Taking Antibiotic Stewardship to the Next Level with Procalcitonin: Exceed the New CMS and TJC Stewardship Requirements and More

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Disclosures

- Consulting / Advisory Boards
  - Thermo Fisher Scientific
  - Roche Diagnostics
- Paid Lecture
  - Thermo Fisher Scientific
  - Roche Diagnostics
  - bioMerieux
- Historically, I have partnered with the healthcare companies bioMerieux, Carefusion, 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

- Describe the pathophysiology and kinetics of Procalcitonin (PCT)
- Compare and contrast PCT to the commonly used biomarkers; WBC, CRP and lactate for management of bacterial infections
- Utilizing actual patient cases, apply use of baseline and serial PCT measurements to better assess initial severity of infection, evaluation of therapy and improve antimicrobial use

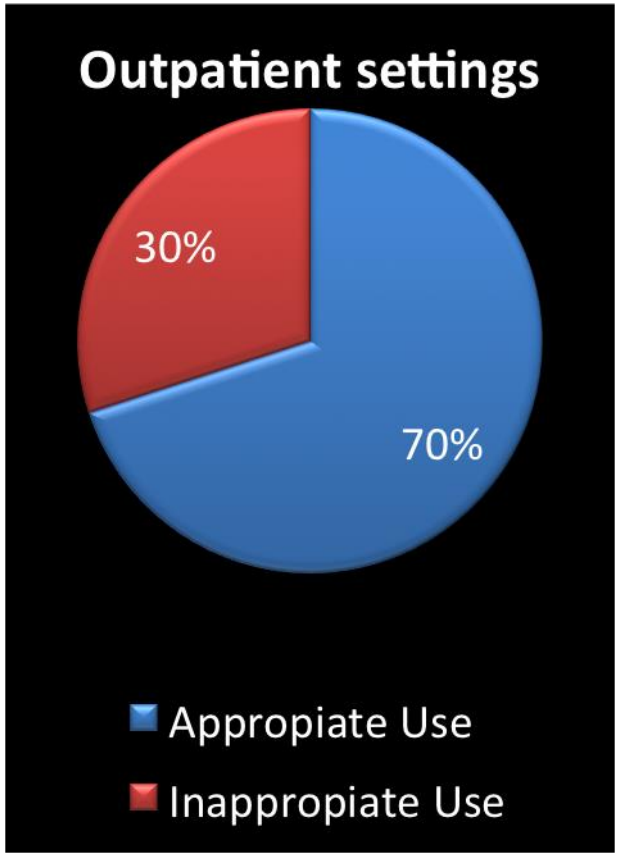
Hospitals Traditionally = Silos

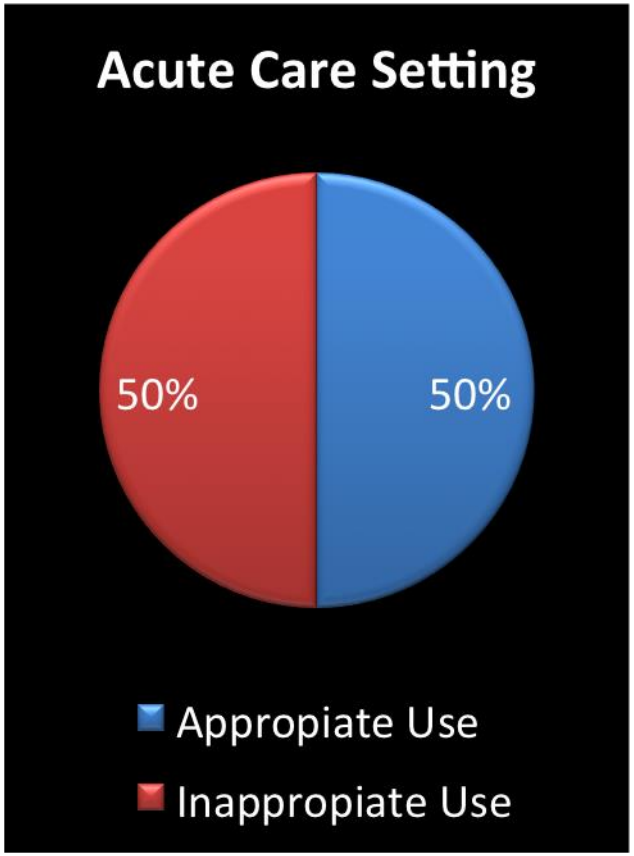
My – Our – Them – Why – Can't - No

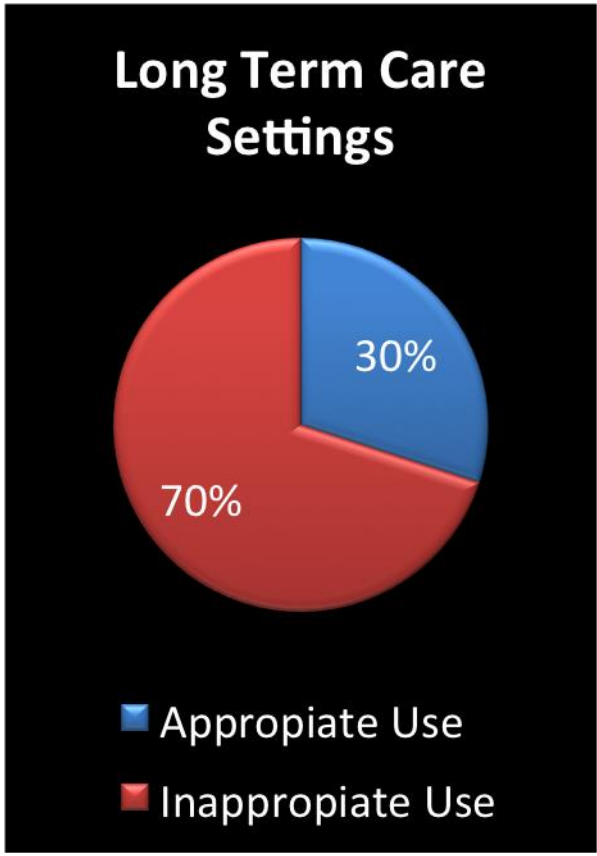
My Personal Goal for all Hospitals

- Get Lab out of the Lab
- Get Pharmacy into the Lab and learn about what Lab can offer them
- Get Lab to have the tools to best serve antibiotic use and stewardship activities
- "All results reviewed – timely" –A result is a wasted resource unless acted on
- Get ID Pharmacists and Physicians to use the results from Lab to obtain "Appropriate Use of Antibiotics"

Antimicrobial Use and “Misuse”







CMS 482.42(b)(2)(i), (ii), and (iii) Meeting the Goals of the AMS Program

CMS states the following goals for an ASP are met:

1. Demonstrate coordination among all components of the hospital responsible for antibiotic use and factors that lead to antimicrobial resistance, including, but not limited to, the infection prevention and control program, the QAPI program, the medical staff, nursing services, and pharmacy services

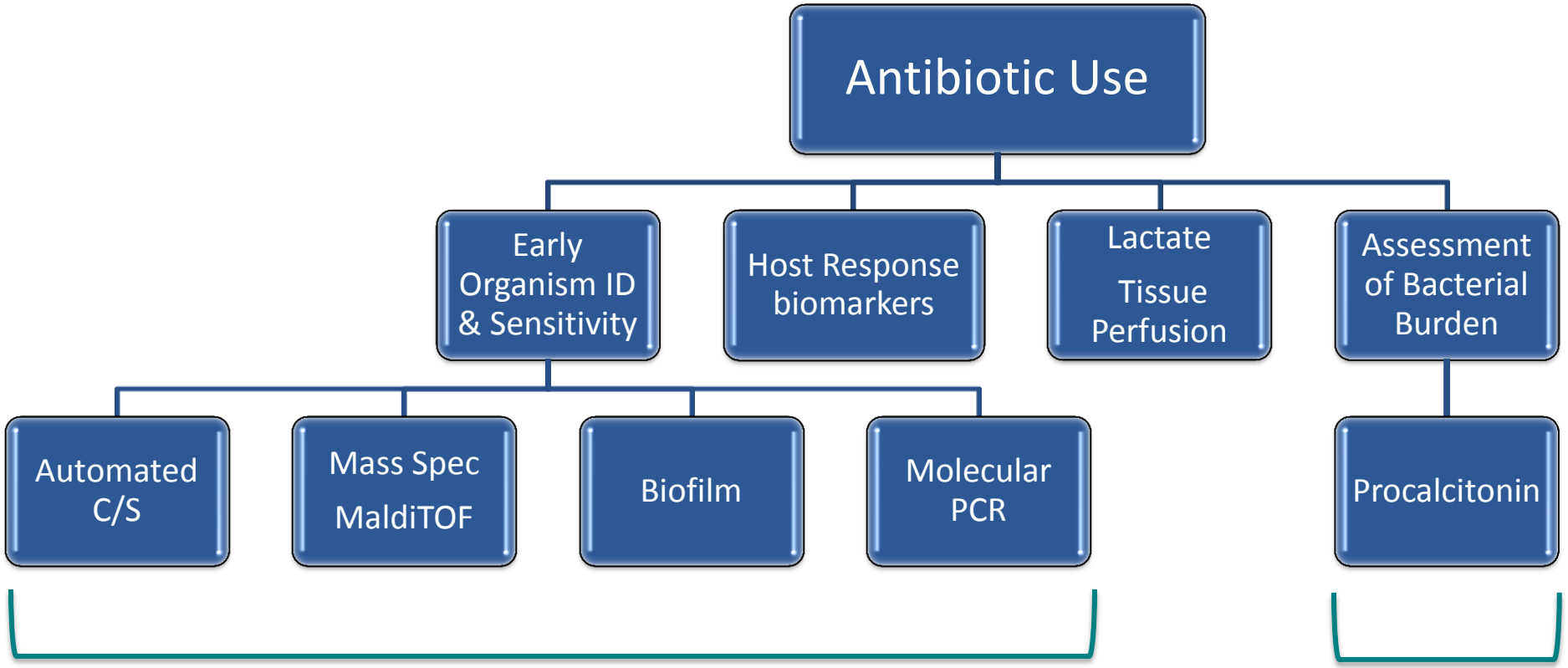
2. Document the evidence-based use of antibiotics in all departments and services of the hospital; and

