

# Nikhil K. Bhayani, MD, FIDSA



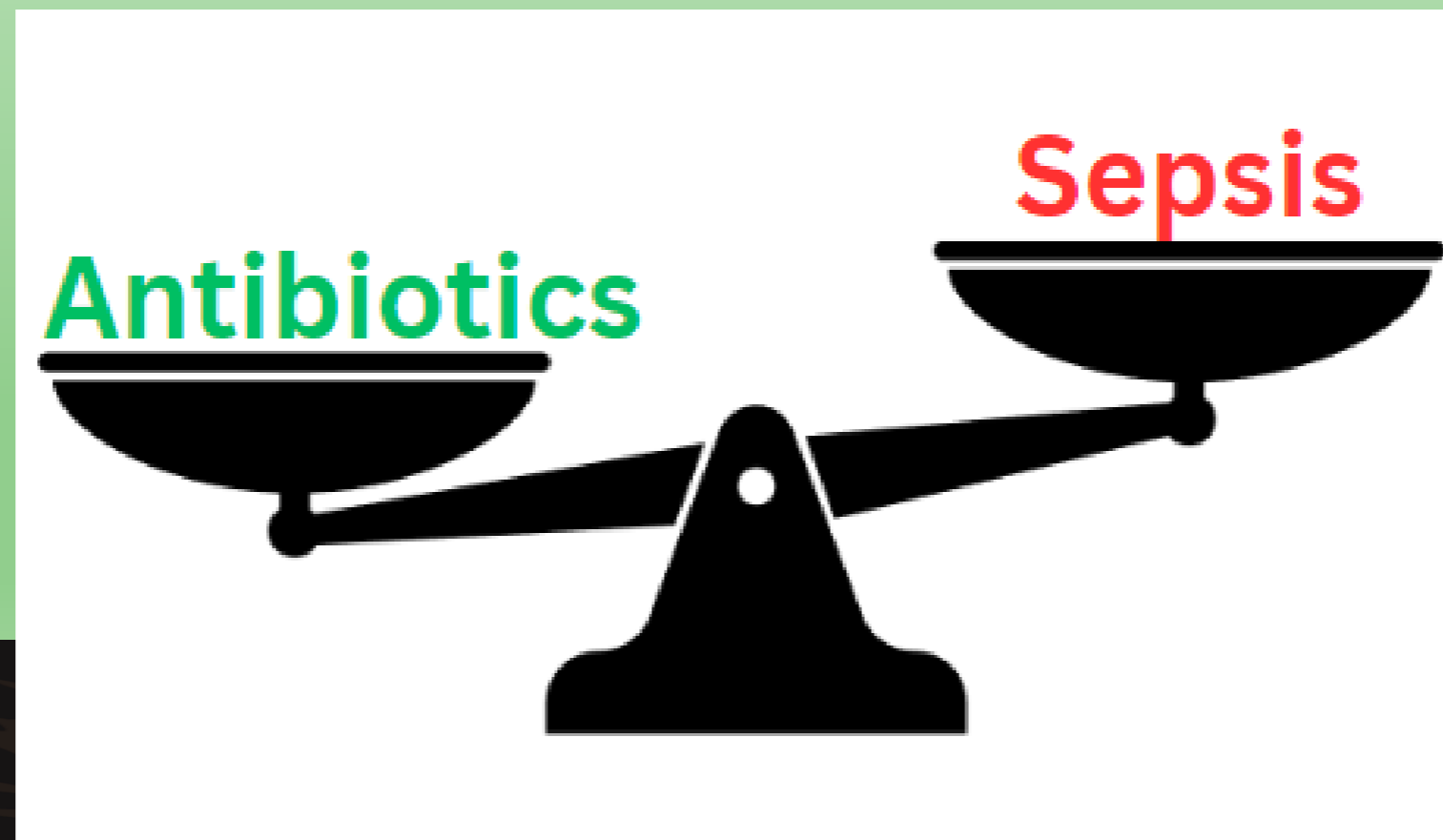
**Texas Health Infection Prevention/  
Epidemiology Physician Advisor**

**Assistant Professor, Department of Internal Medicine  
Anne Burnett Marion School of Medicine at Texas Christian  
University**

**Infectious Disease Consultant (DFWID, PLLC)**



# Antimicrobial Stewardship & Sepsis: “Do We Need More or Less Antibiotics?”



**In March 1942, Mrs. Anne Miller of New Haven, Connecticut, was near death.\*** Infectious germs had made their way into her bloodstream. Desperate to save her, doctors administered an experimental drug: penicillin, which Alexander Fleming discovered 14 years earlier. In just hours, she recovered, becoming the first person in the world to be saved by an antibiotic. Rather than dying in her thirties, Mrs. Miller lived to be 90 years old.

Today, decades later, germs like the one that infected Mrs. Miller are becoming resistant to antibiotics. You could have one in or on your body right now—a resistant germ that, in the right circumstances, could also infect you. But—unlike the bacteria that threatened Mrs. Miller—the bacteria may be able to avoid the effects of the antibiotics designed to kill them.

**Unfortunately, like nearly 3 million people across the United States, you or a loved one may face an antibiotic-resistant infection.**

*Antibiotic Resistance Threats in the United States, 2019*

# Objectives

- Help ease the misunderstanding between antimicrobial stewardship and sepsis
- Importance in deescalation of antimicrobial therapy to help reduce antimicrobial resistance (AMR) & Clostridoides difficile infection
- Utilization of Procalcitonin (PCT) in antimicrobial stewards



# Antimicrobial Stewardship in Context



- Identifying the tipping point between optimal care for a sepsis patient and the importance of antimicrobial stewardship is a balancing act



- Overuse of antibiotics has led to the current situation, with antibiotic resistance as one of the biggest public health challenges of our time



Inpatient

30-50% of antibiotic use in hospitals is unnecessary or inappropriate



Outpatient

80-90% of the volume of human antibiotic use occurs in the outpatient setting  
At least 30% of antibiotics prescribed in outpatient settings are unnecessary

# Big Brother is Watching...

- Joint Commission
  - Standard MM.09.01.01, effective January 2017
  - new antimicrobial stewardship standard is a **hospital priority**, including:
    - Leadership commitment
    - Accountability
    - Drug expertise
    - Action
    - Tracking
    - Reporting
    - Education
- CDC Reporting
- Hospital Penalty from CMS, Medicare
  - Payments to hospitals are directly affected by HAC scores (HAC reduction program-CMS)

# The Threat of Antibiotic Resistance in the United States

Antibiotic resistance—when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them—is one of the greatest global health challenges of modern time.

