Duration of Therapy

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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 a

- 650 non
  - 2 wee
  - appro essary

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**

Trivedi SHEA 2017
Hecker et al. Arch Intern Med 2003

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 right 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

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
Staphylococcus aureus	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
S. aureus or streptococci	75 (97)	70 (96)	>.2[a]
S. aureus 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]

- 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

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)*.

Holmes J Pediatr 2016

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	Placebo		
	no./total no. (%)		*percentage points*	
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

Talan NEJM 2016

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)

Duam NEJM 2017

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"

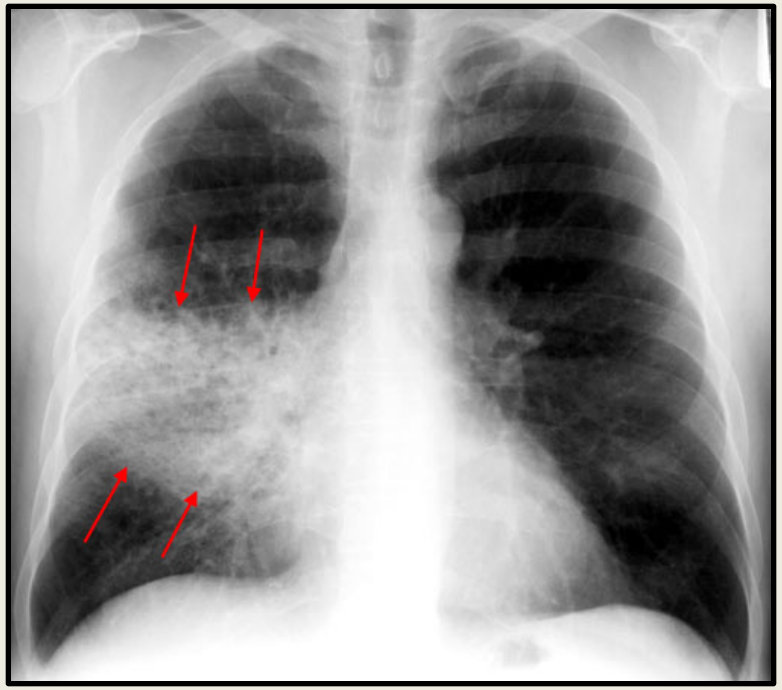
Stevens et al CID 2014
Sanford Guide Antimicrobial Therapy

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

Dunbar CID 2003

Community Acquired Pneumonia

Background Studies

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  - 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 d

> 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.

