Biomarkers and Beyond: An Antimicrobial Stewardship Approach to Fighting Infections in the ICU

Melanie Smith, PharmD

Live Activity Handout

4 slides per page

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Biomarkers and Beyond: An Antimicrobial Stewardship Approach to Fighting Infections in the ICU

ACTIVITY DESCRIPTION

As clinical practitioners, we often struggle to find a balance between appropriate treatment of infectious disease states and antimicrobial stewardship to prevent antimicrobial resistance. In 2016 the Infectious Diseases Society of America published guidelines for the implementation of antimicrobial stewardship programs to help improve the appropriate use of antimicrobials by promoting the selection of the optimal antibiotic drug regimen and duration. As clinicians we often need tools to help with stewardship in treating common disease states such as pneumonia and other ICU infections. This activity will provide practitioners with knowledge of several important biomarkers and tests to help guide the use of antimicrobials and promote stewardship.

TARGET AUDIENCE

The target audience for this activity is **pharmacists, pharmacy technicians,** and **nurses** in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES

After completing this activity, the **pharmacist** will be able to:

- Describe the utility and benefit of antimicrobial stewardship for optimizing treatment of infections in the critically ill.
- Identify clinically useful biomarkers and tests for antimicrobial therapy guidance for bacterial and fungal etiologies of infection.
- Recognize the limitations of these tests as they apply to specific patient populations.

After completing this activity, the **pharmacy technician** will be able to:

- Describe the utility and benefit of antimicrobial stewardship for optimizing treatment of infections in the critically ill.
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ACTIVITY TYPE

Knowledge-Based Live Webinar

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Melanie Smith, PharmD

Medical University of South Carolina

ABOUT THE AUTHOR

Dr. Melanie N. Smith received her Pharm.D. from the University of Arkansas for Medical Sciences in 2015. She then completed a PGY1 pharmacy residency at UF Health Jacksonville in Jacksonville, FL as well as a teaching certificate from the University of Florida College of Pharmacy. She finished her residency training with a PGY2 in Critical Care Pharmacy at the Medical University of South Carolina (MUSC) in Charleston, SC. She currently practices as the Surgery-Trauma ICU Clinical Pharmacy Specialist at MUSC and is an adjunct assistant professor with the MUSC College of Pharmacy. She is actively involved in leadership both nationally and internationally with the American College of Clinical Pharmacy and the Society of Critical Care Medicine. She also enjoys research and scholarship related to critical care pharmacy, infectious diseases, and trauma. In her free time, she enjoys going to Orange Theory Fitness, playing with her dog Pippa, and cheering on the Arkansas Razorbacks and South Carolina Gamecocks.

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faculty

Melanie N. Smith, PharmD, BCPS

Medical University of South Carolina

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Disclosures

- I have no real or apparent conflicts of interest to disclose
- I will not be discussing the off-label use of medications

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Objectives

- Describe the utility and benefit of antimicrobial stewardship for optimizing treatment of infections in the critically ill
- Identify clinically useful biomarkers and tests for antimicrobial therapy guidance for bacterial and fungal etiologies of infection
- Recognize the limitations of these tests as they apply to specific patient populations

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ICU Infections

EPIC II – international point prevalence study

- 1265 ICUs in 75 countries (83 in North America)
- 13,796 adult patients in ICUs
  - 51% infected
  - 71% receiving antibiotics
  - 16% receiving antifungals
- Only 70% of infected patients had positive cultures
  - Gram negative: 62%
    - *Pseudomonas spp.*
  - Gram positive: 47%
    - *Staphylococcus aureus*
  - Fungal: 19%
    - *Candida spp.*

North America (n=1254)	n (%)
Total infections	607 (48.4)
Respiratory tract	345 (56.8)
Bloodstream	157 (25.9)
Renal/urinary	135 (22.2)
Abdominal	101 (16.6)

Vincent et al. *JAMA*. 2009;302(21):2323-9.

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Antimicrobial Stewardship

IDSA Infectious Diseases Society of America

SHEA The Society for Healthcare Epidemiology of America

"Coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen"

Antibiotic › **Dosing** › **Duration** › **Route**

IDSA/SHEA. *CID*. 2016; 62(10):e51-77.

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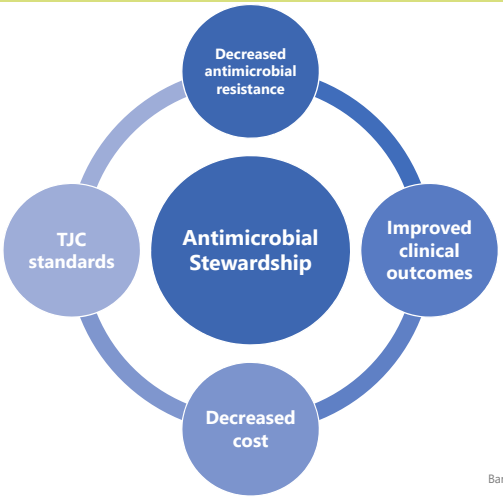
Why Stewardship?

30 – 60% of antibiotics prescribed in ICUs are unnecessary or inappropriate



TJC = The Joint Commission

Barlam, et al. *CID.* 2016; 62(10):e51-77.
Kalil, et al. *CID.* 2016; 63:1-51.
Luyt, et al. *Critical Care;* 2014;18:480.

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Duration of Therapy

Longer Duration

- Adverse effects
- *C. difficile*
- Resistance
- Cost

Shorter Duration

- Treatment failure
- Recurrence

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Obstacles to Stewardship

Diagnosis of infections

- No standardized tests or mechanisms available

Determination of etiology

- Viral, bacterial, or fungal
- Delays to appropriate therapy

Duration of therapy

- Many recommendations based on limited evidence and more on clinical symptoms

Mermel, et al. *Clin Infect Dis*. 2009;49:1-45.
Baddour, et al. *Circulation*. 2005;111:e394-e434.

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Biomarkers of Infection

Soni NJ, et al. AHRQ Publication No. 12(13)-EHC124- EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2012.

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An "Ideal" Biomarker of Infection

Characteristics

- Easy to measure and interpret
- Objective
- Rapidly available
- Reproducible
- High sensitivity and specificity
- Dynamic: rapid increase and decrease
- Unaffected by unrelated treatments or conditions
- Correlates with severity and mortality
- Inexpensive

Povoa P, et al. *Annals of Intensive Care.* 2012;2:32.

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Current Biomarkers of Infection

Biomarker	Marker of	Increases in Relation to	Onset	Peak
White blood cells	Host defense	Infections	--	--
C-reactive protein (CRP)	Acute phase reaction	Infections & inflammation	4 to 6 hours	36 to 50 hours
Procalcitonin (PCT)	Unknown (precursor of calcitonin)	Bacterial infections	2 to 6 hours	6 to 24 hours

Jensen JU, et al. *Crit Care Med.* 2009; 37:2093-94.

