

Duration of Therapy: How Low Can You Go?



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Outline

1. Principles

- “low hanging fruit”
- Goldilocks zone

2. Guideposts

- resources
 - Nelson et al
 - IDSA Guidelines
- data free zone (DFZ)

Outline

3. Infections

- SSTI
- pneumonia
 - CAP
 - HAP/VAP
- urinary infection
 - cystitis
 - pyelonephritis
 - CAUTI
- abdominal abscess
- CLABSI

- Background Studies
- IDSA/Sanford

Principles

“Zero days of therapy is a nice, short duration.”

Hecker et al

- 650 noninfectious days of therapy
 - 2 weeks
 - approx 1/3 of all days of therapy

Table 2. Reasons for Unnecessary Days of Therapy for All Antimicrobials and the Subset of Agents With Antianaerobic Activity

Reason	No. (%) of Patients	
	All Antimicrobials	Antianaerobic Antibiotics
Noninfectious or nonbacterial syndrome	187 (32)	74 (36)
Treatment of colonization or contamination	94 (16)	25 (12)
Duration of therapy longer than necessary	192 (33)	67 (33)
For treatment regimens*	153	56
For empiric regimens†	39	11
Adjustment not made in a timely manner	20 (3)	9 (4)
Redundant antimicrobial coverage	60 (10)	18 (9)
Spectrum of activity not indicated‡	23 (4)	10 (5)
Total	576	203

essary

Principles

SOURCE CONTROL

Principles

Goldilocks Zone

- Q: “How much antibiotics?”
- A: “Just enough.”

Pros

- ↓ resistance
- ↓ adverse reactions
- ↓ length of stay
- ↓ cost

Cons

- blowback
- DFZ

Hot on the Case!

21 yo male wrestler

- 3cm boil on left thigh
- I&D = MRSA
- you're going with TMP/SMX

A. 3 days

B. 5 days

C. 7 days

D. 10 days

E. 14 days

Skin & Soft Tissue Infection

Skin & Soft Tissue

- Jenkins et al 2010

- Holmes et al 2016

- pediatric randomized, non-inferiority (n=249)
- excluded
 - no drainage (ie, only abscesses)
 - immune compromised
 - inpatient
- TMP/SMX 3d vs TMP/SMX 10d

Table 4. Bacteria Isolated from Culture of Abscess Material, Deep Tissue Specimens, or Blood

Isolate	Cutaneous abscess (n = 77)	SSTI with additional complicating factors (n = 73)	P
<i>Staphylococcus aureus</i>	52 (68)	45 (62)	>.2
Methicillin resistant	34 (44)	30 (41)	>.2
Methicillin susceptible	15 (19)	13 (18)	>.2
Susceptibility not assayed	3 (4)	2 (3)	>.2 ^a
Streptococci	29 (38)	31 (42)	>.2
<i>S. aureus</i> or streptococci	75 (97)	70 (96)	>.2 ^a
<i>S. aureus</i> or streptococci only	59 (77)	52 (71)	>.2
Anaerobe(s)	13 (17)	16 (22)	>.2
Aerobic gram-negative bacteria ^b	10 (13)	10 (14)	>.2
Enterococci	3 (4)	2 (3)	>.2 ^a
Other	2 (3)	3 (4)	>.2 ^a

Conclusion Patients with MRSA skin abscesses are more likely to experience treatment failure and recurrent skin infection if given 3 rather than 10 days of trimethoprim-sulfamethoxazole after surgical drainage. (*J Pediatr* 2016;169:128-34).

Skin & Soft Tissue Infection

- Talan et al 2016
 - randomized, double-blind superiority (n=1265)
 - excluded
 - <12 years of age
 - <2cm fluctuant lesion (ie, only abscesses) for < 1 week
 - inpatient

Table 3. Cure Rates among Patients with a Drained Cutaneous Abscess in Three Trial Populations.*

Trial Population	Cure of Abscess		Difference (95% CI)	P Value†
	Trimethoprim–Sulfamethoxazole no./total no. (%)	Placebo no./total no. (%)		
Modified intention-to-treat 1	507/630 (80.5)	454/617 (73.6)	6.9 (2.1 to 11.7)	0.005
Per-protocol‡	487/524 (92.9)	457/533 (85.7)	7.2 (3.2 to 11.2)	<0.001
FDAGEEP	218/601 (36.3)	204/605 (33.7)	2.6 (-3.0 to 8.1)	0.38

Skin & Soft Tissue Infection

- Duam et al 2017
 - randomized, double-blind, superiority (n=786)
 - 281 (36%) children

