How Low Can We Go?

A review of literature supporting shorter duration of antibiotics

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Disclosure Statement

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Objectives

- Discuss the potential negative consequences of excessive durations of antibiotic therapy
- Review the literature supporting the role of shorter durations of antibiotic therapy in common bacterial infections
- Identify scenarios where shorter durations of antibiotic therapy may or may not appropriate

IDSA LECTURE

The Maxwell Finland Lecture: For the Duration—Rational Antibiotic Administration in an Era of Antimicrobial Resistance and *Clostridium difficile*

Louis B. Rice

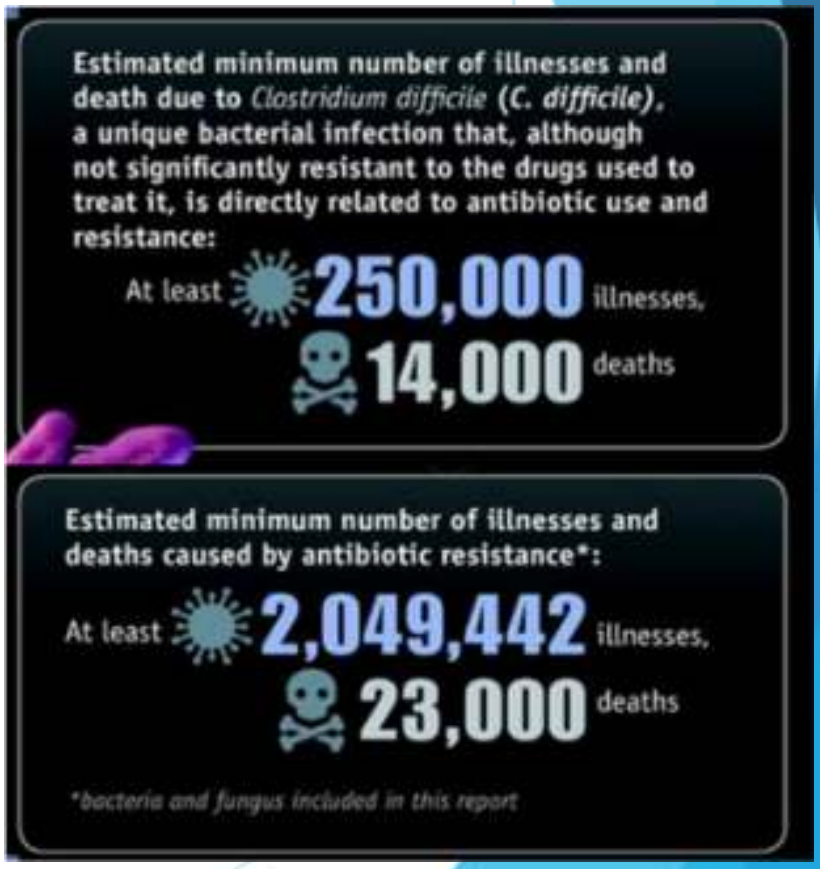
Medical Service, Louis Stokes Cleveland Veterans Affairs Medical Center, and Case Western Reserve University, Cleveland, Ohio

- 45th Annual Meeting of Infectious Diseases Society of America in 2007
- *"The most reasonable strategy to minimize resistance is to stop irritating the bacteria- in other words, to reduce our use of antibiotics to the bare minimum necessary to safely treat patients with serious infections, in hope that this will reduce selective pressure and thereby reduce the prevalence of resistance."*

Rice LB. Clin Infect Dis. 2008;46(4):491-496.

More Antibiotics… More Harm

- Adverse effects
- Superinfections
- Selection of antibiotic resistance



Antibiotics and Adverse Drug Events

- Retrospective, cohort study (n=1,488 medical records)
- Development of antibiotic-associated adverse drug event (ADE) within 30 days of antibiotic initiation

Median age (years)	59 (IQR 49-69)
Female	758 (51%)
Patients developing at least 1 ADE	298 (20%)
Total # of ADEs	324
Clinically significant ADE[1]	314 (97%)
Risk of ADE per 10 antibiotic DOT	3%

1. Clinically significant ADE: new hospitalization, prolonged hospitalization, additional clinic or ED visits, additional labs or imaging
Tamma et al. JAMA Intern Med 2017;177(9):1308-15.

Antibiotics and *C. Difficile*

- Prospective, observational cohort study (n=1,883 patients)
- Assessed the incidence of and risk factors for CDI in patients hospitalized with CAP
- 365 developed diarrhea and 61 had laboratory-confirmed CDI

	CDI (n=61)	No CDI (n=1,822)	P value
Age, years (IQR)	79 (71-83)	67 (50-77)	<0.0001
Length of stay, median days (IQR)	30 (12-46)	5 (2-10)	<0.0001
Duration of antibiotics, median days (SD)	11.5 (3.5)	10.2 (3.1)	0.002
Mortality	21.3%	8.6%	P<0.001

- Multivariate hazard ratio for duration of antibiotics: 1.09 (95% CI 1-1.19), p=0.04

Chalmers et al. Journal of Infection 2016;73(1):45-53.

CDI: *C. difficile* infection
CAP: community acquired pneumonia

Antibiotics and Resistance

- Single-center, retrospective cohort study of patients with sepsis or septic shock who received at least one dose of cefepime, meropenem, or piperacillin-tazobactam (n=7,118), followed for 60 days
- Correlate the duration of exposure to antipseudomonal beta-lactams with development of new resistance in critically ill patients

	Adjusted Hazard Ratio (95% CI)			
	Any anti-pseudomonal beta-lactam	Cefepime	Meropenem	Piperacillin-tazobactam
Each additional day of exposure	1.04 (1.04-1.05)	1.08 (1.07-1.09)	1.02 (1.01-1.03)	1.08 (1.06-1.09)

Teshome et al. Pharmacotherapy 2019;39(3):261-70

The Antibiotic Mantra…
"Shorter is Better"

Spellberg B. The New Antibiotic Mantra-"Shorter Is Better". JAMA Intern Med. 2016;176(9):1254-1255.
Spellberg. Spellberg B. The Maturing Antibiotic Mantra: "Shorter Is Still Better". *J Hosp Med*. 2018;13(5):361.362.
Spellberg B, Rice LB. Duration of Antibiotic Therapy: Shorter Is Better. *Ann Intern Med*. 2019;171(3):210-211.