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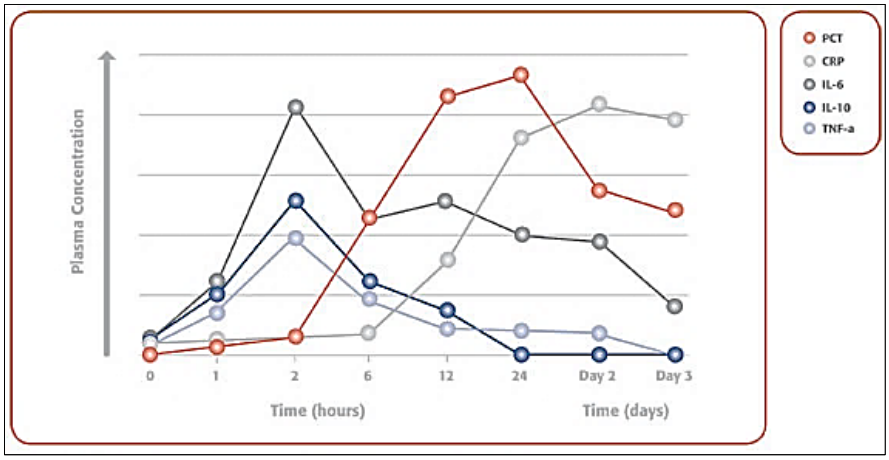
Biomarkers of Infection



Biomarker Kinetics

PCT = Procalcitonin
CRP = C-reactive protein
IL-6 = Interleukin 6
IL-10 = Interleukin 10
TNF-a = Tumor necrosis factor - alpha

Harbarth S. *Am J Resp Crit Care.* 2001;164: 396-402.

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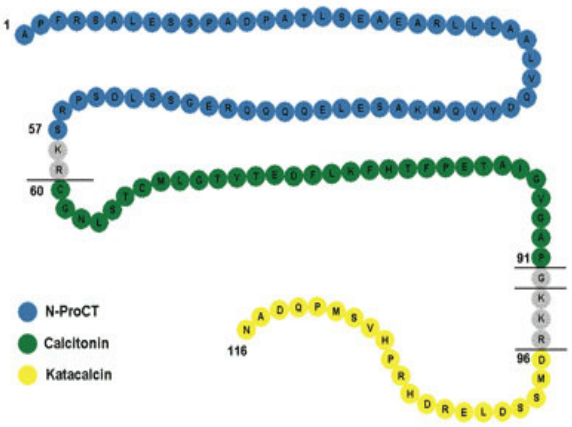
Procalcitonin

Structure discovered in 1975

116 amino acid intracellular precursor to calcitonin

Regulated by *CALC-1* gene on chromosome 11



Maruna P et al. *Physiol Res.* 2000; 49 (Suppl 1): S57-61.
Foushee JA et al. *J Antimicrob Chemother.* 2012;67(11):2560-9.

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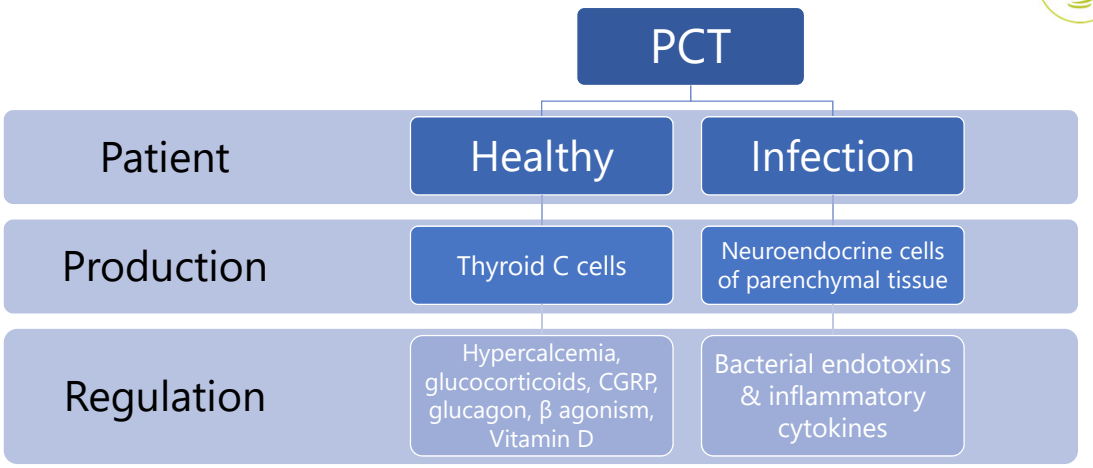
PCT Physiology



CGRP = calcitonin gene related peptide

Maruna P et al. *Physiol Res.* 2000; 49 (Suppl 1): S57-61.
Foushee JA et al. *J Antimicrob Chemother.* 2012;67(11):2560-9.

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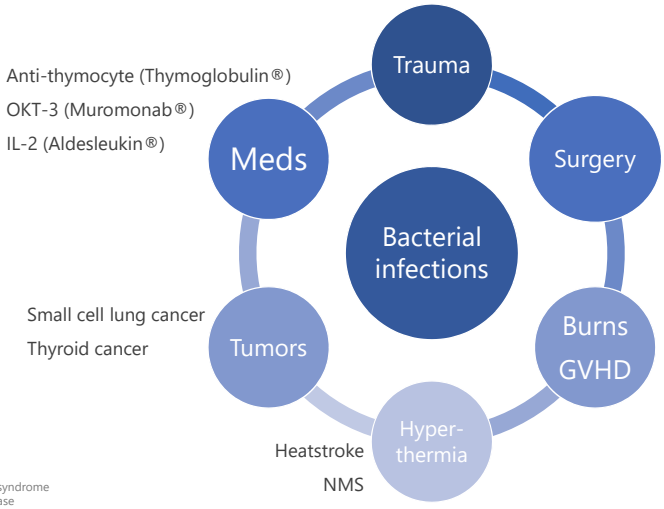
Sources of Increased PCT



NMS = neuroleptic malignant syndrome
GVHD = graft versus host disease

Maruna P et al. *Physiol Res.* 2000; 49 (Suppl 1): S57-61.
Foushee JA et al. *J Antimicrob Chemother.* 2012;67(11):2560-9.