Table 3. Cure Rate at Test-of-Cure Visit in the Overall Population and Relevant Subgroups.*

Group	Clindamycin		TMP-SMX		Placebo	
	No. with Cure/ Total No.	% (95% CI)	No. with Cure/ Total No.	% (95% CI)	No. with Cure/ Total No.	% (95% CI)
All participants						
Intention-to-treat population	221/266	83.1 (78.3–87.9)	215/263	81.7 (76.8–86.7)	177/257	68.9 (62.9–74.9)
Population that could be evaluated	221/238	92.9 (89.3–96.4)	215/232	92.7 (89.0–96.3)	177/220	80.5 (74.8–86.1)
Children						
Intention-to-treat population	90/101	89.1 (82.5–95.7)	75/91	82.4 (74.0–90.8)	61/89	68.5 (58.3–78.7)
Population that could be evaluated	90/92	97.8 (94.3–100.0)	75/81	92.6 (86.3–98.9)	61/74	82.4 (73.1–91.8)

Skin & Soft Tissue Infection

IDSA

RECOMMENDATIONS FOR ERYSIPelas AND CELLULITIS

IV. What Is Appropriate for the Evaluation and Treatment of Erysipelas and Cellulitis?

15. The recommended duration of antimicrobial therapy is 5 days, but treatment should be extended if the infection has not improved within this time period (strong, high).

XXIII. What Is the Appropriate Antibiotic Therapy for Patients With SSTIs During the Initial Episode of Fever and Neutropenia?

65. It is recommended that the duration of treatment for most bacterial SSTIs should be for 7–14 days (strong, moderate).

Sanford

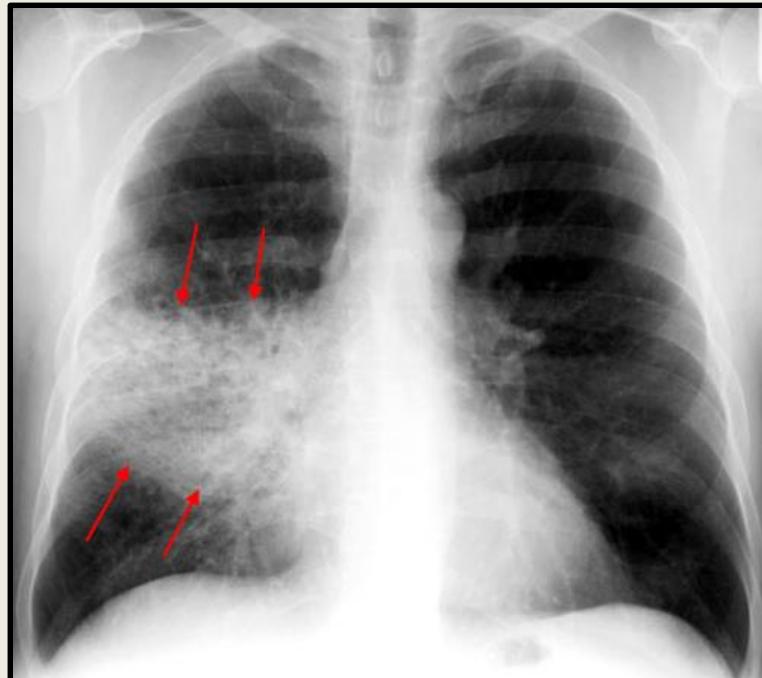
“Until 3 days after acute inflammation disappears”

Hot on the Case!

62 yo retired female librarian

- 9 days of purulent cough + fever
- sputum = Strep. pneumoniae
- you're going with ceftriaxone

- A. 3 days
- B. 5 days
- C. 7 days
- D. 10 days
- E. 14 days



Community Acquired Pneumonia

Community Acquired Pneumonia

Background Studies

- Dunbar et al 2003
 - randomized, double-blind, active-treatment controlled non-inferiority (n=528)
 - excluded
 - known resistance or high risk for *Pseudomonas*
 - aspiration or empyema
 - neutropenia or HIV+
 - meningitis
 - LVQ 750mg daily 5d vs LVQ 500mg daily 10d