## New National Estimate\*


Each year, antibiotic-resistant bacteria and fungi cause at least an estimated:

 **2,868,700** infections

 **35,900** deaths



*Clostridioides difficile*\*\* is related to antibiotic use and antibiotic resistance:

 **223,900** cases

 **12,800** deaths

## New Antibiotic Resistance Threats List

Updated urgent, serious, and concerning threats—totaling 18

**5** urgent threats

**2** new threats

**NEW:** Watch List with **3** threats



Antibiotic resistance remains a significant One Health problem, affecting humans, animals, and the environment. Data show infection prevention and control is saving lives—especially in hospitals—but threats may undermine this progress without continued aggressive action now.

Learn more: [www.cdc.gov/DrugResistance/Biggest-Threats.html](http://www.cdc.gov/DrugResistance/Biggest-Threats.html)

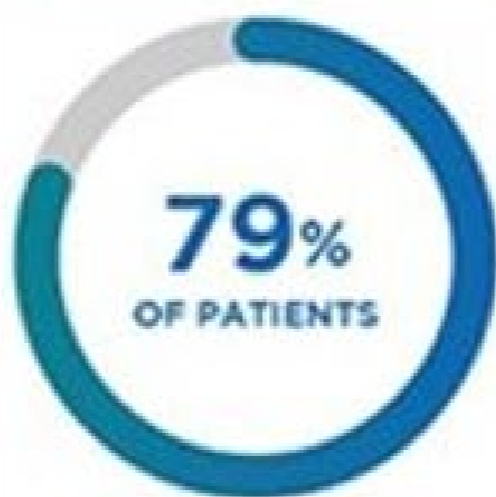


## NEW CDC DATA

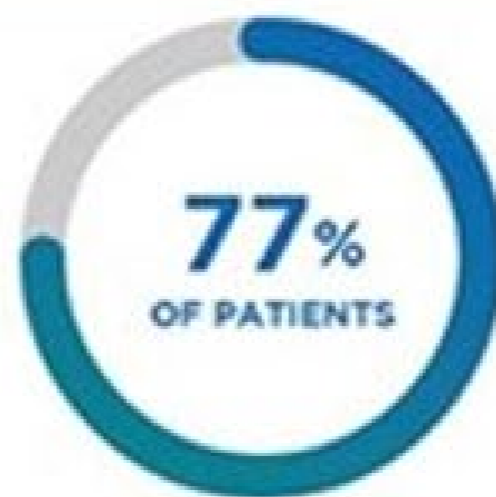
MORE THAN HALF OF ANTIBIOTIC PRESCRIBING FOR SELECTED EVENTS IN HOSPITALS WAS NOT CONSISTENT WITH RECOMMENDED PRESCRIBING PRACTICES



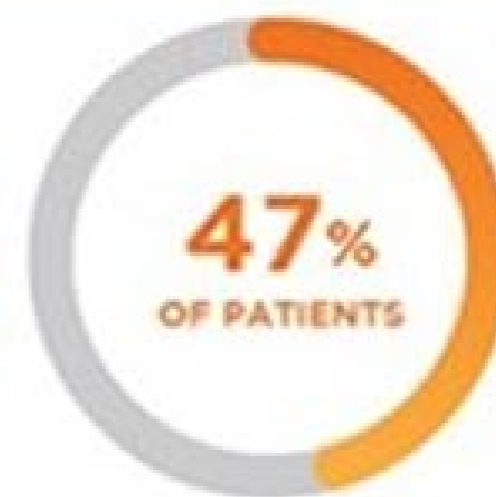
## ANTIBIOTIC PRESCRIBING WAS NOT SUPPORTED IN:



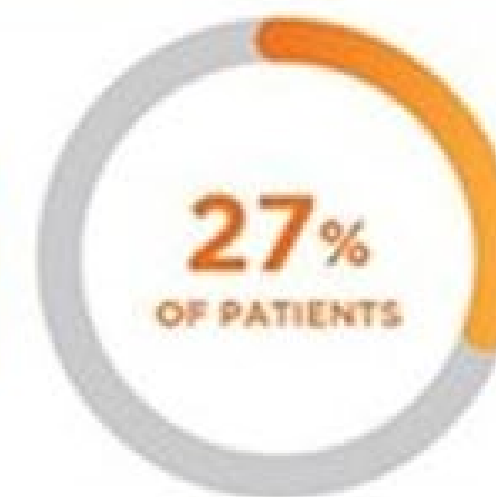
with community-acquired pneumonia



with urinary tract infections



prescribed fluoroquinolone treatment



prescribed intravenous vancomycin antibiotic

## HOSPITAL PRESCRIBERS & PHARMACISTS CAN IMPROVE PRESCRIBING:



Optimize antibiotic selection



Re-assess antibiotic treatment when the results of diagnostic testing are available



Use the shortest effective duration of therapy

FIND RESOURCES ON HOW TO IMPROVE HOSPITAL ANTIBIOTIC USE AND HELP FIGHT ANTIBIOTIC RESISTANCE:  
<http://bit.ly/HospAbx>





METHICILLIN-RESISTANT  
***STAPHYLOCOCCUS AUREUS***  
(MRSA)

# Surviving Sepsis Campaign

- Initiation of broadspectrum antimicrobial therapy within one hour of triage of patients with sepsis/septic shock
- “Administer Antimicrobial First and Ask Questions Later”

# Is there increased mortality in delay of antimicrobial therapy?

- Data supporting delayed administration of antibiotics increases mortality limited.
- Most evidence is based on results from retrospective analyses of data gathered for other purposes.
- Data needs to include important information such as identification of infection site, appropriateness of antibiotic selection, dose of antibiotic administration and source control.




