

Antibiotic Duration for Common Infections

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Learning Objectives

- Understand the rationale for shortest effective durations of antimicrobial therapy for infections.
- Choose appropriate durations of therapy for patients with CAP, HAP, VAP, SSTIs and UTIs.
- Describe the evidence supporting recommendations on duration of therapy for bacteremia in various settings.

Why Does Antibiotic Duration Matter?

- Cure the infection
- Reducing antimicrobial resistance
- Reduces risk of *Clostridium difficile* infection
- Reduces risk of antimicrobial-related organ toxicity
- Reduces hospital costs and length of stay
- Improves drug compliance

LESS IS MORE

Community-Acquired Pneumonia

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

- Patients with CAP should be treated for a minimum of 5 days should be afebrile 48-72 hours and clinically stable
- A longer duration of therapy may be needed if:
 - Initial therapy not active against identified pathogen
 - Loculated fluid collections
 - Complications with extrapulmonary infection

Duration of Antibiotic Treatment in Community-Acquired Pneumonia A Multicenter Randomized Clinical Trial

- 312 inpatients with CAP
- Randomized at day 5 to stopping antibiotics if met clinical stability vs. physician discretion
- 30-day rates of clinical success were significantly higher for short-course vs standard therapy (93.1% vs 80.3%; $P = .04$)
- Readmission rate lower for short-course regimen (1.4% vs 6.6%; $P = .02$)

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MARCH 4, 1944

THE CLINICAL USE OF PENICILLIN

OBSERVATIONS IN ONE HUNDRED CASES

MARTIN HENRY DAWSON, M.D.

AND

GLADYS L. HOBBY, PH.D.

NEW YORK

of cases of this disease was therefore abandoned until such time as larger supplies might become available. In the light of subsequent work it became obvious that the amount of penicillin given in this early group of cases was totally insufficient to secure a significant result.

During this stage of the investigation 3 cases of acute pneumococcal endocarditis came under observation. Since it was known that pneumococcal meningitis was

“Satisfactory results with
1.5-2 days of antibiotics”

The New England Journal of Medicine

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TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN*

MANSON MEADS, M.D.,† H. WILLIAM HARRIS, M.D.,‡ AND MAXWELL FINLAND, M.D.§

WITH THE TECHNICAL ASSISTANCE OF CLARE WILCOX

BOSTON

Average duration of
therapy including
patients in shock was 4-5
days

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

	3 Days	8 Days
Clinical cure at 10 days	93%	93%
Clinical cure at 28 days	90%	88%
Adverse events	11%	21%

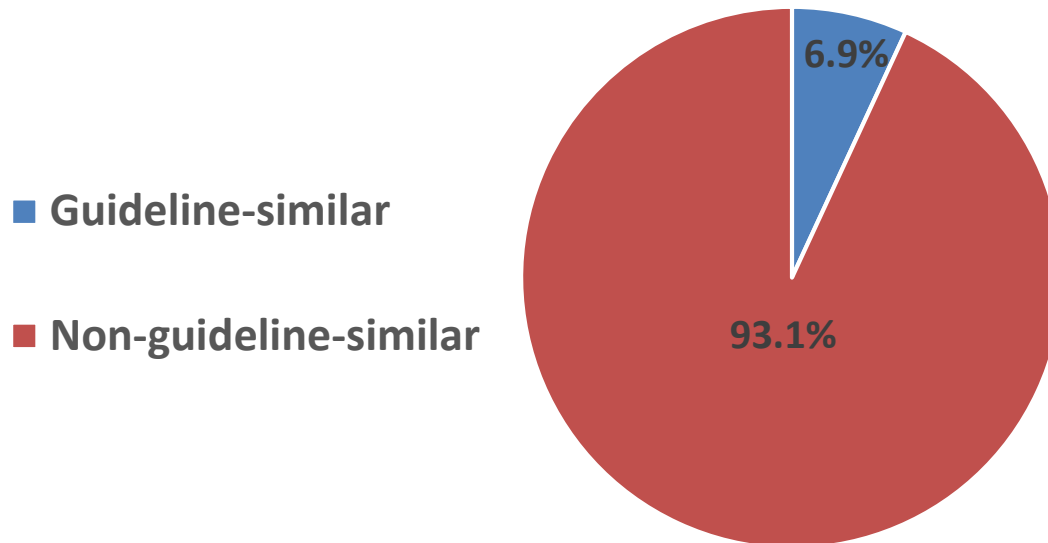
CAP Duration Summary

- IDSA guidelines: ~5 days until clinical stability
- One randomized controlled trial supports 3 days in select patients
 - Another ongoing RCT (3 vs. 8 days)
- Durations < 3 days: no / limited data

What Actually Happens?