3. Demonstrate improvements, including sustained improvements, in proper antibiotic use, such as through reductions in CDI and antibiotic resistance in all departments and services of the hospital

Antimicrobial Stewardship

- IDSA: The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as Clostridium difficile), and the emergence of resistance. Thus, the appropriate use of antimicrobials is an essential part of patient safety and deserves careful oversight and guidance.
- ASHP: Antimicrobial stewardship—the appropriate selection, dosing, route of administration, and duration of antimicrobial therapy—in conjunction with infection prevention and control measures prevents or slows the emergence of antimicrobial resistance and transmission of antimicrobial resistant pathogens

Micro Solutions for Clinicians
ID Management



Opportunities:
Optimize & Narrow Therapy
Organism +/- Sensitivity

Opportunities:
Bacterial?/ABX?
Assess/Stop

Organism ID/Sensitivity Testing: Caveats

Traditional Micro

- Urine
- Blood
- CSF
- Direct from specimen
  - Respiratory – nasal swab
  - Blood (some)
  - Stool
  - CSF
- Wound
- Diabetic foot
- Sputum / Bronchial washing

Biomarkers (PCT)

- Actual pathogen
- Colonization
- Bacterial burden
- Change in bacterial burden over time
- Assess current therapy
- When you may discontinue therapy…. Or not

The Biomarker Catch

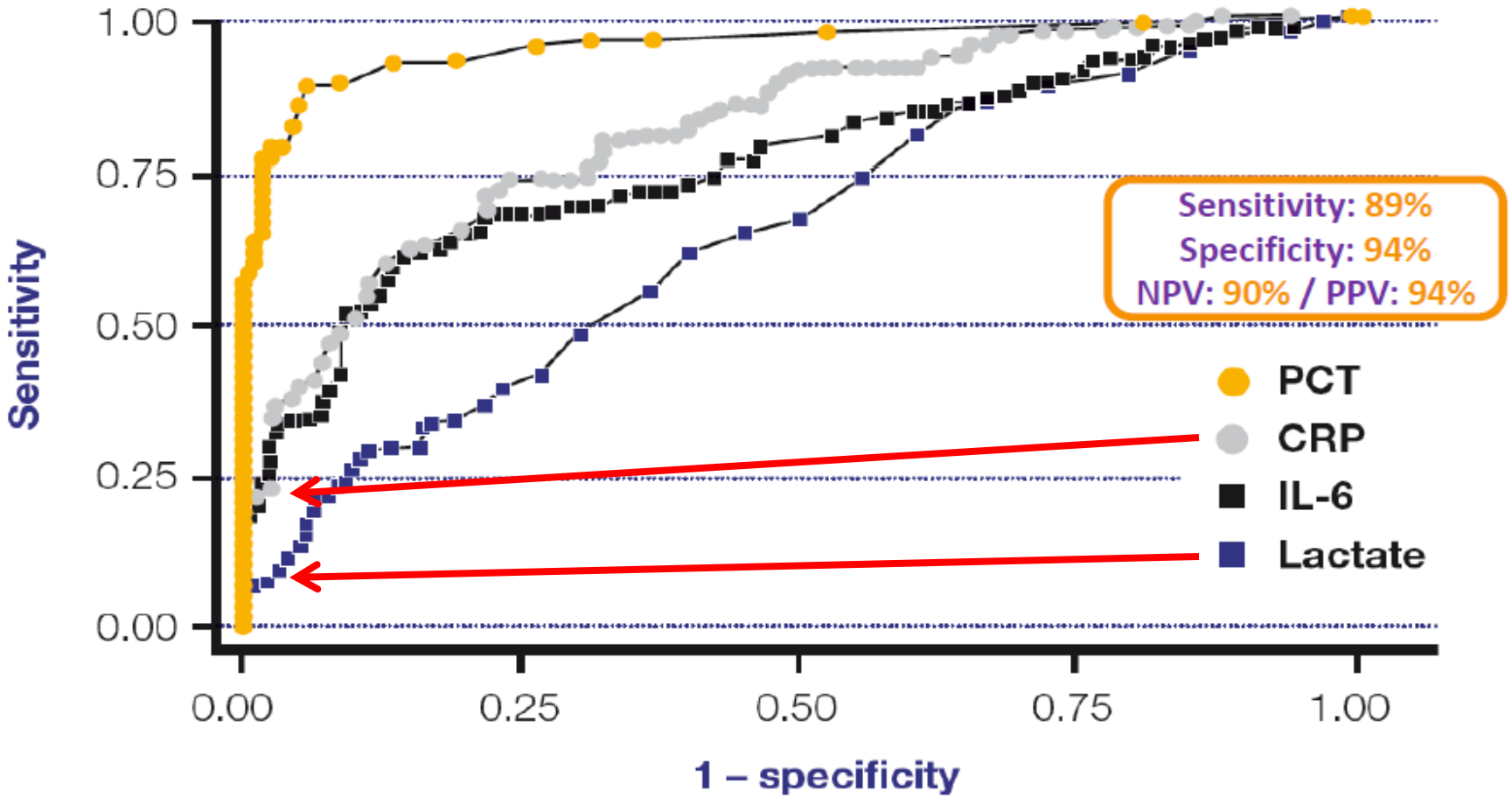
- The clinical phenotype of a patient with significant infection is generally similar to that of a patient with systemic inflammatory response caused by non-infectious or sterile inflammation.
- Most markers are unable to differentiate between bacterial, viral, and fungal infections
- Most are affected in immunocompromised patients
- Most are affected by autoimmune diseases
- Affected by anti-inflammatory, disease modifying drugs, and steroids

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

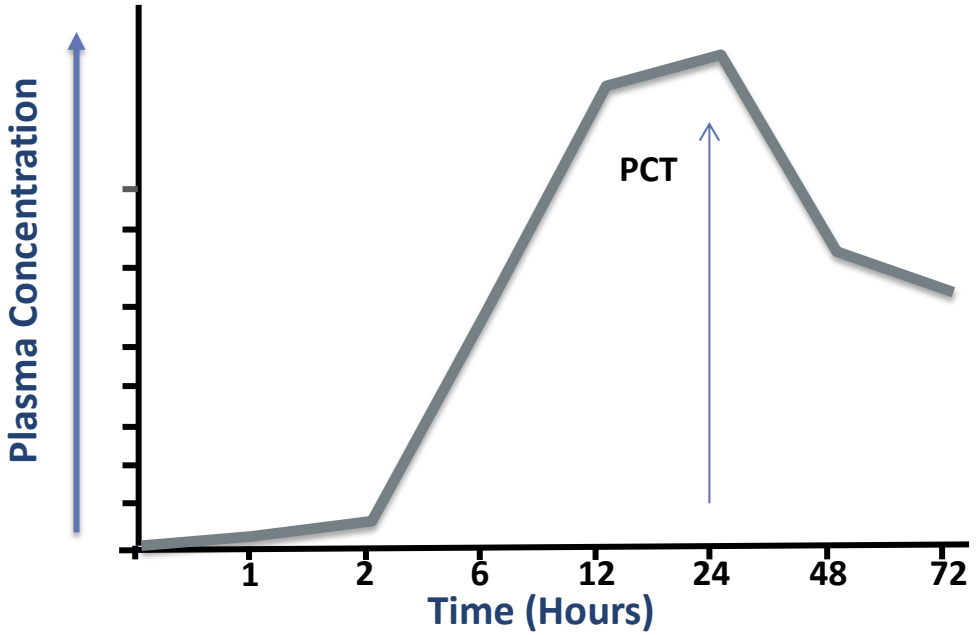
Diagnostic accuracy of PCT compared to other biomarkers used in sepsis for bacteria



- **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.

