Why Do We Persist in Using Outdated Biomarkers for Infection: Procalcitonin Guided Stewardship the New Paradigm

Mike Broyles, BSPharm, PD, PharmD
Director of Pharmacy and Laboratory Services
Five Rivers Medical Center, AR

Disclosures

- Consulting / Advisory Boards / Lecture
  - Thermo Fisher Scientific
  - Roche Diagnostics
  - bioMerieux
  - Fujirebio
  - Abbott
- Information presented is based on my interpretation of the evidence and clinical experience – all original contrent

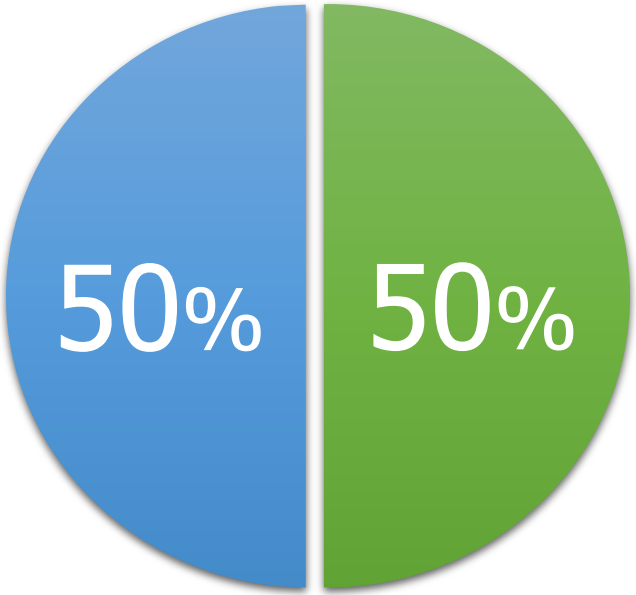
Objectives

- Understand the pathophysiology and kinetics of Procalcitonin
- Review current biomarkers used in the management of bacterial infection
- Describe how Procalcitonin can aid in severity assessment and evaluation of therapy choices
- Understand the role of Procalcitonin in Antibiotic Stewardship
- Appreciate the expected clinical and health economic outcomes of PCT guided therapy

Antimicrobial Use and "Misuse"

Acute Care Setting

Appropriate Use

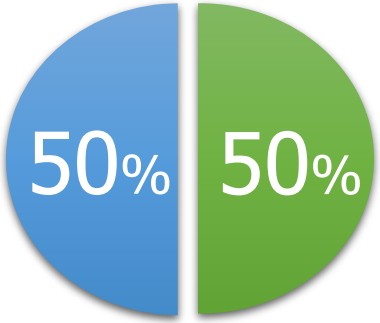


Inappropriate Use

How did we get this way?

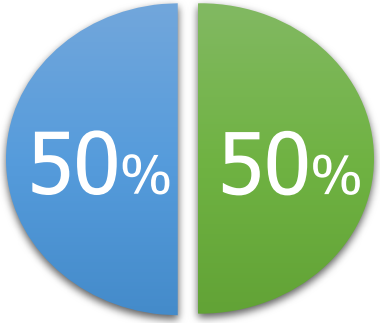
Fridkin S, et al. Morbidity and Mortality Weekly Report. United States Center for Disease Control and Prevention. 2014;63(09):194-200.

How did we get this way?



- Required broad spectrum antibiotic use in sepsis…
- Under appreciation of the effects of antibiotics; assumes no consequences of their use
- Lack of biomarker with high sensitivity and specificity for bacteria alone

Let's save antibiotics so we can use them in the future



- Antibiotics are the "Clinicians anxiolytic of choice. When in doubt give an antibiotic, **just to be sure**". It is time to base antibiotic decisions on objective testing and stop giving them to sooth our conscience.

Mike Broyles, PharmD

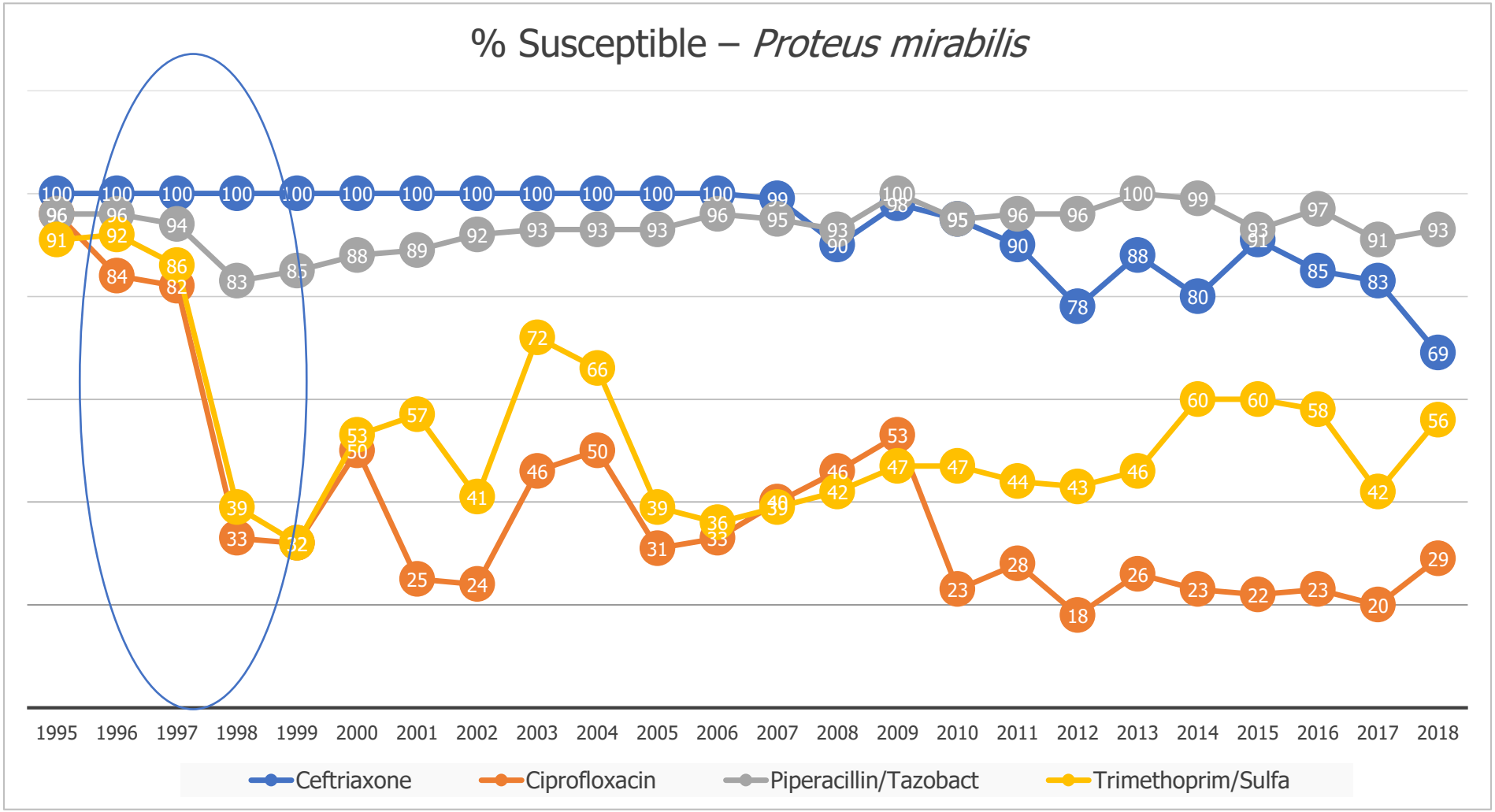
Signs and symptoms of bacterial, viral infection, and even non-infectious diagnoses overlap

Diagnostic methods for septicemia or bacterial infections are inaccurate and present with the similar symptoms: I.E. COPD, Pneumonia, Heart Failure, + possible Coinfection

- Body temperature
- Heart rate
- Respiratory rate
- Leukocyte count are often inadequate to discriminate between bacterial and nonbacterial infections[1,2]
- Chest films
- Elevated PCT level can differentiate parasitic, viral, and localized bacterial infections, as well as septicemia[3]

- With viral, fungal, and parasitic infections PCT remains normal[3]

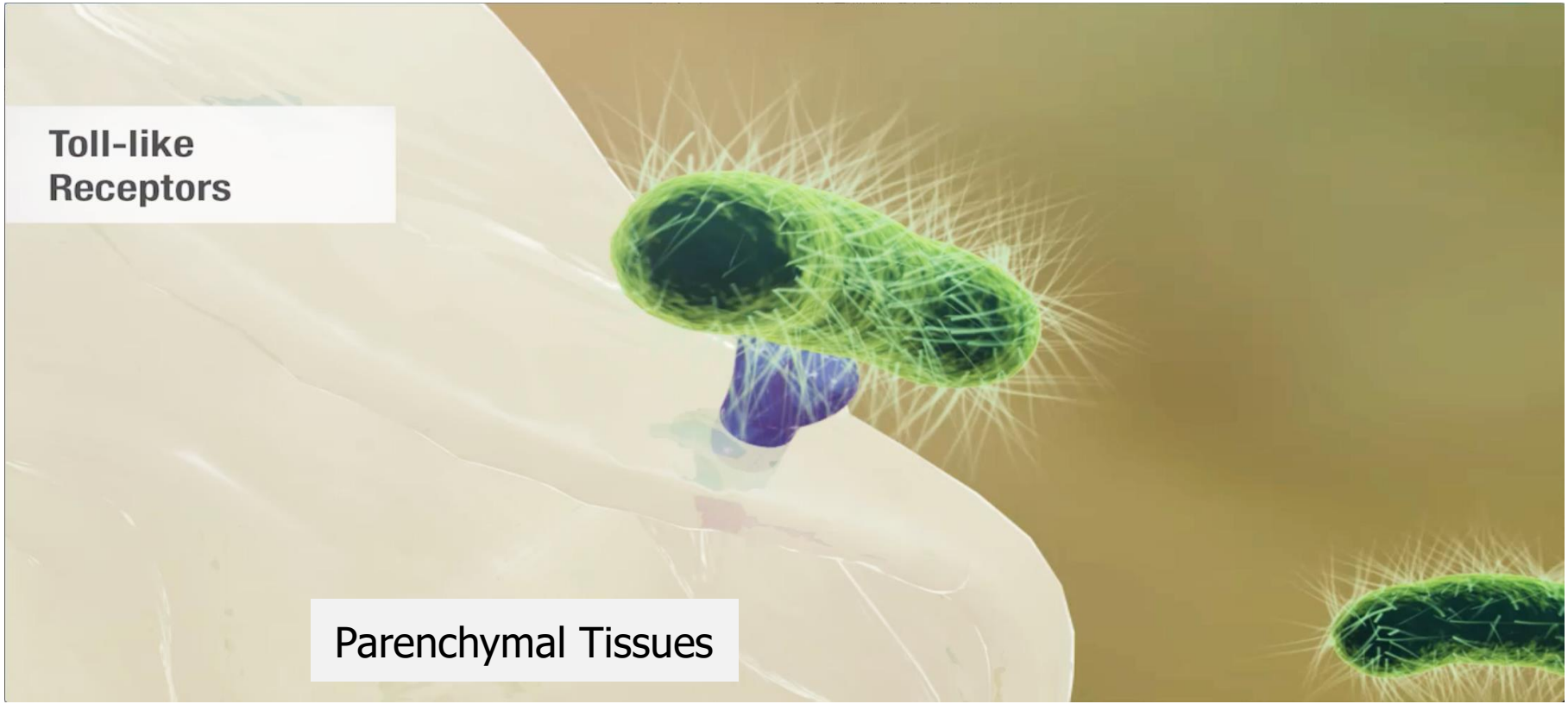
1. Afsar I, et al. *Infect Dis Clin Pract.* 2015;23(1):3-6. 2. Jin M, et al. *Lab Med.* 2010;41(3):173-177. 3. Kelton D, et al. *Nursing Made Incredibly Easy.* 2014;12(1):1-2.