Best Practice Advice on Appropriate Use of Short-Course Antibiotics in Common Infections

Condition	Patient Population	Available Guidelines and Evidence	Best Practice Advice
Acute bronchitis	Adults with COPD	GOLD guideline Meta-analysis of 21 studies comparing ≤5 vs >5 days	Limit antibiotics to 5 days
Community acquired pneumonia (CAP)	Non-immunocompromised adults	IDSA/ATS guideline	Limit antibiotics to minimum of 5 days
UTI, uncomplicated cystitis	Nonpregnant adult women	IDSA/ESCMID guideline	Short course antibiotics: 5 days nitrofurantoin 3 days TMP/SMX 1 day fosfomycin
UTI, uncomplicated pyelonephritis	Nonpregnant adults	IDSA/ESCMID guideline Recent systematic review 3 recent RCTs	Short course antibiotics: 5-7 days fluoroquinolones 14 days TMP/SMX (Based on susceptibility)
Nonpurulent cellulitis	All adults	IDSA guidelines NICE guideline 1 recent RCT	Limit to a 5-6 days course of antibiotics active against streptococci

Lee et al. Ann Intern Med. 2021;174(6):822-827.

Evidence on Shorter Courses of Antibiotics

- Complicated UTI
- Bacteremia
- Pneumonia

Clinical Scenario 1

MJ is a 58-year-old female admitted to the hospital for acute pyelonephritis. Her temperature in the ED was 102F and she reports severe flank pain. She is currently being treated with ceftriaxone and is clinically improving.

- How long should MJ receive treatment for?
  A. 5 days
  B. 7 days
  C. 10 days
  D. 14 days
  E. Not sure

Clinical Scenario 2

JB is a 60-year-old male with a urinary tract infection. He does not have a fever and flank pain. He was prescribed TMP/SMX 3 days ago and is clinically improving.

- How long should JB receive treatment for?
  A. 5 days
  B. 7 days
  C. 10 days
  D. 14 days
  E. Not sure

Challenges with Complicated UTIs

- Outdated IDSA guidelines
- Increasing *E. coli* resistance
- Data on shorter antibiotic courses for uncomplicated UTIs
- Optimal treatment duration in complicated UTIs requiring hospitalization and in men are lacking

5 vs 10 days in Complicated UTIs

- Multicenter, double-blind, randomized, non-inferiority study
- Compared efficacy of levofloxacin 750 mg QD for 5 days versus ciprofloxacin 400/500 mg Q12H for 10 days in patients with complicated UTI (cUTI) or acute pyelonephritis

	Levofloxacin (n=537)	Ciprofloxacin (n=556)	Total (n1093)
Male	207 (38.5%)	220 (39.6%)	427 (39.1%)
Female	330 (61.5%)	336 (60.4%)	666 (60.9%)
cUTI (67 catheterized)	391 (72.3%)	391 (70.3%)	782 (71.5%)
Acute pyelonephritis (1 catheterized)	146 (27.2%)	165 (29.7%)	311 (28.5%)

Peterson et al. Urology. 2008;71(1):17-22.

5 vs 10 days in Complicated UTIs

	Levofloxacin 5 Days (n, %)	Ciprofloxacin 10 Days (n, %)	Difference
Clinical success rates at end of therapy[1]	242/265 (91.3)	210/241 (87.1)	Not significant
Clinical success rates at post therapy[2] cUTI Acute pyelonephritis	229/265 (86.4) 78.9% 86.2%	213/241 (88.4) 79.9% 80.6%	Not significant

- Study demonstrated noninferiority for 5-days of levofloxacin to 10-days of ciprofloxacin in cUTI and acute pyelonephritis

Peterson et al. Urology. 2008;71(1):17-22.

1. End of therapy: study day 11
2. Post therapy: study days 15 to 19

7 vs 14 days in Men with UTIs

- Randomized, double-blind, placebo-controlled non-inferiority trial
- n=272 afebrile men from 2 US VA medical centers
- Intervention: 7 days of ciprofloxacin or TMP/SMX, then randomized to receive continued antibiotics (n=136) or placebo (n=136) for days 8-14
- Primary outcome: resolution of UTI symptoms by day 14

Drekonja et al. JAMA. 2021;326(4):324-331.

7 vs 14 days in Men with UTIs

	7 days antibiotics (n=136)	14 days antibiotics (n=136)
Age, median (IQR)	70 (62-73)	70 (62-75)
UTI-related comorbidities		
Any prior UTI	84 (62)	78 (57)
Prostatic hypertrophy	56 (41)	47 (35)
Urinary incontinence	44 (32)	52 (38)
Intermittent catheter use	24 (18)	23 (17)
Prostate cancer	21 (15)	23 (17)
Urethral stricture	17 (13)	16 (12)
Prior prostatitis	16 (12)	18 (13)
Indwelling catheter use	8 (6)	8 (6)

Drekonja et al. JAMA. 2021;326(4):324-331.

7 vs 14 days in Men with UTIs

- Resolution of UTI symptoms 14 days after stopping antibiotics

	7 days antibiotics	14 days antibiotics	Difference
As-treated population	122/131 (93.1%)	111/123 (90.2%)	NS
As-randomized population	125/136 (91.9%)	123/136 (90.4%)	NS

- Recurrence of UTI symptoms within 28 days of stopping antibiotics

	7 days antibiotics	14 days antibiotics	Difference
As-treated population	13/131 (9.9%)	15/123 (12.9%)	NS
As-randomized population	14/136 (10.3%)	23/136 (16.9%)	NS

- 7-day course of ciprofloxacin or TMP/SMX non-inferior to 14-days in afebrile men with UTI

Drekonja et al. JAMA. 2021;326(4):324-331.

Key Points in Complicated UTIs

- Short course antibiotic therapy can be considered in hospitalized patients with complicated UTIs
- Short course antibiotic therapy of 7 days is an option for afebrile men with UTI
- Limited data on the use of other agents for acute complicated UTI

Clinical Scenario 3

BB is a 75-year-old female on ceftriaxone 2g IV daily for *E.coli* bacteremia. She is afebrile and clinically improving.