PCT Kinetics



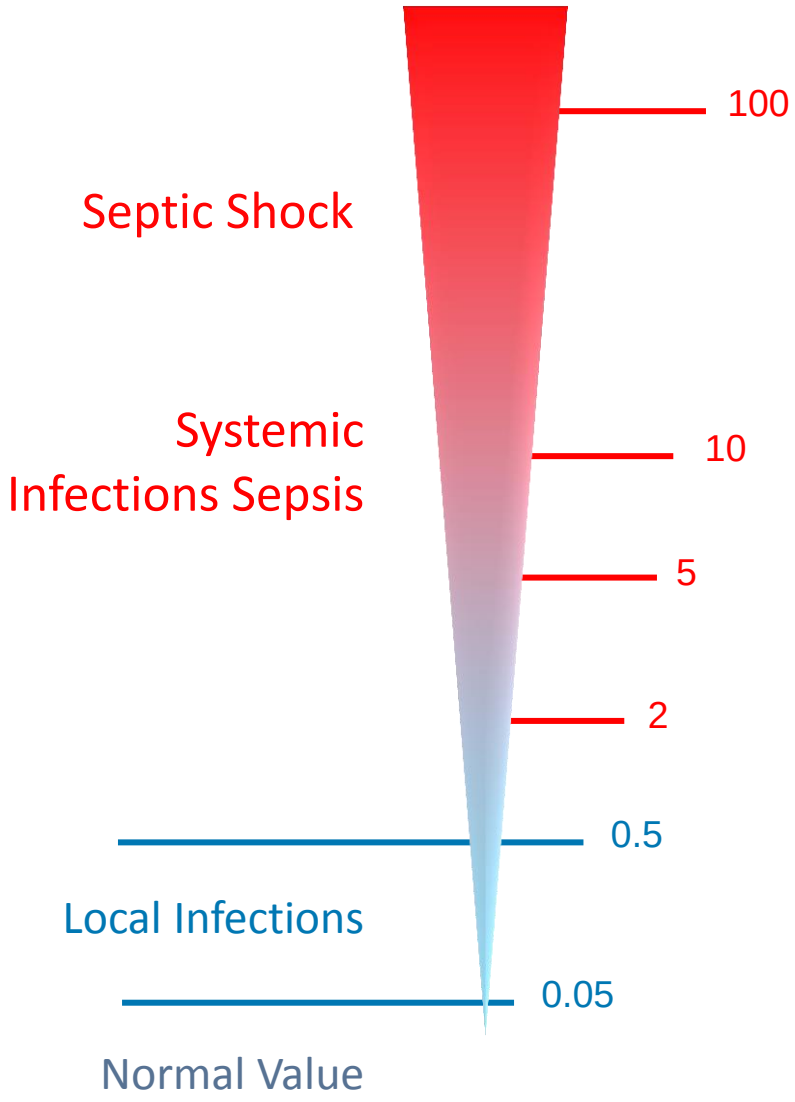
- Rapid kinetics: detectable 3 hours after infection has begun, with a peak after 12 to 24 hours
- Peak values up to 1000 ng/ml
- Half-life: ~ 24 hours

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

Procalcitonin

- PCT is induced in significant quantitates in systemic inflammatory reactions in conjunction with bacterial endo- and exotoxins (IL-1,IL-6, TNF)
- 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 concentrations and sepsis risk

- Less than 0.5ng/ml - low risk for progression to sepsis and septic shock
- Between 0.5 and 2ng/ml – sepsis should be considered
- Greater than 2ng/ml – high risk for progression to sepsis and septic shock
- 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.

What differentiates PCT from the other 175+ biomarkers?

- Approved by the FDA for management of antibiotic therapy in sepsis and LRTI's (February 2017)
- Sensitivity – most always elevates (89%)
- High specificity for bacteria (94%)
- Favorable kinetics
- Measure change of bacterial burden over time
- Use with corticosteroids
- Use with disease modifying drugs
- Use with other drugs affecting inflammatory mediators
- Use in autoimmune diseases
- Use with decreased immune function/oncology

Appropriate Use is Best Determined by: Individual Patient Directed Care

- Organism ID
- Sensitivity
- Procalcitonin
- Biomarkers
- Antibiogram
- Resistance and MIC trending
- Biomarkers
- Comprehensive integrated solution

Appropriate Use

Diagnosis
- Bacterial infection?
- Need for ABX
- Perceived severity or bacterial load

ABX Selection
- Evidenced based medicine
- Early ID – MS or PCR
- Completion of ID/AST
- Formulary selection

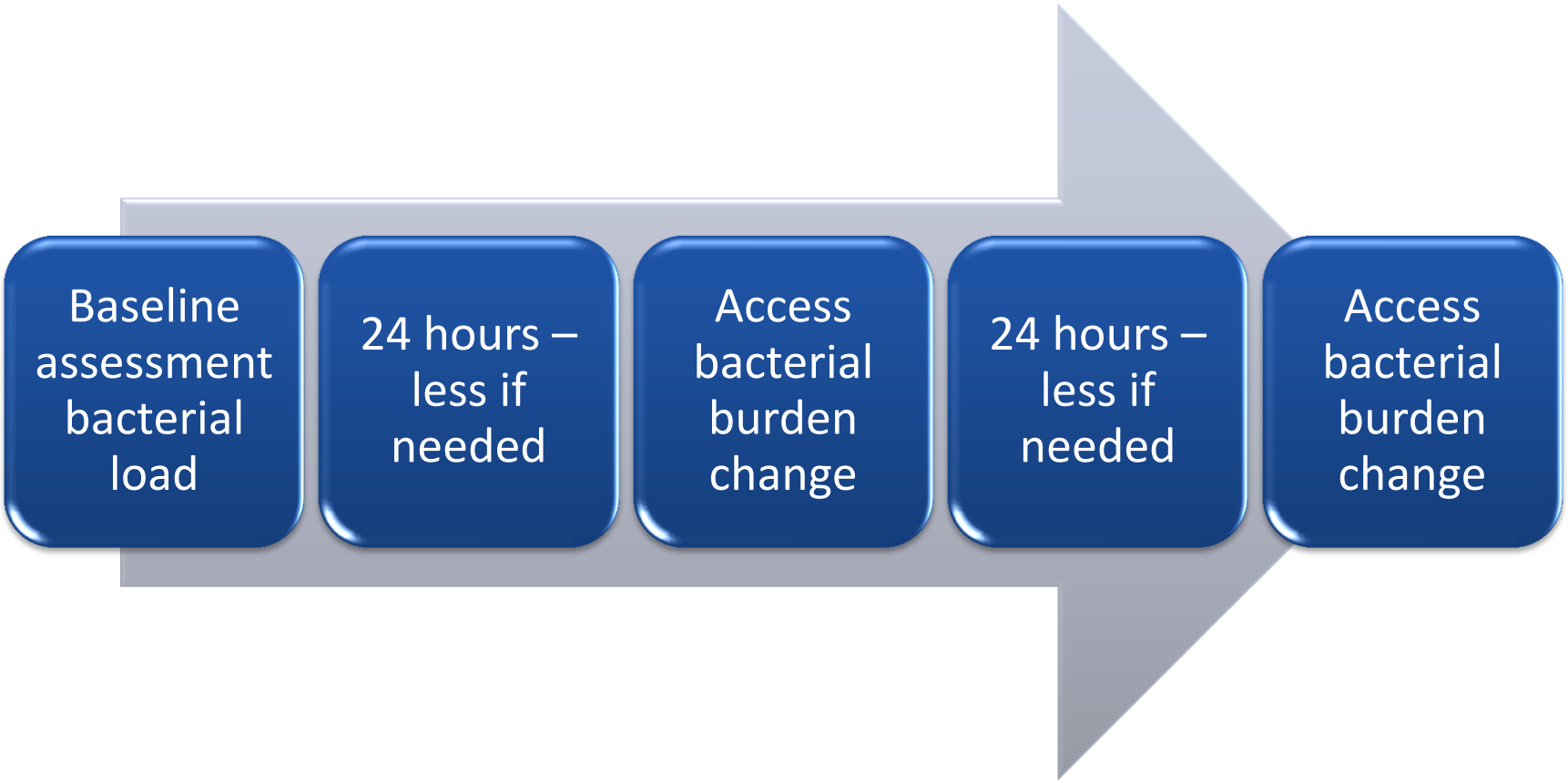
Assess Therapy
- Continue therapy
- Revise therapy