% Susceptible – *Proteus mirabilis*
1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018
Ceftriaxone
Ciprofloxacin
Piperacillin/Tazobact
Trimethoprim/Sulfa

Co

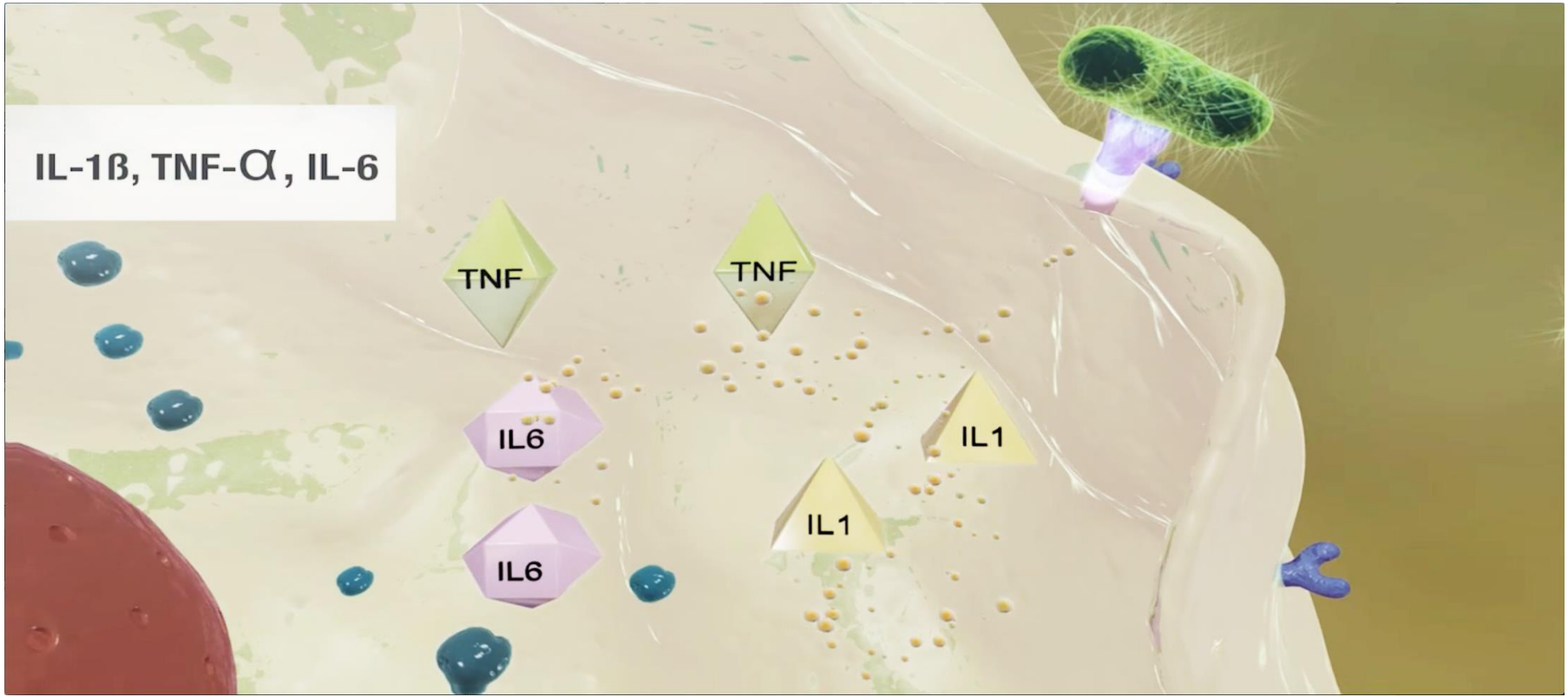
- Shock
  - Distributive
  - Cardiogenic
  - Hypovolemic
  - Obstructive
- Regional Ischemia
  - Mesenteric ischemia
  - Limb ischemia
  - Burns
  - Trauma
  - Compartment Syndrome
  - Necrotizing soft-tissue infections
- Toxins
  - Alcohols
  - Cocaine
  - Carbon monoxide
  - Cyanide
- Heart failure
- Anaerobic muscle activity
  - Seizures
  - Heavy exercise
  - Excessive work of breathing
- Cardiac Arrest
- Diabetic ketoacidosis
- Thiamine deficiency
- Malignancy
- Liver failure
- Mitochondrial disease
- Drugs
  - Linezolid
  - NNRTI's
  - Metformin
  - Epinephrine
  - Propofol
  - Acetaminophen
  - Beta2-agonists

Toll-Like Receptor and Microbial Toxins



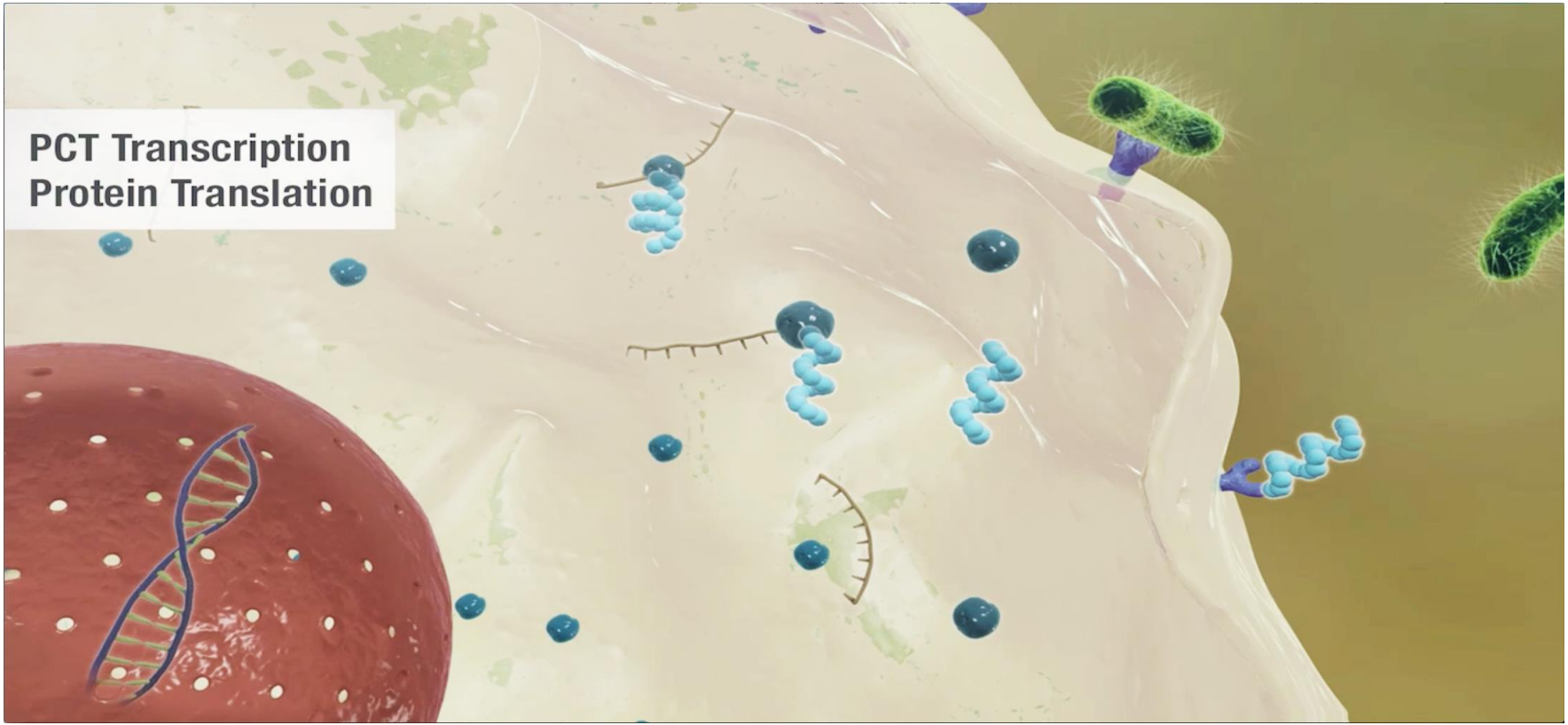
Ryu YH, et al. *Int Immunopharmacol*. (2009) 9:127–133

The key: the toll like receptor



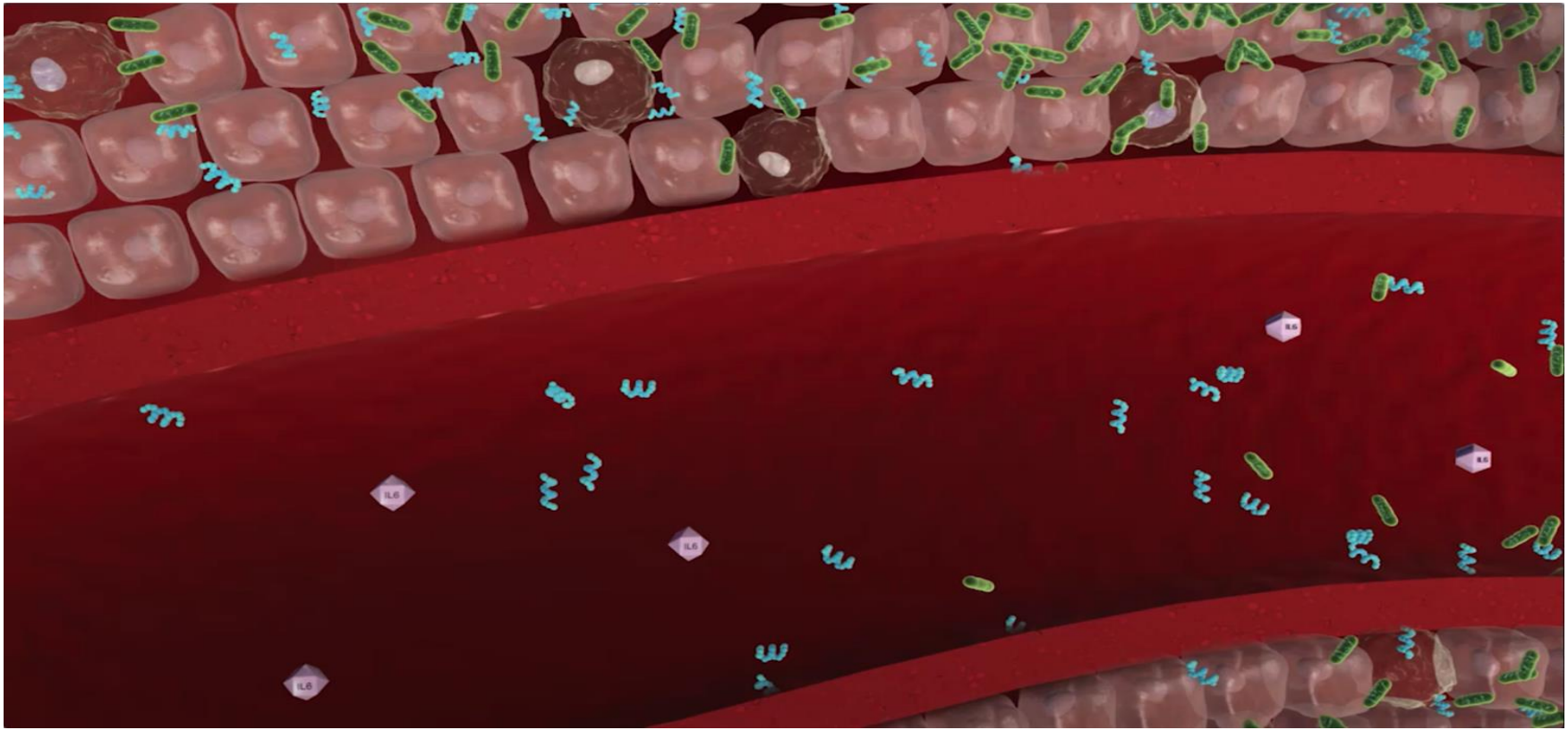
Linscheid P, et al.,*Endocrinology* (2003) 144:5578–5584.