- How long should BB receive treatment for?
  A. 7 days
  B. 14 days
  C. 21 days
  D. Not sure

Clinical Scenario 4

EP is a 50-year-old female with MSSA bacteremia secondary to cellulitis. She is initiated on oxacillin therapy, is afebrile, and clinically improving. Her repeat blood cultures are negative.

- How long should EP receive treatment for?
  A. 7 days
  B. 14 days
  C. 21 days
  D. Not sure

Challenges in Bacteremia

- Gram-negative bacilli account for ~25% of all bloodstream infections, reported mortality ranges from 12% to 38%
- S. aureus is the leading cause of bacteremia, reported mortality ranges from 20% to 40%
- Difficult to minimize antibiotics in this setting
- Current guidelines recommend a range of treatment duration from 7 to 14 days for bacteremia

Kang et al. Antimicrob Agents Chemother. 2005 Feb;49(2):760-6.
Shurland et al. Infect Control Hosp Epidemiol. 2007 Mar;28(3):273-9.

7 vs 14 Days in Uncomplicated Gram-Negative Bacteremia

- Randomized, multicenter, open-label, noninferiority trial
- Hospitalized adult patients with gram-negative bacteremia at day 7 of antibiotics, afebrile and hemodynamically stable for ≥48 hours (n=604)
- Excluded patients with uncontrolled focus of infection, polymicrobial growth, Brucella or Salmonella, or immunosuppression
- Primary outcome: all-cause mortality at 90 days, clinical failure, readmissions, and extended hospitalized > 14 days

Yahav et al. Clin Infect Dis. 2019;69(7):1091-1098.

7 vs 14 Days in Uncomplicated Gram-Negative Bacteremia

	7 Day (n=306)	14 Day (n=298)
Age, median (IQR)	71 (61.8-81)	71 (61-80)
Sex, female	156 (51)	163 (54.7)
Hospital acquired infection	61 (19.9)	72 (24.2)
Devices at baseline		
Urinary device	61 (19.9)	72 (24.2)
Central venous catheter	22 (7.2)	19 (6.4)
Endotracheal tube	8 (2.6)	8 (2.7)
Prosthetic valve/intracardiac implant	14 (4.6)	13 (4.4)

Yahav et al. Clin Infect Dis. 2019;69(7):1091-1098.

7 vs 14 Days in Uncomplicated Gram-Negative Bacteremia

	7 Day (n=306)	14 Day (n=298)
Bacteria type		
E. coli	186 (60.8)	194 (65.1)
Klebsiella spp	47 (15.3)	33 (11.1)
Other *Enterobacterales*	40 (13.1)	43 (14.4)
Acinetobacter spp	2 (0.7)	4 (1.3)
Pseudomonas spp	28 (9.2)	20 (6.7)
Other	3 (1)	4 (1.3)
MDR gram-negative bacteremia	58 (18.9)	51 (17.1)

Yahav et al. Clin Infect Dis. 2019;69(7):1091-1098.

7 vs 14 Days in Uncomplicated Gram-Negative Bacteremia

	7 Day (n=306)	14 Day (n=298)
Source of bacteremia		
Urinary tract	212 (69.3)	199 (66.8)
Primary bacteremia	23 (7.5)	28 (9.4)
Abdominal	37 (12.1)	34 (11.4)
Respiratory	14 (4.6)	10 (3.4)
Central venous catheter	15 (4.9)	23 (7.7)
Skin and soft tissue	5 (1.6)	4 (1.3)

Yahav et al. Clin Infect Dis. 2019;69(7):1091-1098.

7 vs 14 Days in Uncomplicated Gram-Negative Bacteremia

Outcome	7 Day	14 Day	95% CI	P-value
Primary outcome	140 (45.8)	144 (48.3)	-2.6 (-10.5 to 5.3)	.527
90-day all cause mortality	36 (11.8)	32 (10.7)	1.0 (-4.0 to 6.1)	.702
Readmissions	119 (38.9)	127 (42.6)	-3.7 (-11.5 to 4.1)	.363
Extended hospitalization >14 days	15 (4.9)	19 (6.4)	-1.5 (-5.1 to 2.2)	.483
Distant complications	2 (0.7)	1 (0.3)		1
Relapse of bacteremia	8 (2.6)	8 (2.7)	-0.07 (-2.6 to 2.5)	.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (-1.4 to 5.1)	.237
14-day mortality	7 (2.3)	4 (1.3)	0.95 (-1.32 to 3.44)	.288
28-day mortality	15 (4.9)	13 (4.4)	0.54 (-2.98 to 4.06)	.753

- 7-day course non-inferior to 14-days in hospitalized patients with uncomplicated gram-negative bacteremia

Yahav et al. Clin Infect Dis. 2019;69(7):1091-1098.

7 vs 14 Days in Enterobacterales Blood Stream Infection

- Randomized, multicenter, open label, non-inferiority trial
- Hospitalized and outpatient adults with a diagnosis of Enterobacterales Blood Stream Infection (eBSI) (N = 248) randomized to receive 7 or 14 days of any fully active antibiotic therapy (IV or PO) against the organism isolated
- Primary endpoint: Total number of days of antibiotic treatment prescribed to the patient for any reason
- Clinical outcome: Relapse of the eBSI, relapse of fever and clinical cure at the end of follow-up
- Secondary endpoints: Crude mortality, superinfections, & adverse events

Molina et al. Clin Microb and Infect. 2021. E-pub ahead of print.S1198-743X(21)00491-2.

7 vs 14 Days in Enterobacterales Blood Stream Infection

	7 Day (n=119)	14 Day (n=129)
Age, median (IQR)	65 (53-77.5)	68 (53-77)
Sex, female (%)	58 (49.2)	59 (45.7)
Patient Care		
Outpatient (%)	25 (21.6)	36 (28.8)
Inpatient (%)	91 (78.4)	90 (71.2)

Molina et al. Clin Microb and Infect. 2021. E-pub ahead of print.S1198-743X(21)00491-2.

7 vs 14 Days in Enterobacterales Blood Stream Infection

	7 Day (n=119)	14 Day (n=129)
Bacteria type (%)		
E. coli	76 (66.4)	79 (61.2)
Klebsiella pneumoniae	21 (17.6)	18 (14)
Enterobacter spp	11 (9.2)	15 (11.6)
Citrobacter spp	4 (3.4)	3 (2.3)
Serratia spp	3 (2.5)	4 (3.1)
Mechanisms of resistance		
ESBL	16 (13.6)	12 (9.3)
AMP C	4 (3.4)	9 (7.1)

Molina et al. Clin Microb and Infect. 2021. E-pub ahead of print.S1198-743X(21)00491-2.