# Etiology of Illness in Patients with Severe Sepsis Admitted to the Hospital from the Emergency Department

**Alan C. Heffner,<sup>1,3</sup> James M. Horton,<sup>2</sup> Michael R. Marchick,<sup>3</sup> and Alan E. Jones<sup>3</sup>**

Divisions of <sup>1</sup>Critical Care Medicine and <sup>2</sup>Infectious Diseases, Department of Internal Medicine, and <sup>3</sup>Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina

Clinical  
Infectious  
Diseases

Clinical Infectious Diseases 2010; 50:812

# Background

- Patients identified with sepsis in the emergency department often are treated based on the presumption of infection.
- Various noninfectious conditions that require specific treatments have clinical presentations like that of seps

# Methods

- Prospective observational study of patients treated with ~~goal-directed~~ resuscitation for severe sepsis in the emergency department
- Inclusion criteria: suspected infection, 2 or more criteria for systemic inflammation, and evidence of hypoperfusion.
- Exclusion criteria: anyone <18 years of age and need for emergent surgery
- Clinical data prospectively collected for 2 years.

Clinical Infectious Diseases 2010; 50:812-820



# Results

- 211 patients were enrolled
  - 95 (45%) had positive culture results
  - 116 (55%) had negative culture results.
  - The overall mortality rate was 19%
- Patients with negative culture results:
  - 44% had clinical infections, 8% had atypical infections, 32% had noninfectious mimics, & 16% had an illness of indeterminate etiology

# Conclusion

- >50% of patients identified and treated for severe sepsis in the emergency department had negative culture results
- The patients identified with sepsis:
  - 18% had a non-infectious diagnosis that mimicked sepsis
  - The clinical characteristics of these patients were similar to patients with culture-positive sepsis

Clinical Infectious Diseases 2010; 50:814–820



RESEARCH

Open Access



# Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study

Peter M. C. Klein Klouwenberg<sup>1,2,3\*</sup>, Olaf L. Cremer<sup>1</sup>, Lonneke A. van Vught<sup>4</sup>, David S. Y. Ong<sup>1,2,3</sup>, Jos F. Frencken<sup>1,3</sup>, Marcus J. Schultz<sup>5</sup>, Marc J. Bonten<sup>2,3</sup> and Tom van der Poll<sup>4</sup>

13% of 2,579 patients who had been admitted to two ICUs in Netherlands due to a presumptive diagnosis of sepsis, had no infection after further work-up, and 30% of patients were also confirmed to have only the potential of sepsis.



SPECIAL EDITORIAL



# The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy<sup>1\*</sup>, Laura E. Evans<sup>2</sup> and Andrew Rhodes<sup>3</sup>

© 2018 SCCM and ESICM

**Table 1 Bundle elements with strength of recommendations and under-pinning quality of evidence [12, 13]**

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate $\geq$ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mm Hg	Strong recommendation, moderate quality of evidence

**SPECIAL EDITORIAL**



# The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy<sup>1\*</sup>, Laura E. Evans<sup>2</sup> and Andrew Rhodes<sup>3</sup>

© 2018 SCCM and ESICM

“The link between early administration of antibiotics for suspected infection and antibiotic stewardship remains essential to high-quality sepsis management. If infection is proven not to exist, antimicrobials should be discontinued.”

September 30, 2013

# Lower Mortality with De-escalation of Antibiotic Therapy in Sepsis

Thomas Glück, MD, reviewing Garnacho-Montero J et al. *Intensive Care Med* 2013 Sep 12

**NEJM**  
**Journal Watch**

# Results

- To evaluate the effect of antibiotic de-escalation on outcomes, researchers conducted a prospective, observational study involving adults admitted to the intensive care unit (ICU) at a hospital in Seville, Spain, with severe sepsis or septic shock between January 2008 and May 2012 (N=628).



# Results

- Causative pathogen was possible for 481 patients (77%). Bacteremia was present in 241 patients (38%).
  - Antimicrobial therapy was adequate in 88% of the cases.
  - De-escalation of the initial regimen was performed in 219 patients (35%).
  - Common in medical than in surgical patients.
  - Severity of illness during the first 24 hours after ICU admission did not influence antimicrobial-therapy modification.
  - Mortality rate was 27% in patients with therapy de-escalation, 33% in those with no treatment change, and 43% in those with treatment escalation ( $P=0.006$ ).

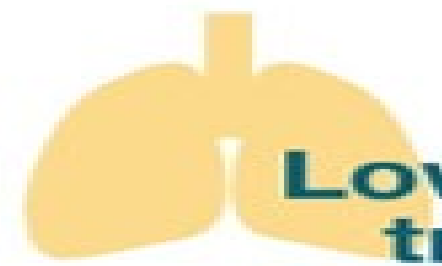
# Conclusion

- Propensity score-adjusted multivariate regression analysis identified septic shock (odds ratio, 1.70), higher Sequential Organ Failure Assessment score on the day of culture results (OR, 1.11), and inadequate empirical antimicrobial therapy (OR, 2.03) as factors independently associated with hospital mortality.
- De-escalating therapy proved to be protective (OR, 0.55).
- De-escalation was also protective against 30-day mortality across the entire cohort, as well as for the subgroup of 403 patients who had received initially inadequate therapy.



