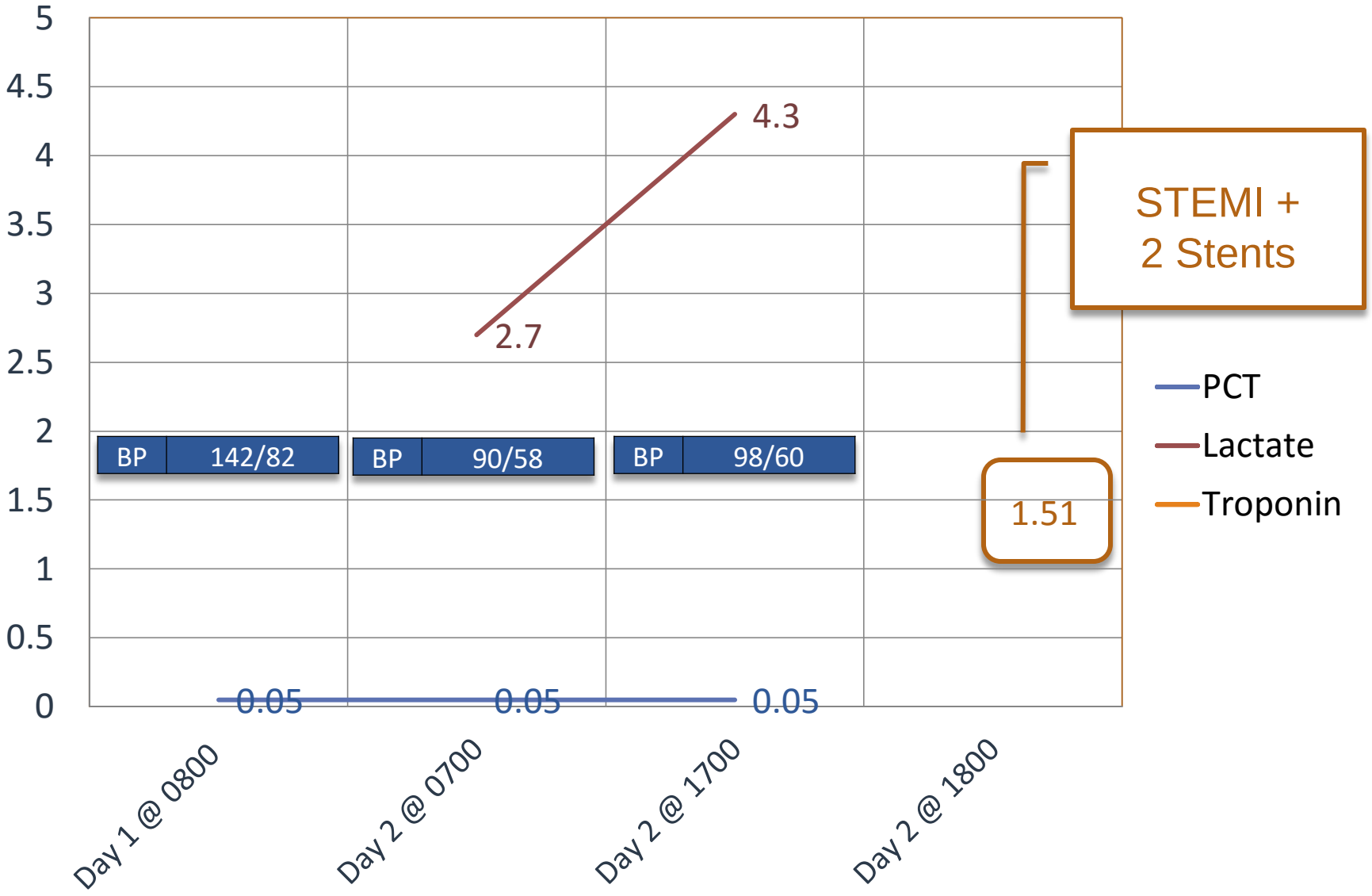
Nitrofurantoin 100mg bid

Hydrocodone/Acetamin 7.5mg/325mg prn q 4 hours

BE

UA collection	Urinalysis	Other Lab
• Mini-Cath - clogged • Required 4 attempts	• Nitrite positive • WBC: 5 • Bacteria 4+ • Dark yellow • Clarity: cloudy	• WBC: 9.6 x 1000 • PCT: 0.05ng/ml