7 vs 14 Days in Enterobacterales Blood Stream Infection

	7 Day (n=119)	14 Day (n=129)
Source of bacteremia (%)		
Urinary tract	70 (59.3)	66 (51.2)
Intraabdominal	16 (13.6)	18 (14)
Vascular	14 (11.9)	16 (12.4)
Respiratory	3 (2.5)	12 (9.3)
Unknown	10 (8.5)	11 (8.5)
Other	5 (4.2)	6 (4.7)

Molina et al. Clin Microb and Infect. 2021. E-pub ahead of print.S1198-743X(21)00491-2.

7 vs 14 Days in Enterobacterales Blood Stream Infection

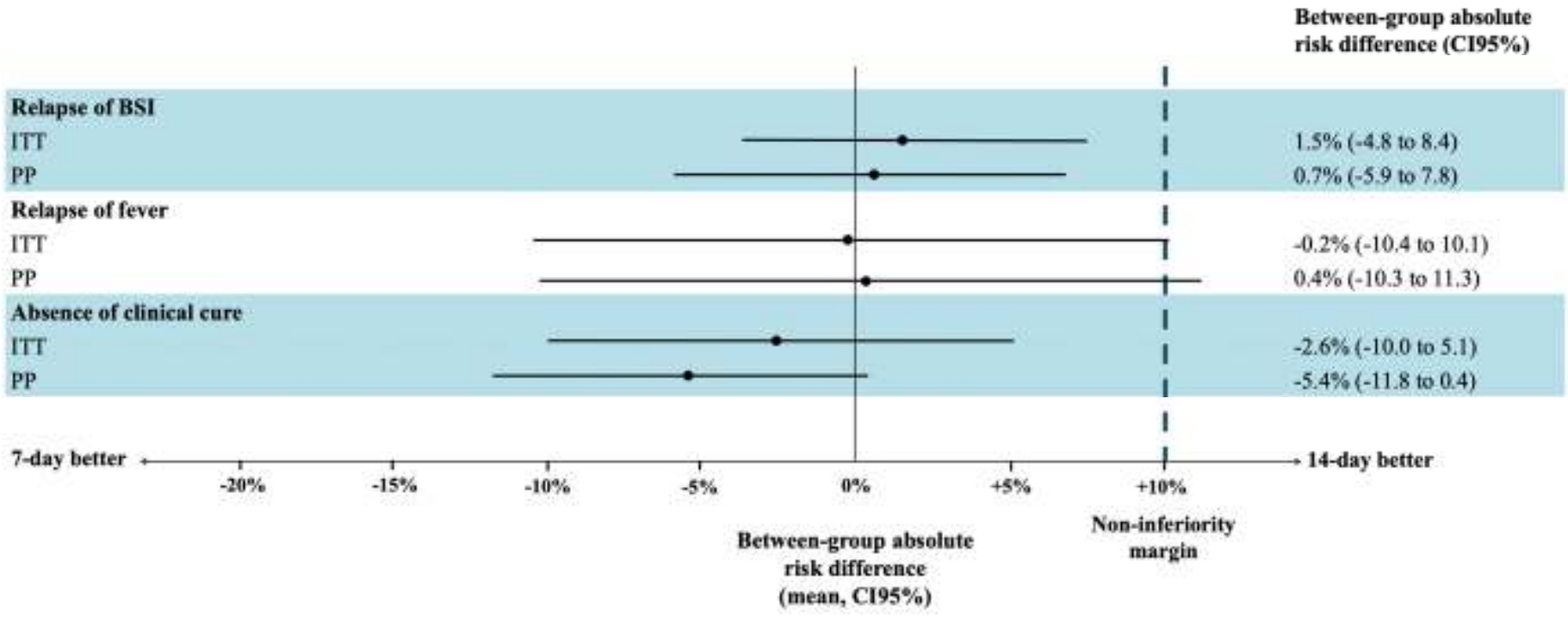


Fig. 3. Non-inferiority analysis for clinical outcome measures.

Molina et al. Clin Microb and Infect. 2021. E-pub ahead of print.S1198-743X(21)00491-2.

7 vs 14 Days in Enterobacterales Blood Stream Infection

- 7-day treatment was non-inferior to 14-day treatment for clinical cure and relapse of eBSI

- Relapse of fever was more frequent in 7-day treatment group
  - No significant differences were observed between groups for the causes of relapsing fever

Molina et al. Clin Microb and Infect. 2021. E-pub ahead of print.S1198-743X(21)00491-2.

Short Course Antibiotics in Catheter-Related Gram-Negative Bacteremia

- Retrospective, observational, single-center study at the University Hospital in Madrid, Spain
- Included patients with monomicrobial gram-negative catheter related bloodstream infection after removal
- Primary outcome: therapeutic failure (composite of one or more of the following: clinical failure, microbiological failure, and 30-day all-cause mortality

Ruiz-Ruigomez at al. J Antimicrob Chemother 2020;75:3049-55.

Short Course Antibiotics in Catheter-Related Gram-Negative Bacteremia

	Overall (n=54)	≤7 Days (n=23)	>7 Days (n=29)
Age, mean (±SD)	57.9±15.9	56.2±13.7	58.2±17.6
Male, gender	32 (59.3)	13 (56.5)	18 (62.1)
Isolated gram-negative bacteria			
Klebsiella pneumonia	13 (24.1)	5 (21.7)	8 (27.6)
Enterobacter cloacae	9 (16.7)	3 (13.0)	5 (17.2)
Serratia marcescens	9 (16.7)	3 (13.0)	6 (20.7)
E. Coli	3 (5.6)	2 (8.7)	1 (3.4)
Pseudomonas aeruginosa	12 (22.2)	6 (26.1)	6 (20.7)
Stenotrophomonas maltophilia	3 (5.6)	2 (8.7)	0
Other	5(9.3)	2 (8.7)	3 (10.3)
MDR bacteria	25 (46.3)	14 (60.9)	10 (34.5)