PCT secretion after PCT transcription



Linscheid P, et al.,*Endocrinology* (2003) 144:5578–5584.

PCT release and severity of infection



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

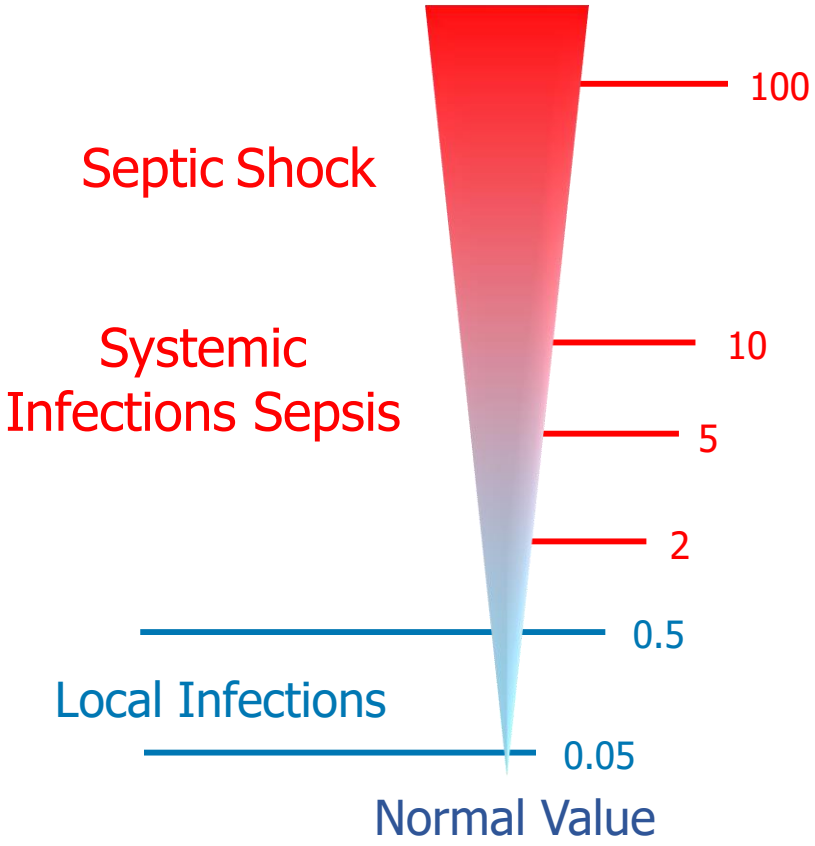
What differentiates B·R·A·H·M·S PCT from the other 175+ biomarkers?

- Sensitivity 89%/Specificity 94%
- Evaluate bacterial burden
- Not affected by corticosteroids
- Can use with disease modifying drugs
- Use with other drugs affecting inflammatory mediators
- Not affected by most autoimmune diseases
- Not affected by decreasing immune function/oncology therapy

Elevations in PCT not requiring ABX

- 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
- Peritoneal and hemodialysis use 0.5ng/ml as normal cutoff instead of 0.05ng/ml > then serial trending

PCT Interpretation

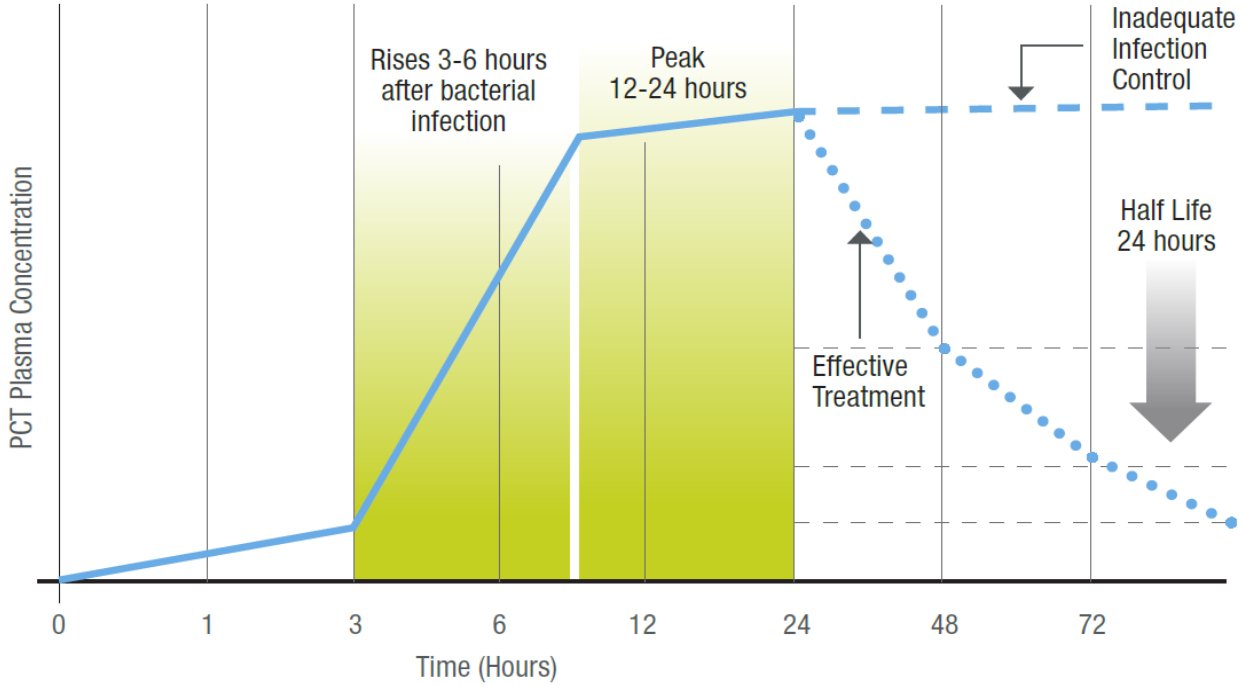


PCT concentrations and sepsis risk

- 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.

Understanding PCT Kinetics

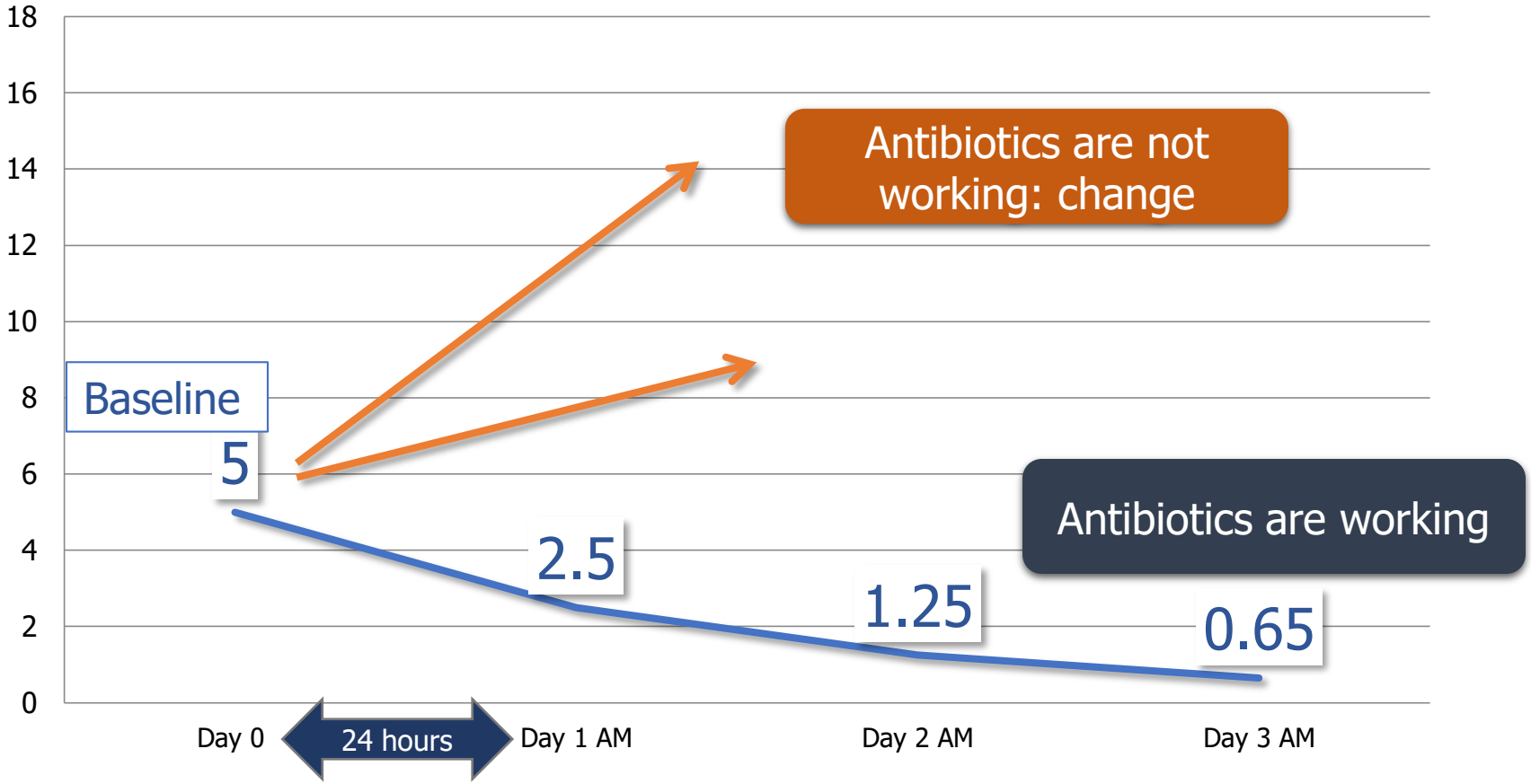


- Rises 3-6 hours after bacterial infection
- Peak occurs 12-24 hours
- Half life of PCT is 24 hours
- Can take 24 hours of appropriate antibiotic therapy to see reduction in serum PCT
- PCT production and serum concentrations will decrease by up to 50% per day with appropriate antibiotic treatment
- If antibiotic therapy is inadequate, PCT levels will remain high

B·R·A·H·M·S PCT is a sensitive and specific biomarker of the inflammatory response to bacterial infection.