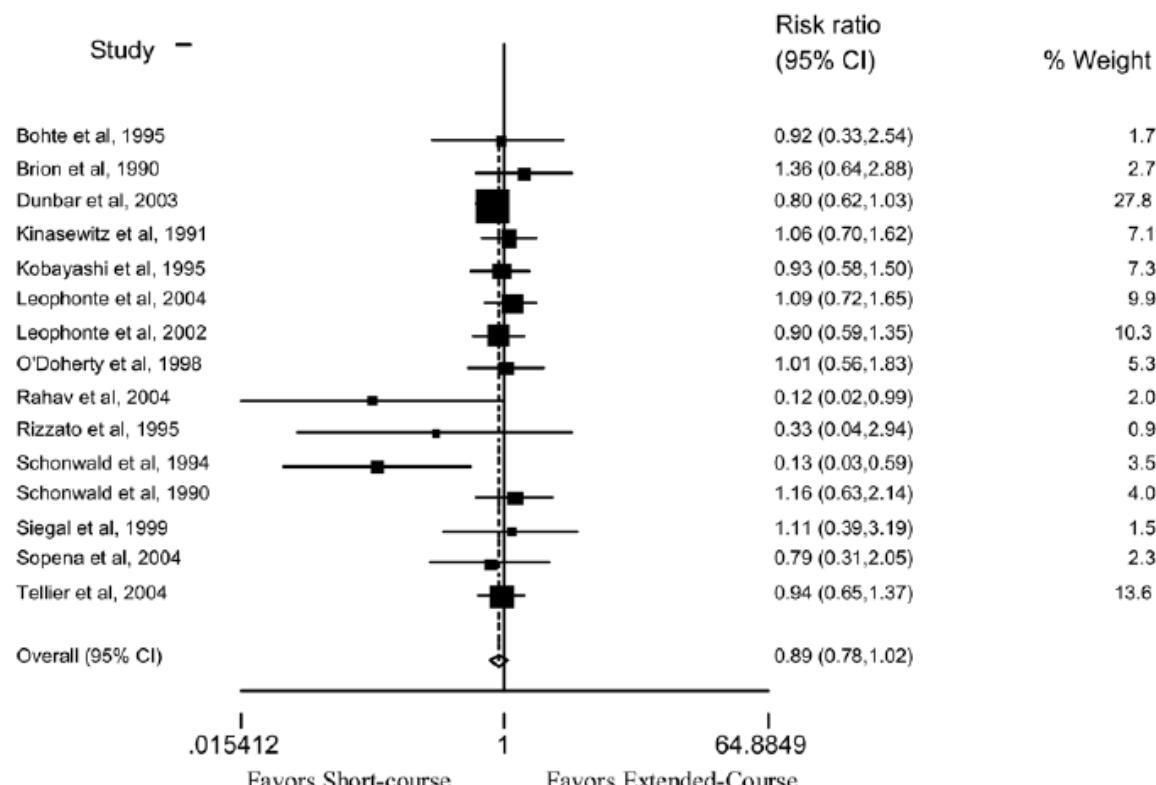
Community Acquired Pneumonia

Background Studies

- Dunbar et al 2003
 - randomized, double-blind, active-treatment controlled non-inferiority (n=528)
 - excluded
 - known resistance or high risk for *Pseudomonas*
 - aspiration or empyema
 - neutropenia or HIV+
 - LV In this study, we demonstrated that treatment with 750 mg of levofloxacin per day for 5 days is at least as effective and well tolerated as treatment with 500 mg of levofloxacin per day for 10 days for the treatment of mild to severe CAP.

Table 1 Characteristics of Included Studies

Study	Short-Course	Extended-Course	n	Mean Age*	Time to Outcome Assessment
Bohte et al, 1995 ²³	Azithromycin, 5 d	Erythromycin, 10 d	42	61	Within 21 days of discharge
Brion et al, 1990 ²⁴	Azithromycin, 5 d	Josamycin, 10 d	97	53	30 days
Dunbar et al, 2003 ³³	Levofloxacin, 5 d	Levofloxacin, 10 d	528	54	7-14 days after last dose of antibiotic
Kinasewitz & Wood, 1991 ²⁵	Azithromycin, 5 d	Cefaclor, 10 d	119	42	10-13 days
Kobayashi et al, 1995 ²⁶	Azithromycin, 3 d	Clarithromycin, 14 d	163	Not reported	14 days
Leophonte et al, 2004 ³⁴	Gemifloxacin, 7 d	Amoxicillin/clav. 10 d	320	54	24-30 days
Leophonte et al, 2002 ³⁵	Ceftriaxone, 5 d	Ceftriaxone, 10 d	244	64	10 days
O'Doherty & Muller, 1998 ²⁷	Azithromycin, 3 d	Clarithromycin, 10 d	203	51	12-16 days

**Figure 2** Relative risk of clinical failure with short-course versus extended course antibiotic regimens.

Community Acquired Pneumonia

IDSA = DFZ

- “The committee chose not to address ...”
 - solid organ/bone marrow/stem cell recipients
 - receiving chemotherapy
 - long-term (>30 days) corticosteroids
 - congenital nor acquired immunodeficiencies
 - CD4 <350
 - <18 years of age

Community Acquired Pneumonia

IDSA

Duration of Antibiotic Therapy

32. Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy (level II evidence). (Moderate recommendation.)