Duration of TX
- How long to treat
- Early cessation

Case Presentations

Application of PCT use for Sepsis and Antibiotic Management

Key Point: Baseline PCT and monitor PCT changes over time to assess therapy



JB - 75 Y/O Female: Comparison of two UTI presentations

JB - 1 CC/Hx/Presentation

CC: dysuria, fever, nausea/vomiting

Temp 103.4

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

JB - 2 CC/Hx/Presentation

CC: dysuria, fever, nausea/vomiting

Temp 102.8

RR 18

BP 156/86

HR 91

WBC 26.4 w/4 bands

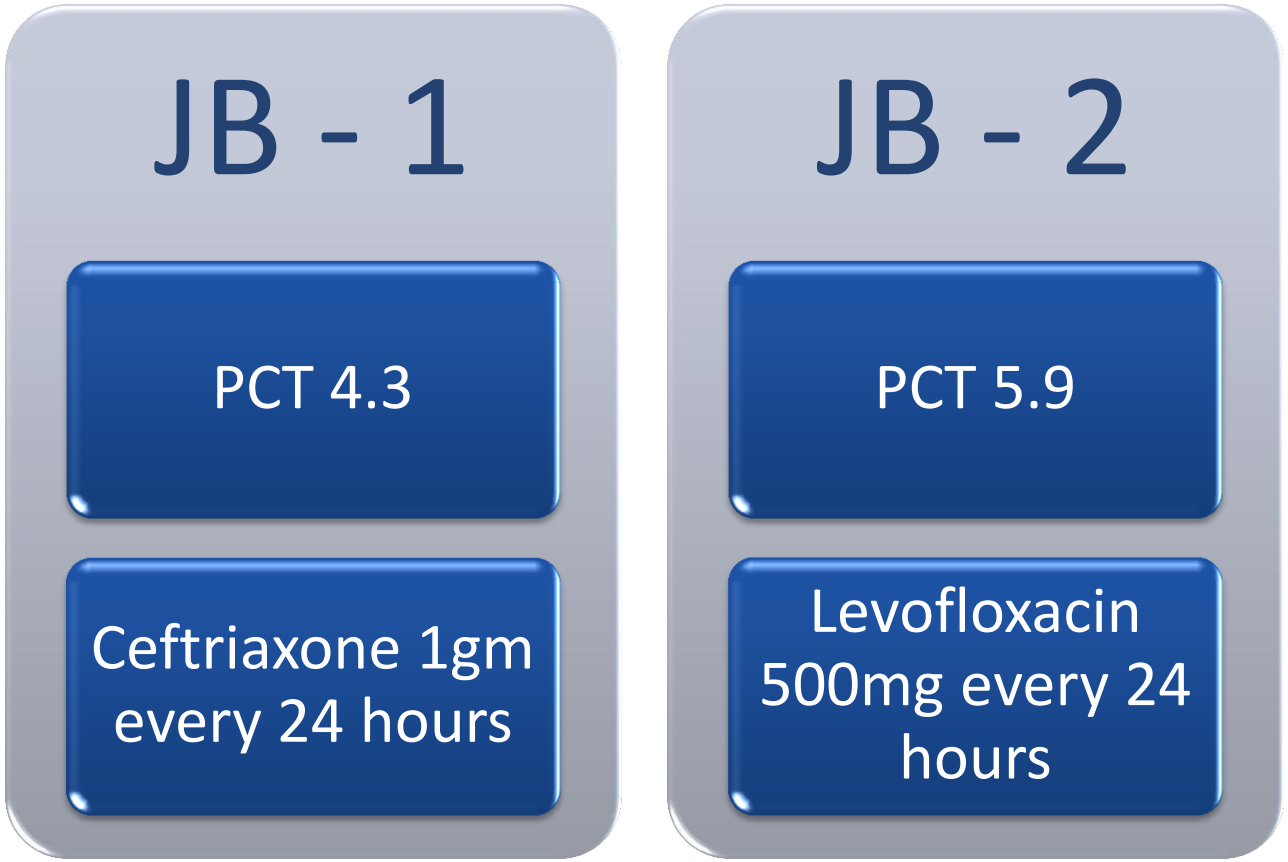
Lactate 1.8 mmol/L

SrCr 1.8 mg/dl w/ BUN 34

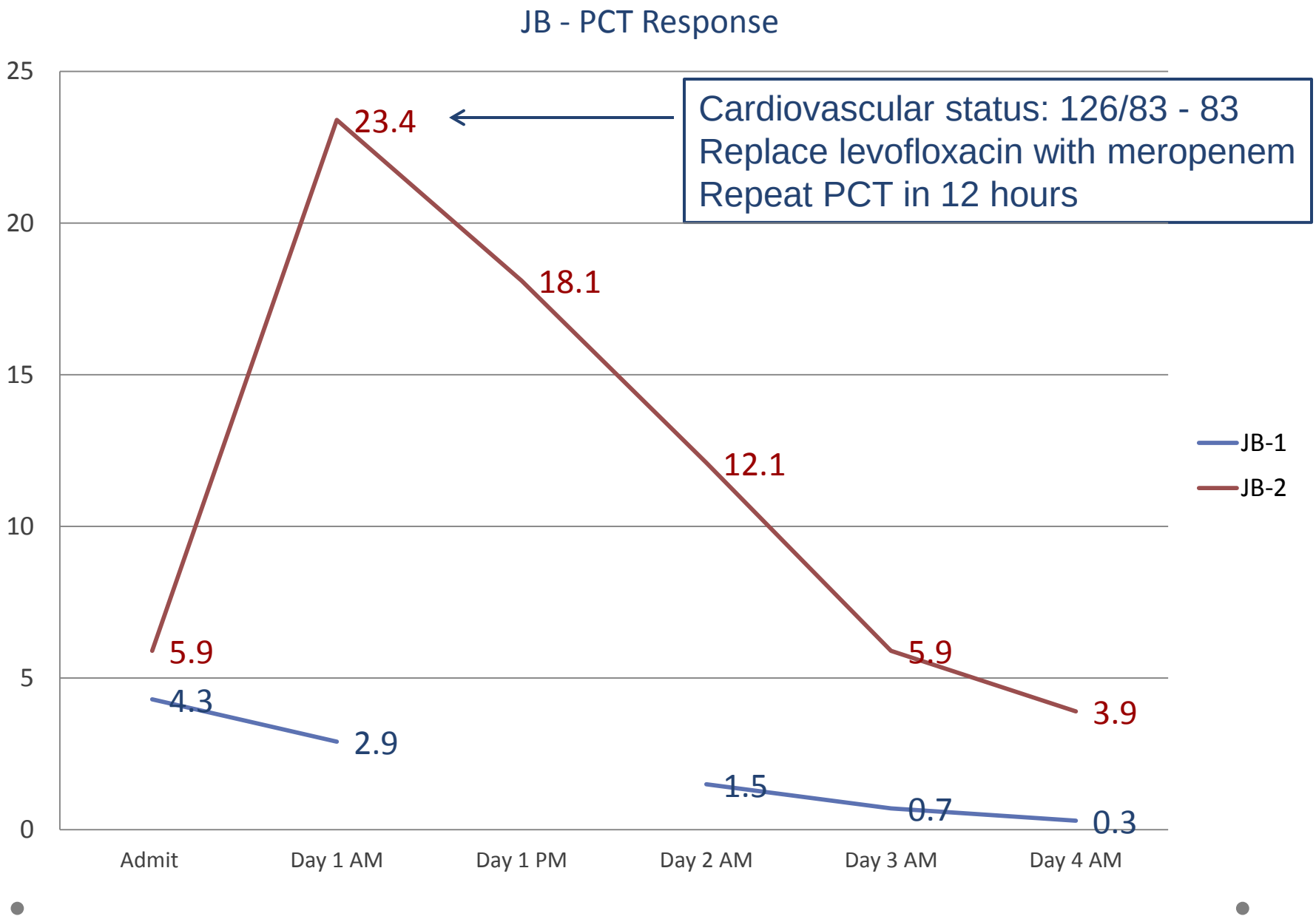
Mini-cath UA

- Nitrite positive
- Leukocyte esterase positive
- 4+ bacteria

JB


JB - 1
PCT 4.3
Ceftriaxone 1gm every 24 hours
JB - 2
PCT 5.9
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
3.9
5.9
4.3
2.9
1.5
0.7
0.3
JB-1
JB-2

TB

CC/Hx

- 80 Y/O female
- CC: dyspnea
- Cough now productive
- Chills
- Rhinorrhea
- Hoarse
- No choking
- No LOC
- No prior Hx of pneumonia, asthma, or lung disease
- Hypertension