Brunkhorst FM et al: Kinetics of Procalcitonin in Iatrogenic Sepsis. Intensive Care Med 1998;24(8):888-889.

Understanding PCT Kinetics



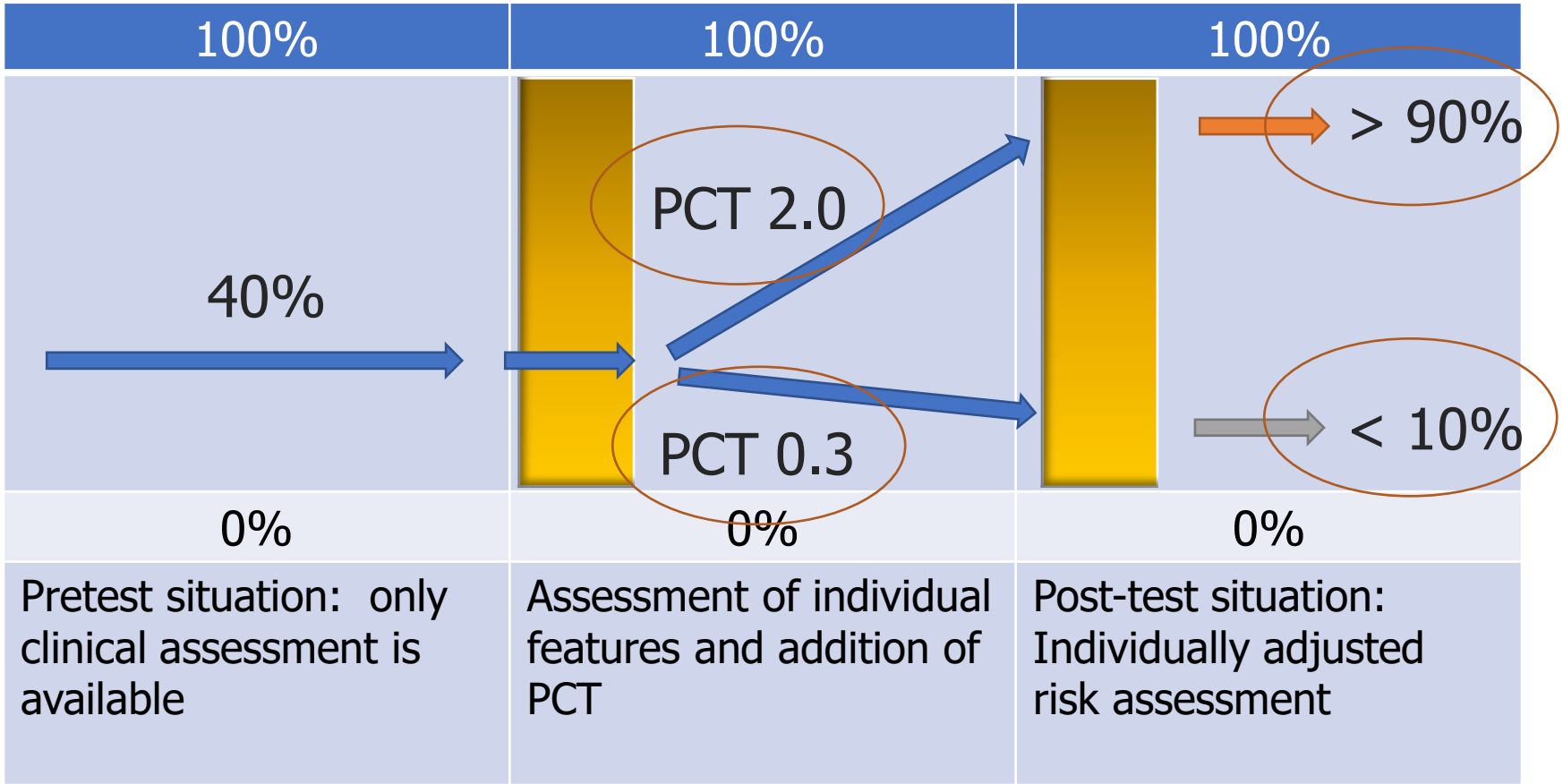
Stewardship opportunities

- Sepsis
- LRTI

Sepsis = Two SIRS Criteria in presence of Infection

- Temperature > 100.4F (38C) or < 96.8F (36C)
- Heart rate > 90 beats/minute
- Respiratory rate > 20 breaths/minute or $PaCO_2$ < 32 mm Hg
- WBC
  - > 12,000/mm^3
  - < 4000/mm^3
  - > 10% immature (band) forms

Probability of a Sepsis Diagnosis: No PCT/PCT



Meisner M, Procalcitonin-Biochemistry and Clinical Diagnosis, UniMed 2010

Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines

International Symposium on Intensive Care and Emergency Medicine

March 22, 2018

Michael Klompas MD, MPH, FIDSA, FSHEA

Professor, Harvard Medical School

Hospital Epidemiologist, Brigham and Women's Hospital

Clinical Infectious Diseases

VIEWPOINTS

Infectious Diseases Society of America (IDSA) POSITION STATEMENT: Why IDSA Did Not Endorse the Surviving Sepsis Campaign Guidelines

IDSA Sepsis Task Force*

IDSA did not endorse the 2016 Surviving Sepsis Campaign Guidelines despite being represented in the working group that drafted the guidelines document. Leadership from the IDSA, the Surviving Sepsis Campaign Guidelines, and the Society of Critical Care Medicine had numerous amicable discussions primarily regarding the bolded, rated guidelines recommendations. Our societies had different perspectives, however, regarding the interpretation of the major studies that informed the guidelines' recommendations, thus leading us to different conclusions and different perspectives on the recommendations. IDSA consequently elected not to endorse the guidelines. IDSA nonetheless hopes to be able to continue collaborating with the Surviving Sepsis Campaign and the Society of Critical Care Medicine to resolve our differences and to develop further strategies together to prevent sepsis and septic shock as well as reduce death and disability from these conditions both nationally and globally.

Keywords. Surviving Sepsis; Guidelines; Endorsement; IDSA.

A Case

67 year old man with severe ischemic cardiomyopathy presents with several days of progressive dyspnea, lower extremity edema, malaise, cough, and subjective fevers.

Vitals: Temp 37.9°C, HR 145 (atrial fibrillation), BP 90/65 mmHg, Resp Rate 24, SaO2 88% room air

Exam: Jugular veins distended, (+) peripheral edema, scattered crackles.

Labs: WBC 12.5, Lactate 2.1, Creatinine 1.3 (baseline 1.0)

Chest x-ray: pulmonary edema, possible LLL infiltrate

Questions

- Would you give fluids?
- Would you give antibiotics?
- Would you start pressors?

Clinical Course

Emergency Department:

- Given 1 L NS bolus, levofloxacin, and 5 mg diltiazem IV
- **BP ↓ 80/60**. Extremities cool. **Repeat lactate ↑ 4.1**
- Worsening hypoxemia and altered mental status → **intubated**
- Central line placed, started on **norepinephrine and dobutamine**
- Initial CVP 16 cm H20 and ScVO2 48%

ICU Course:

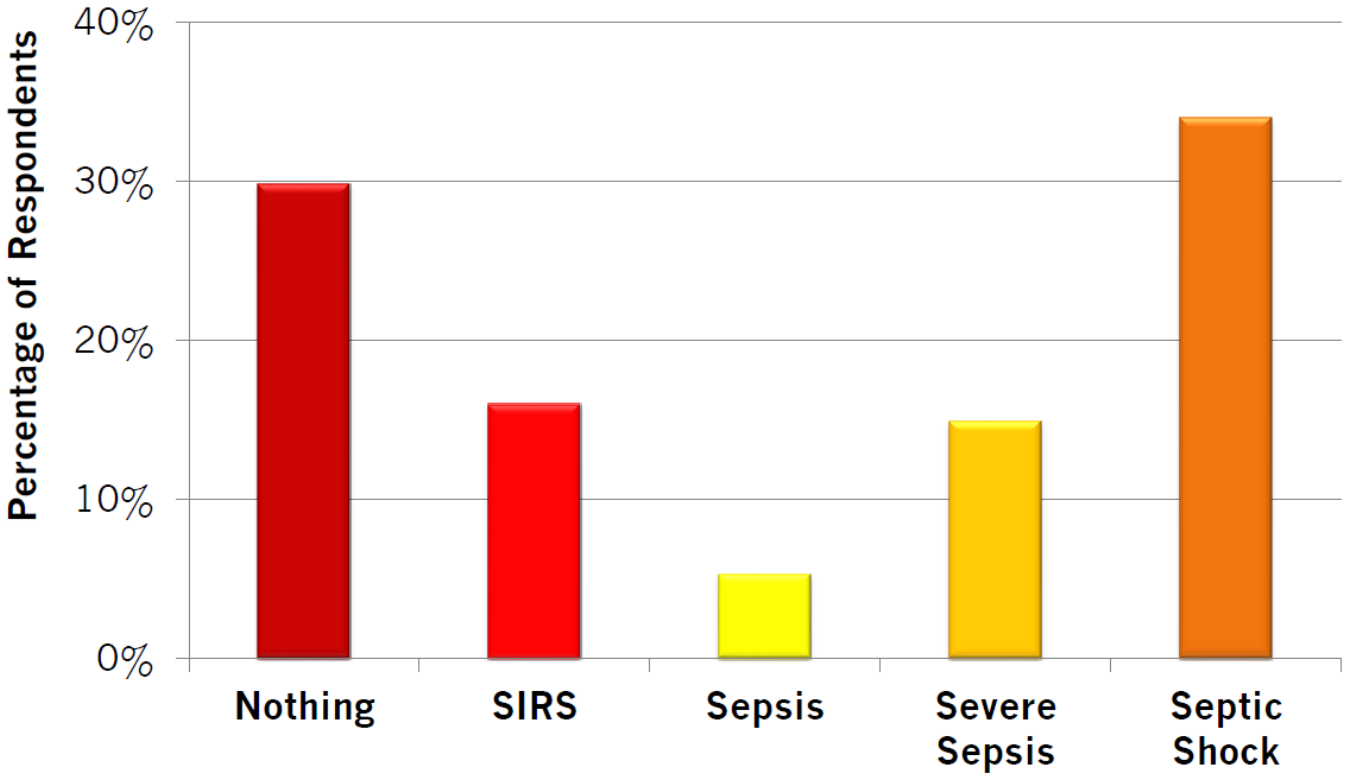
- Continued on pressors, amiodarone and furosemide drips
- Antibiotics broadened to **vancomycin, cefepime, levofloxacin**
- Sputum cultures → mixed respiratory flora;
- Blood cultures → no growth
- Gradually improved, extubated on ICU day 3, weaned off vasoactive agents on ICU day 4
- Completed 7 days of antibiotics, discharged hospital day 10

Questions

Does this patient have:

- SIRS
- Sepsis
- Severe Sepsis
- Septic Shock, *or*
- None of the above?

