Initial Antibiotic Selection and De-escalation in Sepsis

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Disclosure

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Overview

- Sepsis and sepsis shock
- Initial Antibiotic Selection
  - Timing of initiation
  - Specific factors for consideration
- De-escalation based on
  - Culture results
  - Absence of suspicion for resistant pathogens
  - Biomarkers indicating bacterial infection

Sepsis and Septic Shock

Sepsis:

- Life-threatening organ dysfunction caused by a host's response to infection

Septic shock:

- Sepsis with circulatory and cellular/metabolic dysfunction
- Higher risk of mortality

Diagnostic approach:

- Systemic inflammatory response syndrome (SIRS)
- Sequential organ failure assessment (SOFA)
  - qSOFA (at least 2): RR >= 22/min, altered mentation, SBP <= 100 mmHg

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

Cultures

- Before antibiotics, cultures should be obtained if able to do so in a timely manner
- Blood cultures x 2
- Cultures from other suspected sites of infection
- Routine “pan-culture” is not recommended

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

Timing of Antibiotics

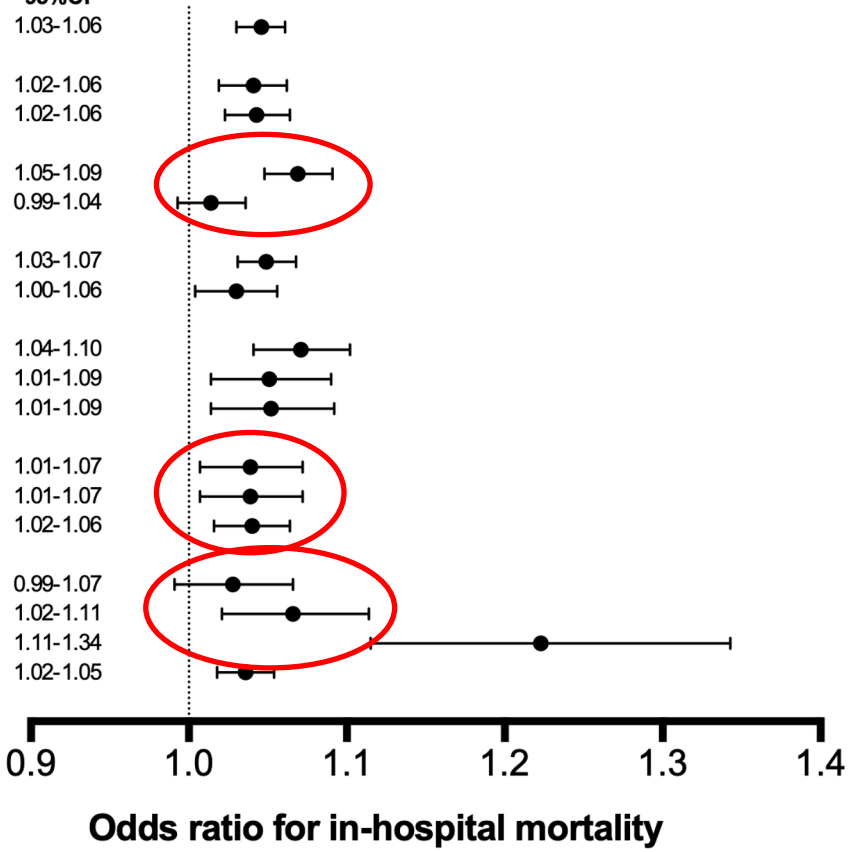
“IV antibiotics should be administered as soon as possible and within one hour of recognition of sepsis and septic shock” - Surviving Sepsis Campaign

- In a study of 49,331 patients with sepsis/septic shock, 82.5% completed the 3-hour bundle within 3 hours
  - Median time to administration of antibiotics was 0.95 hours
  - Each hour delayed in administering antibiotics, resulted in a 4% increase in risk adjusted in-hospital mortality

Rhodes A, et al. *Crit Care Med*. 2017;45(3):486-552; Seymour CW, et al. *N Engl J Med*. 2017;376(23):2235-2244