Presentation/Lab

- Respiratory distress
- Right side decreased breath sounds
- Inspiratory crackles
- JVD
- Chest film: right middle and lower lobe pneumonia
- BP 114/52
- RR 24
- Temp 97.1
- Pulse 112
- Pulse Ox 92% on 2L NC
- PCT 0.75
- WBC 28.2
- Flu negative

TB

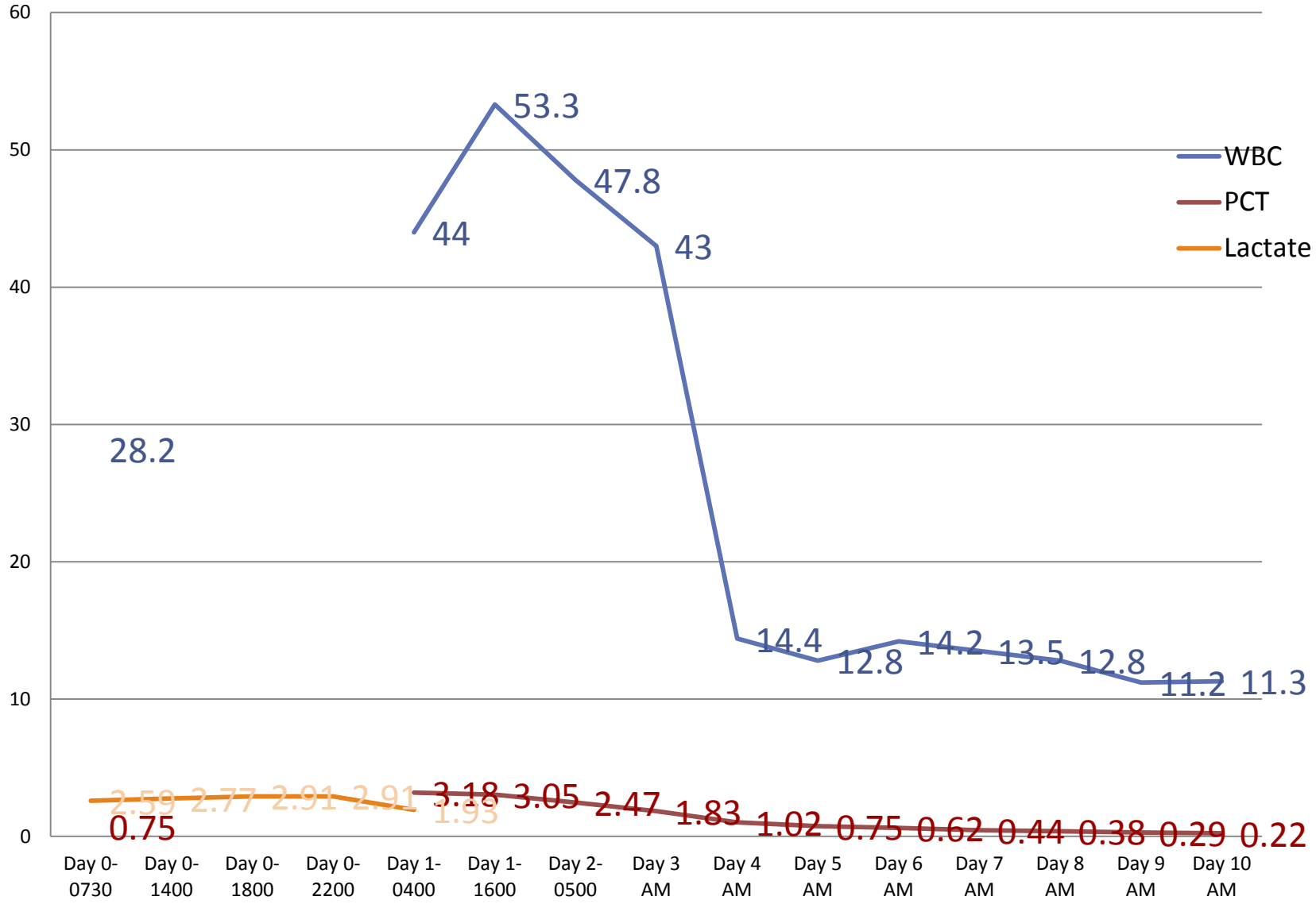
Medications

- Metoprolol 25mg bid
- Hydrochlorothiazide 25mg daily
- Amlodipine 10mg daily
- Omeprazole 20mg daily

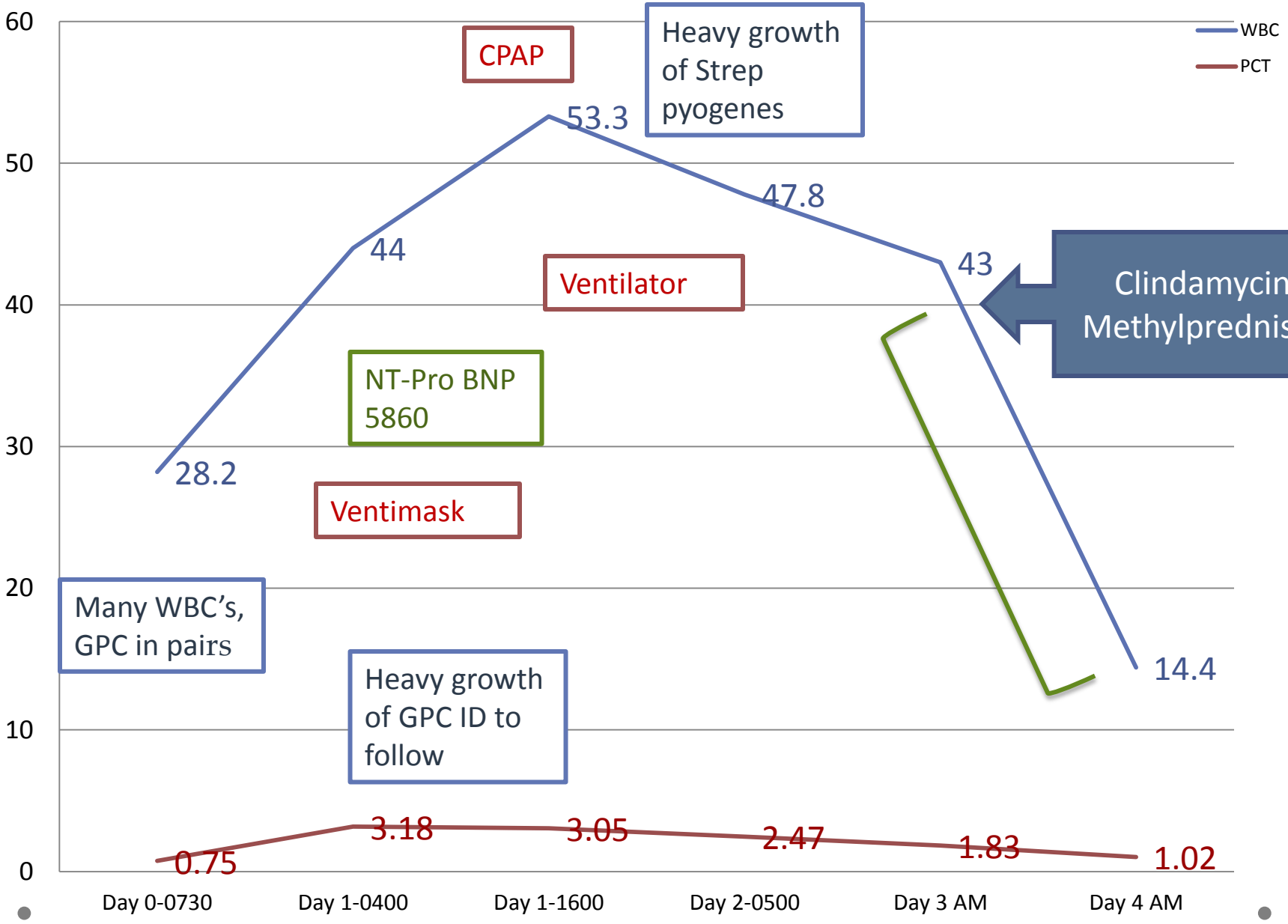
Assessment/Plan

- Community Acquired pneumonia
- Right middle and lower lobe
- Pulmonary edema
- Antibiotics
- Consider diuresis