National Survey of 94 Intensivists



Rhee et al. *Critical Care* 2016;20:89.

Implications

Many patients at **risk of harm**
from antibiotics with no chance of benefit

Because of diagnostic challenges due to overlap of symptoms with etiologies such as AECOPD, pneumonia, and heart failure along with the differentiation between infectious and non-infectious causes of SIRS…. We need more objective information (1) if there is infection (2) if the infection is bacterial and (3) severity of bacterial infection

FDA Indications B·R·A·H·M·S PCT : February 2017

- To aid in decision making on antibiotic discontinuation for patients with *suspected or confirmed sepsis*
- To aid in decision making on antibiotic therapy for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) - defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

B-R-A-H-M-S PCT Guided Therapy*

Antibiotic Initiation for LRTI		
PCT value	Antibiotic Use Recommendation	Discussion
< 0.1 ng/ml	Strongly discouraged	Repeat in 6 to 24 hours if needed < 0.1 ng/ml consider non-bacterial source
0.10 - 0.25 ng/ml	Discouraged	
0.26 – 0.5 ng/ml	Encouraged	Consider repeating every 24 hours to evaluate the opportunity for early cessation
> 0.5 ng/ml	Strongly encouraged	

Antibiotic Discontinuation for Sepsis and LRTI		
PCT Value	Antibiotic Use Recommendation	Discussion
LRTI ≤ 0.25 ng/ml or 80% drop	Cessation strongly encouraged with clinical improvement	Not recommended for endocarditis, osteomyelitis, skin & skin structure infections, and those on chemotherapy
Sepsis ≤ 0.5 ng/ml Or drop by > 80%		

Patient with mild illness outside ICU

(defind by setting specific scores, e.g qSOFA, MEDS, NEWS)

Initial clinical assessment (including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**	
PCT result (µg/L)	**< 0.25**	**≥0.25**	**< 0.25**	**≥0.25**
Probability of bacterial infection based on PCT level?	**Low probability**	**High probability**	**Low probability**	**High probability**
Overall interpretation	**Bacterial infection unlikely**	**Bacterial infection likely**	**Bacterial infection possible**	**Bacterial infection highly likely**
Antibiotic management	withhold Abx, consider other diagnostic tests to establish diagnosis	use Abx based on clinical judgement,	use empiric Abx based on clinical judgement, consider other diagnostic tests	use Abx based on clinical judgement,
Recommendations for follow- up of patients	consider 2nd PCT test within 6-24 hours before sending home	use PCT every 24-48h for monitoring and discontinuation of Abx if PCT <0.25 ug/L or drop by 80%	consider 2nd PCT test within 24 hours to stop Abx if PCT still <0.25 ug/L	use PCT every 24-48h for monitoring and discontinuation of Abx if PCT <0.25 ug/L or drop by 80%

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g., abscess, osteomyelitis, endocarditis)

Patient with moderate illness outside ICU

(defind by setting specific scores, e.g qSOFA, MEDS, NEWS)

Initial clinical assessment (including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**	
PCT result (µg/L)	**< 0.25**	**≥0.25**	**< 0.25**	**≥0.25**
Probability of bacterial infection based on PCT level?	**Low probability**	**High probability**	**Low probability**	**High probability**
Overall interpretation	**Bacterial infection unlikely**	**Bacterial infection likely**	**Bacterial infection possible**	**Bacterial infection highly likely**
Antibiotic management	use empiric Abx based on clinical judgement, consider other diagnostic tests	use Abx based on clinical judgement,	use empiric Abx based on clinical judgement, consider other diagnostic tests	use Abx based on clinical judgement,
Recommendations for follow- up of patients	Use repeated PCT test within 6-24 hours to early stop Abx to if PCT still <0.25 ug/L	use PCT every 24-48h for monitoring and discontinuation of Abx if PCT <0.25 ug/L or drop by 80%	consider 2nd PCT test within 24 hours to stop Abx if PCT still <0.25 ug/L	use PCT every 24-48h for monitoring and discontinuation of Abx if PCT <0.25 ug/L or drop by 80%

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g., abscess, osteomyelitis, endocarditis)

Patient with severe illness in ICU

(defind by setting specific scores, e.g qSOFA, SOFA, APACHE)

Initial clinical assessment (including microbiology)	**Bacterial infection uncertain**		**Bacterial infection highly suspected**	
PCT result (µg/L)	**< 0.5**	**≥0.5**	**< 0.5**	**≥0.5**
Probability of bacterial infection based on PCT level?	**Low probability**	**High probability**	**Low probability**	**High probability**
Overall interpretation	**Bacterial infection unlikely**	**Bacterial infection likely**	**Bacterial infection possible**	**Bacterial infection highly likely**
Antibiotic management	use empiric Abx based on clinical judgement, consider other diagnostic tests	use Abx based on clinical judgement,	use empiric Abx based on clinical judgement, consider other diagnostic tests	use Abx based on clinical judgement,
Recommendations for follow- up of patients	use PCT within 24-48h for monitoring and discontinuation of Abx if PCT still <0.5 ug/L	use PCT every 24-48h for monitoring and discontinuation of Abx if PCT <0.5 ug/L or drop by 80%	consider 2nd PCT test within 24 hours to stop Abx if PCT still <0.5 ug/L	use PCT every 24-48h for monitoring and discontinuation of Abx if PCT <0.5 ug/L or drop by 80%

* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g., abscess, osteomyelitis, endocarditis)

Pneumonia in the Postantibiotic Era

- Pinpointing the source of infection in community-acquired pneumonia (CAP) can be a daunting task that more often than not results in failure. Although *Streptococcus pneumoniae* are the most frequently isolated bacterial pathogens, they are no longer the most common cause of CAP. In fact, despite extensive testing, no pathogen is detected in 60% of patients with CAP.[1] Even when a pathogen is isolated, it's usually a rhinovirus, influenza virus, or human metapneumovirus. This shift to viral causes of pneumonia is probably due in part to the pneumococcal conjugate vaccination of children.

https://www.medscape.com/viewarticle/914104?nlid=130230_805&src=WNL_mdplsfeat_190618_mscpedit_infd&uac=161631CJ&spon=3&impID=1998946&faf=1

Case Presentations

Application of PCT use for Sepsis and Antibiotic Management

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

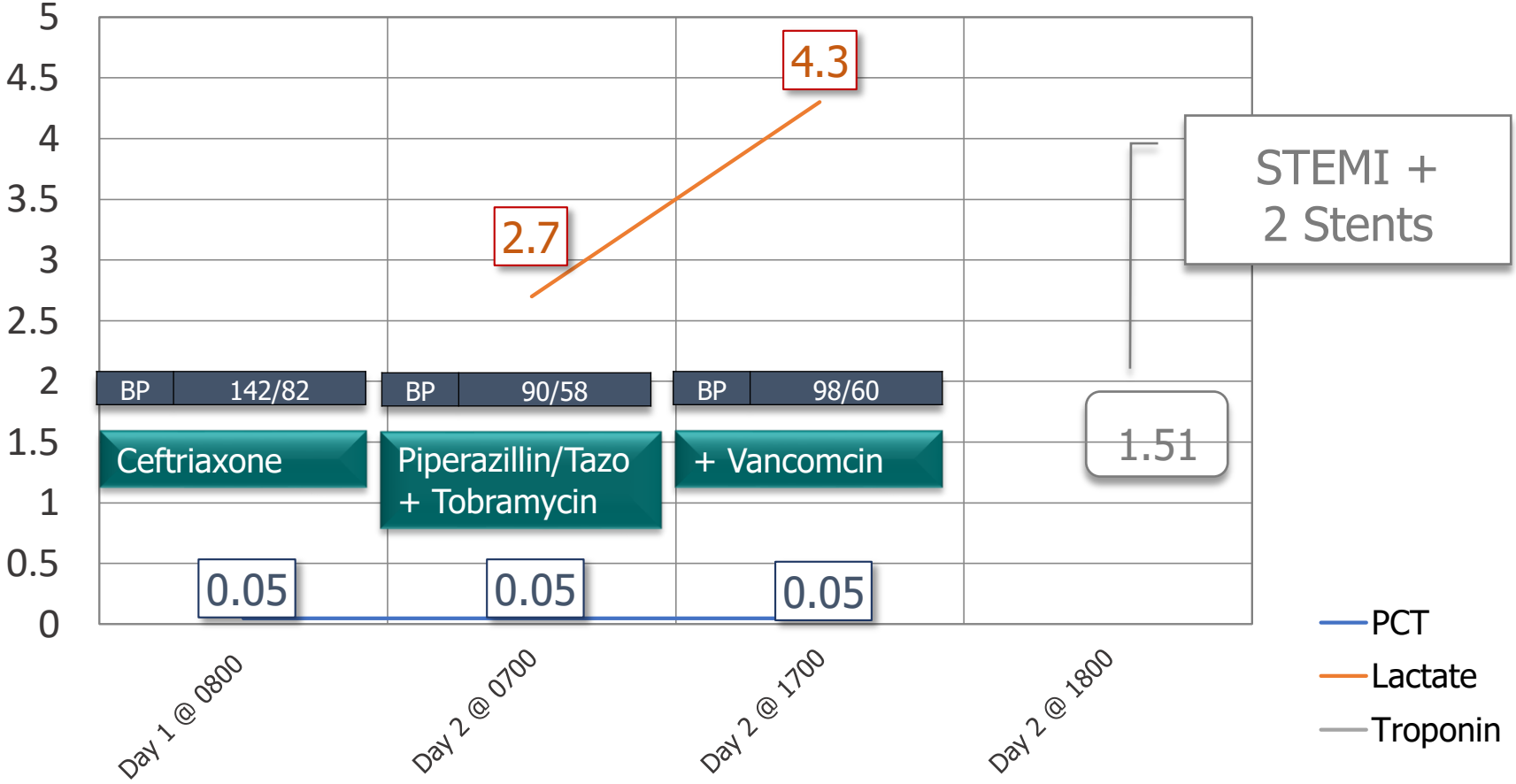
Fibromyalgia

Restless leg syndrome

BE

Urinalysis	Other Lab
• Sq Epi 4-6 • Nitrite positive • Leuk 1+ • WBC: 4-6 • Bacteria +2 • pH 6 • SG 1.025 • Dark yellow • Clarity: cloudy	• WBC: 9.6 x 1000 • Neutrophils 62 • PCT: 0.05ng/ml

BE: UTI and Lactate Specificity



BE Clinical Pearls

- Lactate is a marker of anaerobic metabolism
- Low sensitivity and specificity for bacteria and should not guide antibiotic therapy; elevations do not guarantee infection
- If lactate is elevated in bacterial infections, the patient must be in sepsis or septic shock
- Useful assessment of reperfusion
- UA/Culture “positive” plus normal PCT ?