Risk-adjusted OR for Each Hour until Administration of Antibiotics

Model	No.	Odds ratio	95%CI
All cases	49,331	1.04	1.03-1.06
Gender			
Male	25,689	1.04	1.02-1.06
Female	23,634	1.03	1.02-1.06
Vasopressors			
Yes	16,721	1.07	1.05-1.09
No	32,610	1.01	0.99-1.04
Admission source			
Home	33,464	1.05	1.03-1.07
Other	15,867	1.03	1.00-1.06
Comorbidities			
Congestive heart failure	10,092	1.07	1.04-1.10
Hemodialysis	5,207	1.05	1.01-1.09
Chronic respiratory failure	5,738	1.05	1.01-1.09
Source of infection			
Respiratory	19,839	1.04	1.01-1.07
Urinary	13,439	1.04	1.01-1.07
Other	16,053	1.04	1.02-1.06
Bacteremia			
Gram positive	7,175	1.03	0.99-1.07
Gram negative	6,431	1.07	1.02-1.11
Other	965	1.22	1.11-1.34
None	34,757	1.04	1.02-1.05



Seymour CW, et al. *N Engl J Med*. 2017;376(23):2235-2244

Empiric Antimicrobial Recommendation

"We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)"

- Surviving Sepsis Campaign

- Risk of antimicrobial resistance
- Clostridium difficile colitis
- Acute kidney injury

- Increased morbidity and mortality

Over use of broad-spectrum antibiotics

Inadequate antibiotic coverage

Considerations for Choosing Empiric Therapy

What is the likely source of infection?

What is/are the likely pathogen(s)?

How catastrophic would the outcome be if antibiotics were incorrectly withheld?

Required Coverage

Empiric Therapy should include broad coverage against:

- Gram (+) Organisms
- Gram (-) Organisms

Routine coverage of multidrug-resistant organisms (MDRO) is not necessary unless patient has risk factors

- Methicillin resistant *Staphylococcus aureus* (MRSA)
- *Pseudomonas aeruginosa*

Host Risk Factors to Assess

- Severity of illness
- Travel history
- Patient location at the time of infection acquisition
  - Community vs. long-term care vs. hospital
  - MDRO coverage not needed for most community acquired sources of infection without risk factors
- Comorbidities: chronic illness, chronic organ dysfunction
- Presence of indwelling devices
- Immunosuppression or immunocompromised
- Recent known infection
- Use of recent antibiotics within previous 3 months
- Colonization with specific pathogens

Risk Factors for MDROs

- Recent hospitalization or prolonged hospitalization
- Recent administration of broad-spectrum antibiotics
- History of prior infection/colonization
- Resides in a long-term care facility

MRSA

- Catheter related infections
- Skin and soft tissue infections (SSTI)

Pseudomonas

- Ventilator associated pneumonia (VAP)
- Structural lung disease (HAP/VAP)

HAP = hospital acquired pneumonia

Broad-Spectrum Antibiotic Coverage

TABLE 1. SELECTED ANTIMICROBIAL AGENTS AND SPECTRUM OF COVERAGE

	Gram +	*Gram −*	*Anaerobes*	*Pseudomonas*	*MRSA*	*ESBL*	*VRE*
Vancomycin	X				X		
Linezolid	X				X		X
Daptomycin	X				X		X
Piperacillin-tazobactam	X	X	X	X			
Meropenem	X	X	X	X		X	
Doripenem	X	X	X	X		X	
Imipenem-cilastatin	X	X	X	X		X	
Ertapenem	X	X	X			X	
Ceftriaxone	X	X					
Cefepime	X	X		X			
Ciprofloxacin	X	X		X			
Levofloxacin	X	X		X			
Metronidazole			X				

ESBL = extended-spectrum β-lactamase producer; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

Buckman SA, et al. *Surg Infect*. 2018;19(2):147-154.

Combination Antibiotic therapy

- The use of at least two different antibiotics from different classes with the intent to cover a specific known or suspected pathogen with more than one antibiotic (a.k.a. “double coverage”) to *accelerate clearance*

  - Initial use for patients in septic shock with a suspected gram-negative infection based on local epidemiology (increased local resistance)
    - E.g., Beta-lactam with aminoglycoside
    - Weak evidence for improved survival
  - Not recommended in sepsis or bacteremia without shock
    - No difference seen in outcomes
    - Increased risk for renal failure