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PCT Kinetics

- Half-life: 24 hours
- Levels ↑ 2-6 hours after onset of bacterial infections
  - Peak within 6-24 hours
- Transient ↑ up to 12-24 hours post-surgery or trauma
  - Prolonged increases after surgery indicate infection and possible sepsis

PCT Levels	
	<0.1 µg/L = healthy
	0.1 to <0.25 µg/L = infection unlikely
	0.25 to <0.5 µg/L = possible infection
	>0.5 µg/L = bacterial infection likely
	>2.0 µg/L = sepsis likely

Jensen JU et al. *BMC Infectious Diseases.* 2008;8:91.
Maruna P et al. *Physiol Res.* 2000; 49 (Suppl 1): S57-61.
Foushee JA et al. *J Antimicrob Chemother.* 2012;67(11):2560-9.

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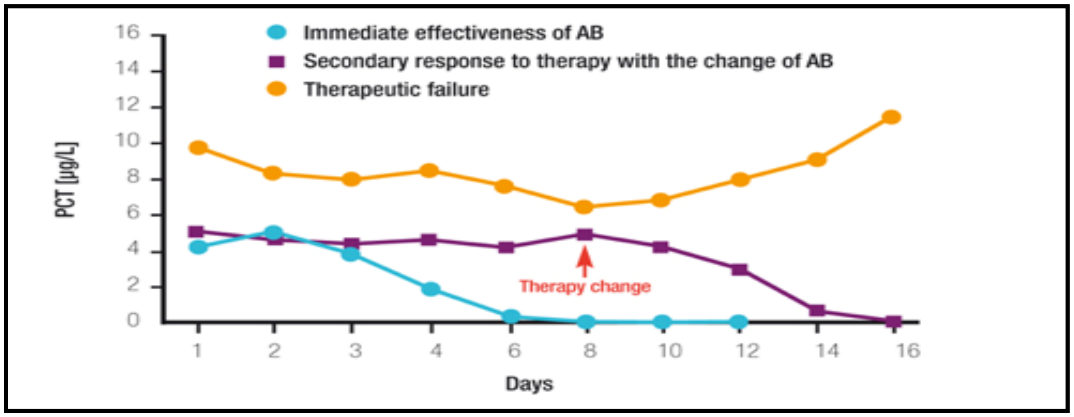
PCT Kinetics

Serum PCT level according to response to antibiotic (AB) treatment (n=109)



Schuetz P et al. *Expert Rev Anti Infect Ther.* 2010;8 (5): 575-87.

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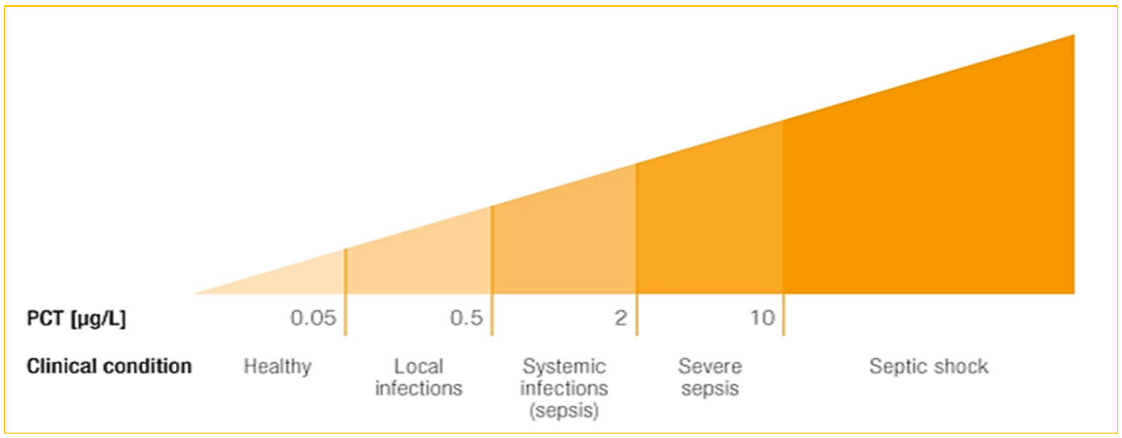
PCT Levels and Infection Severity



Sepsis Marker PCT. <http://www.procalcitonin.com>

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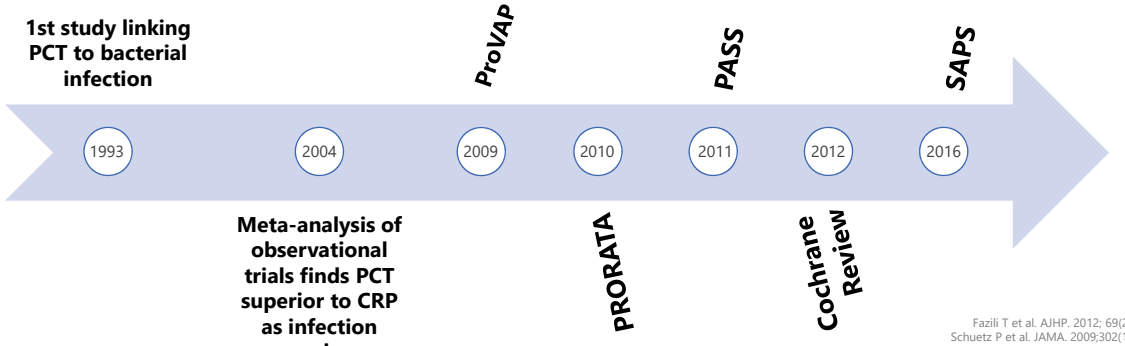
PCT Clinical Trials



Fazili T et al. AJHP. 2012; 69(23):2057-61.
Schuetz P et al. JAMA. 2009;302(10):1059-66.
Bouadma L et al. Lancet. 2010;375:463-74.
Jenson J et al. Crit Care Med. 2011;39(9):2048-58.
De Jong E et al. Lancet Infect Dis. 2016; 16(7):819-27.
Schuetz P et al. Cochrane Database 2012.

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ProVAP

- **Patients**: 101 adults with newly diagnosed VAP
- **Design**: multi-center, superiority, RCT in 7 ICUs
- **Intervention**: antibiotic (ABX) discontinuation strategy guided by serum PCT concentrations or standard of care (control)
- **Primary Endpoint**: ABX-free days alive at 28 days
- **Secondary Endpoints**: MV-free days, ICU-free days, change in respiratory status, hospital LOS, VAP-related adverse effects, mortality at 28 days

LOS = length of stay
MV = mechanical ventilation
RCT = Randomized controlled trial

Schuetz P, et al. *JAMA*. 2009;302(10):1059-66.

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ProVAP PCT Algorithm

<0.25 µg/L	0.25 – 0.5 µg/L or decrease by ≥ 80%	≥ 0.5 µg/L or decrease by < 80%	> 1 µg/L
Absence of VAP	Bacterial infection unlikely	Unresolved bacterial infection	Strongly suggests unresolved bacterial infection
Discontinuation of ABX strongly encouraged	Reduction or discontinuation of ABX encouraged	Reduction or discontinuation of ABX discouraged	Reduction or discontinuation of ABX strongly discouraged

Schuetz P, et al. *JAMA*. 2009;302(10):1059-66.