CC/Hx

62 y/o male FW

Smoker – 2 ppd

AECOPD

CC: Severe dyspnea more time on prn 0_2, increase in sputum production, n/v

RR 24

Pulse 94

Chest film : "emphysema w/out acute pulmonary process"

Auscultation: rhonchi

Expiratory wheezing

$PaCO_2$ 30 mm Hg

Presentation/Lab

BP 110/62

Temp 99.2

Pulse Ox 92 @ 2 L NC

SrCr 1.6 – BUN 33

WBC 13.6

PCT 0.05 ng/ml on admission

Tiotropium daily

Fluticasone/salmeterol 250/50 bid

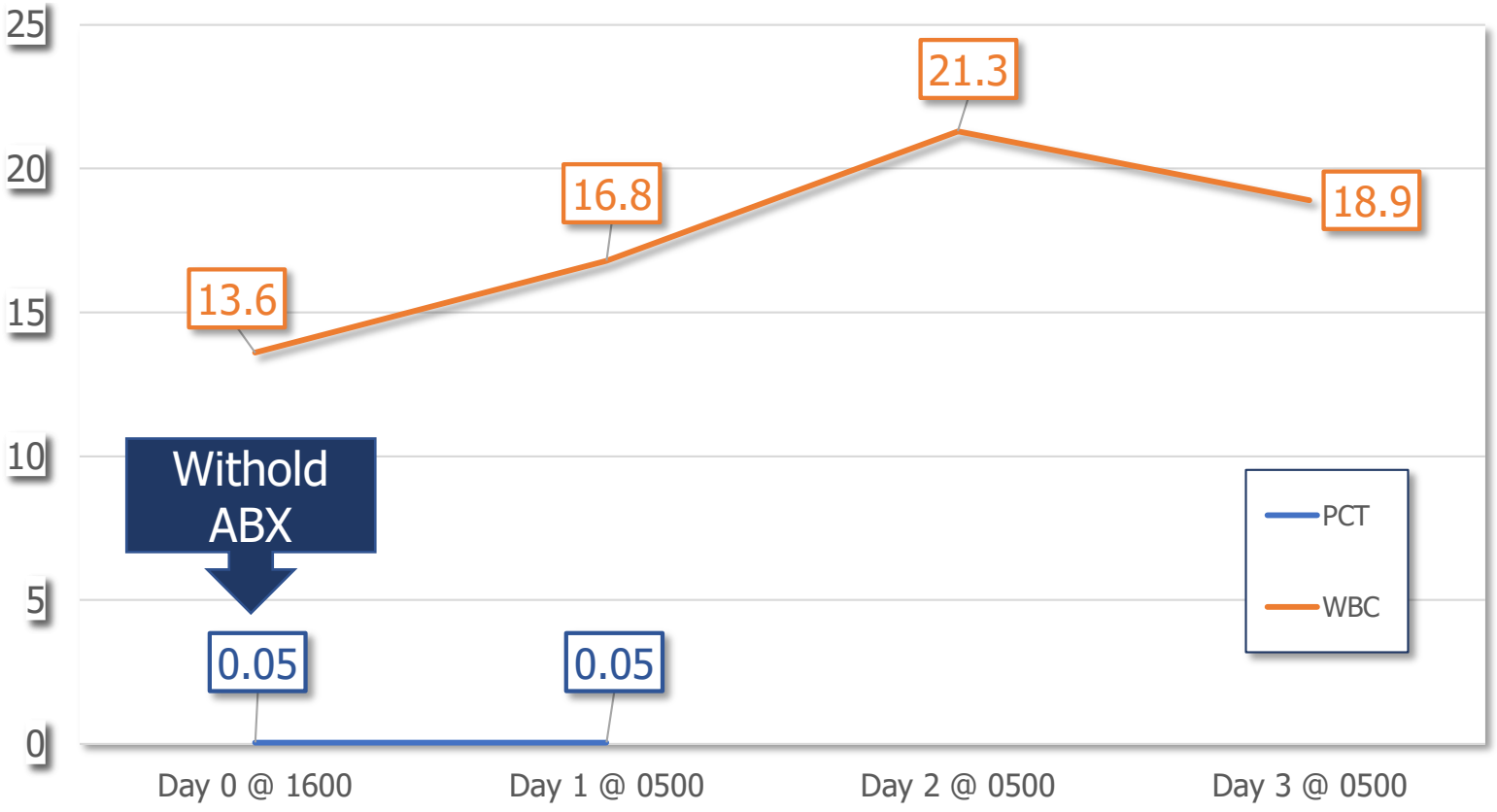
Albuterol MDI 2 puffs prn every 2 hours SOB

FW

Pertinent History

- PMH indicates four acute exacerbations within last year, last one six months ago
- Episodes are clustered during fall and winter months
- Further questioning indicates patient uses wood heat in wood furnace to supplement heating home
- Exacerbation coincides mostly with onset of cooler temperatures for fall
- All previous episodes treated outpatient with azithromycin (Z-Pak)

FW PCT and WBC



FW

Clinical Course

Treatment

- O_2 management
- Ipratropium and albuterol via nebulization qid
- Budesonide via nebulization bid
- Rehydration with 0.9% sodium chloride
- Methylprednisolone 125 mg IV on admission, 60 mg IV every 6 hours initially on titration schedule

No antibiotics prescribed

Antibiotic exposure prevented

AJ a 68 Y/O male

CC/Hx

CC increasing dyspnea on exertion, now worsening

Recent weight gain

Trace BLE pitting edema

Productive cough

10 history of osteoarthritis managed with NSAID's

Depression

Hypertension x 15 years (furosemide + amlodipine)

Heart failure x 7 years (carvedilol + lisinopril)

AJ Presentation 1

BP 135/78

RR 26

Temp 100.6

Pulse 98

Pulse Ox 91% on RA

NT-proBNP 1920

WBC 11.6

PCT 0.05 ng/ml

Flu negative

Lactate 1.9

CXR: Findings consistent with pulmonary edema, no large effusions

AJ Presentation 2

BP 145/85

RR 27

Temp 100.9

Pulse 98

Pulse Ox 89% on RA

NT-proBNP 2030

WBC 13.1

PCT 2.4

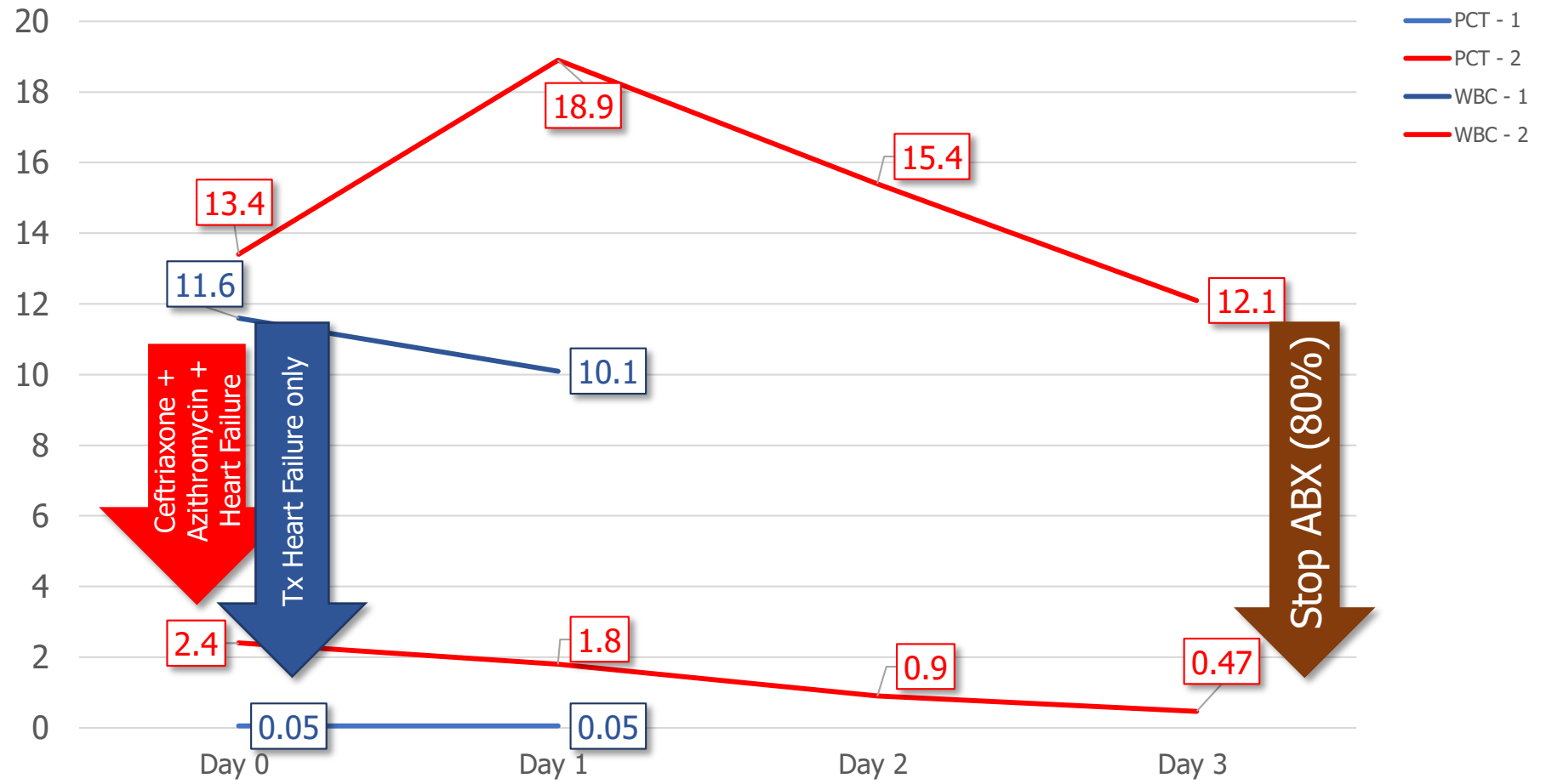
Start ABX based on PCT

Flu negative

Lactate 2.0

CXR: cardiomegaly, pulmonary edema, no definite focal consolidation

AJ PCT & WBC


20
18
16
14
12
10
8
6
4
2
0
Day 0
Day 1
Day 2
Day 3
PCT - 1
PCT - 2
WBC - 1
WBC - 2
18.9
15.4
13.4
12.1
11.6
10.1
2.4
1.8
0.9
0.47
0.05
0.05
Ceftriaxone + Azithromycin + Heart Failure
Tx Heart Failure only
Stop ABX (80%)

AJ

Clinical Pearls

- 10% of heart failure patients have superimposed pneumonia
- 20% of heart failure patients will have a secondary infection
- AJ-1's laboratory presentation was indicative of heart failure only (no bacterial infection*) and confirmed with a second PCT
- AJ-2's laboratory presentation was indicative of a bacterial infection based on PCT
- AJ-2's PCT response to ABX was typical with appropriate therapy
- Opportunity to stop at 80% reduction from max value

JW

Question:
What is your Tx plan if the procalcitonin was 0.7?
Now:
Would your plan be different if the procalcitonin was 15?

