UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

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10/27/18

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Fortnights and Football Scores: Evaluating Evidence Based Durations of Antibiotic Therapy

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Disclosure

CE Presenter, Brandon Tritle: No relevant disclosures
CE Mentor, Tristan Timbrook: No relevant disclosures

I will be discussing off label uses of medications throughout the presentation
Amoxicillin
Daptomycin
Ceftibuten
Imipenem

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Learning Objectives for Pharmacists

- Recognize the benefits of appropriate durations of antimicrobial therapy
- Identify infectious disease states with studies into appropriate duration of antimicrobial therapy
- Compare guideline recommended durations of therapy with primary literature
- Distinguish patients appropriate for shorter durations of therapy

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Learning Objectives for Pharmacy Technicians

- Recognize the benefits of appropriate durations of antimicrobial therapy
- Criticize myths around antibiotic treatment courses
- Differentiate patients who may have longer courses of antibiotics dispensed

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"If you take an antibiotic, always complete the full prescription, even if you feel better because stopping treatment early promotes the growth of drug-resistant bacteria"
-WHO 2015

World Health Organization. Global action plan on antimicrobial resistance 2015

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Similar Statements

- National Prescribing Service (Department of Health-Australia)
- National Collaborating Centre for Infectious Diseases (Canada)
- FDA/CDC (USA)
- European Centre for Disease Prevention and Control (EU)

NPS Medicinewise. Antibiotic resistance: the facts
National Collaborating Centre for Infectious Diseases. Antibiotic use and resistance:information for patients
Federal Drugs Administration. Combatting antibiotic resistance. Follow directions for proper use
European Antibiotic Awareness Day. Factsheet for general public
Centers for Disease Control. Get smart about antibiotics. What you can do

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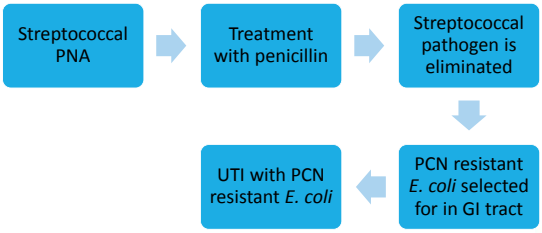
Resistance Simplified



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Historical Basis for Treatment Courses

- 1940's: early days of penicillin for pneumonia
  - Typical courses 1-4 days based on symptoms
  - 30,000-40,000 units/day
  - 3 relapses in 44 patients
- Roman Emperor Constantine the Great
  - AD 321
  - Officially declared a week would be 7 days

Meads et al. *N Engl J Med* 1945
Tillett et al. *Bull NY Acad Med* 1944
Spellberg, B. *JAMA Intern Med* 2016
https://www.flickr.com/photos/47329792@N06/4338544773/

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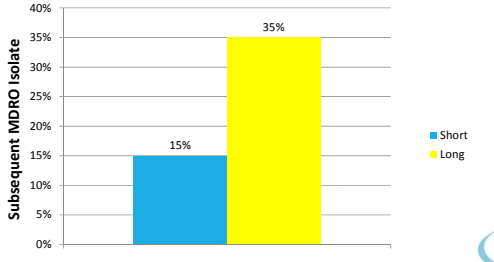
Longer Durations of Therapy Lead to More Antimicrobial Resistance



Singh et al. *Am J Respir Crit Care Med* 2000

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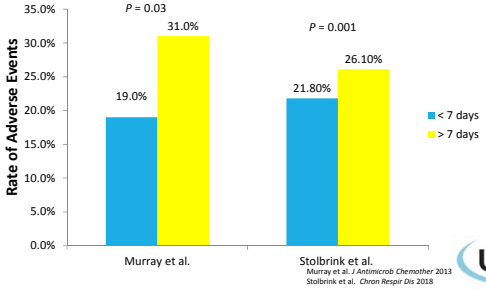
…and Adverse Effects



Murray et al. *J Antimicrob Chemother* 2013
Stolbrink et al. *Chron Respir Dis* 2018

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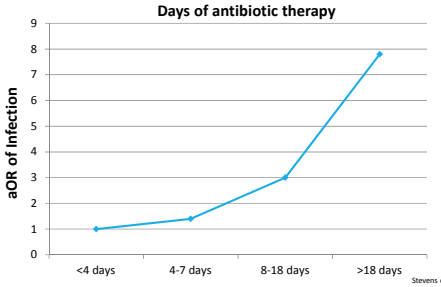
…and More *C. difficile* Infections



Stevens et al. *Clin Infect Dis* 2011.
https://www.flickr.com/photos/encinas1987/5512755104/

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For Pharmacists and Technicians:
Extended antibiotic durations put your patients at risk for which of these?