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ProVAP Results

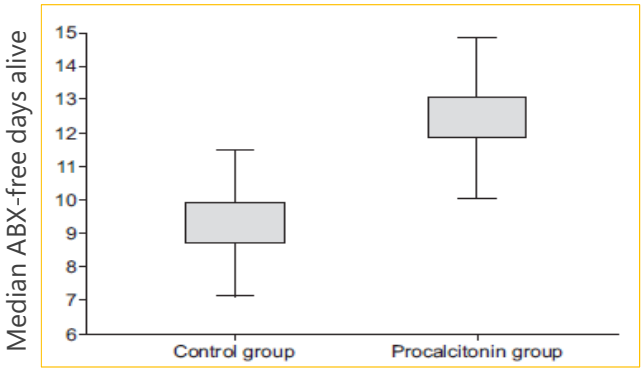
Median (IQR) ABX-free days alive at 28 days:

PCT 13 (2-21) vs. 9.5 days (1.5-17)

Reduction of 27% of overall duration in the PCT group:

10 vs. 15 days (p=0.038)

No difference in secondary endpoints



Schuetz P, et al. *JAMA*. 2009;302(10):1059-66.

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PRORATA

Patients: 621 adults with suspected bacterial infections in the ICU; >70% respiratory infections, >50% hospital acquired

Design: multi-center, non-inferiority, RCT in 7 ICUs (5 medical & 2 surgical)

Intervention: ABX initiation and discontinuation strategy based on PCT or standard of care (control); ultimately at provider discretion in both arms

Primary Endpoint: Mortality at 28 and 60 days; ABX-free days at 28 days

Secondary Endpoints: Relapse, superinfection, MV-free days, ICU LOS, hospital LOS

Bouadma L, et al. *Lancet*. 2010;375:463-74.

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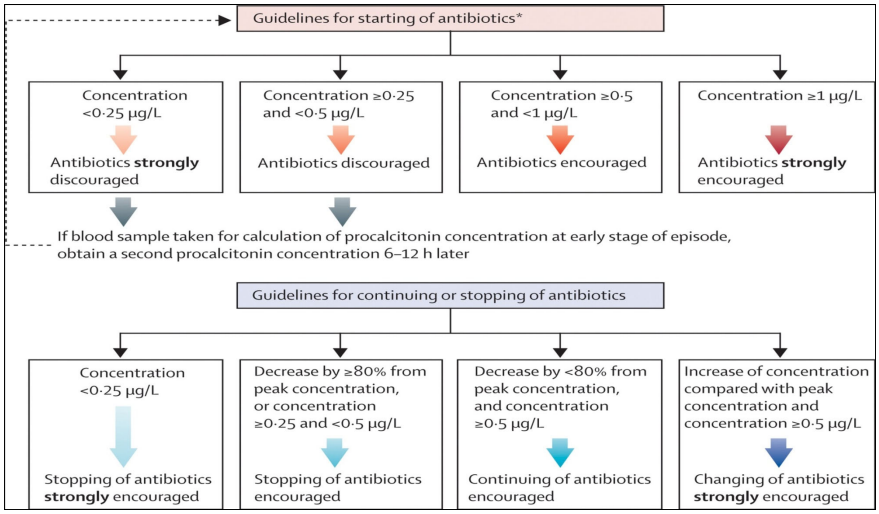
PRORATA PCT Algorithm



Bouadma L, et al. *Lancet*. 2010;375:463-74.

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PRORATA Results

Mortality non-inferior at both 28 and 60 days (PCT vs. Control)

- 28 days: 21.2% vs. 20.4%
  - Absolute difference: 0.8% (90% CI: -4.6 to 6.2%)
- 60 days: 30.0% vs. 26.1%
  - Absolute difference: 3.8% (90% CI: -2.1 to 9.7%)

Antibiotic free alive days non-inferior at 28 days

- PCT vs Control: 14.3 vs. 11.6 days
  - Absolute difference: 2.7 days (90% CI: 1.4 to 4.1 days)

Bouadma L, et al. *Lancet*. 2010;375:463-74.

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PASS

- **Patients**: 1200 critically ill adults with suspected bacterial infections; 55% respiratory infections
- **Design**: multi-center, non-inferiority, RCT in 9 ICUs (mixed medical & surgical) in Denmark
- **Intervention**: ABX escalation or discontinuation strategy based on PCT or standard of care (control)
- **Primary Endpoint**: Mortality at 28 days
- **Secondary Endpoints**: MV-duration, ICU LOS, adverse events, healthcare utilization

Jenson J, et al. *Crit Care Med.* 2011;39(9):2048-58.

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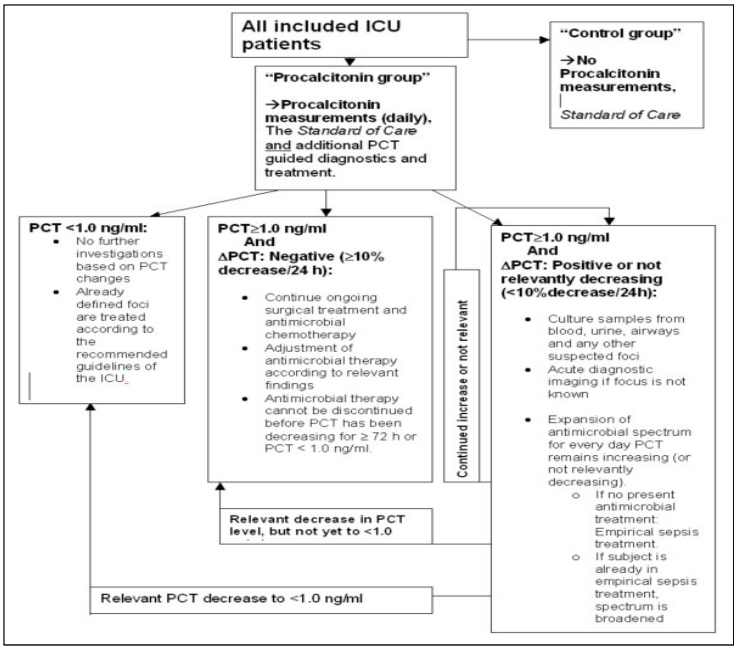

PASS Algorithm

Jenson J, et al. *Crit Care Med.* 2011;39(9):2048-58.