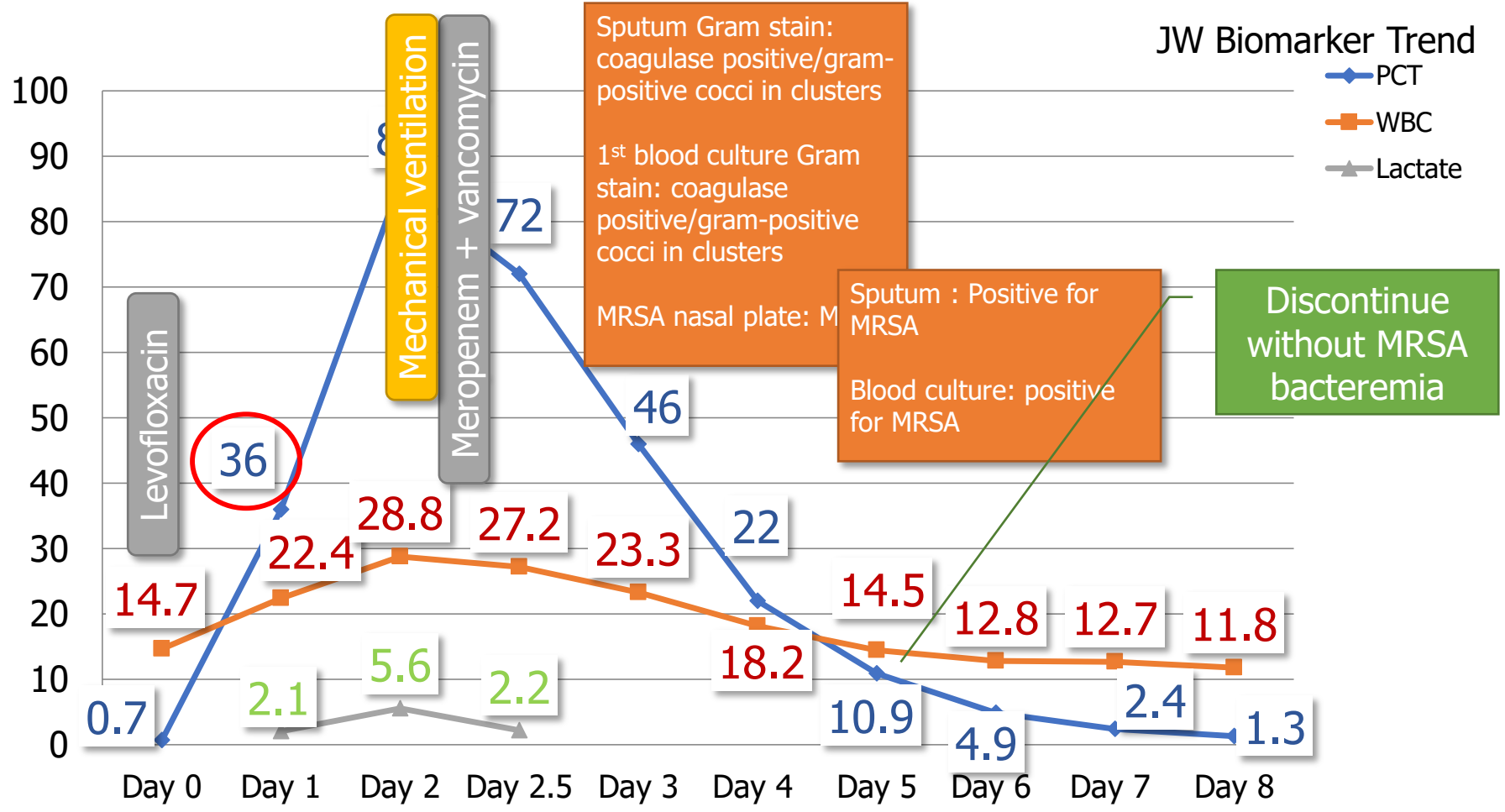
CC/Hx/Presentation

- ale,
- ion worker
- ince childhood
- smoker
- productive
- alaise, fever
- of 12-14 days
- ycin Z-Pak
- ne 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

JW clinical course



JW Clinical Pearls

- 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
- Suggest therapy modification and re-evaluate with serial measurements.

ST a 66 Y/O female

CC/Hx/Presentation

CC: pain, tenderness, and fever with recurrent cellulitis of left great toe and shin just superior to ankle

Second day of recurrent infection that had "resolved" two weeks ago

Adult onset insulin dependent diabetic

Neuropathy in legs/feet

Mild CHF

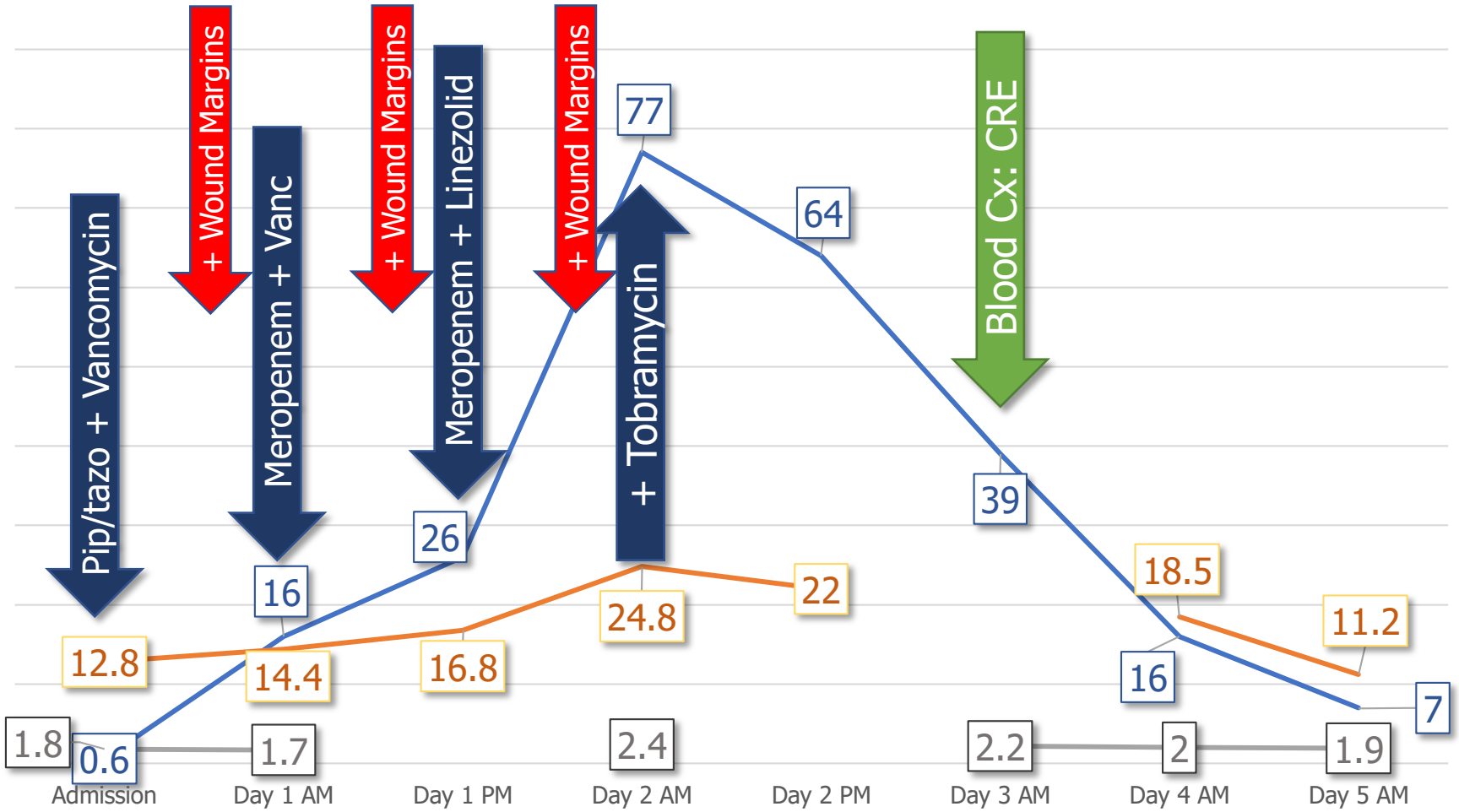
HTN

ST clinical course

Admission – AM

- Plain film
- Scheduled MRI
- WBC 12.8 X 1000
- PCT 0.6 ng/ml
- Piperacillin/Tazobactam
- Vancomycin

ST


Pip/tazo + Vancomycin
+ Wound Margins
Meropenem + Vanc
+ Wound Margins
Meropenem + Linezolid
+ Wound Margins
+ Tobramycin
Blood Cx: CRE
77
64
39
26
16
18.5
11.2
12.8
14.4
16.8
24.8
22
16
7
1.8
0.6
1.7
2.4
2.2
2
1.9
Admission
Day 1 AM
Day 1 PM
Day 2 AM
Day 2 PM
Day 3 AM
Day 4 AM
Day 5 AM

ST Blood Culture #1 and #2

Culture Report	
Organism 01 Escherichia coli (esccol)	
Antibiotics	
Ampicillin	R
Ampicillin/Sulbactam	R
Ceftizoxime	R
Gentamicin	R
ESBL	POS
Cefoxitin	R
Ceftazidime	R
Ceftriaxone	R
Cefepime	R
Imipenem	R
Meropenem	R
Amikacin	S
Tobramycin	S
Piperacillin/Tazobactam	R
Levofloxacin	R
Trimethoprim/Sulfamethox	R

ST Clinical Pearls

- Understanding PCT principles will allow effective monitoring and shorten time to evaluate therapy
- Elucidation of organisms and sensitivity offers huge benefits for clinicians and patients
- Reducing intervention time can preempt more serious disease progression
- Narrow and define therapy
- Interesting fact…..

Real World Data

- The following real world data was presented at November 10, 2016 for the FDA and to CID Open Forum
- Added to a mature stewardship program of 18 years

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

Open Forum Infectious Diseases

MAJOR ARTICLE

Impact of Procalcitonin-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real-world Evidence

Michael R. Broyles[1]

[1]Department of Clinical Pharmacy and Laboratory Services, Five Rivers Medical Center, Pocahontas, Arkansas

Background. Delayed pathogen identification and nonspecific clinical findings make definitive decisions regarding antibiotics challenging. The stimuli of bacterial toxins and inflammation make procalcitonin (PCT) unique in its ability to differentiate bacterial infection from other causes of inflammation, and thus it is useful for antibiotic management. The objective of our study was to evaluate the impact of a PCT algorithm (PCT-A) on current practice.

Methods. A single-center, retrospective cohort study was conducted to evaluate the impact of adding PCT-A to stewardship practices. Data from 4 years prior to and after PCT-A implementation were compared in critical and acute care patients of all ages receiving parenteral antibiotics for a DRG coded for infection. A baseline PCT was obtained on admission in patients with suspected bacterial infection. Serial PCT measurements were repeated daily to evaluate effectiveness of therapy. Outcomes of interest were antibiotic exposure, hospital mortality, 30-day readmission, *Clostridium difficile* infection (CDI), and adverse drug events during hospitalization.