- National VA evaluation: duration of therapy in Veterans hospitalized with pneumonia
- 1195 patients with CAP

Duration of Therapy in CAP Patients



Hospital-acquired and Ventilator-associated Pneumonia

American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

“A shorter duration of antibiotic therapy (7 to 8 days) recommended for patients with [VAP] who have received initially appropriate therapy and have had a good clinical response, with no evidence of infection with nonfermenting Gram-negative bacilli”

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

- HCAP gone
- Local antibiograms to reduce unnecessary use of dual Gram-negative coverage and empiric MRSA coverage
- De-escalation
- **Short course therapy for everyone = 7 days**
 - Regardless of infecting organism (ex. *Pseudomonas* and *Acinetobacter*)

Skin and Soft Tissue Infections

IDSA Guidelines: SSTI & MRSA

2014 IDSA Skin & Soft Tissue Infection Guidelines

Cellulitis	5 days (strong, high) Extend if no improvement within 5 days
Abscess / carbuncle / furuncle	Not specifically addressed
Recurrent abscess	5 – 10 days (weak, low)

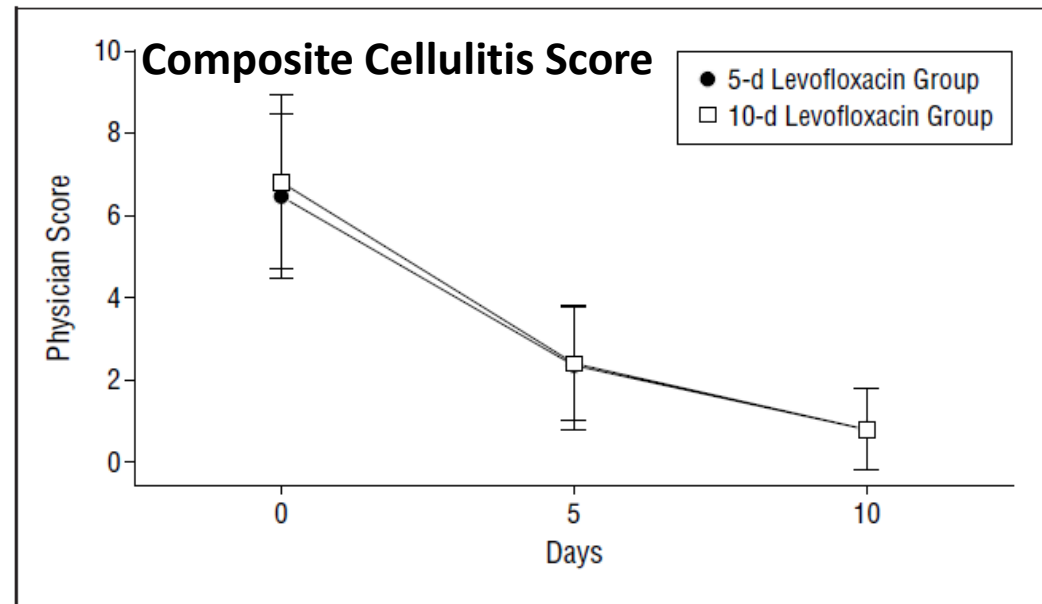
2010 IDSA MRSA Guidelines

Cellulitis (outpatients)	5 – 10 days
Purulent SSTI (outpatients)	5 – 10 days
SSTI (hospitalized)	7 – 14 days