MULTIDRUG-RESISTANT  
*PSEUDOMONAS AERUGINOSA*

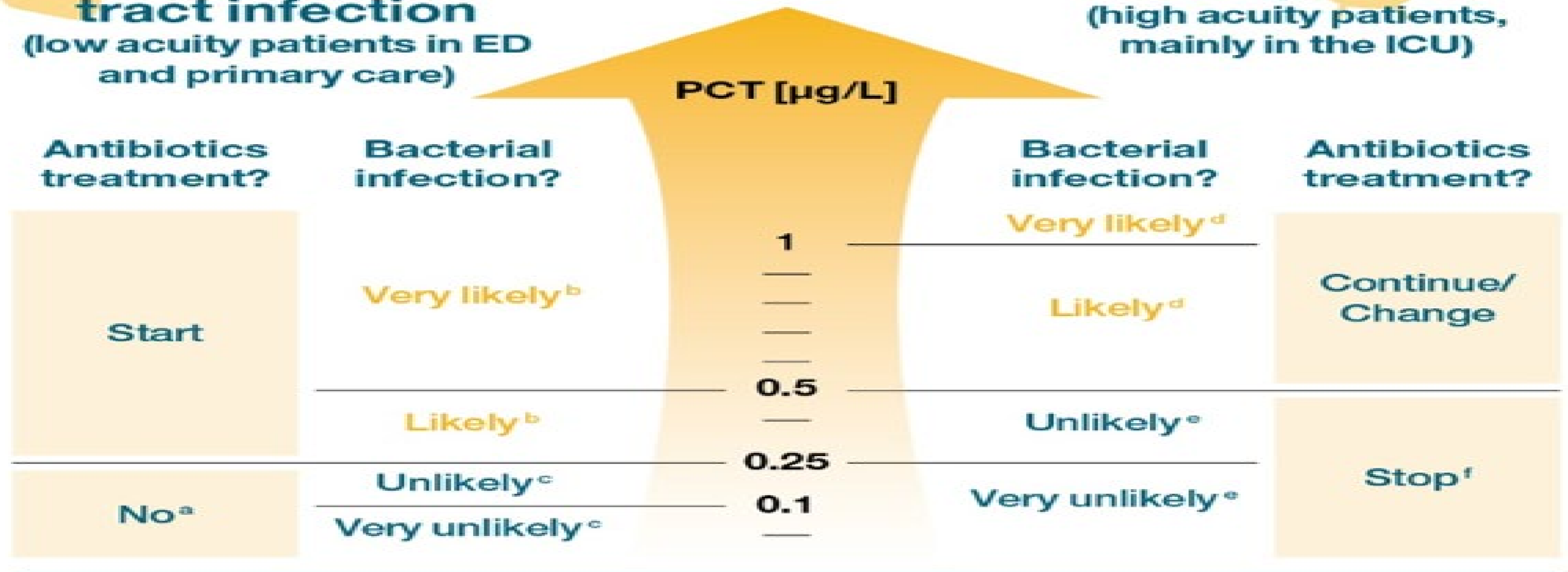
# Procalcitonin: a Tool in Antimicrobial Stewardship



**Lower respiratory tract infection**  
(low acuity patients in ED and primary care)



**Sepsis**  
(high acuity patients, mainly in the ICU)

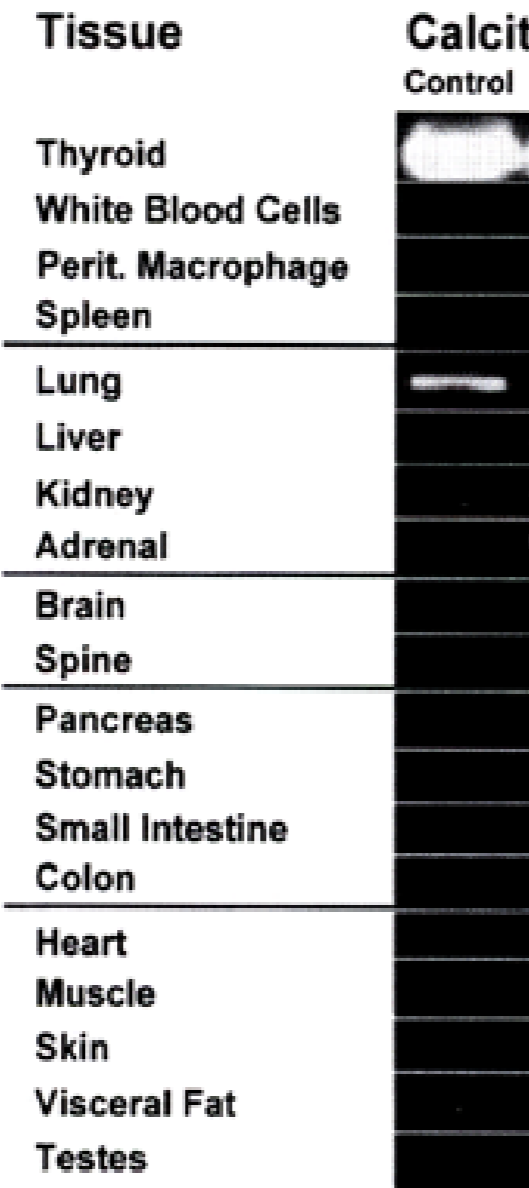


**Figure** PCT algorithm for guidance of antibiotic therapy\*  
(Adapted from Schuetz et al., Arch Intern Med 2011, 171(15): 1322-1331)