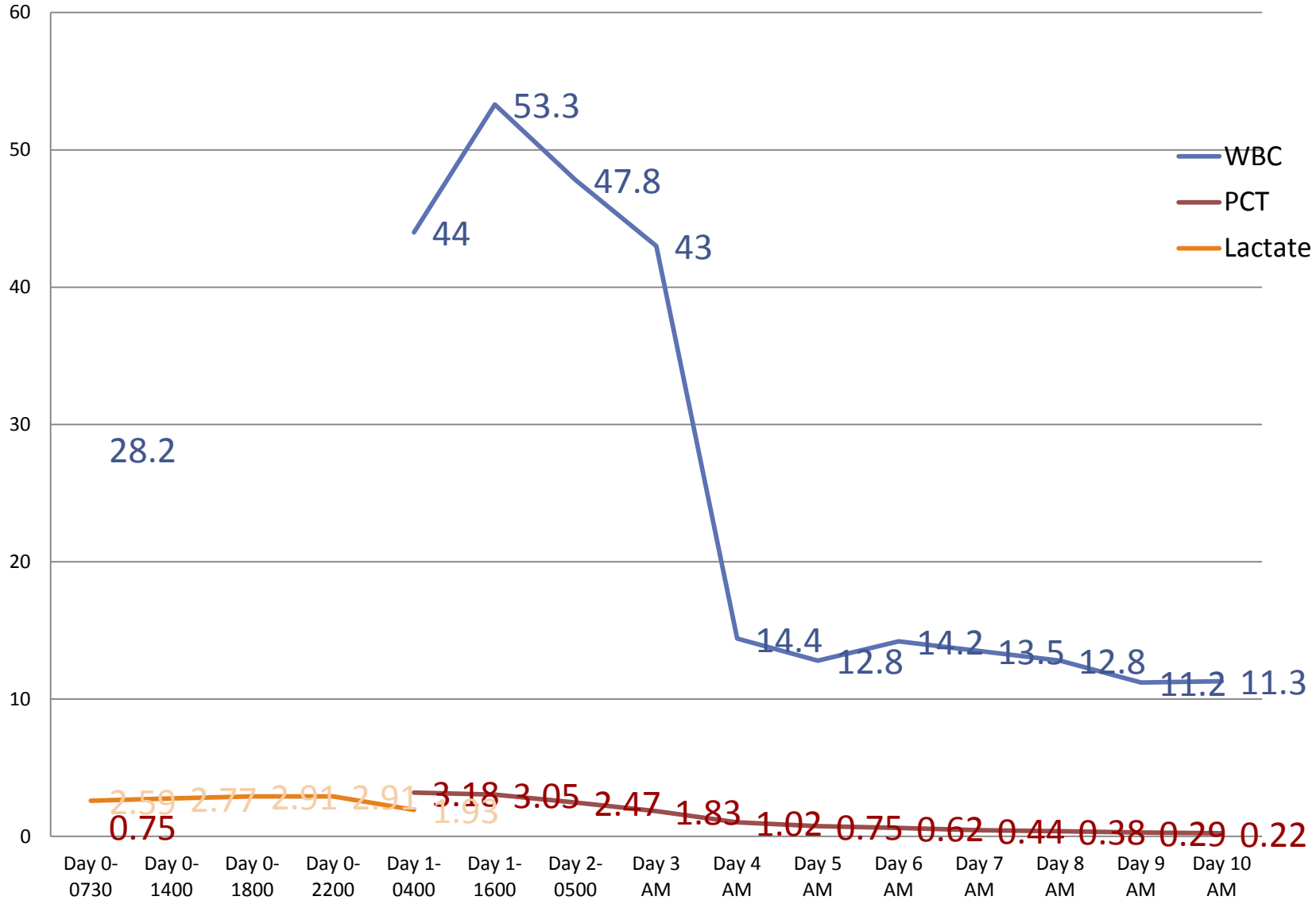
TB


60
50
40
30
20
10
0
WBC
PCT
Lactate
28.2
44
53.3
47.8
43
14.4
12.8
14.2
13.5
12.8
11.2
11.3
2.59
2.77
2.91
2.91
1.93
0.75
3.18
3.05
2.47
1.83
1.02
0.75
0.62
0.44
0.38
0.29
0.22
Day 0-0730
Day 0-1400
Day 0-1800
Day 0-2200
Day 1-0400
Day 1-1600
Day 2-0500
Day 3 AM
Day 4 AM
Day 5 AM
Day 6 AM
Day 7 AM
Day 8 AM
Day 9 AM
Day 10 AM

TB Lab


60
50
40
30
20
10
0
WBC
PCT
CPAP
Heavy growth of Strep pyogenes
53.3
47.8
44
43
Ventilator
Clindamycin + Methylprednisone
NT-Pro BNP 5860
28.2
Ventimask
Many WBC's, GPC in pairs
Heavy growth of GPC ID to follow
14.4
3.18
3.05
2.47
1.83
1.02
0.75
Day 0-0730
Day 1-0400
Day 1-1600
Day 2-0500
Day 3 AM
Day 4 AM

TB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Lactate
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2.91
2.91
1.93
0.75
3.18
3.05
2.47
1.83
1.02
0.75
0.62
0.44
0.38
0.29
0.22
Day 0-0730
Day 0-1400
Day 0-1800
Day 0-2200
Day 1-0400
Day 1-1600
Day 2-0500
Day 3 AM
Day 4 AM
Day 5 AM
Day 6 AM
Day 7 AM
Day 8 AM
Day 9 AM
Day 10 AM

TB Clinical Perles

- Expected 3 day LOS from CAP > 7 days ICU > 5 on ventilator > DC home after 59 days
- Uncommon lung pathogen
- Tremendous inflammatory response > WBC vs. PCT which indicated bacterial burden
- Allowed decisions for ABX and corticosteroids
- Required information from all disciplines for best management
- Micro, biomarkers, and radiology were all important

MB

CC/Hx

82 Y/O female

Geri-Psych Ward

Referred Hospital after Tx for UTI for mental status changes

Agitation

Delusional

Confused

CVA

Diabetes Mellitus Type 2

Allergies

- Penicillins
- Quinolones
- Neomycin
- Propoxyphene
- Codeine

Presentation

Unable to give clear history – unsure patient is not symptomatic

Alert

Will not initially answer questions

Combative

Yelling

Delusional

UA on admission

Cognitive Disorder NOS

R/O Vascular Origin

MB Lab & UA

Test	Value #1 Day 01	Value #2 Day 05
PCT	< 0.05	< 0.05
WBC	11.3	10.1
BASP	1	1.1
LYMP	17.7	18.3
MONP	7.7	8.7
NUTP	70	67.4

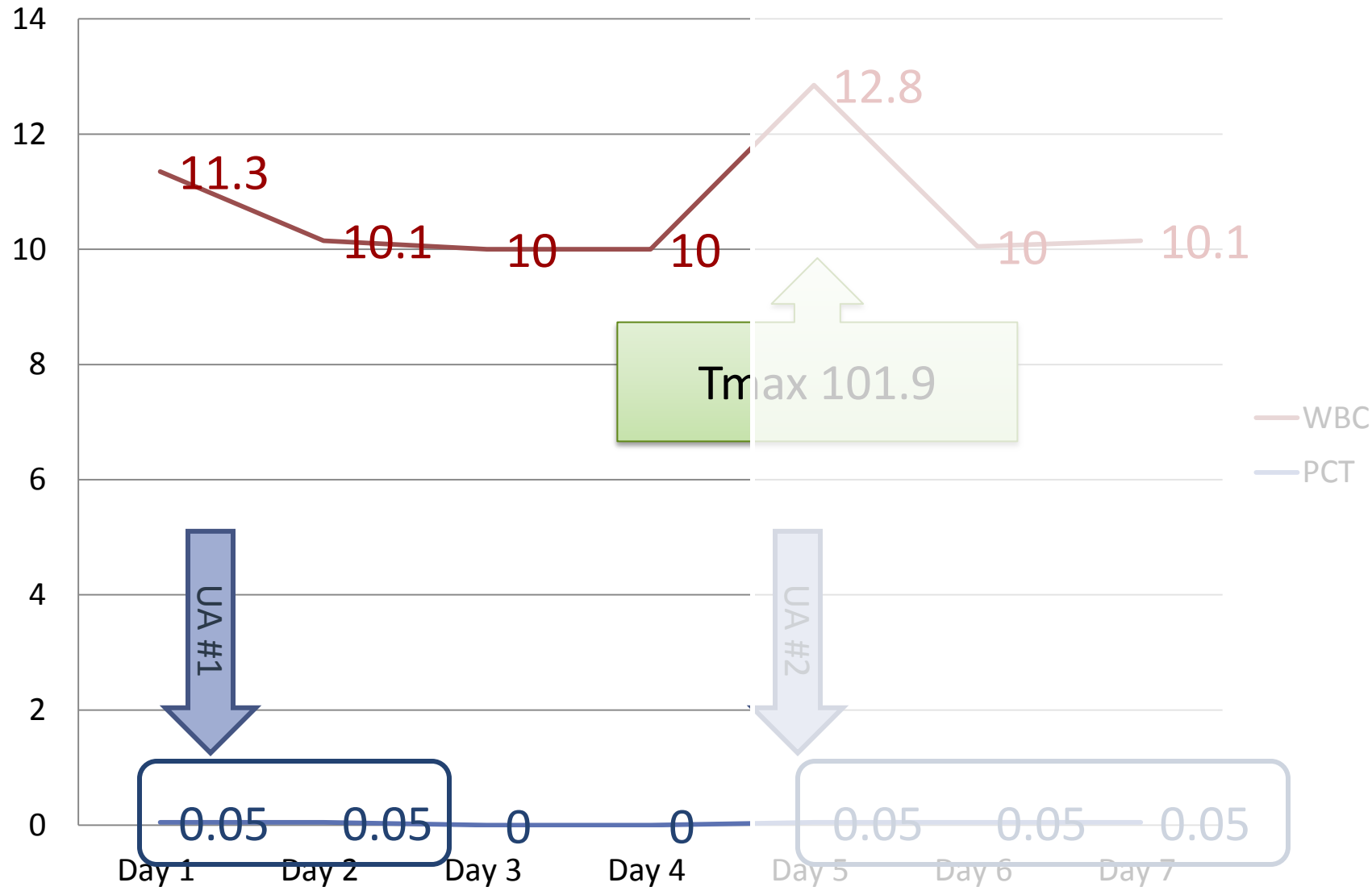
Test	Result #1 Day 01	Result #2 Day 05
Color	Yelow	Yelow
Clarity	Cloudy	Cloudy
pH	5	5
Occbld	2+	2+
Nitrite	Neg	Neg
Leuk	3+	3+
Rbcua	4-6	4-6
Wbcua	0-5	0-5
Squepi	0-6	0-6
Bacteria	2+	2+
Mucus	Neg	Neg