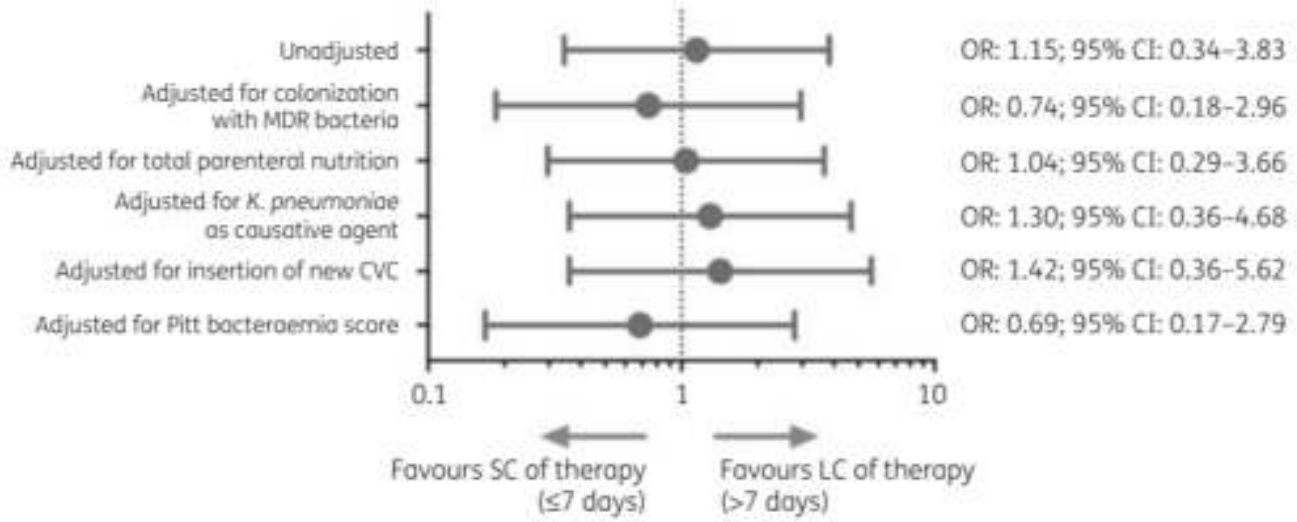
Ruiz-Ruigomez at al. J Antimicrob Chemother 2020;75:3049-55.

Short Course Antibiotics in Catheter-Related Gram-Negative Bacteremia

Study Outcome	Overall (n=54)	≤7 Days (n=23)	>7 Days (n=29)	P-value
Therapeutic failure	15 (27.8)	7 (30.4)	8 (27.6)	0.822
Clinical failure	11 (20.4)	5 (21.7)	6 (20.7)	1
Microbiological failure	2 (3.7)	1 (4.3)	1 (3.4)	1
All-cause 30-day mortality	4 (7.4)	3 (13)	1(3.4)	0.310

Ruiz-Ruigomez at al. J Antimicrob Chemother 2020;75:3049-55.

Short Course Antibiotics in Catheter-Related Gram-Negative Bacteremia



- Short course therapy (≤7 days) not associated with increased odds of therapeutic failure

Ruiz-Ruigomez at al. J Antimicrob Chemother 2020;75:3049-55.

Short Course Antibiotics in Uncomplicated MSSA Bacteremia

- Multicenter, retrospective, pooled cohort study in Copenhagen, Denmark
- ≥18 years and older with ≥1 methicillin-susceptible *S. aureus* blood isolate
- Excluded >16 days of treatment, endocarditis, meningitis, osteomyelitis, arthritis, spondylodiscitis, other secondary manifestation, infection involving foreign body, pneumonia, or positive follow-up blood culture for S. aureus obtain >48 hours after treatment initiation

Thorlacius-Ussing et al. CID 2021;73(5):866-72.

Short Course Antibiotics in Uncomplicated MSSA Bacteremia

	Cohort 1 Jan 2009-Dec 2018 (n=645)	Cohort 2 Jan 2006-Dec 2008 (n=219)	Cohort 3 Jan 1995-Dec 2010 (n=197)
Short-course (SC) therapy (6-10 days)	166	74	51
Prolonged-course (PC) therapy (11-16 days)	479	145	90

- Primary focus of *S. aureus* bacteremia (SAB): intravenous device, dialysis, drug injection, postop infection, skin infection, UTI, unknown

Thorlacius-Ussing et al. CID 2021;73(5):866-72.

Short Course Antibiotics in Uncomplicated MSSA Bacteremia

- Median duration (days)

	SC	PC
Cohort 1	8 (7-10)	14 (13-15)
Cohort 2	9 (8-10)	14 (13-15)
Cohort 3	8 (7-10)	13 (12-15)

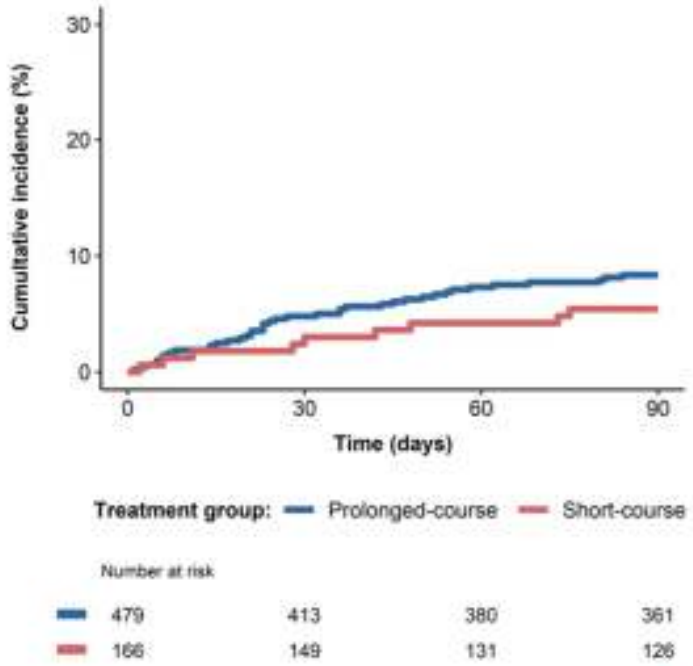
- Primary outcome: 90-day all-cause mortality

- Primary outcome in cohort 1
  - SC: 32/166 (19.3%)
  - PC: 91/479 (19%)
  - No difference
- Primary outcome in cohort 2
  - SC: 17/74 (23%)
  - PC: 30/145 (20.7%)
  - No difference
- Primary outcome in cohort 3
  - SC: 9/51 (17.6%)
  - PC: 18/90 (20%)
  - No difference

Thorlacius-Ussing et al. CID 2021;73(5):866-72.