Sanford

Community Acquired Pneumonia

IDSA

Duration of Antibiotic Therapy

32. Patients with CAP should receive antibiotic therapy for at least 5 days (level I evidence). The duration of therapy should be longer if there is evidence of bacteremia, septic shock, and should have no improvement in clinical instability (time to resolution of fever and signs of clinical instability) by day 3 of therapy (level II evidence). (See Table 1 for specific recommendations.)

Short-duration therapy may be suboptimal for patients with bacteremic *S. aureus* pneumonia (because of the risk of associated endocarditis and deep-seated infection), for those with meningitis or endocarditis complicating pneumonia, and for those infected with other, less common pathogens (e.g., *Burkholderia pseudomallei* or endemic fungi). An 8-day course of therapy for nosocomial *P. aeruginosa* pneumonia led to relapse more commonly than did a 15-day course of therapy [279]. Whether the same results would be applicable to CAP cases is unclear, but the presence of cavities or other signs of tissue necrosis may warrant prolonged treatment.

Sanford

“5 days (minimum) and until afebrile for 2-3 days”

Hospital/Ventilator Pneumonia

Table 4. Primary Study Outcomes 28 Days After Bronchoscopy as a Function of Duration of Antibiotic Administration

Event	No./Total (%)		Between-Group Risk Difference (90% CI), %
	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)	
Death from all causes*			
All patients	37/197 (18.8)	35/204 (17.2)	1.6 (-3.7 to 6.9)
Nonfermenting GNB†	15/64 (23.4)	19/63 (30.2)	-6.7 (-17.5 to 4.1)
MRSA	6/21 (28.6)	5/21 (23.8)	4.8 (-13.9 to 23.4)
Other bacteria	16/112 (14.3)	11/120 (9.2)	5.1 (-0.7 to 10.9)
Pulmonary infection recurrence*			
All patients	57/197 (28.9)	53/204 (26.0)	2.9 (-3.2 to 9.1)
Superinfection‡	39/197 (19.8)	38/204 (18.6)	1.2 (-4.3 to 6.6)
Relapse‡	33/197 (16.8)	23/204 (11.3)	5.5 (0.7 to 10.3)
Nonfermenting GNB†	26/64 (40.6)	16/63 (25.4)	15.2 (3.9 to 26.6)
Superinfection‡	13/64 (20.3)	8/63 (12.7)	7.6 (1.1 to 14.2)
Relapse‡	21/64 (32.8)	12/63 (19.0)	13.8 (7.8 to 19.7)
MRSA	7/21 (33.3)	9/21 (42.9)	-9.5 (-30.1 to 11.1)
Superinfection‡	6/21 (28.6)	5/21 (23.8)	4.8 (-8.8 to 18.3)
Relapse‡	3/21 (14.3)	4/21 (19.0)	-4.8 (-9.9 to 0.4)
Other bacteria	24/112 (21.4)	28/120 (23.3)	-1.9 (-9.5 to 5.6)
Superinfection‡	20/112 (17.9)	25/120 (20.8)	-3.0 (-8.2 to 2.2)
Relapse‡	9/112 (8.0)	7/120 (5.8)	2.2 (-1.3 to 5.7)

Hospital/Ventilator Pneumonia

IDSA

LENGTH OF THERAPY	XXII. What Is the Optimal Duration of Antibiotic Therapy for HAP
<p>XXI. Should Patients With VAP Receive Therapy?</p> <p><i>Recommendation</i></p> <p>1. For patients with VAP, we recommend antimicrobial therapy rather than a longer duration (<i>strong recommendation, moderate-quality evidence</i>).</p>	<p>Remarks: There exist situations in which a shorter or longer duration of antibiotics may be indicated, depending upon the rate of improvement of clinical, radiologic, and laboratory parameters.</p> <p>We recommend a 7-day course of therapy rather than a longer duration (<i>strong recommendation, very low-quality evidence</i>).</p>

Sanford

“Not well defined”

- 8d for “relatively susceptible pathogens”
- 14d for MRSA, PSA, Acinetobacter, Stenotrophomonas, etc.

Hot on the Case!