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PASS Results

Primary Outcome (PCT vs. control):

- 28-day mortality: 31.4% vs. 32%
  - ARR 0.6% (95% CI: - 4.7% to 5.9%)

Secondary Outcomes (PCT vs. control):

- ICU LOS: 6 vs. 5 days (p=0.004)
- Duration of MV increased 4.9% in PCT group
  - 95% CI: 3 to 6.7%
- Days of renal dysfunction increased 5% in PCT group
  - 95% CI: 3 to 6.9%
- Increased use of broad spectrum antibiotics, combination therapy, cultures, and imaging in PCT group

Jenson J, et al. *Crit Care Med.* 2011;39(9):2048-58.

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Why the Difference?

Higher PCT cut off (1.0 µg/mL)

- Not as sensitive
- Too high to reliably detect candidemia

Routine escalation of therapy and diagnostics

- Low resistance rates may not have required escalation
- Treatment driven only by PCT not clinical indicators

Population differences (vs. PRORATA)

- Deviations from protocol guidelines (18% vs. 50%)
- More surgical patients (10% vs. 41%)

Bouadma L, et al. *Lancet* .2010;375:463-74.
Jenson J, et al. *Crit Care Med.* 2011;39(9):2048-58.

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PCT, Should We PASS?

2012 Cochrane Review

- 14 RCTs including 4221 patients with acute respiratory infections

PCT Group	
Decreased all cause mortality	OR 0.94 (95%CI 0.71 to 1.23)
Decreased treatment failure	OR 0.82 (95%CI 0.71 to 0.97)
Decreased ABX exposure	-3.47 days (95%CI -3.78 to -3.17)

Schuetz P, et al. *Cochrane Database of Systematic Reviews*. 2012.

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PCT, Should We PASS?

2016 SAPS Study

- RCT including 1575 ICU patients with ~64% acute respiratory infections and ~25% hospital-acquired infections

PCT Group	
Decreased 28 day mortality	19.6 vs. 25% (p<0.012)
Decreased 1 year mortality	34.8 vs. 40.9% (p<0.015)
Decreased median ABX duration	5 vs. 7 days (p<0.0001)

De Jong E, et al. *Lancet Infect Dis*. 2016; 16(7):819-27.

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PCT for Initiation or Cessation?

2018 Meta Analysis

- 15 RCTs including 3 for initiation, 9 for cessation, and 3 mixed studies
- Primary outcome: short-term (30 day) all cause mortality

PCT Group	Mortality, RR (95% CI)	Antibiotic duration, days (95% CI)
Initiation	1.00 (0.86 – 1.15)	NR
Cessation	0.87 (0.77 – 0.98)	-1.26 (-1.98 to -0.54) p<0.001
Mixed	1.01 (0.80 – 1.29)	-3.10 (-6.09 to -0.11) p=0.04

Lam SW, et al. *Crit Care Med* 2018;46:684-90.

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Limitations of PCT

- Other sources of increased PCT
- Limited data:
  - Febrile neutropenia & immunosuppression
  - Post-surgical infections
- Renal function affects PCT levels
  - Baseline PCT elevation in chronic kidney disease
  - PCT cleared by continuous renal replacement therapy

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2016 IDSA/ATS HAP/VAP Guidelines

For patients with suspected HAP/VAP, we recommend **using clinical criteria alone** rather than using serum PCT plus clinical criteria **to decide whether or not to initiate** antibiotic therapy *(strong recommendation, moderate-quality evidence)*

For patients with HAP/VAP, we suggest **using PCT levels plus clinical criteria to guide the discontinuation** of antibiotic therapy, rather than clinical criteria alone *(weak recommendation, low-quality evidence)*

Kalil, et al. *CID.* 2016; 63:1-51.

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2016 Surviving Sepsis Guidelines

We suggest that measurement of **PCT levels can be used to support shortening the duration** of antimicrobial therapy in sepsis patients *(weak recommendation, low quality of evidence)*

We suggest that **PCT levels can be used to support the discontinuation of empiric antibiotics** in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection *(weak recommendation, low quality of evidence)*

Rhodes, A. *Crit Care Med.* 2017; 45(3): 486-552.

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PCT: The Bottom Line

PCT is the most specific biomarker and has several advantages over previous markers

PCT is well studied in respiratory infections and in the critically ill

- Algorithms have been developed for both lower respiratory tract infections and sepsis based on the PRORATA study design

PCT isn't perfect

- Interpret in the clinical context of the patient
- Serial measurements are preferred and provide more useful information
- Be aware of conditions which may affect PCT levels
- Good clinical judgement should always be applied

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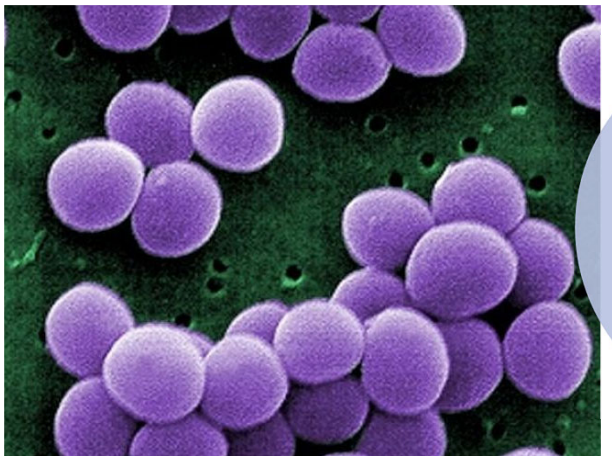
Methicillin Resistant *Staphylococcus aureus*



MRSA

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Methicillin Resistant *Staphylococcus aureus*

- Recommend empiric coverage based on local antibiogram and risk factors
- Empiric MRSA coverage
  - Risk factors for MRSA HAP/VAP: Prior IV antibiotic use within 90 days
  - *Staphylococcus aureus* >10 – 20% MRSA or prevalence unknown
  - High risk for mortality
    - Need for ventilator support in HAP
    - Septic shock

2018 Hospital Antibiogram	Systemic isolates (n=700)
Staphylococcus aureus	Nafcillin 48%

Kalil, et al. *CID.* 2016; 63:1-51.

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MRSA Nares Swabs

Nares Swab	Polymerase Chain Reaction (PCR)	mecA gene Results: 2 hours
	Culture	Chromogenic agar (CA) or disk diffusion Results: 24-48 hours

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PCR vs Culture

Method (# studies)	Sensitivity (95% CI)	Specificity (95% CI)
PCR (n=15)	92.5% (87.4–95.9)	97.0% (94.5–98.4)
CA 18-24 h (n=28)	78.3% (71.0–84.1)*	98.6% (97.7–99.1)
CA 48 h (n=24)	87.6% (82.1–91.6)	94.7% (91.6–96.8)
Disk diffusion 48 h (n=7)	86.9% (74.7–93.7)	89.7% (77.7–95.6)*

*Significantly lower than PCR
CA = chromogenic agar
PCR = polymerase chain reaction

Luteijn JM, et al. *Clin Microbiol Infect* .2011;17:146 -54.