Cellulitis 5 vs. 10 Days

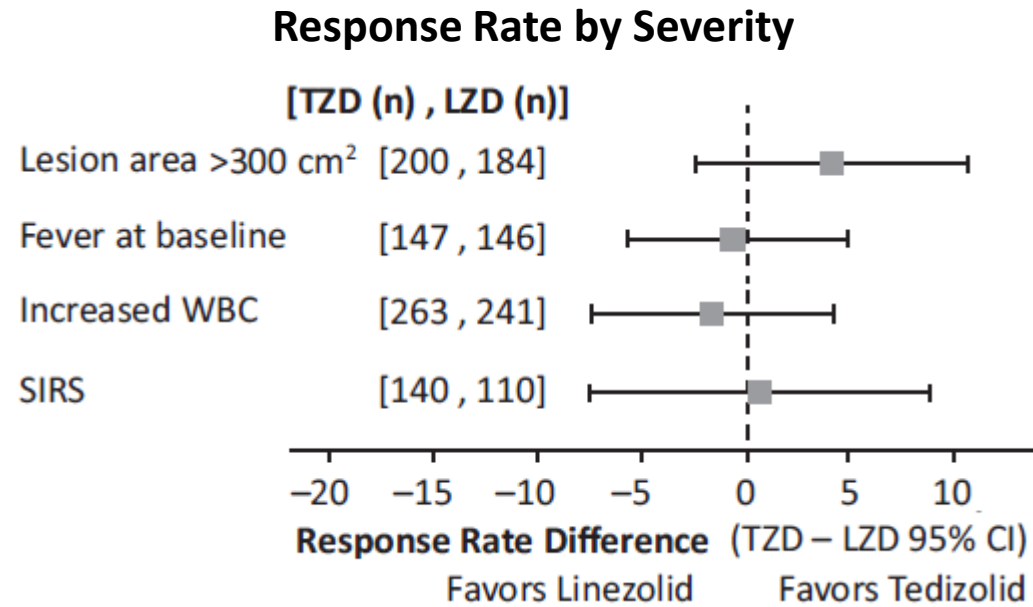
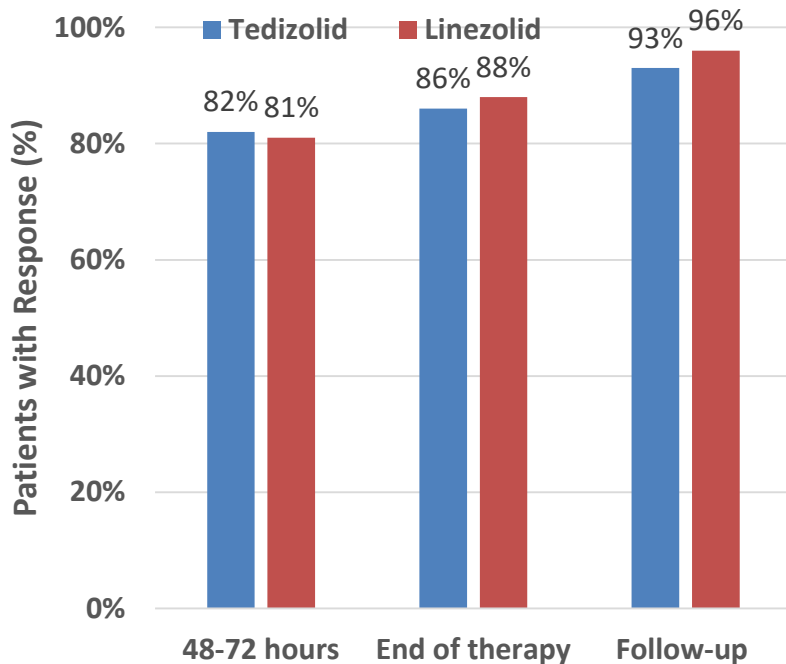
- Randomized, controlled, single-center trial
- Cellulitis (primarily outpatient)
- Levofloxacin 500 mg PO x 5 vs. 10 days
- Residual cellulitis did not exclude stopping at day 5

	5-day n = 44	10-day n = 43
Age (mean)	56	49
Diabetes	7 (16%)	5 (12%)
Hospitalized	8 (18%)	4 (12%)
Cure	43 (98%)	42 (98%)



ABSSI 6 vs. 10 Days

- 2 Randomized, controlled, multi-center trials
- Tedizolid 6 days (n=569) vs. linezolid 10 days (n=560)
- Cellulitis, major cutaneous abscess, infected wounds



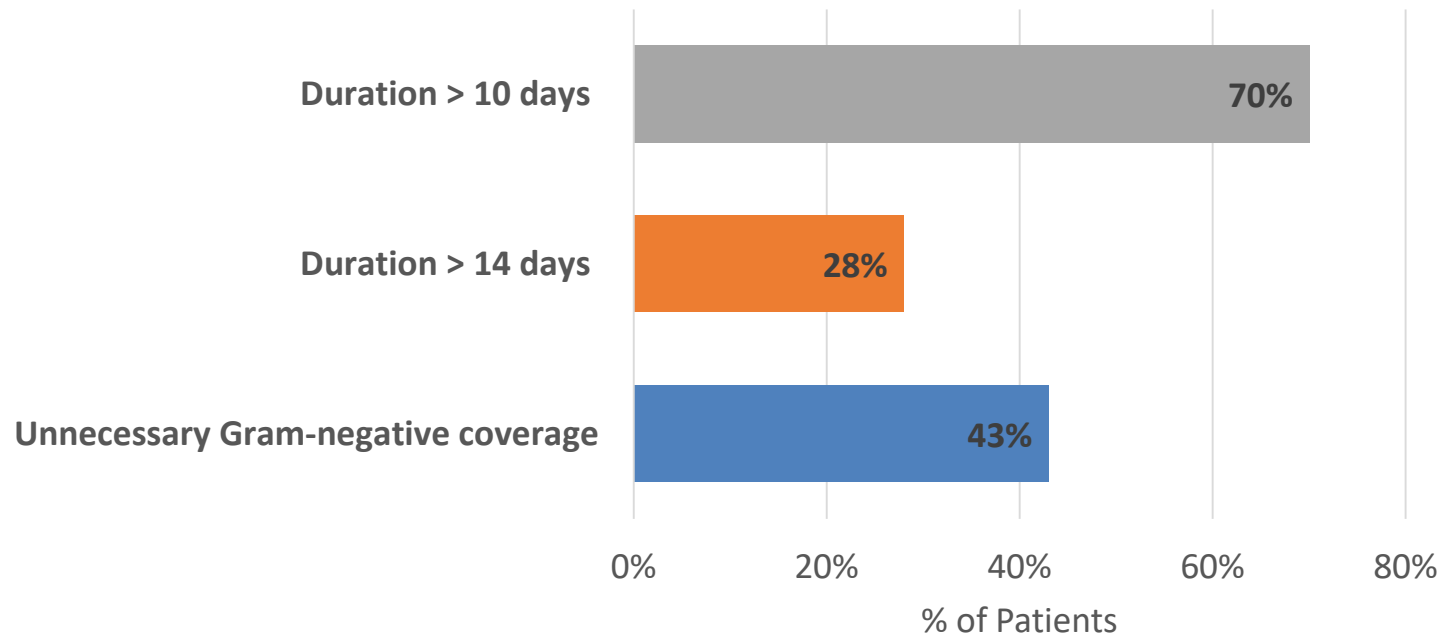
Prokocimer P, et al JAMA 2013;308(6):559