30 yo female medicine resident

- 2 days of dysuria
- UA = >600 WBCs growing E. coli
- you're going with nitrofurantoin

- A. 3 days
- B. 5 days
- C. 7 days
- D. 10 days
- E. 14 days

Cystitis

Background Studies

- Trienekens et al 1989

TABLE II—*Response of symptoms in patients with urinary tract infection treated with co-trimoxazole. Figures are numbers (percentages) of patients*

	Symptoms present		Symptoms present and bacteriologically proved	
	Three days' treatment	Seven days' treatment	Three days' treatment	Seven days' treatment
Symptoms absent or improved one week after entry	131/142 (92)	129/145 (89)	88/97 (91)	89/97 (92)
Symptoms absent or improved two weeks after entry	110/121 (91)	108/121 (89)	77/83 (93)	74/81 (91)
Symptoms absent six weeks after entry	97/116 (84)	106/123 (86)	74/85 (87)	72/80 (90)

- 3d v /d TMP/SMX
 - no recurrence at 1, 2 and 6 weeks

Cystitis

- Iravani et al 1999

randomized double-blind ($n = 521$)

3d

•

• ciprofloxacin vs nitrofurantoin

in

Outcome	Patients, No./Total No. (%)		
	TMP-SMX Group (n = 148)	Nitrofurantoin Group (n = 160)	Difference (95% CI), %
Primary outcome			
Overall clinical cure	117/148 (79)	134/160 (84)	-5 (-13 to 4)
Secondary outcomes			
Early clinical cure	133/148 (90)	144/160 (90)	-0.1 (-7 to 7)
Early microbiological cure	131/144 (91)	141/154 (92)	-1 (-7 to 6)

- clinical cure at 30 days

Cystitis

IDSA + Sanford

Nitrofurantoin monohydrate/macrocrystals 100 mg bid X 5 days
(avoid if early pyelonephritis suspected)

OR

Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid X 3 days
(avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months)

OR

Fosfomycin trometamol 3 gm single dose
(lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

Cystitis

IDSA + Sanford

Nitrofurantoin

(avoid if early
pyelonephritis
suspected)

6. β -Lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3–7-day regimens are appropriate choices for therapy when other recommended agents cannot be used (B-I). Other β -lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III). The β -lactams generally have inferior efficacy and more adverse effects, compared with other UTI antimicrobials (B-I).

Trimethoprim-sulfamethoxazole
(one daily dose)
(avoid if renal function
exceeds 20% of normal)

months)

OR

Fosfomycin trometamol 3 gm single dose
(lower efficacy than some other recommended
agents; avoid if early pyelonephritis suspected)