Dunbar CID 2003

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

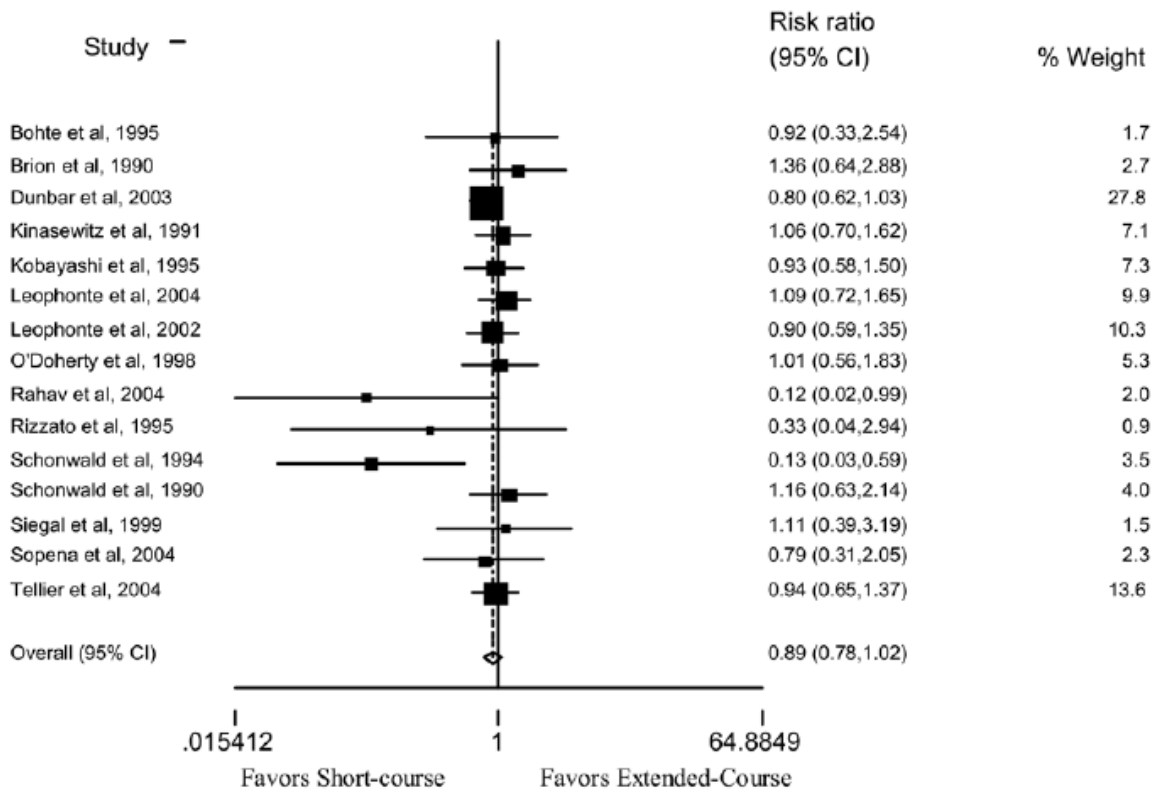


Figure 2 Relative risk of clinical failure with short-course versus extended course antibiotic regimens.

Li Am J Med 2007

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

Mandell CID 2007

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

Mandell CID 2007

Community Acquired Pneumonia

IDSA

Duration of Antibiotic Therapy

32. Patients with CAP shou
5 days (level I evidence
h, and should have no n
of clinical instability (t
of therapy (level II
mendation.)

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"

Mandell CID 2007

Hospital/Ventilator Pneumonia

-

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

Event	No./Total (%) 8-Day Regimen (n = 197)	No./Total (%) 15-Day Regimen (n = 204)	Between-Group Risk Difference (90% CI), %
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)

Chastre JAMA 2003

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
Fekth 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 abbreviation.
[a]Refers to 21-d mortality.
[b]Mortality for nonfermenting gram-negative bacteria was 12 of 47 (25.5) and 4 of 38 (10.5) for short- and long-course therapy, respectively.
[c]Mortality 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

Hedrick Surg Infect 2007
Dimopoulos Chest 2013

Hospital/Ventilator Pneumonia

IDSA

LENGTH OF THERAPY

XXI. Should Patients With VAP Rece
Therapy?

Recommendation

1. For patients with VAP, we r
timicrobial therapy rather than a longer duration *(strong recommendation, moderate-quality evidence).*

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.

XXII. What Is the Optimal Duratio

quality evidence).

Sanford

"Not well defined"

- 8d for "relatively susceptible pathogens"
- 14d for MRSA, PSA, Acineto, Steno, etc.

Kalil CID 2016

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 7d TMP/SMX
  - no recurrence at 1, 2 and 6 weeks

Trienekens BMJ 1989

Cystitis

- Iravani et al 1999
  - ran
  - 3d
    -
  - cip
- Gupta
  - ran
  - 3d
    - clinical cure at 30 days

Table 3. Treatment Outcomes by Treatment Group[a]

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)

Iravani J Antimicrob Chemother 1999
Gupta Arch Intern Med 2007

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)

Gupta CID 2011

Cystitis

IDSA + Sanford

Nitrofurantoin

(avoid if ea

Trimethoprim
(one
(avoid if res
exceed 20%
months)