Results. A total of 985 patients (pre-PCT-A group) were compared with 1167 patients (post-PCT-A group). Antimicrobial stewardship alone (pre-PCT-A) resulted in a median days of therapy (DOT) of 17 (interquartile range [IQR], 8.5–22.5) vs 9.0 (IQR, 6.5–12) in the post-PCT-A group ($P < .0001$). Secondary outcomes were also significantly reduced in the post-PCT-A group.

N = 2152 Patients
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

Five Rivers Medical Center Study Outcomes (N = 2152)

	Pre-PCT n=985	Post-PCT n=1167	Between-Group Difference	% Reduction	P value
Primary Outcome					
Days of Therapy DOT, median (IQR)	17.0 (8.5-22.5)	9.0 (6.5-12.0)	-8.0	47%	<0.001
Secondary Outcomes					
Hospital All-Cause Mortality, n (%) Hospital Mortality from Infection, n (%)	75 (7.6) 68 (6.9)	35 (2.9) 33 (2.8)	4.7% 4.1%	62% 59%	<0.001 <0.001
30-day All-Cause Readmission*, n (%) 30-day Readmission for Infection*, n (%)	204 (22.4) 177 (19.5)	119 (11.1) 111 (9.8)	11.3% 9.5%	50% 49%	<0.001 <0.001
Hospital C. difficile Infection, n (%)	25 (2.5)	10 (0.9)	1.6%	64%	0.002
ADEs from Antimicrobials**, n (%)	160 (16.2)	94 (8.1)	8.1%	50%	<0.001

*30-day hospital readmission rate calculated by eligible readmissions (e.g. # readmissions/(# patients in cohort – # in-hospital deaths));

**Adverse Drug Events (ADEs) during hospitalization from Antimicrobials defined as: infusion related injury or irritation, nausea, vomiting, diarrhea, Q-T interval prolongation, or arthralgia.

OMICS A Journal of Integrative Biology
Volume 23, Number 0, 2019
Mary Ann Liebert, Inc.
DOI: 10.1089/omi.2019.0113

Research Article

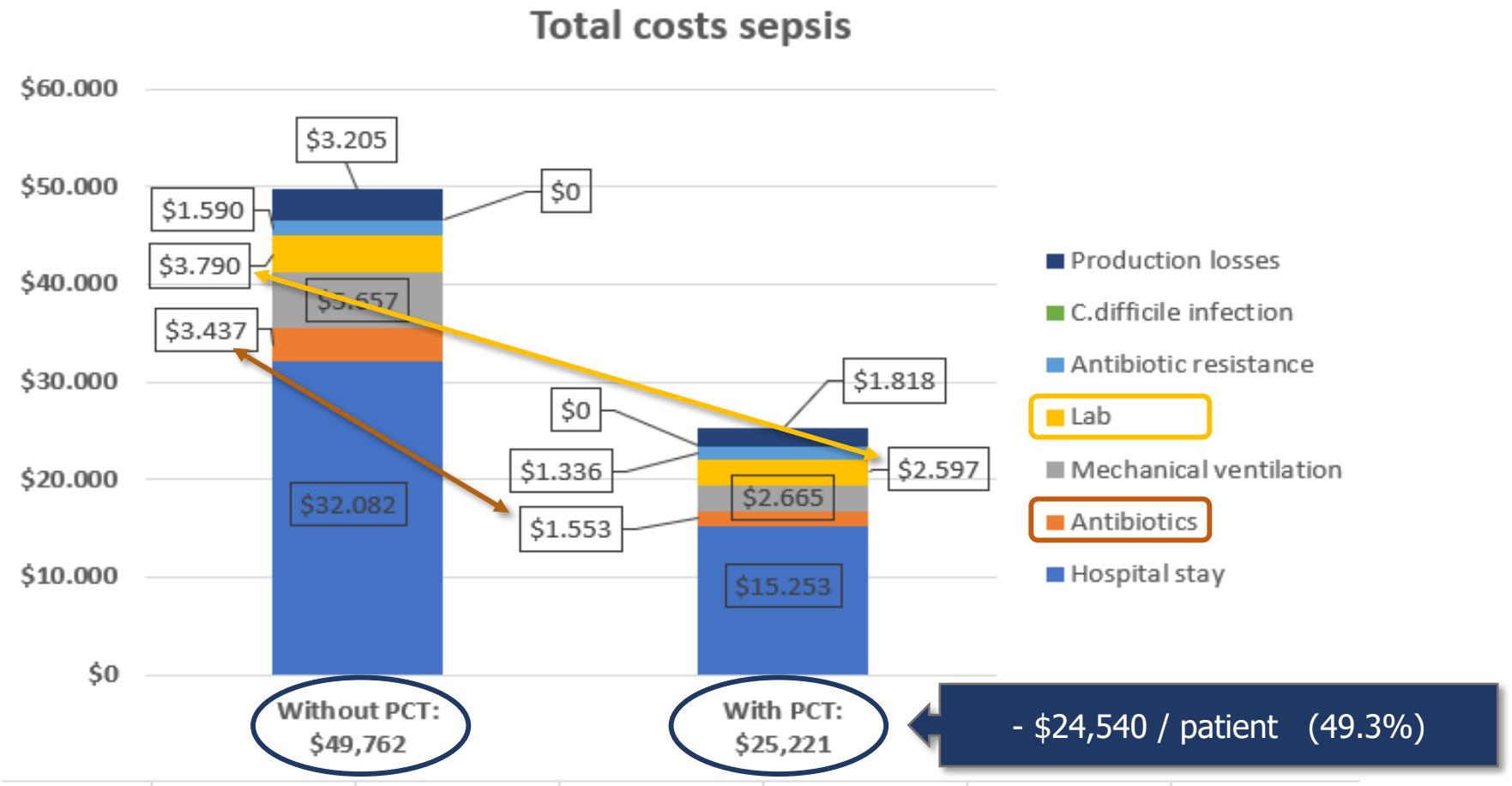
Cost-Effectiveness Analysis of a Procalcitonin-Guided Decision Algorithm for Antibiotic Stewardship Using Real-World U.S. Hospital Data

Anne M. Voermans,[1] Janne C. Mewes,[1] Michael R. Broyles,[2] and Lotte M. G. Steuten[3,*]

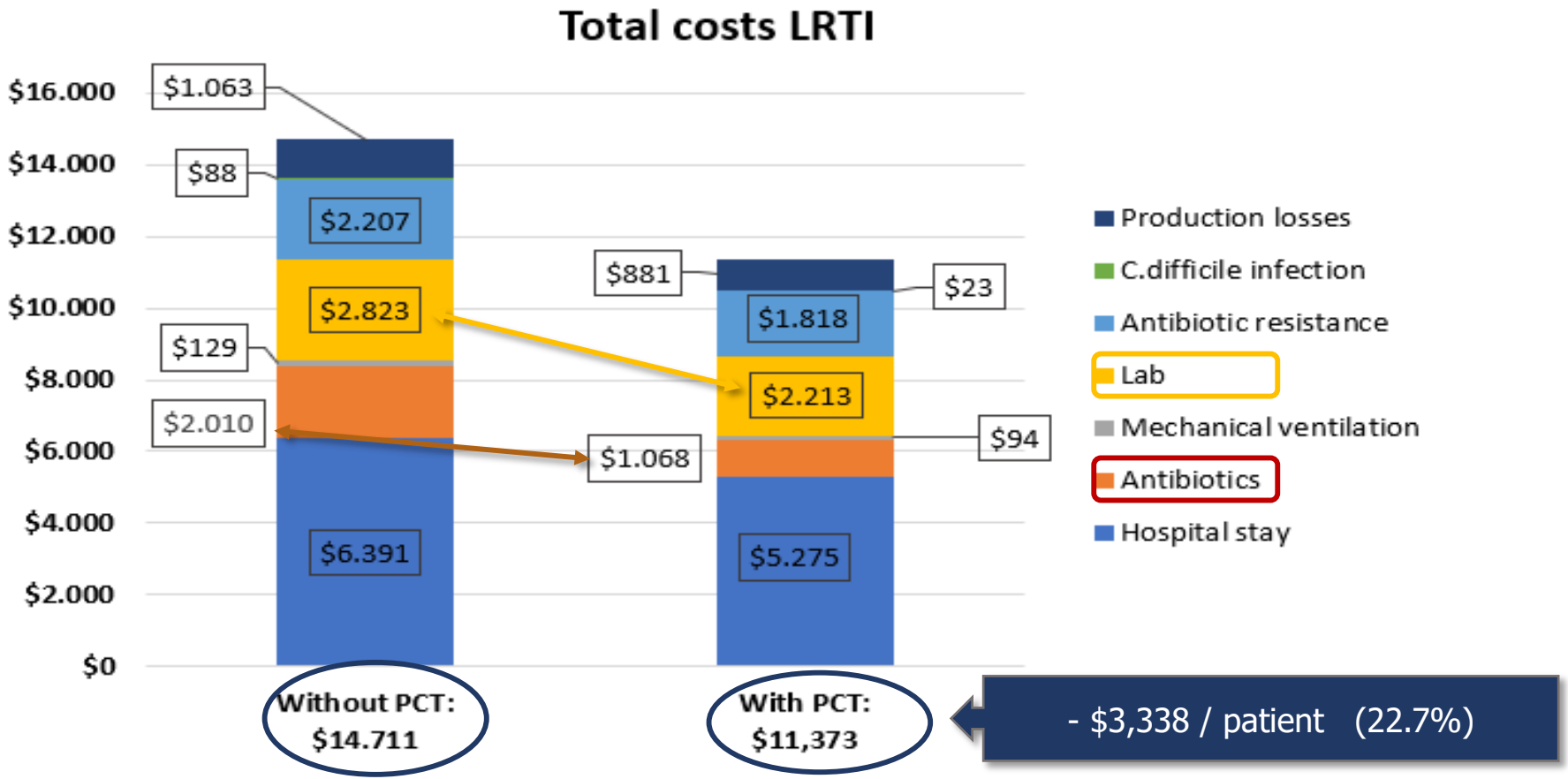
Abstract

Medical decision-making is revolutionizing with the introduction of artificial intelligence and machine learning. Yet, traditional algorithms using biomarkers to optimize drug treatment continue to be important and necessary. In this context, early diagnosis and rational antimicrobial therapy of sepsis and lower respiratory tract infections (LRTI) are vital to prevent morbidity and mortality. In this study we report an original cost-effectiveness analysis (CEA) of using a procalcitonin (PCT)-based decision algorithm to guide antibiotic prescription for hospitalized sepsis and LRTI patients versus standard care. We conducted a CEA using a decision-tree model before and after the implementation of PCT-

Results: Sepsis



Results: LRTI



The ideal biomarker or laboratory marker for bacterial infections would…

- Have the ability to differentiate bacterial from viral infection
- Have good positive and negative predictive value
- Stratify patients as to severity of infection
- Have a defined cutoff value for diagnosis
- Risk-stratify patients for appropriate disposition
- Change or support therapeutic decision making
- Determine when to start and stop antibiotic therapy
- Monitor progress of disease and response to therapy
- Improve emergency department and hospital resource utilization

Blomkalns AL. https://pdfs.semanticscholar.org/1f67/eb51f3f9d88c83af59b0fbaf01a4ef237eeb.pdf. 2007;7:1-11. Accessed April 16, 2018.

Questions

mrbroyles@suddenlink.net