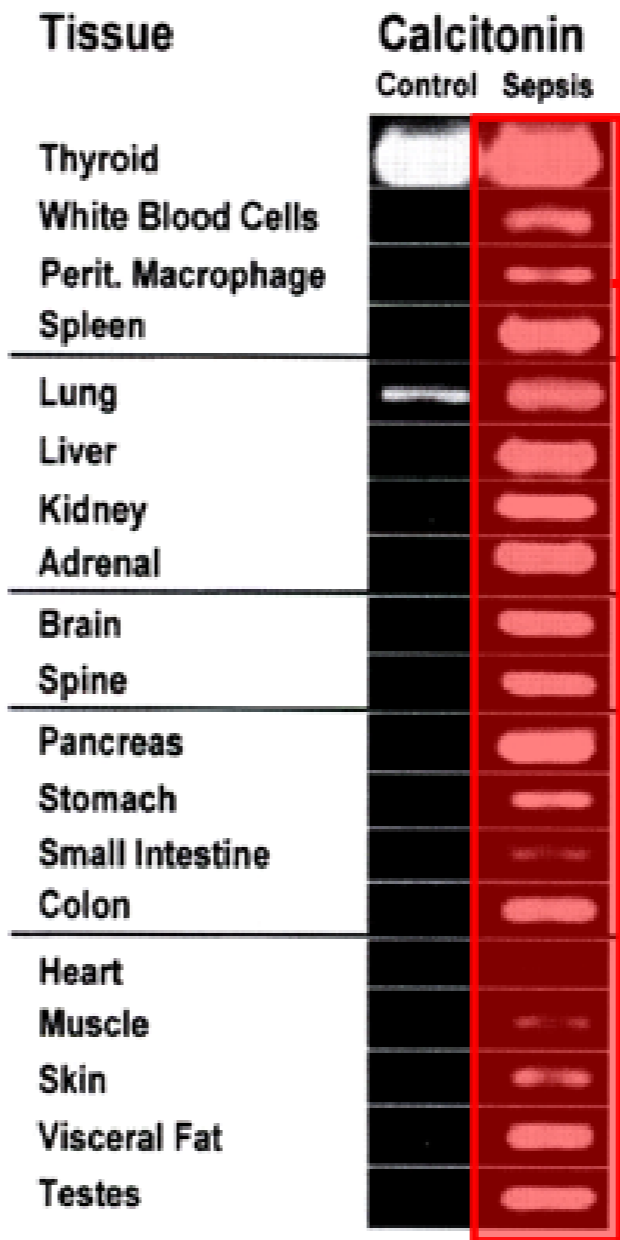
# PCT is a marker of systemic bacterial infection

## Healthy Individuals



Calcitonin

## Individuals with Systemic Bacterial Infection



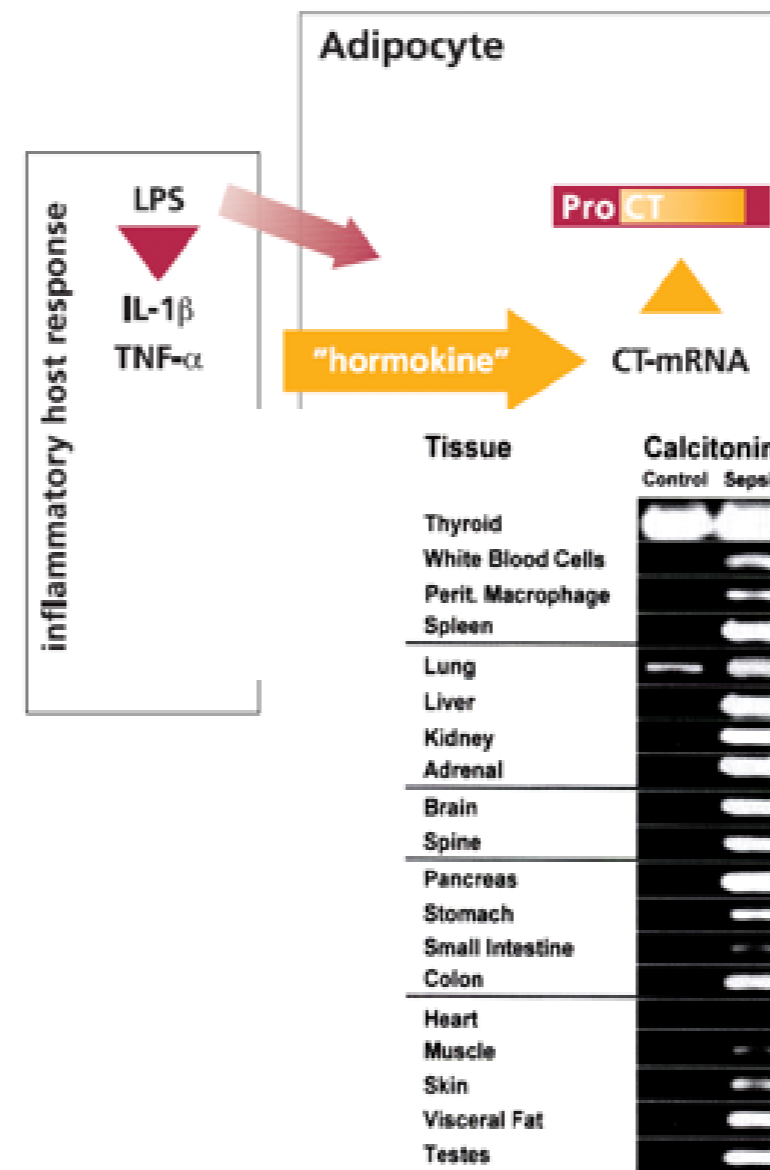
→ PCT

In systemic bacterial infection, PCT is rapidly induced in almost every organ and released into circulation

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

# PCT induction & release during clinically relevant bacterial infection

- Bacterial toxins (gram+/-) and cytokines stimulate induction pathway of Calcitonin mRNA in almost all parenchymal tissues
- Release of the prohormone into circulation