BE: UTI and Lactate Specificity



HW & CK

HW CC/Hx/Presentation

73 Y/O female

CC: dysuria, fever, nausea/vomiting

Temp 103.4

Hx: Recurrent UTI's last 3 years

RR 19

BP 142/84

HR 95

WBC 28.4 w/4 bands

Lactate 1.9 mmol/L

SrCr 1.6 mg/dl w/ BUN 38

Mini-cath UA

- Nitrite positive
- Leukocyte esterase positive
- 4+ bacteria

CK CC/Hx/Presentation

75 Y/O female

CC: dysuria, fever, nausea/vomiting

Temp 102.8

Hx: Recurrent UTI's last 4 years

RR 18

BP 156/86

HR 91

WBC 26.4 w/4 bands

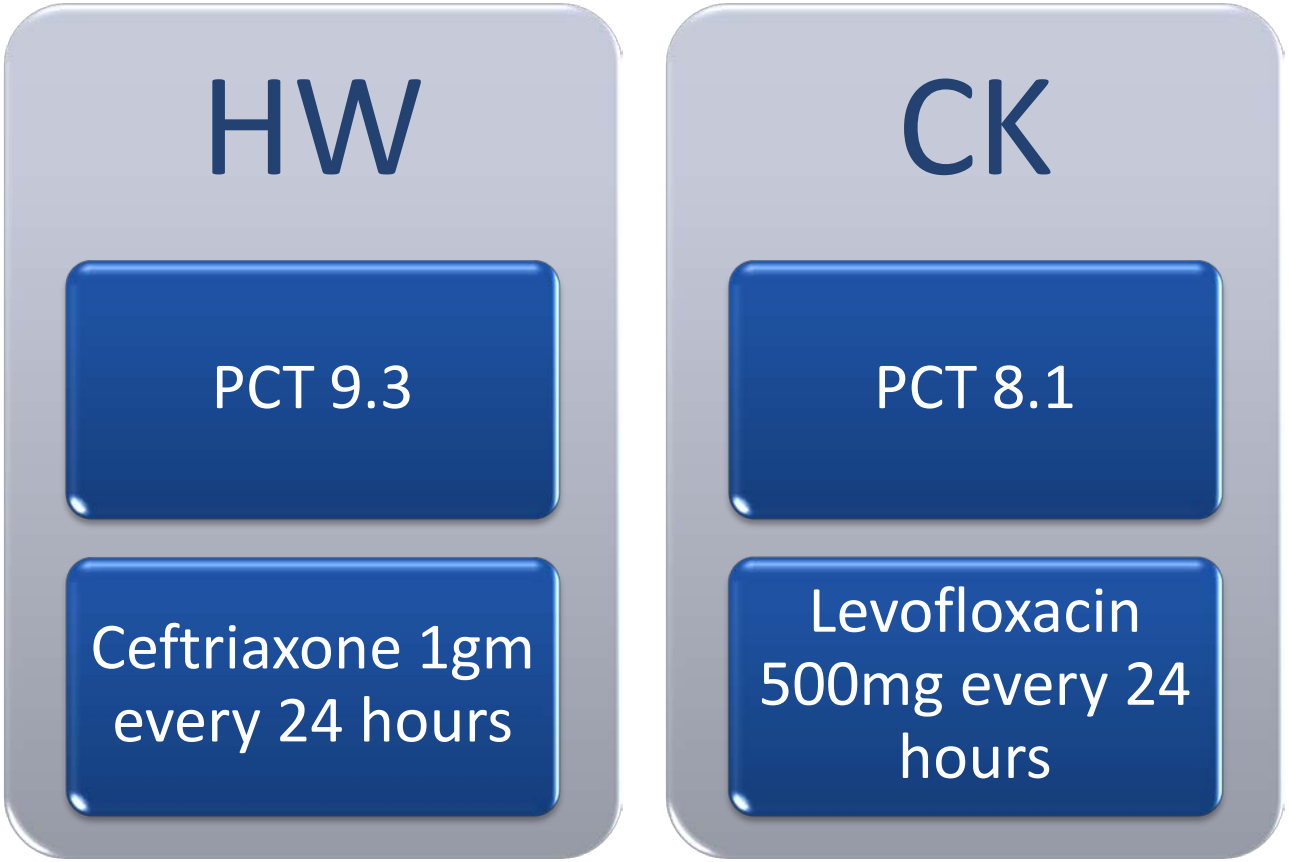