OR

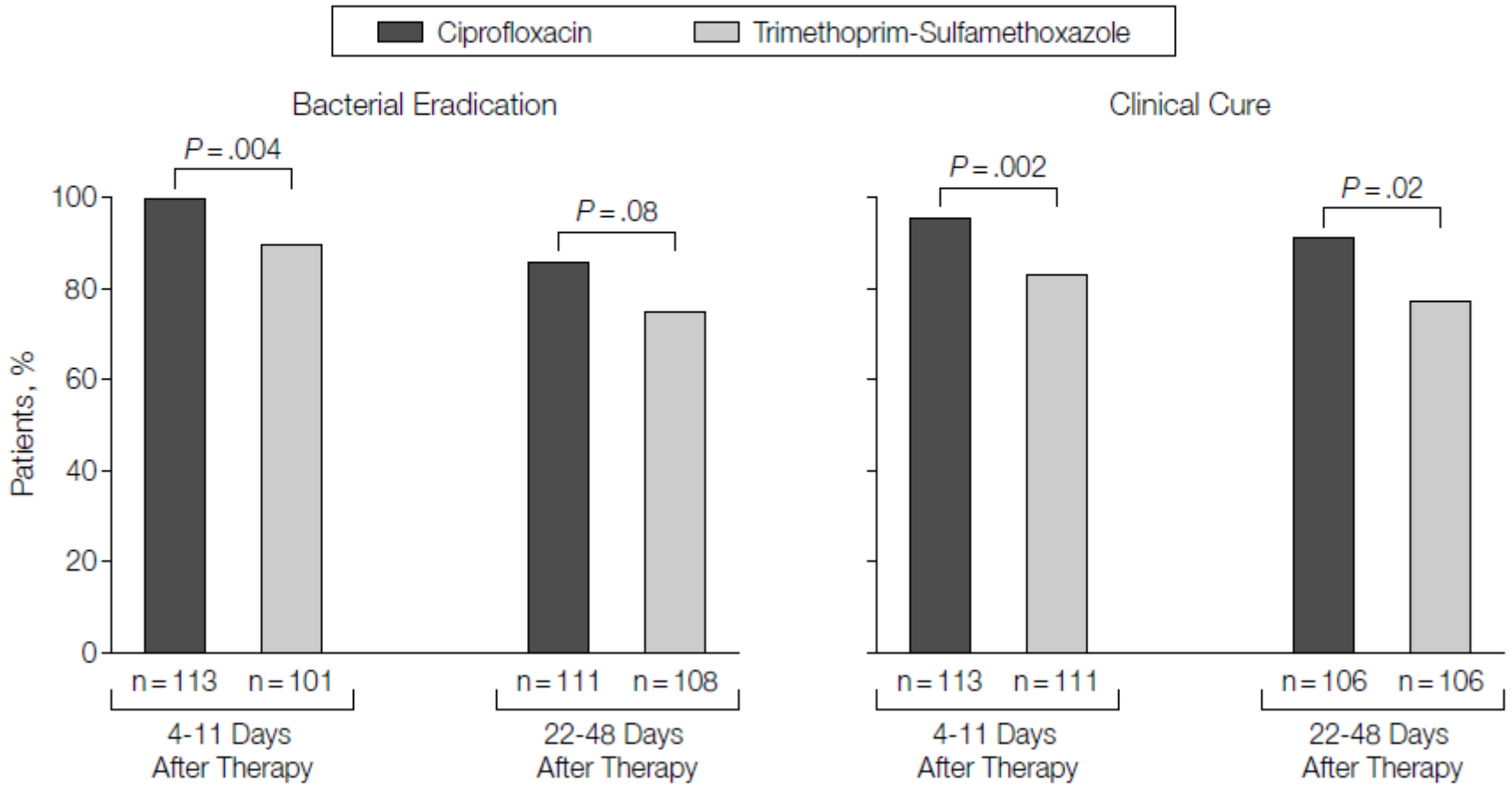
Fosfomycin trometamol 3 gm single dose
(lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

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).

Gupta CID 2011

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



Talen JAMA 2000

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)*
mITT		$n = 94$			$n = 98$		
	Eradicated	Persisted	Unknown	Eradicated	Persisted	Unknown	
Microbiologic outcome	78 (83.0)	6 (6.4)	10 (10.6)	78 (79.6)	8 (8.2)	12 (12.2)	–3.4 (–14.4, 7.6)
	Success	Failure	Unable to evaluate	Success	Failure	Unknown	
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		$n = 80$			$n = 76$		
	Eradicated	Persisted		Eradicated	Persisted		
Microbiologic outcome	74 (92.5)	6 (7.5)		71 (93.4)	5 (6.6)		0.9 (–7.1, 8.9)
	Success	Failure		Success	Failure		
Clinical outcome	74 (92.5)	6 (7.5)		68 (89.5%)	8 (10.5)		–3.0 (–12.0, 6.0)

Klausner Curr Med Res Opin 2007

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

Gupta CID 2011

CAUTI

"The most common healthcare-associated infection worldwide."