Short Course Antibiotics in Uncomplicated MSSA Bacteremia

- Cumulative incidence of 90-day relapse of patients with low-risk MSSA bacteremia receiving SC or PC therapy
- Relapse: deep-seated infection or new SAB episode within 90 days of treatment
- Short-course duration of therapy not associated with increased risk of relapse



Thorlacius-Ussing et al. CID 2021;73(5):866-72.

Key Points in Bacteremia

- For uncomplicated infections with Enterobacterales, 7-day duration is as effective as longer courses
- For catheter related gram-negative bacteremia, 7-day duration is as effective as longer courses if catheter is removed
- For uncomplicated MSSA bacteremia, short course antibiotics yielded similar outcomes as prolonged courses in retrospective pooled cohort-- need RCT
- Non-Enterobacterales? Immunocompromised? MRSA bacteremia? ICU population?

Clinical Scenario 5

- PS, a 65 year-old male, is currently on amoxicillin/clavulanate for community acquired pneumonia. He is on day 2 of therapy and is clinically improved.

- How long should PS receive treatment for?
  A. 3 days
  B. 5 days
  C. 7 days
  D. Not sure

Challenges in Pneumonia

- >1 million hospitalized for pneumonia each year
- 1:4 patients require admission to the ICU
- 1:4 admitted to the ICU with pneumonia die
- IDSA recommends a minimum of 5-day course of antibiotics for community acquired pneumonia (CAP)
- IDSA recommends 7-day course of antibiotics for nosocomial pneumonia

Cavallazzi et al. *Chest*. 2020;158(3):1008-1016.
Bordon et al. *Chest*. 2010;138(2):279-283.

3-Day Course for CAP?

- Double-blind, randomized, placebo-controlled, non-inferiority trial in 16 centers in France

- Patients ≥18 years old hospitalized with moderately severe CAP (non-ICU), who met clinical stability criteria, were randomized (1:1) to receive amoxicillin-clavulanate 1,000/125mg TID or placebo for 5 extra days
  - Clinical stability criteria: afebrile, HR <100, RR <24, O2 sat ≥90%, SBP ≥90 mm Hg, and normal mental status

- Primary outcome: cure 15 days after initiation of antibiotics

Dinh et al. Lancet. 2021;397:1195-1203.

3-Day Course for CAP?

	3 day BL group (n=152)	8 day BL group (n=151)
Age, years	72.5 (54-85.3)	74 (58-83)
Female sex	66 (43%)	57 (38%)
Oxygen therapy	60 (39%)	59 (39%)
2 comorbidities	34 (22%)	39 (36%)
Active smoking	30 (20%)	25 (17%)
PSI score	80.5 (57-103)	83 (58-104)
Radiological findings		
Multilobar	30 (20%)	23 (15%)
Pleural effusion	11 (7%)	16 (11%)
Procalcitonin	0.55 (0.20-2.23)	0.20 (0.10-0.60)

Dinh et al. Lancet. 2021;397:1195-1203.