Lactate 1.8 mmol/L

SrCr 1.8 mg/dl w/ BUN 34

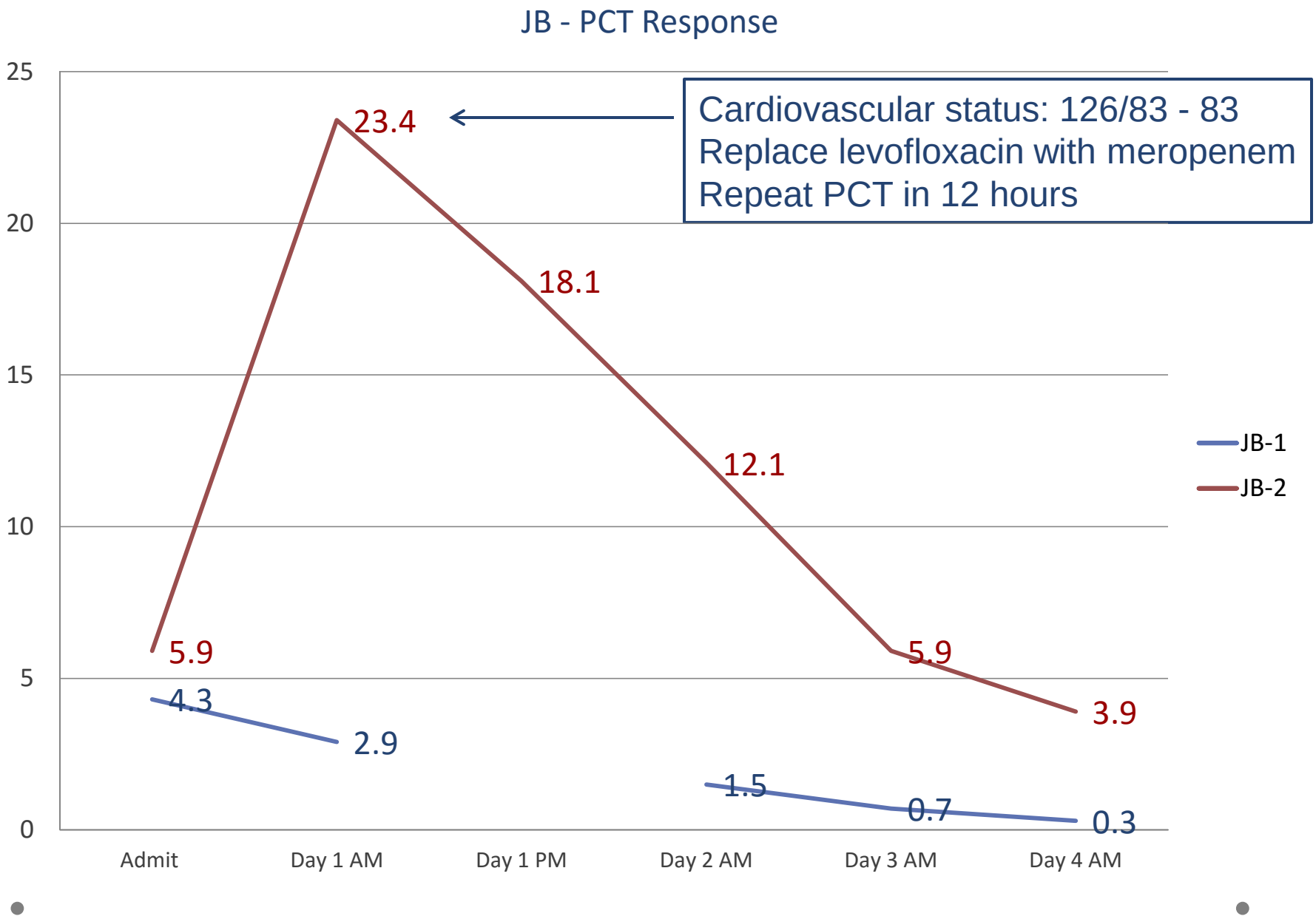
Mini-cath UA

- Nitrite positive
- Leukocyte esterase positive
- 4+ bacteria

HW & CK


HW
PCT 9.3
Ceftriaxone 1gm every 24 hours
CK
PCT 8.1
Levofloxacin 500mg every 24 hours

JB


JB - PCT Response
25
20
15
10
5
0
Admit
Day 1 AM
Day 1 PM
Day 2 AM
Day 3 AM
Day 4 AM
Cardiovascular status: 126/83 - 83
Replace levofloxacin with meropenem
Repeat PCT in 12 hours
23.4
18.1
12.1
5.9
5.9
3.9
4.3
2.9
1.5
0.7
0.3
JB-1
JB-2