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

Gram-Negative Organisms

Percent Susceptible (Number of isolates tested)	# of all isolates from all sources	Penicillins			Cephalosporins				Carbapenems			Quinolones	
		Amoxicillin/ Clavulanic Acid	Ampicillin/ Sulbactam	Piperacillin/ Tazobactam	Cefuroxime	Ceftriaxone	Ceftazidime	Cefepime	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Levofloxacin
Acinetobacter sp.	859		93 (805)	75 (843)		17 (841)	77 (795)	83 (154)		98 (794)	99 (795)	90 (859)	94 (795)
Citrobacter freundii†	452		*	*	*	*		97 (412)	100 (312)	99 (274)	100 (314)	92 (447)	92 (314)
Citrobacter koseri†	1,214			97 (1,213)	78 (434)	98 (1,205)	99 (622)	99 (1,026)	100 (893)	100 (436)	98 (622)	99 (1,213)	99 (474)
Enterobacter sp.	2,948	*	*	*	*	*	86 (,1740)	95 (2,593)	100 (1,796)	98 (1,419)	100 (1,740)	96 (2,787)	98 (1,740)
Escherichia coli	49,745	88 (43,611)	64 (30,677)	98 (46,444)	73 (4,077)	95 (49,745)	93 (26,568)	97 (43,477)	100 (24,411)	100 (24,412)	95 (28,482)	83 (49,742)	82 (28,468)
Klebsiella pneumoniae	10,640	95 (4,475)	85 (6,391)	96 (10,209)	87 (2,798)	97 (10,305)	95 (6,085)	96 (8,803)	100 (5,522)	100 (5,167)	100 (5,167)	96 (10,327)	96 (5,981)
Proteus mirabilis	4,872	99 (2,199)	95 (2,765)	100 (4,813)	97 (805)	98 (4,867)	99 (2,714)	98 (4,349)	100 (2,249)	87 (2,199)	99 (1,318)	92 (4,872)	94 (2,714)
Pseudomonas aeruginosa	7,413			99 (6,822)			91 (3,409)	93 (6,573)	*	90 (6,536)	95 (4,251)	87 (7,413)	81 (4,250)

2017 Hawaii Statewide Antibiogram. https://health.hawaii.gov/docd/files/2019/05/2017-Hawaii-Statewide-Antibiogram.pdf. Accessed 6/25/2021.

Appropriate Antibiotic Use

Optimal antimicrobial use

- Early initiation of appropriate antimicrobial therapy
- Utilizing the most narrow spectrum agent to provide adequate coverage for causative pathogens
- Utilizing shortest duration of therapy to ensure efficacy while minimizing adverse drug events

Antibiotic De-escalation

“We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted” - Surviving Sepsis Campaign

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

Antibiotic De-escalation (ADE)

- Should be part of the standard process of patient care in sepsis
- Includes:
  - Discontinuation of one or more components of combined empirical therapy
  - Changing broad spectrum agents to a more narrow spectrum agent
  - Shortening antibiotic duration
- Only an estimated 16% of ICU patients have their treatment de-escalated during the first 72 hours of admission

De Bus L, et al. *Intensive Care Med*. 2020;46:1404-1417.

Discontinuing Coverage Against MDRO

- Patient does not meet criteria for initial MRSA / Pseudomonas coverage
- Lack of clinical evidence (i.e. cultures and sensitivities) of MRSA/Pseudomonas
- MRSA PCR (Pneumonia)

MRSA PCR

AAC
Journals.ASM.org

Predictive Value of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Swab PCR Assay for MRSA Pneumonia

Benjamin Dangerfield,[a] Andrew Chung,[b] Brandon Webb,[c] Maria Teresa Seville[d]

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- Negative predictive value of 99.2%

MRSA PCR

- Should not be used to confirm MRSA infection
- Strong negative predictive value in patients with definitive or high suspicion for pneumonia
- Should not be used for infections of unknown source or other non-pulmonary sources (i.e. SSTI, catheter-related infection, etc)

Likelihood of Infection in Presumed Sepsis

- Nearly half of all patients with presumed sepsis lack infection or only have “possible” infection