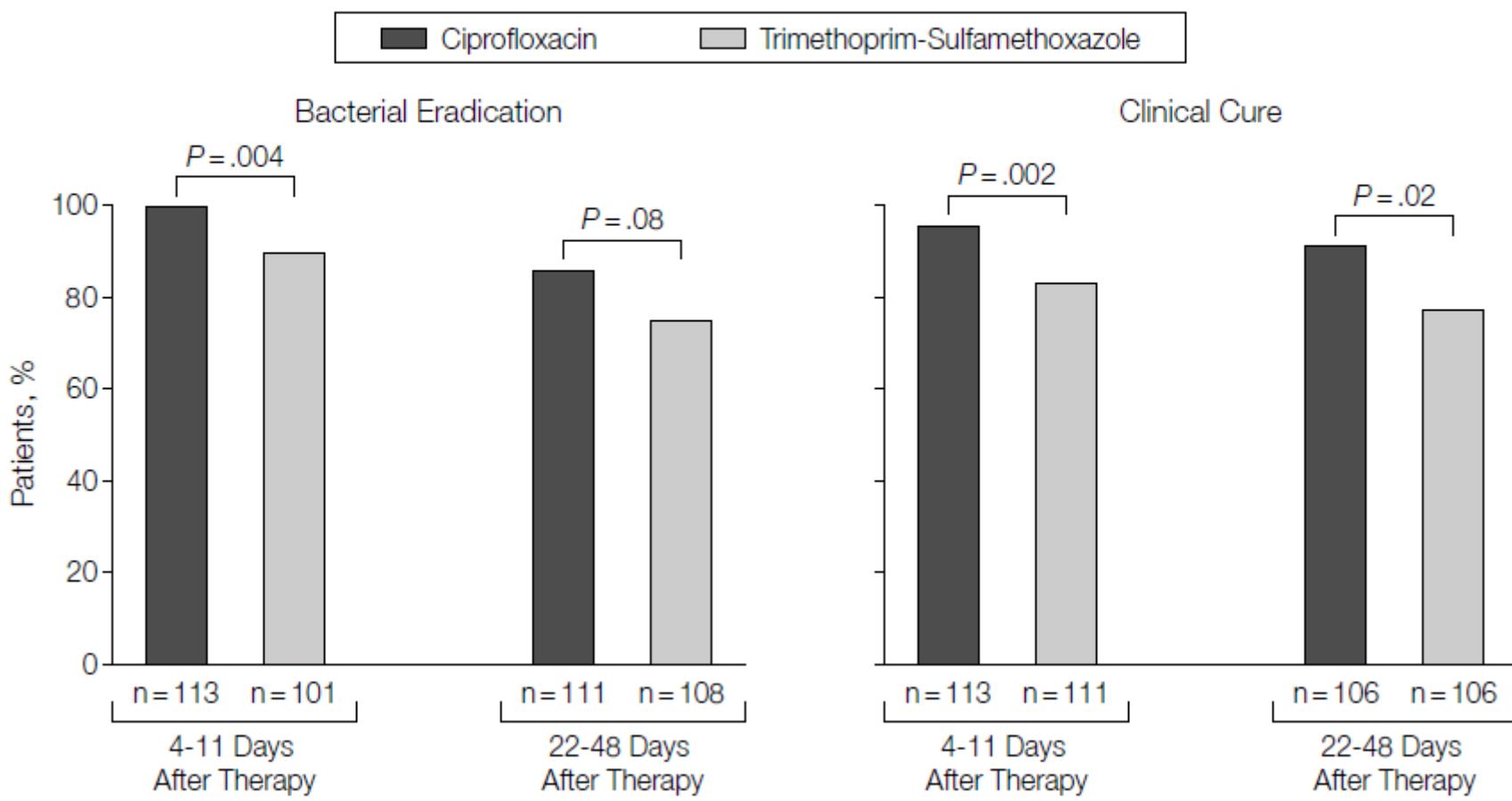
Pyelonephritis

Background Studies

- Talen et al 2000
 - randomized, double-blind, placebo-controlled (n=255)
 - CVA tenderness + fever + pyuria
 - excluded
 - <18 years of age
 - sepsis
 - GU abnormality/pregnant
 - immune compromised (including diabetes)
 - renal dysfunction
 - 7d ciprofloxacin + 7d placebo vs 14d TMP/SMX

Pyelonephritis

Figure 2. Continued Bacteriologic and Clinical Cure Rates Through the 4- to 11-Day and 22- to 48-Day Posttherapy Visits for Women with Acute Uncomplicated Pyelonephritis



Pyelonephritis

- Klausner et al 2007
 - double-blind, non-inferiority (n=311)
 - excluded

Table 3. Microbiologic and clinical responses at post-therapy visit (study days 15–19)

	Levofloxacin (10–14 days after end of active therapy)			Ciprofloxacin (5–9 days after end of active therapy)			Difference (95% CI)*
	Eradicated	Persisted	Unknown	Eradicated	Persisted	Unknown	
mITT							
Microbiologic outcome	78 (83.0) Success	6 (6.4) Failure	10 (10.6) Unable to evaluate	78 (79.6) Success	8 (8.2) Failure	12 (12.2) Unknown	-3.4 (-14.4, 7.6)
Clinical outcome	81 (86.2)	6 (6.4)	7 (7.4)	79 (80.6)	9 (9.2)	10 (10.2)	-5.6 (-16.0, 4.9)
ME							
Microbiologic outcome	74 (92.5) Success	6 (7.5) Failure		71 (93.4) Success	5 (6.6) Failure		0.9 (-7.1, 8.9)
Clinical outcome	74 (92.5)	6 (7.5)		68 (89.5%)	8 (10.5)		-3.0 (-12.0, 6.0)

Pyelonephritis

IDSA

- 5d LVQ 750mg PO daily
- 7d ciprofloxacin 500mg PO BID
- 14d TMP/SMX PO BID
- “oral β lactams are less effective”
 - “insufficient data” = 10-14d

Sanford

- 5d LVQ or 7d ciprofloxacin or 14d other

CAUTI

“The most common healthcare-associated infection worldwide.”