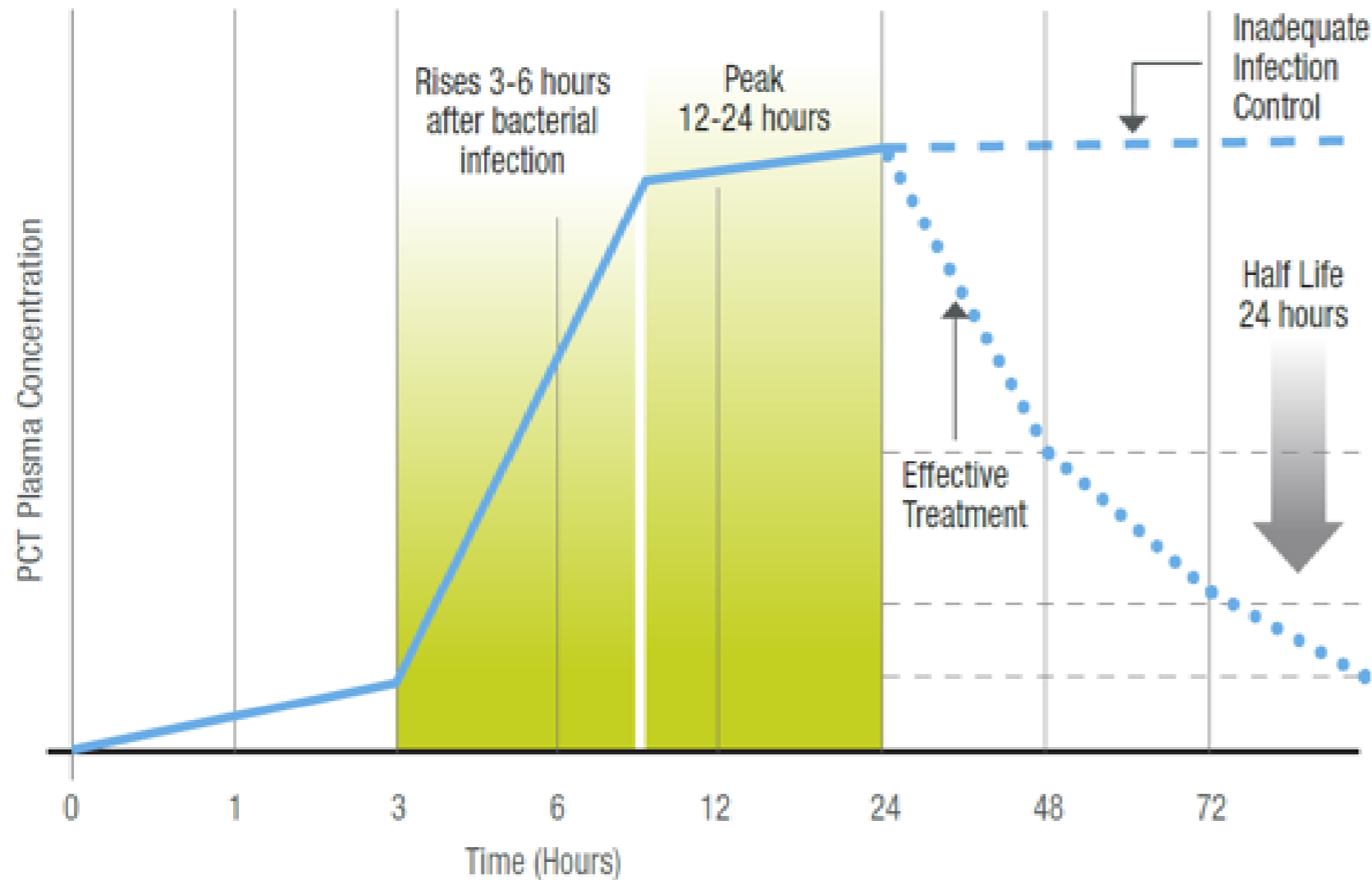


**In systemic bacterial infection, PCT is rapidly induced in almost every organ and released into circulation**

24. Linscheid et al. 2003

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

# PCT Kinetics



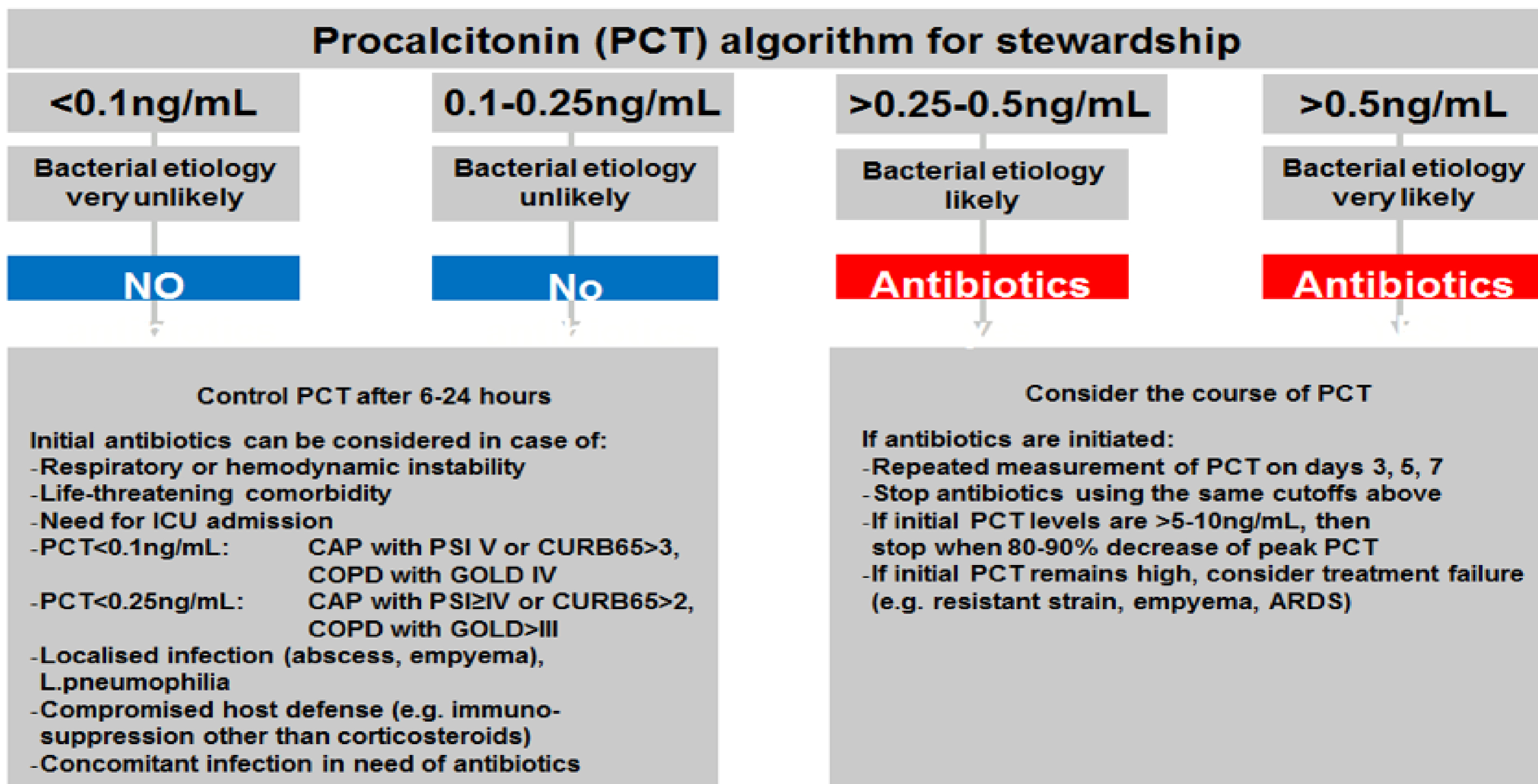
- Rises 2-3 hours after bacterial infection
- Peak occurs 12-24 hours
- Half life of 24 hours
- Can take 24 hours of appropriate antibiotic therapy to see reduction in serum PCT
- PCT production and serum concentrations will decrease by up to 50% per day
- If antibiotic therapy is inadequate, PCT levels will remain high