Moran GJ, et al. Lancet Infect Dis 2014;14:696

Sandison T, et al. Antimicrob Agents Chemother 2017;61(5):e02687

What Actually Happens?

- Multicenter, retrospective evaluation
- Antibiotic prescribing for SSTI in hospitals
- 492 SSTIs in pediatrics or adults



Urinary Tract Infections

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America

Category	Duration of treatment	RCT Evidence
Acute cystitis	TMP/SMX 1 DS tab PO Q12h for 3 days	4 RCTs
	Nitrofurantoin 100 mg PO Q12h for 5 days	4 RCTs
	Cephalexin 500 mg PO Q6h for 7 days	---
	Cefpodoxime 100 mg BID x 3 days	Gupta Arch Intern Med 2007
Acute pyelonephritis	Cipro 500 mg PO Q12h for 7 days	Talan JAMA 2000
	TMP/SMX 1DS tab PO Q12h for 14 days	
	Cipro 1000 mg ER Q24h for 7 days	Talan J Urol 2004
	Levofloxacin 750 mg Q24 h for 5 days	Peterson Urol 2008
Catheter-associated UTI	-Catheter removal, female, lower tract, <65 years of age: 3 days -Prompt symptom resolution: 7 days -Delayed response: 10-14 days	Harding Ann Intern Med 1991; Dow Clin Infec 2004; Mohler J Urol 1987

Shorter Works!

- Uncomplicated cystitis
 - 3 days with TMP/SMX
 - 5 days with nitrofurantoin
 - 3-7 days with beta-lactam
 - *7 days for men*
- CA-UTI
 - 7 days
 - 3 days if a woman ≤ 65 with catheter removed
- Pyelonephritis
 - 5-7 days
 - 10 days if delayed response

Hooton TM et al. Clin Infect Dis. 2010;50:635.

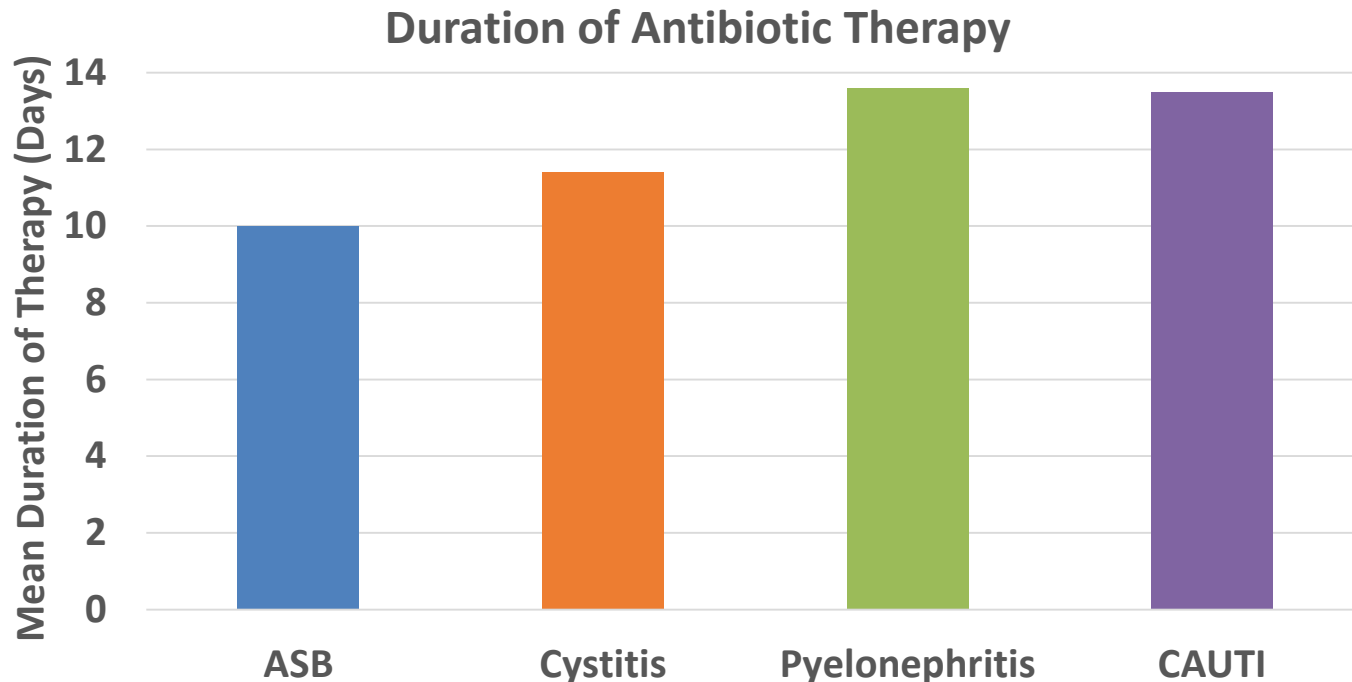
Talan DA et al. JAMA. 2000;283:1583-90.