IDSA

- 7d if "prompt resolution"
  - 3d if woman ≤65 years old wi
  - 5d LVQ if not "severely ill"
- 10-14d if "delayed response"

Sandford

- see Hooton et al CID 2010

Hooton CID 2010

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

Solomkin CID 2010

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

Sawyer NEJM 2015

Hot on the Case!

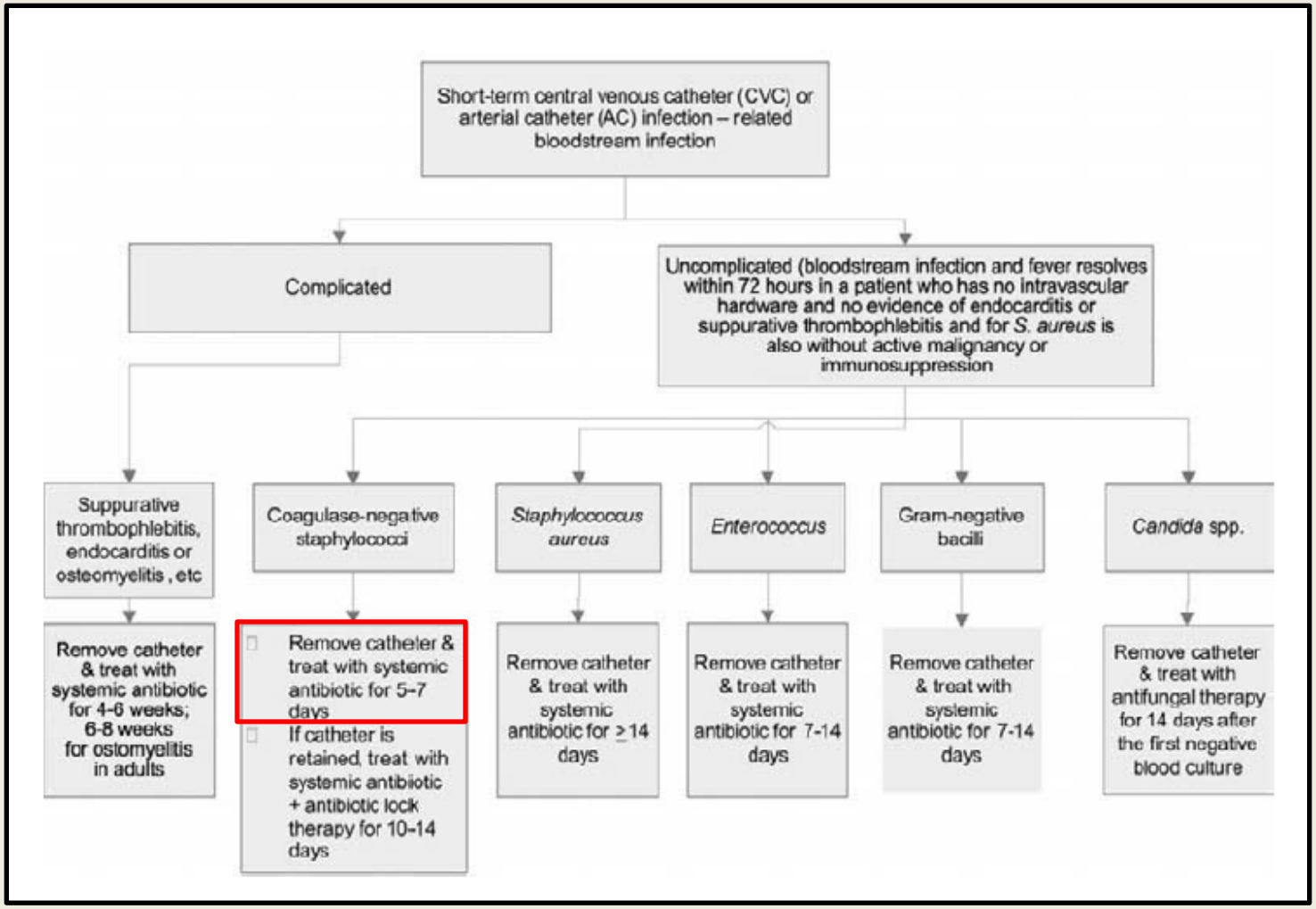
71 yo male nursing home resident

- 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



Mermel CID 2009

Questions?