IDSA

- 7d if “prompt resolution”
 - 3d if woman ≤65 years old without UUTS
 - 5d LVQ if not “severely ill”
- 10-14d if “delayed response”

Sanford

- see Hooton et al CID 2010



Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score-Matched Cohort

- Chotiprasitsakul et al 2018
 - retrospective cohort (n=385)
 - monomicrobial Enterobacteriaceae septicemia
 - matched 1:1 to “nearest neighbor”
 - excluded
 - >16d of antibiotics
 - death or Hospice
 - aminoglycoside therapy
 - transplant patients
 - short course (6-10d) vs prolonged course (11-16d)

Comparing the Outcomes of Adults With Enterobacteriaceae Bacteremia Receiving Short-Course Versus Prolonged-Course Antibiotic Therapy in a Multicenter, Propensity Score-Matched Cohort

Source of bacteremia						
Pneumonia	36 (9.4)	109 (7.9)	.35	36 (9.4)	33 (8.6)	.71
Skin and soft tissue	14 (3.6)	43 (3.1)	.60	14 (3.6)	17 (4.4)	.58
Urinary tract	134 (34.8)	566 (40.9)	.03	134 (34.8)	144 (37.4)	.45
Biliary	60 (15.6)	156 (11.3)	.02	60 (15.6)	65 (16.9)	.63
Gastrointestinal	87 (22.6)	261 (18.9)	.24	87 (22.6)	66 (17.1)	.12
Catheter-associated	54 (14.0)	240 (17.3)	.12	54 (14.0)	52 (13.5)	.83

Table 3. Thirty-Day All-Cause Mortality for Hospitalized Adult Patients With Enterobacteriaceae Bacteremia in a Propensity Score-Matched Cohort

Variable	Unadjusted HR (95% CI)	PValue	Adjusted HR ^a (95% CI)	PValue
Short-course therapy (6–10 d)	1.12 (.70–1.80)	.64	1.00 (.62–1.63)	.97
Urinary source	0.36 (.19–.67)	.001	0.49 (.26–.94)	.03
Pneumonia	3.06 (1.73–5.42)	<.001	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.31 (1.21–1.42)	<.001	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	2.38 (1.48–3.81)	<.001	0.99 (.56–1.76)	.98
End-stage liver disease	3.58 (2.05–6.06)	<.001	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.03 (.63–1.70)	.89	1.40 (.83–2.36)	.21

Abdominal Abscess

IDSA

- 4-7d after “adequate source control”
- 24h for perforation controlled <24hrs
- ≤24hrs for penetrating injury repaired <12hrs
- only pre-operative for simple appendicitis
 - i.e., no perforation nor abscess

Abdominal Abscess

- Sawyer et al 2015

Duration of outcome — days

Antimicrobial therapy for index infection	<0.001	
Median	8	4
Interquartile range	5–10	4–5

Table 2. Primary and Major Secondary Outcomes.*

Variable	Control Group (N=260)	Experimental Group (N=257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Surgical-site infection	23 (8.8)	17 (6.6)	0.43
Recurrent intraabdominal infection	36 (13.8)	40 (15.6)	0.67
Death	2 (0.8)	3 (1.2)	0.99

Hot on the Case!