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Definitions

- **Negative predictive value (NPV):** percentage of patients with a negative test who do not have the disease
- **Positive predictive value (PPV):** percentage of patients with a positive test who actually have the disease
- **Sensitivity:** ability of a test to correctly classify an individual as *diseased*
- **Specificity:** ability of a test to correctly classify an individual as *disease-free*

Parikh. *Indian J Ophthalmol.* 2008;56(1):45–50.

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MRSA Nares for Stewardship

Clinical Infectious Diseases
MAJOR ARTICLE

The Clinical Utility of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications

Diane M. Parente,[1] Cheston B. Cunha,[2,3] Eleftherios Mylonakis,[2,3] and Tristan T. Timbrook[4]

- Included 22 studies and 5,163 patients with suspected pneumonia (CAP, HCAP, HAP, VAP)
- Pooled prevalence of MRSA pneumonia
  - 10% (95% CI, 8-13%)
- Detection method
  - Polymerase chain reaction: 50%
  - Culture methods: 18.2%

Parente D, et al. *Clin Infect Dis.* 2018 Jan 11. doi: 10.1093/cid/ciy024.

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MRSA Nares for Stewardship

Type of pneumonia	No. of studies	Sensitivity, % (95%CI)	Specificity, % (95%CI)	PPV, %	NPV, %
All	22	70.9 (58.8 – 80.6)	90.3 (86.1 – 93.3)	44.8	96.5
CAP/HCAP	4	85.0 (59.7 – 95.6)	92.1 (81.5 – 96.9)	56.8	98.1
VAP	5	40.3 (17.4 – 68.4)	93.7 (77.1 – 98.4)	35.7	94.8

Overall negative likelihood ratio (95%CI): 0.32 (0.22 – 0.46)

Parente D, et al. *Clin Infect Dis.* 2018 Jan 11. doi: 10.1093/cid/ciy024.

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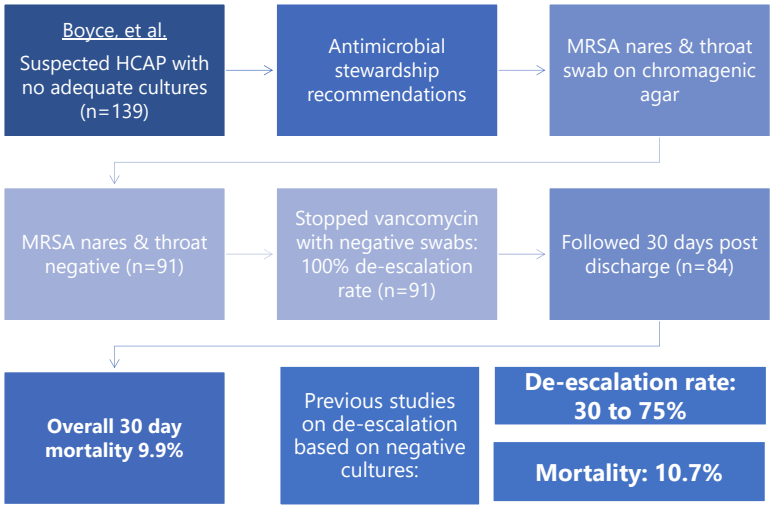
What About Outcomes?



Boyce JM, et al. *AAC*. 2013; 57(3):1163-8.

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MRSA Nares Considerations

Timing

- Majority of studies ≤ 48 hours between nares swab and respiratory culture
- Some studies have shown similar NPV between 7-14 days

Cultures

- No culture, whether invasive or noninvasive (BAL, ET aspirate, sputum), has shown superior correlation
- Correlation with other cultures (blood) have limited evidence

Prevalence

- Accuracy of NPV depends on individual institution prevalence
- Previous studies had MRSA prevalence of 5-20%

Cost & Outcomes

- Potential area for future research

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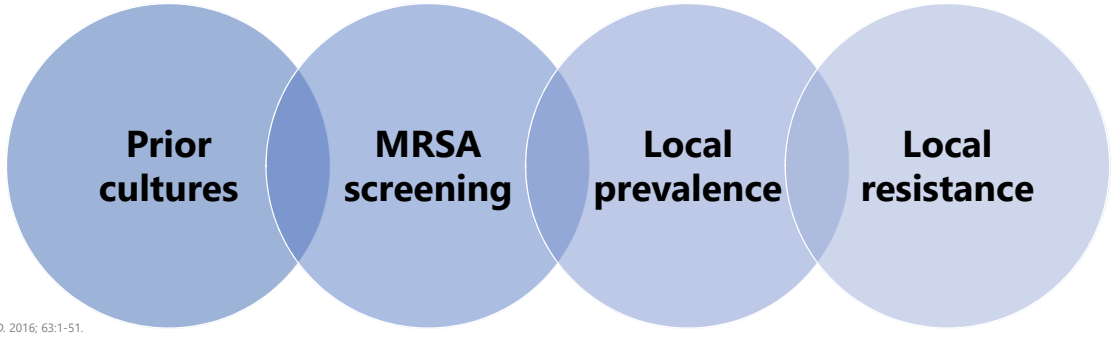
2016 IDSA/ATS HAP/VAP Guidelines

"The panel strongly encourages clinicians to consider all relevant, available data about both their individual patient and their practice environment to tailor empiric choices for each patient."



Kalil, et al. *CID.* 2016; 63:1-51.

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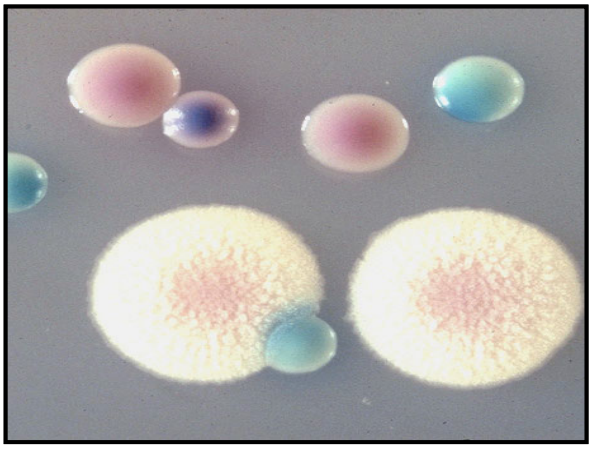
Fungal Diagnostics



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Invasive Candidiasis Review

- *Candida species* are the fourth most common cause of nosocomial bloodstream infections
- Candidemia
  - Increases mortality by 15%
  - Increases hospital length of stay an average 10 days
- Up to 60% mortality of invasive candidiasis in critically ill patients
- Fungal cultures from non-sterile sites may be positive without clinical implication

Pfaller MA. J Clin Microbiol. 2001 Sep;39(9):3254-9.
Zaoutis TE. Clin Infect Dis. 2005 Nov 1;41(9):1232-9.