Peterson J et al. Urology. 2008;71:17-22.

Drekonja DM et al. JAMA Intern Med. 2013;173(1):62-68

What Actually Happens?

- National VA evaluation: management of bacteriuria in hospitalized patients
- 2225 patients @ 25 VA hospitals – fiscal year 2014



**Bacteremia:
How much is enough?**

Duration for Bacteremia

- Duration is style, not substance
- Unencumbered by data
- Equipoise
- Clinical trial is needed
- *S. aureus bacteremia is different...*

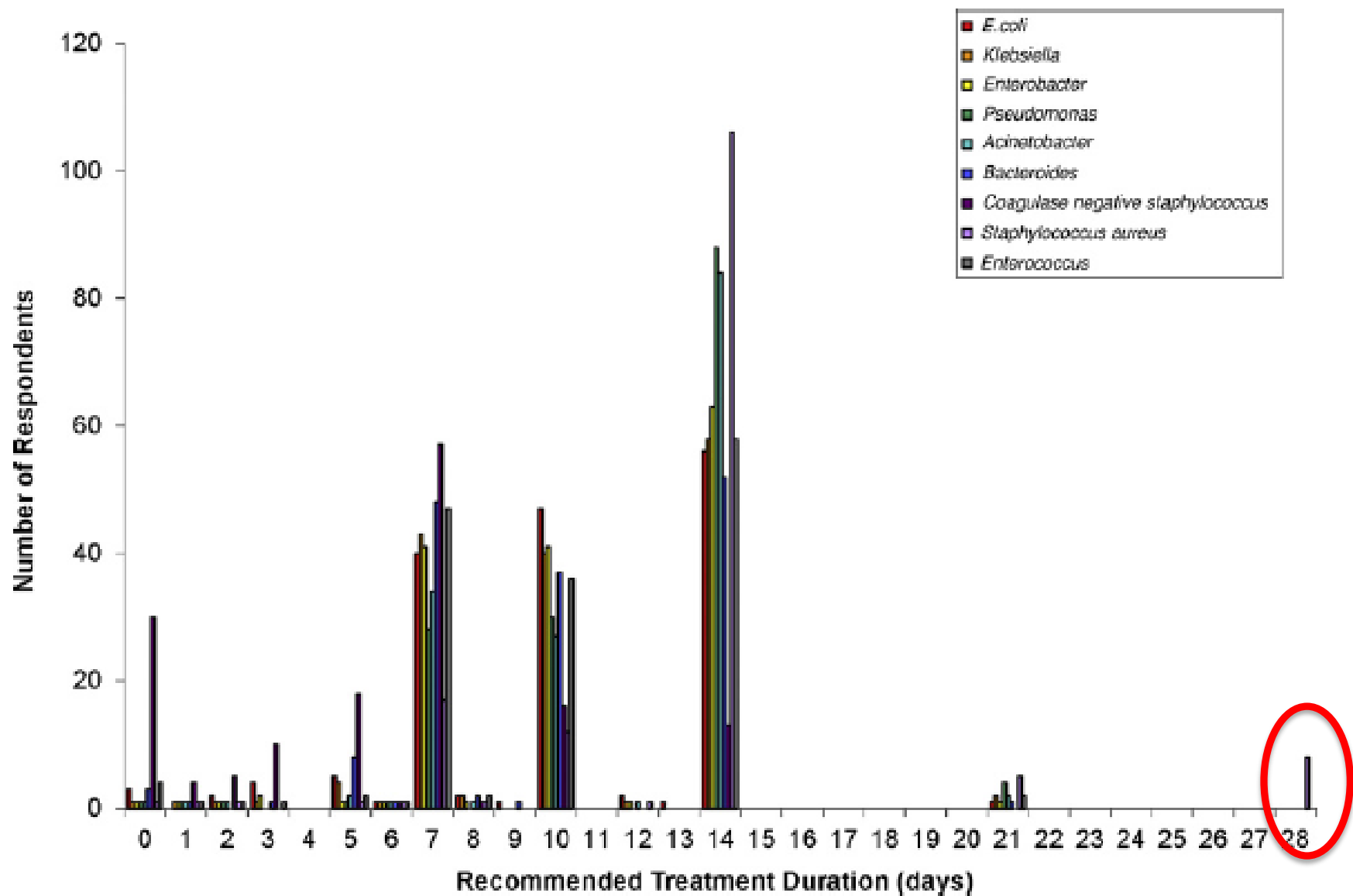
Guidelines & Bacteremia

- *Staphylococcus aureus* is different

Guideline	Duration Recommendation
IDSA 2007 CAP	Not specifically addressed
IDSA 2010 uncomplicated UTI	Not addressed
IDSA 2009 CAUTI	Not addressed
IDSA 2014 SSTI	Not addressed
IDSA 2010 Intra-abdominal infection	Not addressed
SIS 2017 Intra-abdominal infection	Consider limiting to 7 days (2-B)

Antibiotic treatment duration for bloodstream infections in critically ill patients: a national survey of Canadian infectious diseases and critical care specialists