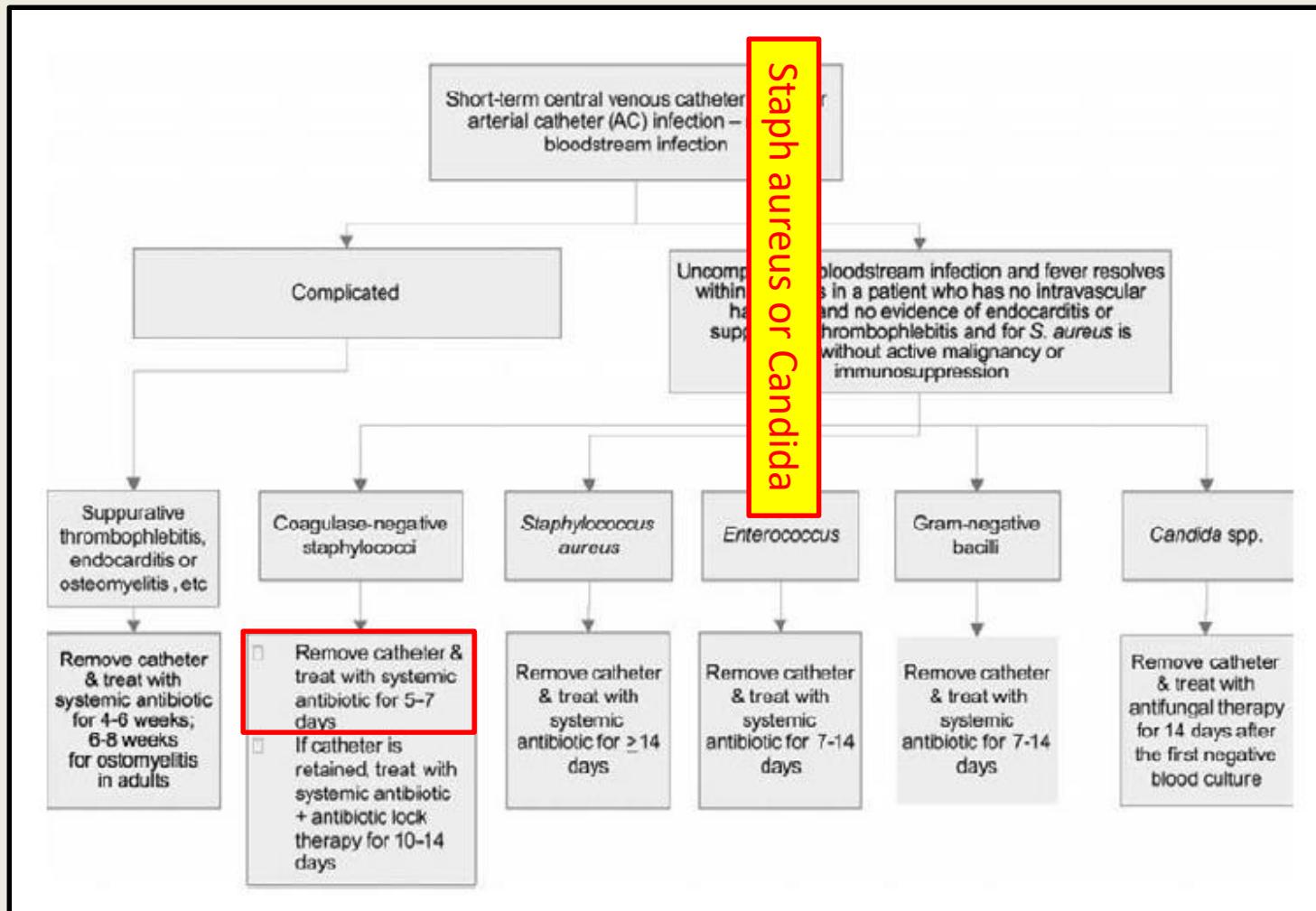
71 yo male nursing home resident

- 3 days of fever and chills
- blood cultures + PICC = MRSE
- you're going with vancomycin

- A. 3 days
- B. 7 days
- C. 10 days
- D. 14 days
- E. 28 days

CLABSI

IDSA



Hospital/Ventilator Pneumonia

- Hedrick et al 2007
 - retrospective subgroup NFGNB (n=154)

Table 2—Primary and Secondary Outcomes of the Included Trials

Study/Year	Mortality, n of N (%)		Abx-Free Days (Mean ± SD)		Relapses, n of N (%)		MV-Free Days (Mean ± SD)		Duration of MV (Mean ± SD)		LOS in ICU (Mean ± SD)	
	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long	Short	Long
Capellier et al ²³ /2012	10 of 116 ^a (8.6)	9 of 109 ^a (8.3)	NR	NR	6 of 116 (5.2)	2 of 109 (1.8)	NR	NR	13.6 ± 5.3	13.4 ± 5.9	15.9 ± 5.1	15.7 ± 5
Kollef et al ²² /2012	26 of 115 ^b (22.6)	18 of 112 ^b (16.1)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fekh Hassen et al ²¹ /2009	5 of 14 (35.7)	6 of 16 (37.5)	4.1 ± 1.9	1.8 ± 1.6	1 of 16 (6.3)	1 of 14 (7.1)	3.4 ± 1.9	2.1 ± 1.8	18.9 ± 3.3	18.9 ± 3.8	26.1 ± 3.8	27.7 ± 4.6
Chastre et al ²⁰ /2003	37 of 197 ^c (18.8)	35 of 204 ^c (17.2)	13.1 ± 7.4	8.7 ± 5.2	33 of 197 (16.8)	23 of 204 (11.3)	8.7 ± 9.1	9.1 ± 9.4	NR	NR	30 ± 20	27.5 ± 17.5

Abx = antibiotic; LOS = length of stay; MV = mechanical ventilation. See Table 1 legend for expansion of other abbreviations.

^aRefers to 21-d mortality.

^bMortality for nonfermenting gram-negative bacteria was 12 of 47 (25.5) and 4 of 38 (10.5) for short- and long-course therapy, respectively.

^cMortality for nonfermenting gram-negative bacteria was 15 of 64 (23.4) and 19 of 63 (30.2) for short- and long-course therapy, respectively.

- 7-8d vs 10-15d