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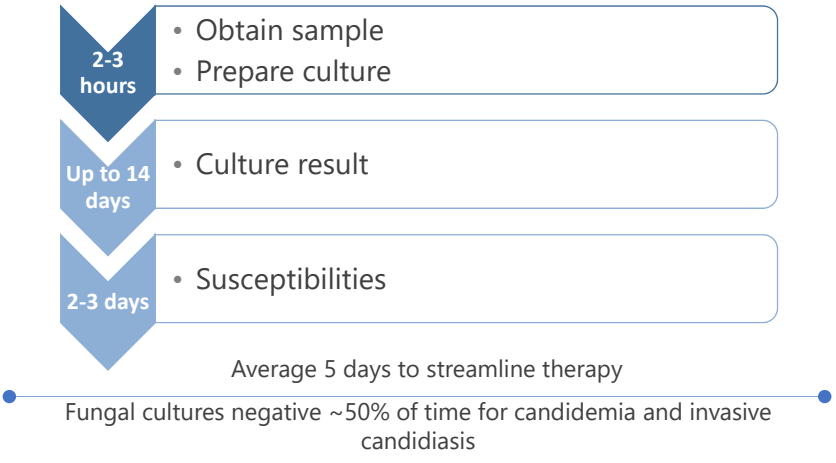
Current Strategy – Fungal Cultures



Shah DN. Antimicrob Agents Chemother. 2012 Jun;56(6):3239-43.
Berenguer J. Diagn Microbiol Infect Dis. 1993 Aug-Sep;17(2):103-9.
Wenzel RP. Clin Infect Dis. 1995 Jun;20(6):1531-4.

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Other Fungal Diagnostics

- (1,3) β-D Glucan Assay (BDG)
- T2 Candida Assay
- Galactomannan (aspergillus antigen) Assay
- Cryptococcal Antigen

Associates of Cape Cod International, Inc. Fungitell (2011).
T2 Candida Panel (2015).
Platelia *Aspergillus* EIA, Bio-Rad (2003).
CrAg Lateral Flow Assay, IMMY (2016).

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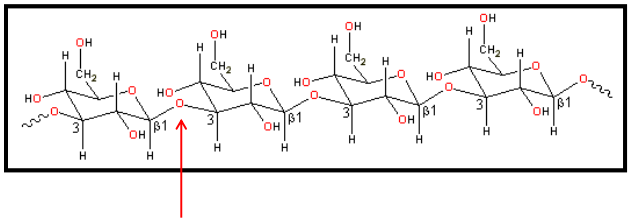
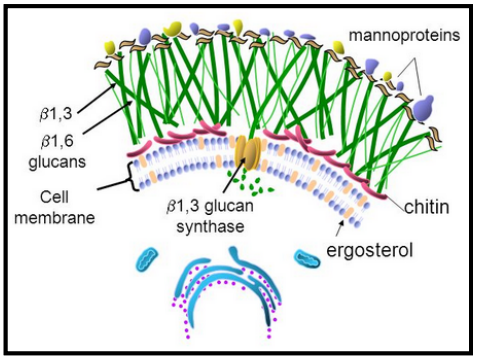
(1,3) β-D-Glucan

Component of fungal cell walls

- *Candida sp.*
- *Aspergillus sp.*
- *Fusarium sp.*
- *Trichosporon sp.*
- *Coccidioides immitis*
- *Histoplasma capsulatum*
- *Pneumocystis sp.*





Associates of Cape Cod International, Inc. (2011) Fungitell.

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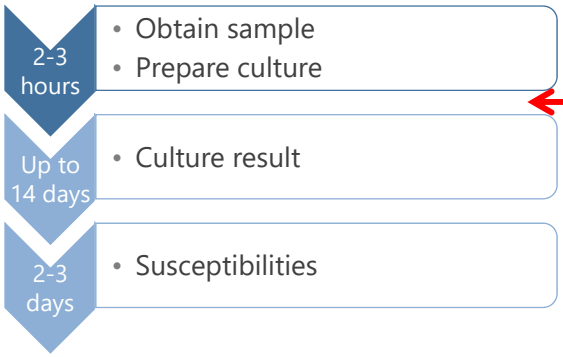
β-D-Glucan – Fungitell Assay



BDG

Results within 1 hour

Result	Level
Normal	10 – 40 pg/mL
Negative	< 60 pg/mL
Indeterminate	60 – 79 pg/mL
Positive	> 80 pg/mL

Associates of Cape Cod International, Inc. (2011) Fungitell.

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Early Diagnosis of Candidemia

Design	Patients	Methods
• Prospective study of non-neutropenic ICU patients at risk for invasive fungal infection (IFI) • Compared BDG, *Candida* score, and *Candida* colonization index	• 95 patients with signs of sepsis and requiring at least 5 days in the ICU, without baseline IFI • 16.8% (n=14) incidence of proven IFI	• Fungal surveillance cultures obtained (day 0, day 3, and twice weekly thereafter) • At signs of sepsis blood cultures and blood samples for BDG were obtained • BDG >80 pg/mL considered positive

Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
92.9 (66.1 – 99.8)	93.7 (85.8 – 97.9)	72.2 (46.5 – 90.3)	98.7 (92.8 – 99.9)

Postero B. Crit Care. 2011;15(5):R249.

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FUNGINOS

Design

- Assessment of BDG as a diagnostic marker for deep-seated invasive candidiasis in culture negative patients
- Cohort study in two intensive care units in Switzerland
- Included patients with abdominal surgery or necrotizing pancreatitis requiring ICU stay ≥ 72 hours

Patients

- 89 patients requiring at least 72 hours in ICU
  - 68 recurrent GI perforation
  - 21 necrotizing pancreatitis
- 29 / 89 confirmed intraabdominal candidiasis
- 27 of 29 patients had negative blood fungal cultures

Methods

- Cultures from nonsterile sites obtained twice weekly
- 2 blood cultures were obtained at onset of fever and with persistent fever in setting of antibacterial therapy
- **BDG Measurements**
  Blood samples drawn at study inclusion and three times weekly thereafter

Tissot F. Am J Respir Crit Care Med. 2013 Nov 1;188(9):1100-9.