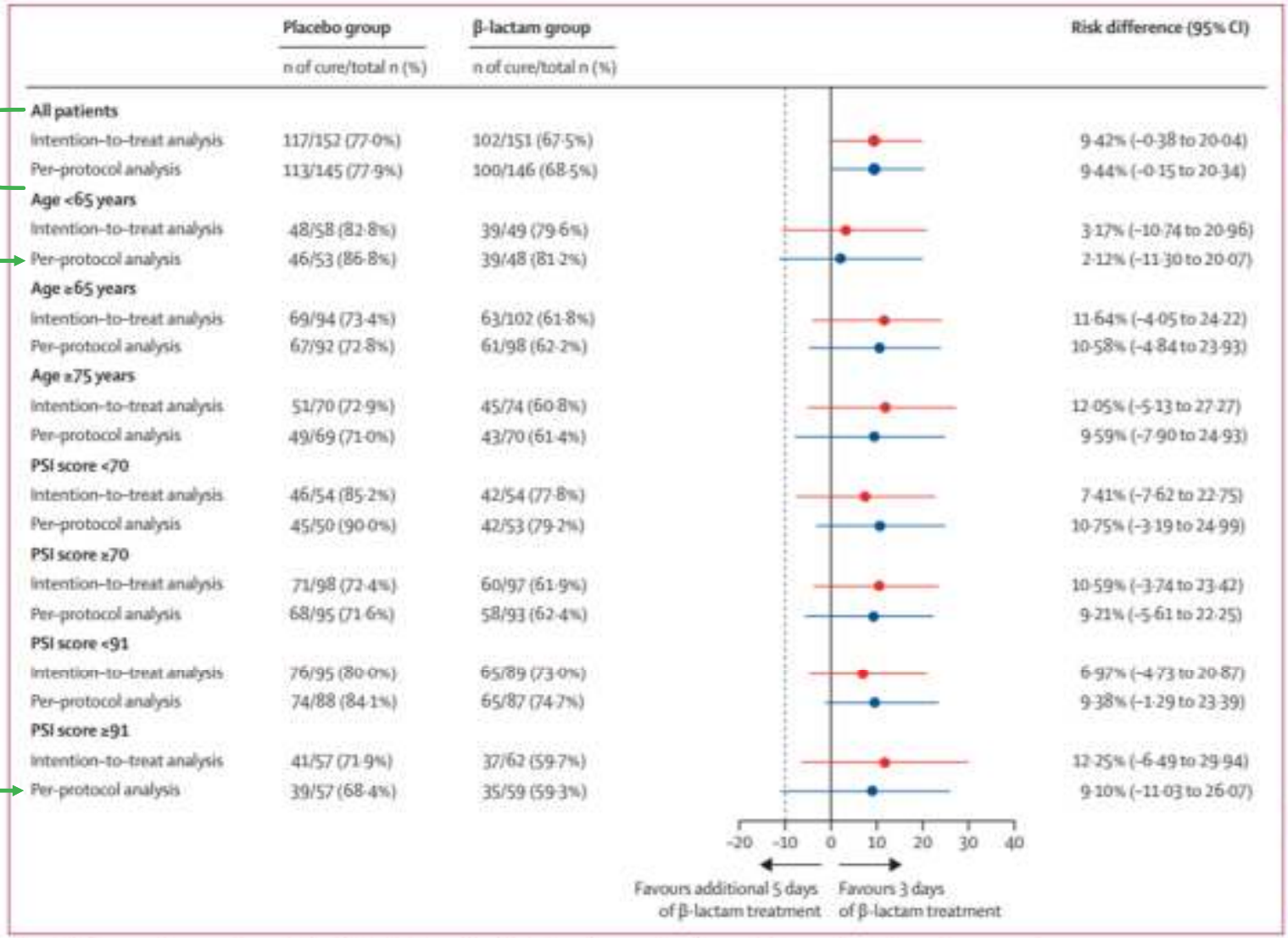


Figure 2: **Primary outcome of cure at day 15, in the intention-to-treat and per-protocol population, and post-hoc subgroup analyses**
Data are n/N (%) and risk difference with 95% CI in parentheses. Vertical dotted line indicates non-inferiority margin. PSI=Pneumonia Severity Index.

Dinh et al. Lancet. 2021;397:1195-1203.

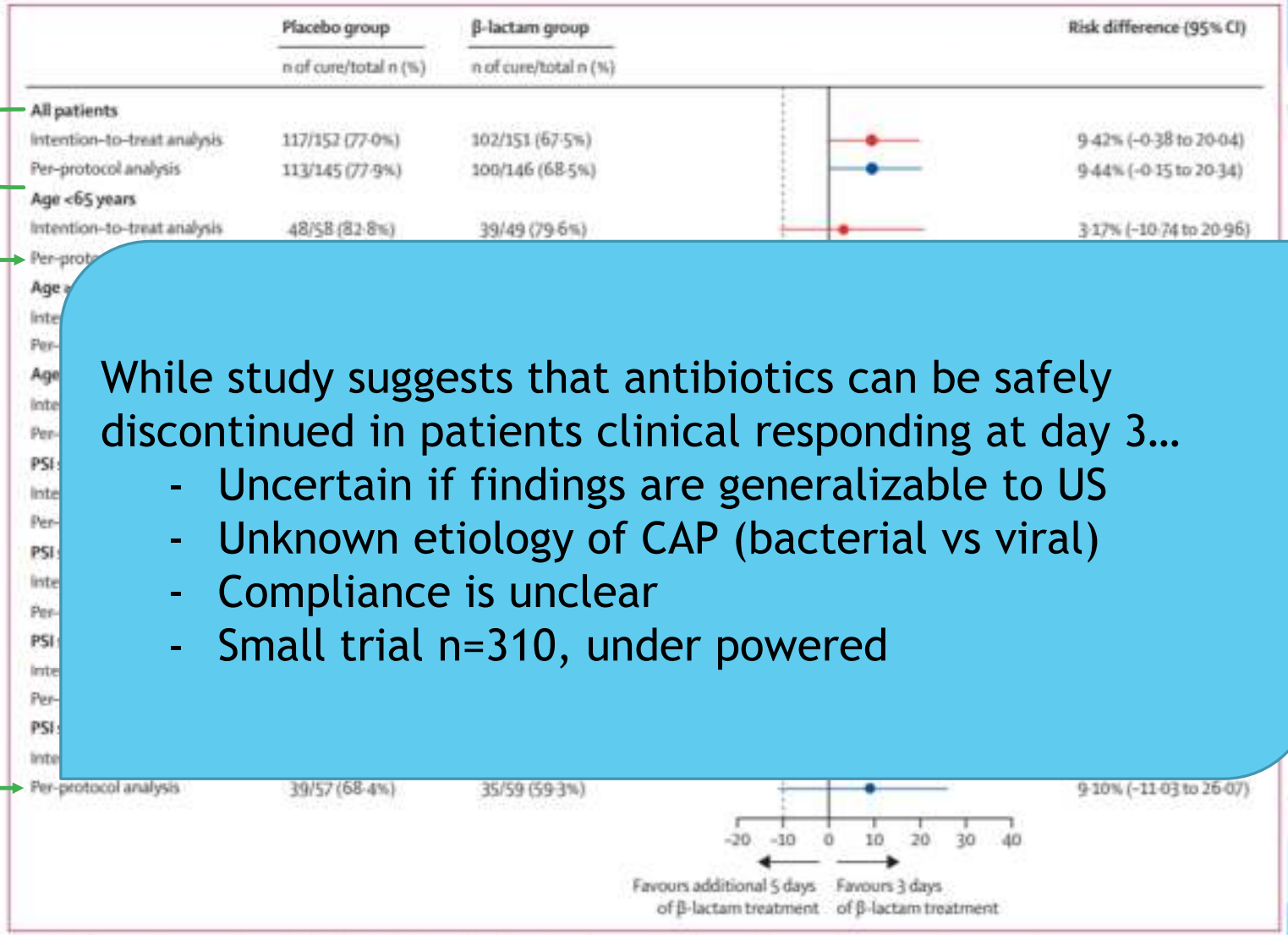


Figure 2: **Primary outcome of cure at day 15, in the intention-to-treat and per-protocol population, and post-hoc subgroup analyses**
Data are n/N (%) and risk difference with 95% CI in parentheses. Vertical dotted line indicates non-inferiority margin. PSI=Pneumonia Severity Index.

While study suggests that antibiotics can be safely discontinued in patients clinical responding at day 3…

- Uncertain if findings are generalizable to US
- Unknown etiology of CAP (bacterial vs viral)
- Compliance is unclear
- Small trial n=310, under powered

Dinh et al. Lancet. 2021;397:1195-1203.