JW

CC/Hx/Presentation

56 Y/O male, construction worker

Asthma since childhood

CC: SOB, productive cough, malaise, fever

Duration of 12-14 days

Azithromycin Z-Pak

Benazepril 20 mg daily

Nebivolol 5 mg daily

Citalopram 20 mg daily

Furosemide 80 mg daily

Omeprazole 20 mg daily

Prednisone 5 mg daily

Mometasone 220 mcg daily

Albuterol MDI prn q 4 hours for SOB/wheezing

Labs/X-Ray/Plan

Temp 99.8

BP 145/86

Pulse 90

RR 20

Pulse Ox 92% on RA

WBC 14.7 x 1000

Bands 6

Lactate 1.3mmol/L

Chest film and auscultation: early bilateral pneumonia

Stop azithromycin

Start levofloxacin 750mg daily

Question:
What is your Tx plan if the procalcitonin was 0.7?
Now:
Would your plan be different if the procalcitonin was 17?

JW clinical course

Day 1 (22 hours)

- Temp 101.8
- BP 138/82
- RR 22
- WBC 22.4 x 1000
- Bands 10
- Lactate 2.1 mmol/L

PCT = 36 ng/ml

Day 2

- Temp 103.6
- BP 106/62
- RR 26
- WBC 28.8
- Bands 12
- Lactate 5.6 mmol/L
- PCT 86 ng/ml
- Blood gases

JW clinical course

Day 2 continued

- Increase fluids
- DC Levofloxacin
- Start Vancomycin
- Start Meropenem
- CPAP > Ventilator
- Sputum Gram stain: coagulase positive/gram-positive cocci in clusters
- 1st blood culture Gram stain: coagulase positive/ gram-positive cocci in clusters
- Nasal culture plate: MRSA