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

11. Dandona P. et al., J. of Endocrinology and Metabolism, 1994; 79 (5): 1605-160

20. Kinetics Image: Adapted from Meisner M: Procalcitonin: a new, innovative infection parameter; biochemical and clinical aspects; Georg Thieme Verlag; 2000 in Thermo Scientific Brochure "B.R.A.H.M.S PCT-A Valuable Tool for Sepsis Risk Assessment and Critical Care Management"

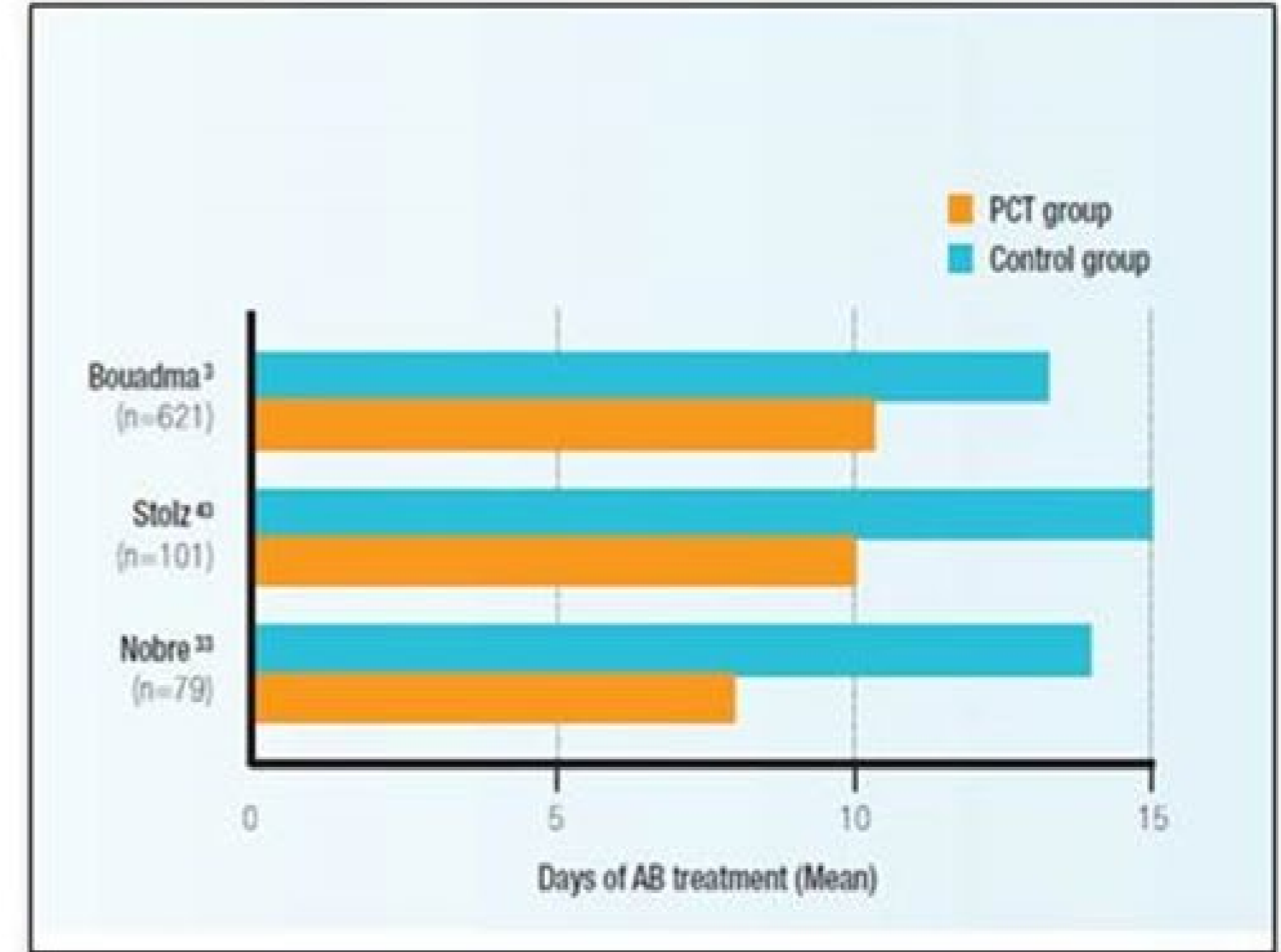
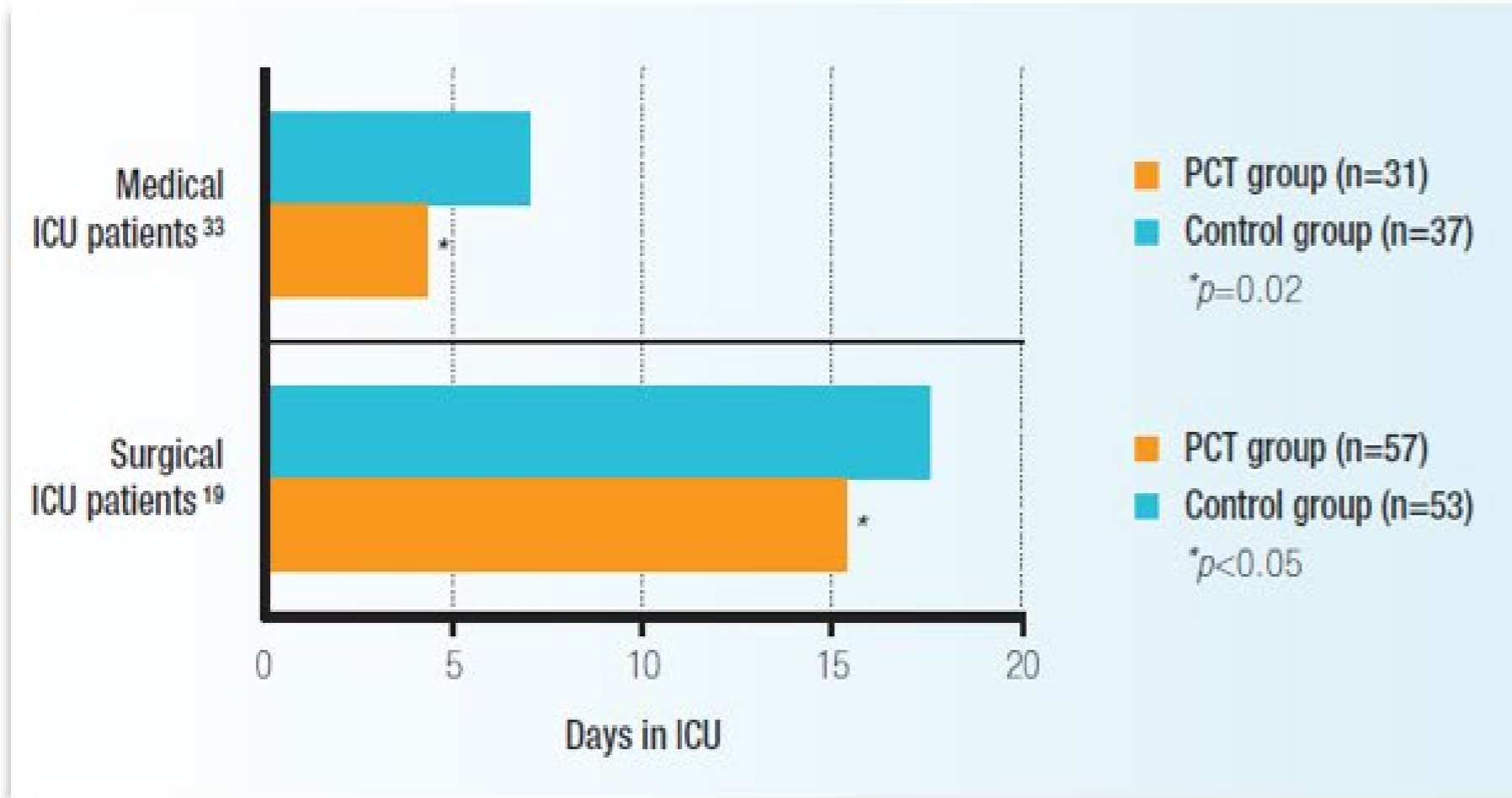
# Example of Antibiotic Stewardship Protocol



16. Adapted from: Schuetz et al., JAMA.2009;302(10):1059-66 University of Nebraska Algorithm adaptation



# Reduction of Length of Stay and Duration of Abx Treatment in PCT-Guided Protocols



8. Thermo Scientific Brochure "B-R-A-H-M-S PCT Improving infection management".

# Impact of Antibiotic Stewardship

- ↓ Antimicrobial Resistance
  - Reducing use of antibiotics reduces the development of resistant strains of bacteria
- ↓ *Clostridioides difficile* (*C. diff*) infections
  - *C. diff* is of particular concern due to its antibiotic resistant nature
  - Avoiding *c. diff* and other HAI
- ↓ Cost
  - Antibiotics
- ↑ Quality of Life
  - Reduced adverse events, productivity gain, reduced exposure to potential HAI
- ↑ Outcomes
  - Reduced LOS, Improved patient flow and triage

<https://www.cdc.gov/antibiotic-use/healthcare/evidence.html>





**Thank you!**



# References

- Garnacho-Montero J et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med* 2013 Sep 12; <http://dx.doi.org/10.1007/s00134-013-3077-7>
- Heffner et al. Etiology of Illness in Patients with Severe Sepsis Admitted to the Hospital from the ED. *Clinical Infectious Diseases* 2010; 50:882-890
- Klein Klouwenberg et al. Likelihood of infection in patients with presumed sepsis at the time of ICU admission: a cohort study. *Critical Care* (2015) 19:319
- Levy et al. The Surviving Sepsis Campaign Bundle: 2018 Update. *Intensive Care Med* (2019) 24:925
- Park et al. *Infect Chemother*. 2020 Mar;52(1):30-39 <https://doi.org/10.3947/ic.2020.52.1.19>