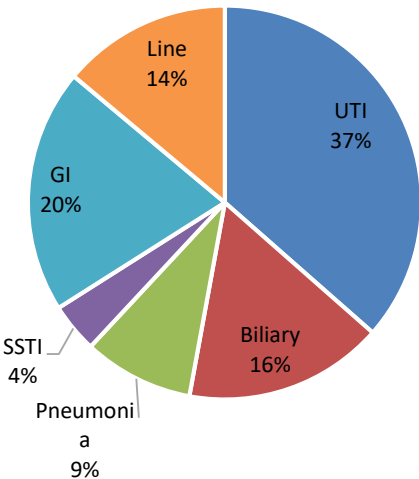
N
a L
b S
c S
d S



Enterobacteriaceae Bacteremia

- Retrospective, 3-center, propensity score-matched cohort study
- Hospitalized adults with Enterobacteriaceae bacteremia
- Duration 6-10 days (median 8) vs. 11-16 days (median 15 days)

Source of Infection



Characteristic / Outcome*	6-10 days (n=385)	11-16 days (n=385)
Immune compromise	127 (33%)	134 (35%)
ICU (day 1)	113 (29%)	122 (32%)
Source control	382 (99%)	381 (99%)
30-day mortality	37 (10%)	39 (10%)
Recurrent bacteremia	5 (1%)	9 (2%)
Future resistance	17 (4%)	28 (7%)

30-Day All-Cause Mortality (Propensity-Score Matched Cohort)

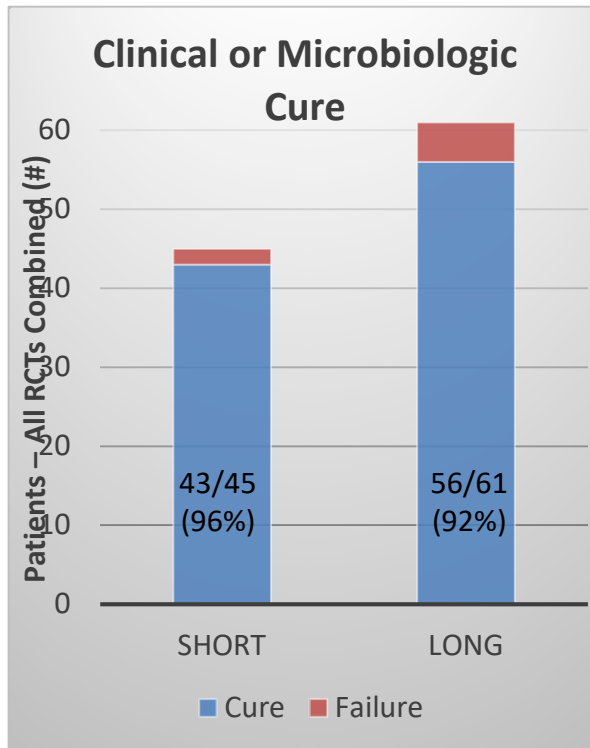
Variable	Adjusted HR* (95% CI)	P Value
Short-course therapy (6–10 d)	1.00 (.62–1.63)	.97
Urinary source	0.49 (.26–.94)	.03
Pneumonia	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	0.99 (.56–1.76)	.98
End-stage liver disease	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.40 (.83–2.36)	.21