Urine Culture(s) MB

Specimen Source: Urine c/c	
Organism #01: Enterobacter cloacae > 100,000 col/ml	
cefazolin	R
cefoxitin	R
ceftazidime	R
ceftriaxone	R
cefepime	R
meropenem	R
amikacin	S
tobramycin	R
ciprofloxacin	R
levofloxacin	R
TMP/SMZ	R
Piperacillin/Tazo	R

Specimen Source: Urine c/c	
Organism #02: Enterobacter cloacae > 100,000 col/ml	
cefazolin	R
cefoxitin	R
ceftazidime	R
ceftriaxone	R
cefepime	R
meropenem	R
amikacin	S
tobramycin	R
ciprofloxacin	R
levofloxacin	R
TMP/SMZ	R
Piperacillin/Tazo	R

MB - WBC & PCT


14
12
10
8
6
4
2
0
11.3
10.1
10
10
12.8
10
10.1
Tmax 101.9
WBC
PCT
UA #1
UA #2
0.05
0.05
0
0
0.05
0.05
0.05
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7

MB Lab & UA

Test	Value #2 Day 05	Value #1 Day 01
PCT	< 0.05	< 0.05
WBC	10.1	11.3
BASP	1.1	1
LYMP	18.3	17.7
MONP	8.7	7.7
NUTP	67.4	70

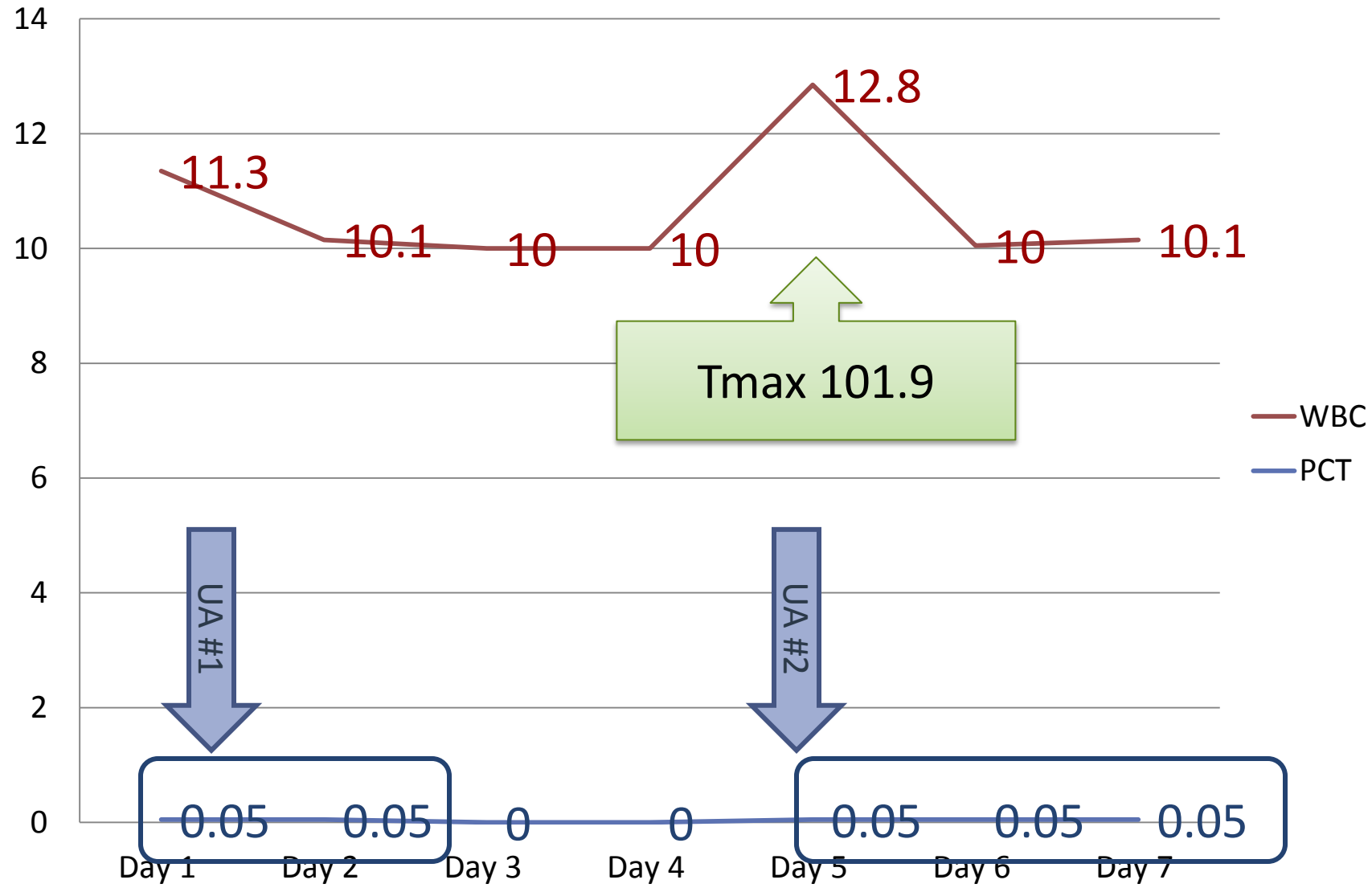
Test	Result #2 Day 05	Result #1 Day 01
Color	Yelow	Yelow
Clarity	Cloudy	Cloudy
pH	5	5
Occbld	2+	2+
Nitrite	Neg	Neg
Leuk	3+	3+
Rbcua	4-6	4-6
Wbcua	0-5	0-5
Squepi	0-6	0-6
Bacteria	2+	2+
Mucus	Neg	Neg

Urine Culture(s) MB

Specimen Source: Urine c/c	
Organism #01: Enterobacter cloacae > 100,000 col/ml	
cefazolin	R
cefoxitin	R
ceftazidime	R
ceftriaxone	R
cefepime	R
meropenem	R
amikacin	S
tobramycin	R
ciprofloxacin	R
levofloxacin	R
TMP/SMZ	R
Piperacillin/Tazo	R

Specimen Source: Urine c/c	
Organism #02: Enterobacter cloacae > 100,000 col/ml	
cefazolin	R
cefoxitin	R
ceftazidime	R
ceftriaxone	R
cefepime	R
meropenem	R
amikacin	S
tobramycin	R
ciprofloxacin	R
levofloxacin	R
TMP/SMZ	R
Piperacillin/Tazo	R

MB - WBC & PCT


14
12
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11.3
10.1
10
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12.8
10
10.1
Tmax 101.9
UA #1
UA #2
0.05
0.05
0
0
0.05
0.05
0.05
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
WBC
PCT