Day 2 PM

- PCT 72 ng/ml

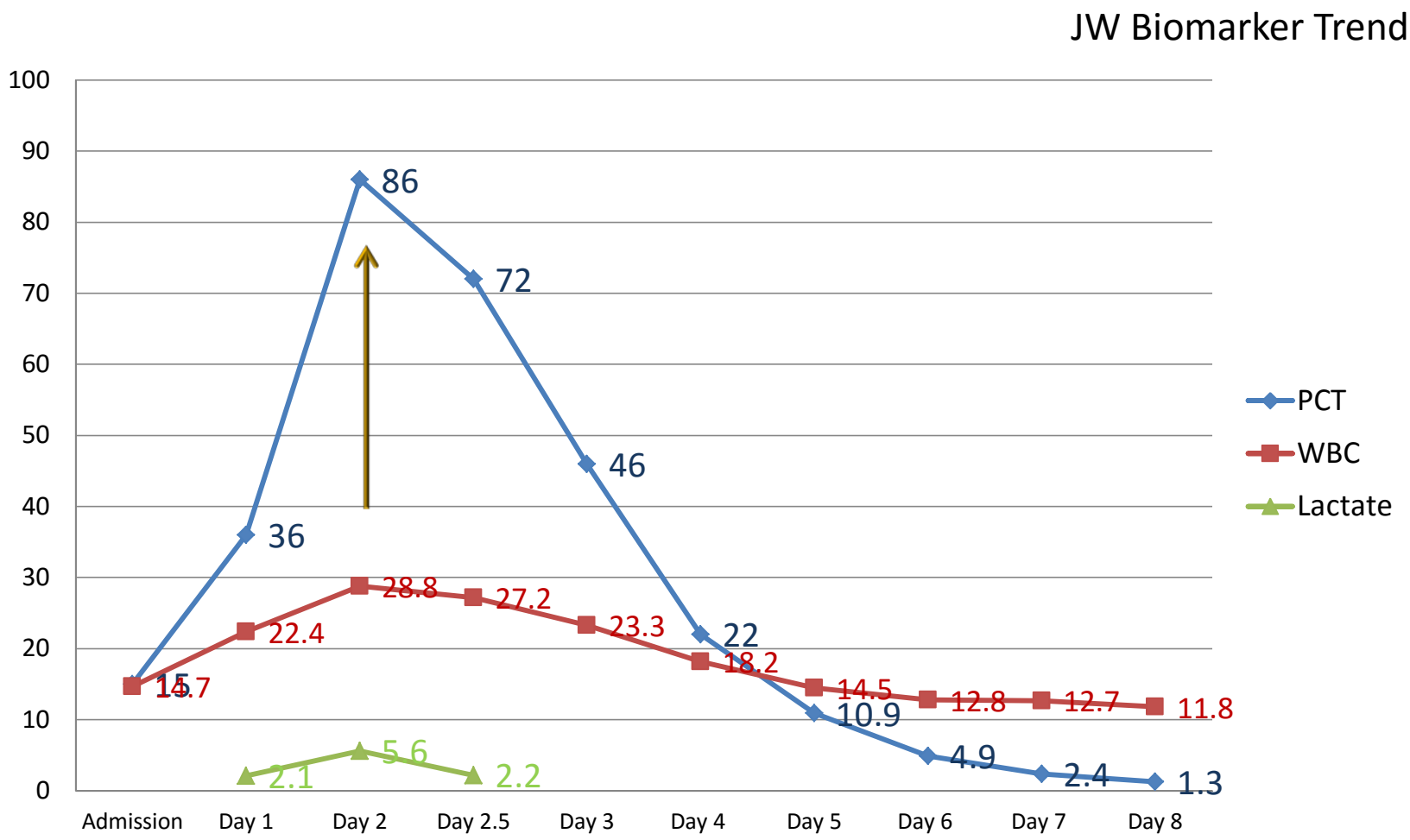
JW clinical course

Day 3

- Temp 101.2
- BP 120/68
- WBC 23.3 x 1000
- Bands 10
- Lactate 2.2mmol/L
- BP 120/68
- PCT 46 ng/ml
- Sputum: MRSA
- Blood Cx: MRSA

JW clinical course

Summary



JW Clinical Perles

- The pneumonia diagnosis is a based on three pillars (1) clinical symptoms (2) tissue infiltration (3) signs of inflammation, suspicion of infection – elevated PCT is not absolutely essential, but be aware of significant elevations (1/3rd / 0.5ng/ml)
- Significant elevations in procalcitonin after 24 hours is always cause for concern and that the infectious organism in not being adequately treated

Retrospective Analysis: Before and After

Years 2006 thru 2009 4 years	2010 PCT implementation	Years 2011 thru 2014 4 years
N = 985		N = 1167
Lower Respiratory Tract COPD Biliary tract Osteomyelitis SSSI GU Septicemia Other	Implementation Education	Lower Respiratory Tract COPD Biliary tract Osteomyelitis SSSI GU Septicemia Other

Inclusion and Exclusion Criteria

- Inclusion:
  - All patients with ID diagnosis requiring parenteral administration of antibiotics at onset of therapy
  - All age groups (pediatric through aged)
- Exclusion:
  - Patients admitted for surgical prophylaxis
  - Patients transferred to other facilities
- Process Implemented:
  - PCT at baseline (ED or admission) and every 24 hours and as needed
  - PCT placed in all ID related order sets and protocols
- Pharmacy reviewed:
  - All PCT orders
  - All antimicrobial orders
  - Communicated with prescribers to close loop of missed lab and/or therapy changes

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Statistical Analysis

Clinical factor	p-value	Applied test
Age	0.2505	Mann–Whitney U test
Gender	0.6149	Chi-square test Gender vs. time (before/after)
Diagnosis	0.9124	Mann-Whitney U test
Adverse drug events	4.47E-09	Chi-square test
C difficile	0.002128	Chi-square test
Death within 30 days	8.43E-06	Chi-square test
30 day readmissions	9.39E-09	Chi-square test
Antimicrobial days of therapy per patient:	0.00018	Mann-Whitney U test

Five Rivers Medical Center

- Outcomes Comparison: Control Vs. Procalcitonin
- 4 years Pre (n=985) and Post Procalcitonin (n=1167) implementation with one year for education between patient groups

42% **Reduction in Antimicrobial Days of Therapy**	**57.6%** **Reduction in Mortality Due to Infectious Diseases**	**47.2%** **Reduction in 30-day Readmissions**	**64.6%** **Reduction in *C. difficile* Infections**	**50%** **Reduction in Adverse Drug Events**
Days of Therapy/Patient **Pre:** 16.43 DOT **Post:** 9.52 DOT	Mortality due to Infectious Diseases **Pre**:6.9% **Post:** 2.8%	30-Day Readmission for Infection **Pre:** 18% **Post:** 9.5%	C. difficile Rate **Pre:** 9.5% **Post:** 0.9%	Adverse Drug Events **Pre:** 16.2% **Post:** 8.1%
P < 0.00018	**P< 0.000001**	**P < 0.000001**	**P < 0.002128**	**P < 0.000001**

Questions

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