*Outcome differences not statistically significant

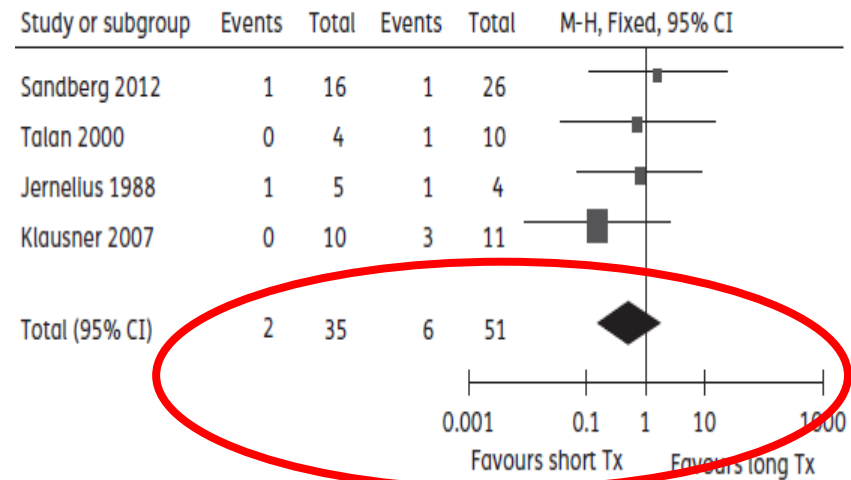
UTI RCTS & Bacteremia

- Short (≤ 7 days) vs. long & outcomes reported in bacteremic subset

Studies
Pivamecillinam 7 days Pivamecillinam 21 days
Ciprofloxacin 7 days TMP-SMX 14 days
Levofloxacin 5 days Ciprofloxacin 10 days
Levofloxacin 5 days Ciprofloxacin 10 days
Ciprofloxacin 7 days Ciprofloxacin 14 days



Meta-Analysis Clinical Failure of Bacteremic Patients (End of Follow-up)



TMP-SMX: trimethoprim-sulfamethoxazole

RCT: randomized, controlled trial

Talan D, et al. JAMA 2000;283(12):1583

Peterson J, et al. Urology 2008;71:17

Jernelius H, et al Acta Med Scand
1988;223(5):469

Klausner H, et al. Curr Med Res Opin
2007;23(11):26387

Sandberg T, et al. Lancet 2012;380:484

Eliakim-Raz N. J Antimicrob Chemother
2013;68:2183

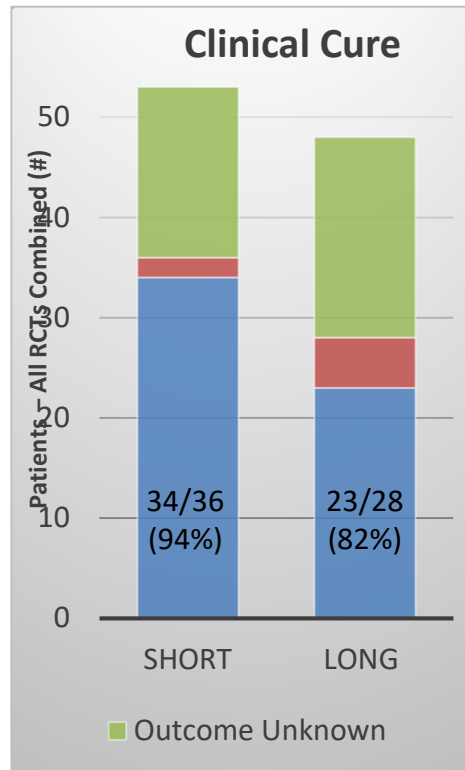
van Nieuwkoop C, et al. BMC Infect Dis
2017;15:70