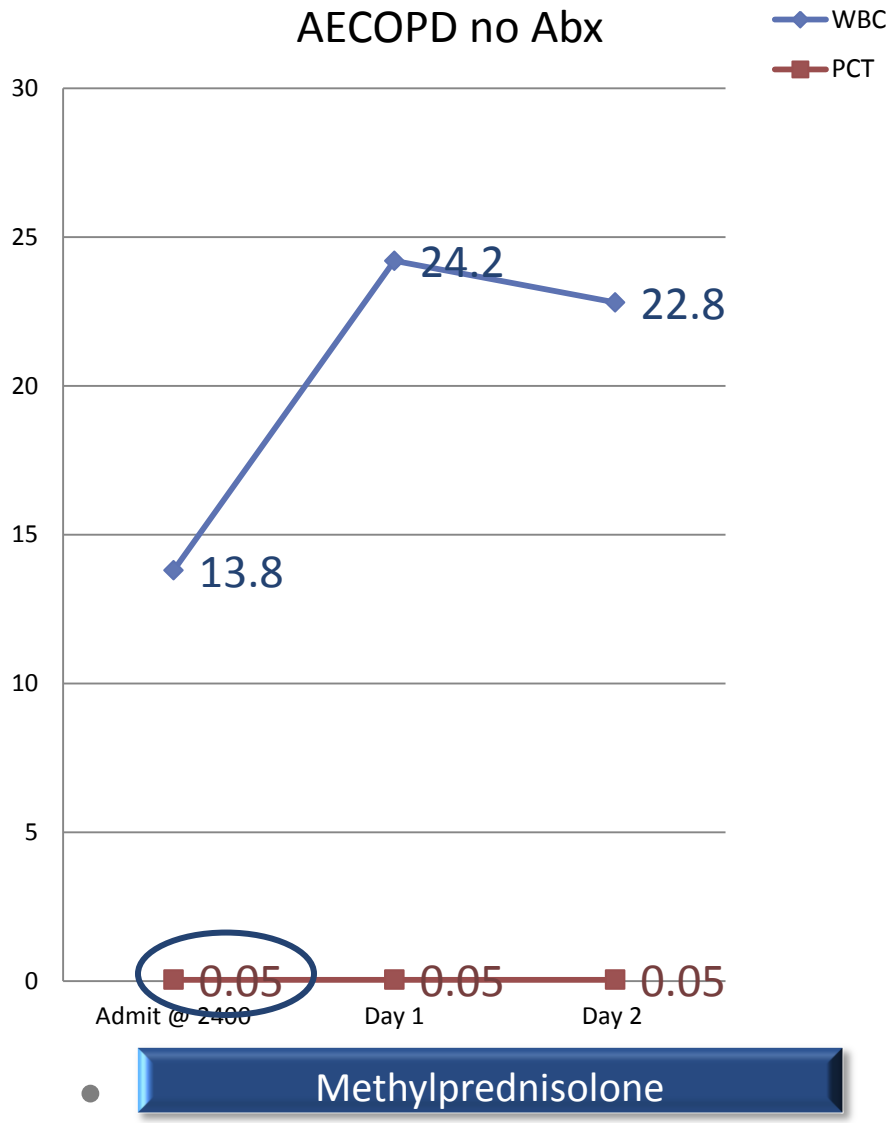
MB Clinical Perles

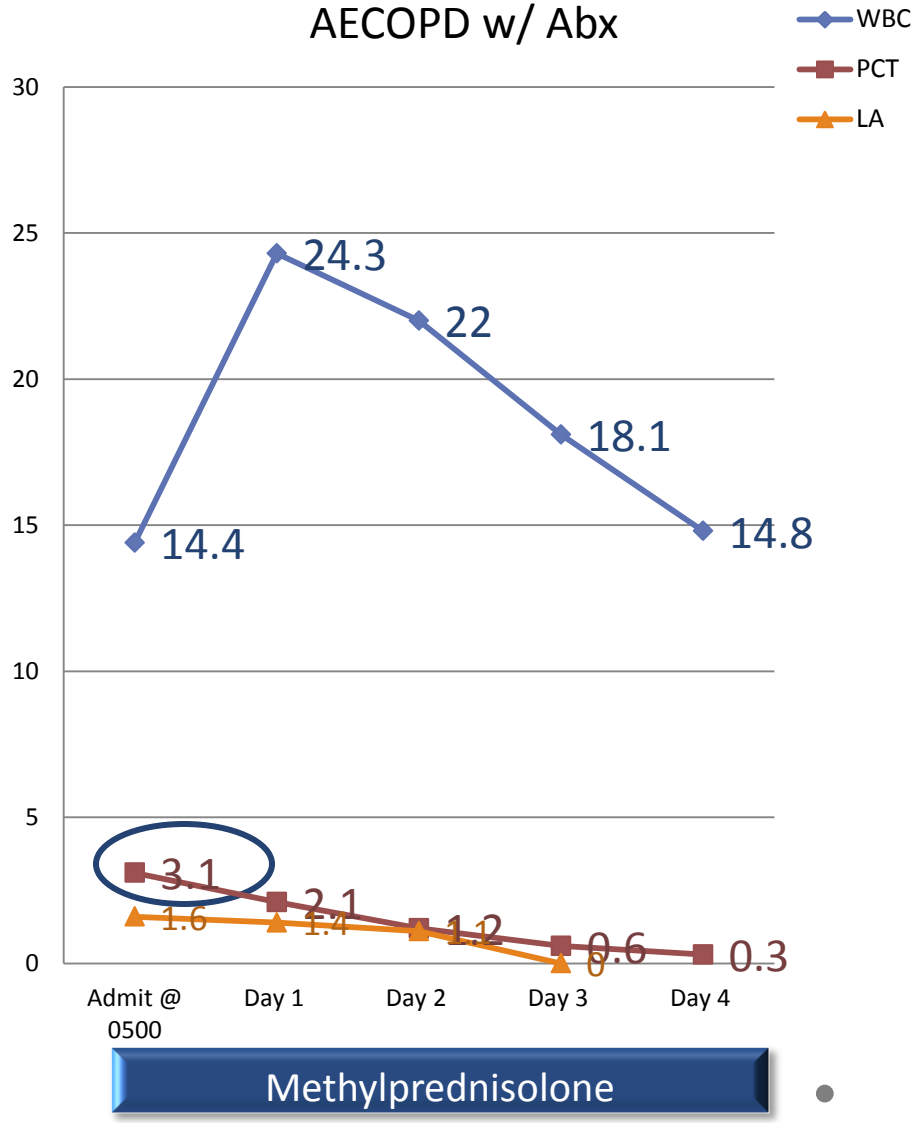
- Guidelines for treatment of UTI
  - Not required to treat
    - > 100,000 col/ml unless symptomatic
    - MDRO's
- Treat if symptomatic
- Treat if UA indicates and patient cannot communicate if symptomatic
- PCT is indicative of bacterial effects on the body at that time
- Baseline and serial measurement(s)
- PCT is very helpful to prevent ABX use (*)

JM Antibiotic Exposure with AECOPD Presentations

2008-2009 PRE PROCALCITONIN 15 PRESENTATIONS		2012-2013 POST PROCALCITONIN 24 PRESENTATIONS	
ED DC to Home	*IP Admissions*	*ED DC to home*	*IP Admissions*
7	8	9	15
Antibiotics Prescribed		*Antibiotics Prescribed*	
100%	100%	56%	87%
Average Abx Duration		*Average Abx Duration*	
10 Days	10 Days	7 Days	5.5 Days
Antibiotic Exposure		*Antibiotic Exposure*	
70 Days	153 Days	50 Days/61%	89 Days/41%

JM: Comparison of two same patient: Two admissions with diagnosis of AECOPD





Early Cessation of Therapy

- PCT reduction of 80 to 90%
- Absolute PCT value of 0.5 to 0.25ng/ml
- Immunocompetent
- Excluding
  - Skin and skin structure infections
  - Endocarditis
  - Osteomyelitis

Michael Meisner; Procalcitonin-Biochemistry and Clinical Diagnosis
www.nebraskamed.com/.../asp/procalcitonin-pct-guidance

Real World Data

- The following real world data was presented at November 10, 2016 for the FDA

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm515517.htm

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

Pre/Post Data Extraction Comparison

Variable	Pre PCT Group N= 985	Post PCT Group N=1167	p-value
Mean Age (years)	70	70	0.2505
% Male	42.4%	43.6%	0.6149
Diagnosis Sepsis/RTI	No difference in case mix index	No difference in case mix index	0.9124
Antimicrobial days of therapy per patient	16.43	9.52	0.00018

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
Study Outcomes

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 *Clostridium difficile* Infections	**50%** Reduction in Adverse Drug Events
Days of Therapy per 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%	Clostridium 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**

Procalcitonin Use: Keys to Success

- Education – Education - Education
- Ultimate program ownership
- Order sets
- Ensure PCT is ordered
- Follow all PCT resulting
- Communication among clinicians
- Tracking results

Questions

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