Keys Points in Pneumonia

- Data supports shorter courses of antibiotics in CAP (5 days) and HAP/VAP (7days)
- Insufficient data to support shorter course (<5 days) of antibiotics in CAP
- Awaiting surveillance data for treatment outcomes in all severities of pneumonia with shorter courses of antibiotics

Situations Where Shorter Duration May Not Be Appropriate

- Severe infections, critically ill
- Immunocompromised patients
- No source control
- Delay in microbiology results

Antimicrobial Stewardship Strategies for Reducing Durations of Antibiotics

Early Infectious Diseases Consult

Open Forum Infectious Diseases
MAJOR ARTICLE

Early Infectious Disease Consultation Is Associated With Lower Mortality in Patients With Severe Sepsis or Septic Shock Who Complete the 3-Hour Sepsis Treatment Bundle

Theresa Madaline,[1,2] Francis Wadskier Montagne,[1] Ruth Eisenberg,[2] Wenzhu Mowrey,[2] Jaskiran Kaur,[2] Maria Malik,[2] Inessa Gendlina,[1] Yi Guo,[1] Deborah White,[3] Liise-anne Pirofski,[1,3] and Uzma Sarwar[1]

- In-hospital mortality was lower in early ID consult group
- There was no significant difference in 30-day readmission or mean LOS
- There was a trend towards shorter time to antibiotic de-escalation in early ID group

Madaline et al. Open Forum Infect Dis. 2019;6(10):ofz408.

American Journal of Infection Control
Volume 47, Issue 12, December 2019, Pages 1409-1414

Major Article

Influencing duration of antibiotic therapy: A behavior change analysis in long-term care

Bradley J. Langford BscPhm, PharmD [a], Jacquelyn Quirk MPH [a], Stacie Carey MA [a], Nick Daneman MD, MSc [a, b, c, d], Gary E. Garber MD [a, d, e, f]

- Themes identified that influenced duration of antibiotic in long-term care:
  - Environmental context and resources
  - Knowledge
  - Beliefs and consequences
  - Social influences
  - Behavioral regulation

Langford et al. Am J Infect Control. 2019;47(12):1409-1414.

Clinical Infectious Diseases

MAJOR ARTICLE

Late-career Physicians Prescribe Longer Courses of Antibiotics

Cesar I. Fernandez-Lazaro,[1,2,3] Kevin A. Brown,[1,3] Bradley J. Langford,[1] Nick Daneman,[1,4,5] Gary Garber,[1,6] and Kevin L. Schwartz[1,3,7]

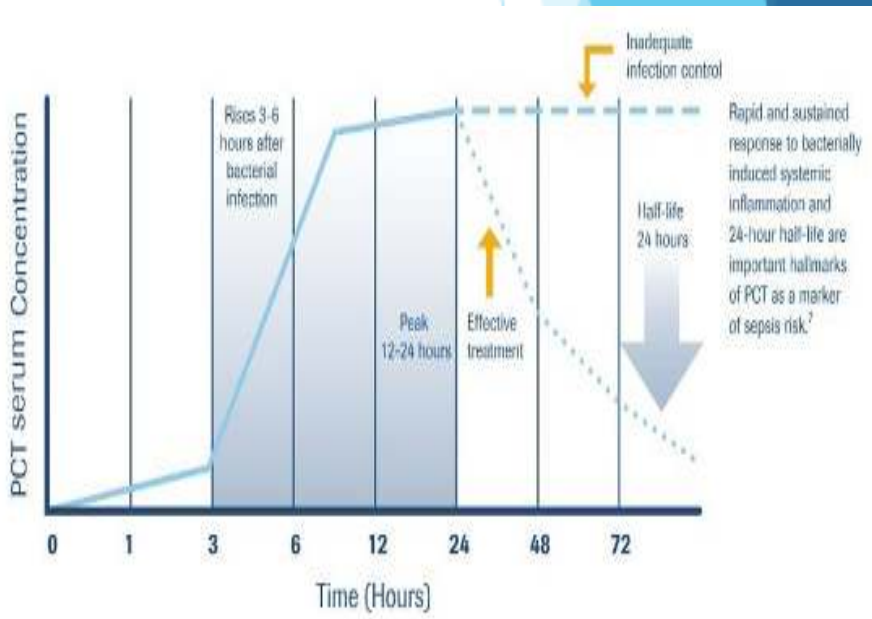
[1]Infection Prevention and Control, Public Health Ontario, Toronto, Canada; [2]Department of Biomedical and Diagnostic Sciences, University of Salamanca, Spain; and [3]Dalla Lana School of Public Health, University of Toronto, and [4]Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Canada; [5]Institute of Health Policy, Management and Evaluation, University of Toronto, Canada [6]Department of Medicine, Ottawa Hospital Research Institute, Canada; and [7]Department of Medicine, St. Joseph's Health Centre, Toronto, Canada

- Retrospective cohort analysis of family physicians in Ontario, Canada (n=10,616)
- Prolonged courses (>8 days) of antibiotics were more likely prescribed by late-career (>24 years) physicians

Fernandez-Lazaro et al. Clin Infect Dis 2019;69:1467-75

Role of Procalcitonin

- Increases within 3-6 hours after onset of bacterial infection, peaks 12-14 hours
- Persists for duration of inflammatory process
- Normalizes with recovery
- Remains low in viral infections and nonspecific inflammatory diseases



https://diagnostics.roche.com/us/en/products/params/elecsys-brahms-procalcitonin-pct.html

Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis

A Randomized Trial

Evdoxia Kyriazopoulou[1], Lydia Liaskou-Antoniou[1], George Adamis[2], Antonia Panagaki[1], Nikolaos Melachroinopoulos[1], Elina Drakou[2], Konstantinos Marousis[2], Georgios Chrysos[3], Andronikos Spyrou[2], Nikolaos Alexiou[4], Styliani Symbardi[4],

- Multicenter trial of patients with sepsis secondary to lower respiratory tract infections, acute pyelonephritis, or primary bloodstream infection (n=266)

	PCT Guided Discontinuation	Standard of Care	P-value
Infection associated ADE	7.2%	15.3%	0.045
28-day mortality	15.2%	28.2%	0.02
Median length of therapy, days	5 (5-7)	10 (7-15)	<0.001

Kyriazopoulou E et al. Am J Respir Crit Care Med. 2021;203(2):202-210.

Conclusions

- Shorter durations of antibiotics prevents adverse events, super infections, and antibiotic resistance
- Growing evidence to support short-course antibiotics to be equivalent to longer therapy
- Some situations warrant longer courses of antibiotic therapy- durations should be determined based on individual clinical picture
- Food for thought…. can we customize antibiotic durations to patient's response?

How Low Can We Go?

A review of literature supporting shorter duration of antibiotics

NYSCHP Annual Assembly 2022

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