Pneumonia RCTs & Bacteremia

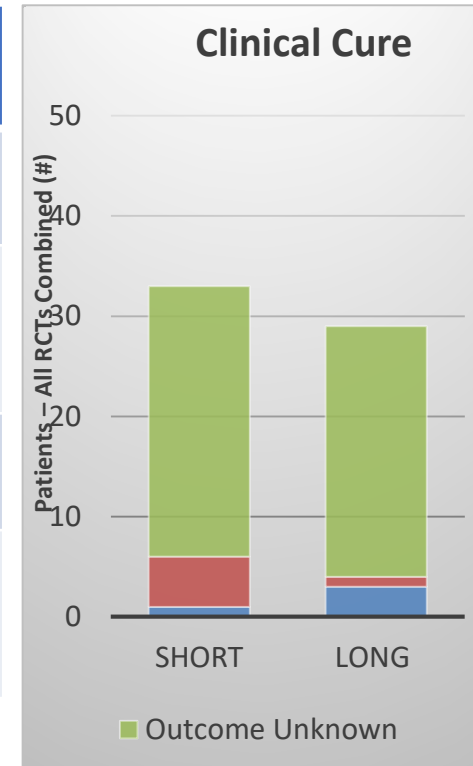
- Community-acquired pneumonia

- Ventilator-associated pneumonia

Studies
Cefuroxime 7 vs. 14 days
Ceftriaxone 5 vs. 10 days*
Levofloxacin 5 vs. 10 days
Amoxicillin 3 vs. 8 days*
Telithromycin 5-7 vs. Clarithromycin 10 days
Gemifloxacin 7 vs. Amoxicillin-clavulanate 10 days



Studies
Ciprofloxacin 3 vs. Guideline 10-21 day
Guideline antibiotics 8 vs. 15 days
Doripenem 7 vs. Imipenem 10 days
Guideline antibiotics 8 vs. 15 days*



- 88% pathogens = *Streptococcus pneumoniae*
- *Bacteremic patients included – outcomes not reported

- Pathogen distribution unclear
- *No mortality difference bacteremic vs. non-bacteremic

Siegel R, et al. Am J Ther 1999;6:217
 Leophonte P, et al. Med Mal Infect 2002;32:369
 Dunbar LM, et al. Clin Infect Dis 2003;37:752
 el Moussaoui R, et al BMJ 2006;332(7554):1355
 Teller G, et al. J Antimicrob Chemother 2004;54:515
 Singh M, et al. Am J Respir Crit Care Med 2000;162:505
 Chastre J, et al. JAMA 2003;290(19):2588
 Lephonte P, et al. Resp Med 2004;98:708
 Kollef M, et al. Crit Care 2012;16:R218
 Capellier G, et al. PLoS One 2012;7(8):e41290

Intra-Abdominal Infection RCTs & Bacteremia

Infection Type	Groups	Cure / Bacteremic	
		Short	Long
Spontaneous bacterial peritonitis	Cefotaxime 5 days Cefotaxime 10 days	9/9 (100%) ¹	16/17 (94%)
Spontaneous bacterial peritonitis	Cefoperazone 5 days Cefoperazone 10 days	5/6 (83%) ²	7/8 (88%)
Complicated (various)	Ertapenem 3 days Ertapenem ≥5 day	?	?
Complicated (various)	Guideline antibiotics 4 days Guideline antibiotics 10 days	?/3	?/5
Total bacteremic population:		14/15 (93%)?	23/25 (92%)?

¹Clinical cure

²Survival

Runyon B, et al. Gastroenterology
1991;100(6):1737
Chaudhry Z, et al. JCPSP 2000;10:284

Basoli A, et al. J Gastrointest Surg
2008;12:592
Sawyer RG, et al. N Engl J Med
2015;372:1996

The New Antibiotic Mantra—“Shorter Is Better”

Brad Spellberg, MD

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

Disease	Treatment, Days	
	Short	Long
Community-acquired pneumonia ¹⁻³	3-5	7-10
Nosocomial pneumonia ^{6,7}	≤8	10-15
Pyelonephritis ¹⁰	5-7	10-14
Intraabdominal infection ¹¹	4	10
Acute exacerbation of chronic bronchitis and COPD ¹²	≤5	≥7
Acute bacterial sinusitis ¹³	5	10
Cellulitis ¹⁴	5-6	10
Chronic osteomyelitis ¹⁵	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

Useful Links

Why antibiotic duration matters*	http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2536180
HAP and VAP	http://cid.oxfordjournals.org/content/early/2016/07/06/cid.ciw353.full.pdf+html
Skin and soft tissue infections	http://cid.oxfordjournals.org/content/early/2014/06/14/cid.ciu296.full.pdf+html
Urinary tract infections	https://www.ncbi.nlm.nih.gov/pubmed/23212273
Bacteremia NOS	https://www.ncbi.nlm.nih.gov/pubmed/22085732

Questions?

emily.spivak@hsc.utah.edu

Short vs. Long Summary in Males

- Trials from previous slide
 - de Gier R, et al. *Int J Antimicrob Agents* 1995;6:27
 - Klimberg IW, et al. *Urology* 1998;51:610
 - Klausner H, et al. *Curr Med Res Opin* 2007;23(11):237
 - Peterson J, et al. *Urology* 2008;71:17
- Additional studies supporting ~7 days in males
 - Drekonja D, et al. *JAMA Intern Med* 2013;173(1):62
 - Eliakim-Raz N. *J Antimicrob Chemother* 2013;68:2183
 - Wagenlehner F, et al. *Lancet* 2015;385:1949