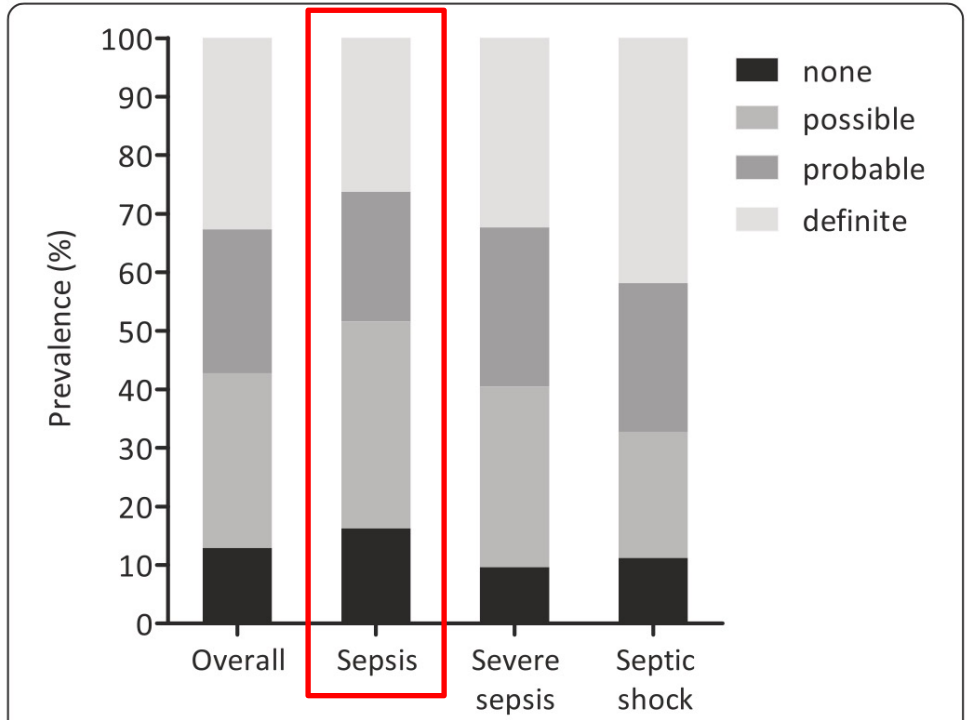


Fig. 1 Plausibility of infection stratified by clinical severity upon presentation in patients with presumed sepsis. Comparison between the clinical diagnosis of infection at the time of ICU admission and the actual presence of infection as determined by post-hoc evaluation

Klein Klouwenberg PM, et al. *Crit Care*. 2015;19:319.

Procalcitonin Test (PCT)

Precursor hormone to calcitonin triggered by systemic inflammation as the result of severe infection

Surviving Sepsis Campaign:

- We suggest that measurement of procalcitonin levels can be used to support:
  - Shortening the duration of antimicrobial therapy in sepsis patients
  - 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, et al. *Crit Care Med*. 2017;45(3):486-552.

Concerns regarding PCT

- Delay in elevations during early stages of infection
- Utility in patients with impaired immune systems/ organ failure
- Agreement on standardized cut off values
- Delayed initiation of antimicrobial therapy

Procalcitonin Test (PCT)

- Used to complement **NOT** replace clinical judgement
- Decisions should be based on changes in levels, not single values in the context of pre-test probability of severe bacterial infection
- PCT should not be used to determine initial antibiotic therapy
- Use of assays with high sensitivities is recommended (KRYPTOR)

Procalcitonin Test (PCT)

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial

Evelien de Jong, Jos A van Oers, Albertus Beishuizen, Piet Vos, Wytze J Vermeijden, Lenneke E Haas, Bert G Loef, Tom Dormans, Gertrude C van Melsen, Yvette C Kluiters, Hans Kemperman, Maarten J van den Elsen, Jeroen A Schouten, Jörn O Streefkerk, Hans G Krabbe, Hans Kieft, Georg H Kluge, Veerle C van Dam, Joost van Pelt, Laura Bormans, Martine Bokelman Otten, Auke C Reidinga, Henrik Endeman, Jos W Twisk, Ewoudt M W van de Garde, Anne Marie G A de Smet, Jozef Kesecioglu, Armand R Girbes, Maarten W Nijsten, Dylan W de Lange

Sept 18 2009- July 1, 2013

N = 1575 (761 Procalcitonin vs 785 Standard of Care)

Recommended antibiotics be discontinued if PCT decreased 80% or < 0.5 μg/L

Procalcitonin Test (PCT)

Discontinuation of Antibiotics based on decline in PCT level has been associated with:

- Decreased antibiotic duration and earlier discontinuation of antibiotics
- No change or improvements in mortality