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FUNGINOS

Patient groups

- Not colonized (n=2)
- Colonized, not receiving antifungals (n=40)
- Colonized and receiving preemptive antifungals (n=18)
- Documented intraabdominal candidiasis (n=29)

Results

- BDG positive even when cultures were negative
- Patients with severe sepsis/septic shock had higher BDG compared to patients with less severe infection
  - 313 pg/mL vs 100 pg/mL ($p < 0.007$)
- BDG was positive median 5 days before cultures
- BDG declined in 20/22 (91%) patients who responded to antifungal therapy

Tissot F. Am J Respir Crit Care Med. 2013 Nov 1;188(9):1100-9.

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FUNGINOS

BG: β-D-Glucan, PPV: positive predictive value, NPV: negative predictive value

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
BG >/= 80 x1 at inclusion	76 (56 – 90)	59 (43 – 74)	56 (40 – 72)	78 (60 – 90)
BG >/= 80 x1 at infection	83 (64 – 94)	40 (26 – 57)	49 (34 – 64)	77 (55 – 92)
BG >/= 80 x2 at inclusion	66 (45 – 82)	83 (69 – 93)	73 (52 – 88)	78 (63 – 89)
BG >/= 80 x2 at infection	65 (46 – 82)	78 (63 – 90)	68 (48 – 84)	77 (61 – 88)

Tissot F. *Am J Respir Crit Care Med.* 2013 Nov 1;188(9):1100-9.

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BDG + PCT for Fungal Infections

Design	Patients	Methods
• Multicenter, retrospective study of critically ill adults with candidemia or bacteremia • Compared BDG and PCT for the differential diagnosis of candidemia and bacteremia	• 166 patients • 73 with candidemia • 93 with bacteremia • Excluded mixed infections	• Index culture: day of first positive blood culture • BDG: within 48 hours of index culture • PCT: within 24 hours of index culture

Giacobbe et al. *Critical Care* (2017) 21:176

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BDG + PCT for Fungal Infections

Cutoff	Candidemia	Bacteremia	Sensitivity(%)	Specificity (%)	PPV (%)	NPV (%)
BDG ≥80 pg/mL and/OR PCT <2 ng/mL	70/73	56/93	96	60	65	95
BDG ≥80 pg/mL AND PCT <2 ng/mL	48/73	91/93	66	98	96	78

Giacobbe et al. *Critical Care* (2017) 21:176

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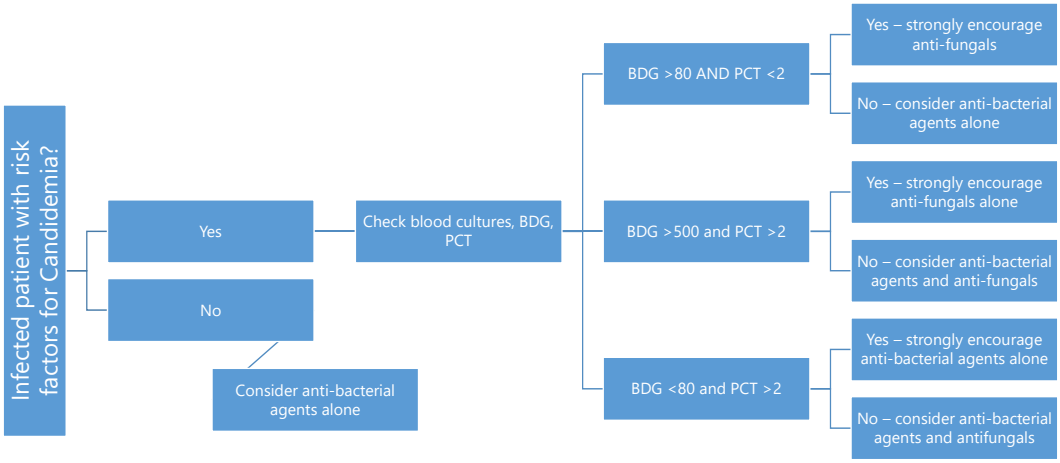
Potential clinical tools



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2016 IDSA Candidiasis Guidelines

Empiric antifungal therapy should be considered in critically ill patients with risk factors for invasive candidiasis and no other known cause of fever and should be based on clinical assessment of risk factors and surrogate markers for invasive candidiasis (strong recommendation; moderate-quality evidence).

For patients who have no clinical response to empiric antifungal therapy at 4–5 days and who do not have subsequent evidence of invasive candidiasis after the start of empiric therapy or have a negative non-culture-based diagnostic assay with a high NPV, consideration should be given to stopping antifungal therapy (strong recommendation; low-quality evidence).

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2016 Surviving Sepsis Guidelines

Rapid diagnostic testing using β-D-glucan assays to minimize inappropriate anti-*Candida* therapy may have an evolving supportive role. However, the NPV of such tests is not high enough to justify dependence on these tests for primary decision-making.

Rhodes, A. *Crit Care Med*. 2017; 45(3): 486-552.

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β-D-Glucan Considerations

Potential False Positive Results	Consideration
Hemodialysis filters and surgical gauze	Contain cellulose (Should determine institution use of cellulose HD or CRRT filters)
Bacteremia (S. pneumoniae, P. aeruginosa)	BDG in cell wall may produce mildly elevated BDG assay (average 17 pg/mL)
IVIG, Albumin, coagulation factors, and plasma	Filtered through BDG-containing filters
Mucositis or disruptions in gastrointestinal mucosa	Translocation of gut flora
Use of certain antibiotics	Made from fungal sources. Clinical significance is debatable.

Associates of Cape Cod International, Inc. (2011) Fungitell: Instructions for use.
Marty FM. *AAC.* 2006;50(10):3450-3453.

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Antibiotics containing BDG

Antibiotic	Concentration of BDG (pg/mL)	
	Reconstituted vial Concentration	Maximum plasma concentration
Colistin	4,348	<4
Ertapenem	3,472	<32
Cefazolin (vials)	2,054	<4
Trimethoprim-sulbactam	1,187	<8
Cefotaxime	560	<8
Cefepime	425	<8
Ampicillin-sulbactam	519	<8
Piperacillin-tazobactam	<80	<8

Marty FM. *AAC.* 2006;50(10):3450-3453.

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Cost Considerations‡

Diagnostic test cost	Antibiotic cost per patient day
MRSA nares $150*	Vancomycin $140ɣ
Procalcitonin $275	Linezolid (IV) $350
β-D glucan assay $300	Piperacillin-tazobactam $600
Cryptococcal antigen $100	Micafungin $800
Galactomannan $300	Fluconazole (IV) $200

‡ Approximate patient charge
*No extra charge if done for infection control surveillance
ɣ Does not include cost of levels

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In Summary

- Antimicrobial stewardship decreases resistance and cost and leads to improved patient outcomes
- Procalcitonin should be interpreted in context with clinical picture and is more useful when trended
- MRSA nares swabs are useful for ruling out MRSA but depend on prevalence
- β-D-glucan assay can be useful as a diagnostic marker for invasive candidiasis but has clinical limitations

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