Special Populations

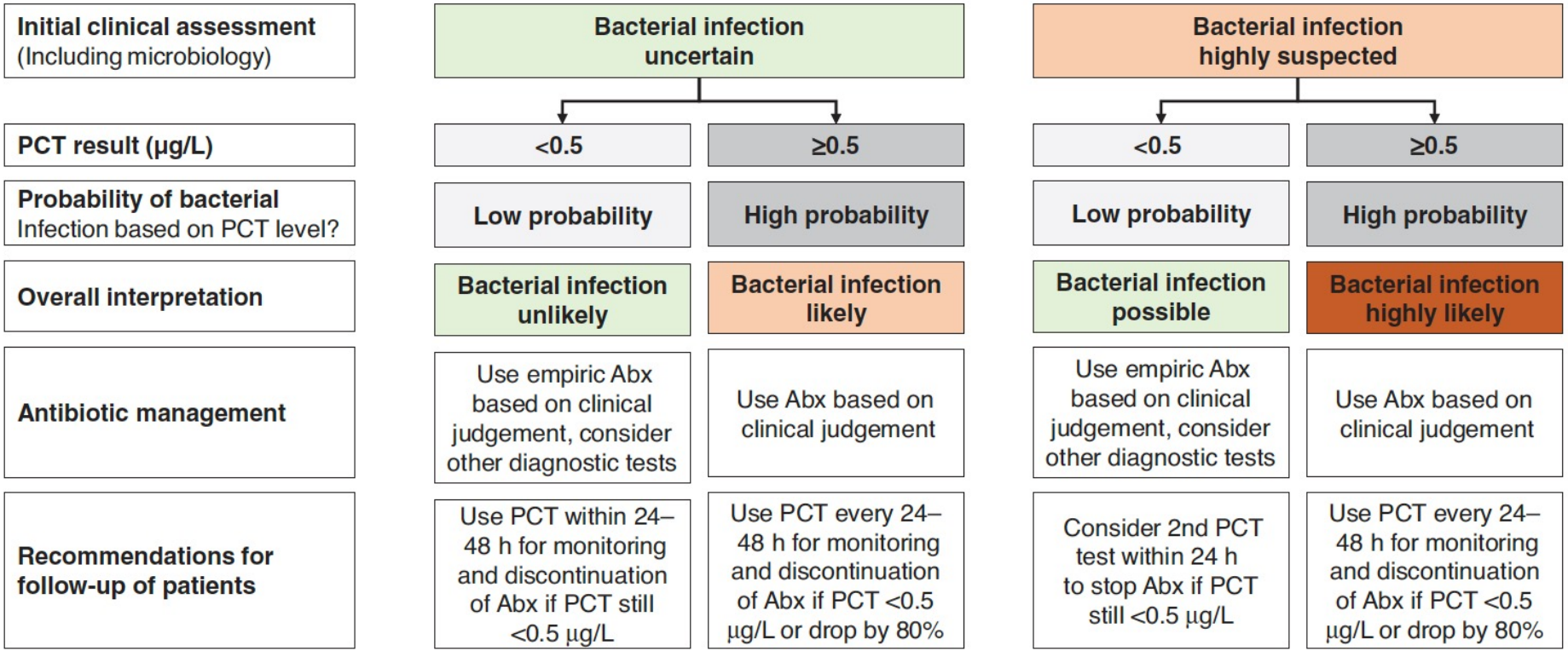
- Cystic Fibrosis
- Pancreatitis
- Immunosuppression
- Trauma
- High-volume transfusion
- Renal dysfunction
- Patients with chronic infections

Opinion Paper

Philipp Schuetz*, Albertus Beishuizen, Michael Broyles, Ricard Ferrer, Gaetan Gavazzi, Eric Howard Gluck, Juan González del Castillo, Jens-Ulrik Jensen, Peter Laszlo Kanizsai, Andrea Lay Hoon Kwa, Stefan Krueger, Charles-Edouard Luyt, Michael Oppert, Mario Plebani, Sergey A. Shlyapnikov, Giulio Toccafondi, Jennifer Townsend, Tobias Welte and Kordo Saeed

Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use

Patient with severe illness in ICU
(Defined by setting specific scores, e.g. qSOFA, SOFA, APACHE)



Schuetz P, et al. *Clin Chem Lab Med*. 2019;57(9):1308-1318. doi:10.1515/cclm-2018-1181

Summary

- Empiric treatment of sepsis should be initiated as soon as possible and within 1 hour of identification of sepsis
- Empiric treatment of sepsis should be based on suspected source of infection, severity of illness, patient specific risk factors, and local antibiogram
- MDRO coverage may be de-escalated with negative culture and MRSA PCR results in most infections
- Antibiotic de-escalation should be standard of care for patients with sepsis and antibiotics stopped when bacterial infection is no longer suspected

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