A. Increased development of resistant organisms

B. Increased risks of adverse effects

C. Increased rates of *C. difficile* infections

D. All of the above

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For Pharmacists and Technicians:
Your friend sees a physician after having a cough for 2 weeks. She is given 14 days of antibiotics. After taking them for 5 days, she tells you she feels better. What advice would you give her?

A. Finish your course or you will create antibiotic resistance

B. Horde them along with the 2 years worth of canned food in your basement

C. Call your physician and discuss whether it is appropriate to stop your antibiotics

D. Finish your course or you will have a relapse

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Hospital Acquired Pneumonia/Ventilator Associated Pneumonia (HAP/VAP)

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HAP/VAP: Defined

- HAP: PNA occurring at least 48 hours after admission
- VAP: PNA occurring at least 48 hours after intubation

Kalil et al. Clin Infect Dis. 2016

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HAP/VAP: Guidelines

2016 IDSA guidelines

- HAP: 7 days of antimicrobial therapy (strong recommendation, very low-quality evidence)
- VAP: 7 days of antimicrobial therapy (strong recommendation, moderate-quality evidence)

Kalil et al. Clin Infect Dis. 2016

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HAP/VAP: Chastre 2003

- Design
  - Prospective, double-blind RCT
- Patients
  - Adults with culture positive VAP
  - Excluded: Pregnant, neutropenia (ANC<500), AIDS, immunosuppressive therapy
- Intervention
  - 8 days vs. 15 days of antibiotics
- Outcomes: assessed at 28 days
  - All cause mortality
  - Recurrence
  - Antibiotic free days

Chastre et al. *JAMA* 2003

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HAP/VAP: Chastre 2003

Characteristic	8-day Regimen (n=197)	15-day Regimen (n=204)
SAPS II score (mean)	40	39
Shock present	33.5%	35.8%
Bacteremia	7.1%	6.9%
ARDS present	25.9%	20.6%

Organism	8-day Regimen (n=197)	15-day Regimen (n=204)
P. aeruginosa	18.4%	19.6%
E. Coli	7.6%	10.7%
MSSA	13.6%	11.7%
MRSA	7.0%	7.3%
Streptococcus	13.9%	12.6%

Chastre et al. *JAMA* 2003

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HAP/VAP: Chastre 2003

Outcome	8-day Regimen (n=197)	15-day Regimen (n=204)	Risk Difference (90% CI)
Mortality (28 days)	18.8%	17.2%	1.6 (-3.7 to 6.9)
Mortality (60 days)	25.4%	27.9%	2.6 (-5.6 to 10.7)
Recurrence or superinfection	28.9%	26%	2.9 (-3.2 to 9.1)
MV-free days	8.7	9.1	-0.4 (-1.9 to 1.1)
Organ failure-free days	7.5	8.0	-0.5 (-1.9 to 1.0)

Chastre et al. *JAMA* 2003

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HAP/VAP: Chastre 2003

Outcome	8-day Regimen	15-day Regimen	Difference (90% CI)
Recurrence or superinfection (Non-fermenters sub-group)	26/62 (40.6%)	(16/63) 25.4%	15.2% (3.9 to 26.6)
Recurrence before end of treatment	13/197 (6.9%)	21/204 (11.5%)	-4.6% (-9.5 to 0.4)
Development of MDRO pathogen	24/57 (42.1%)	33/53 (62.3%)	*P* = 0.04

Chastre et al. *JAMA* 2003

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HAP/VAP: Meta-analyses

- Findings of Chastre et al. confirmed by a Cochrane meta-analysis
  - Found no difference in mortality or recurrence with ≤ 8 days compared with longer durations
- Additional meta-analysis performed by IDSA guideline authors
  - No difference in mortality, recurrence, or clinical cure with 7-8 days compared with 10-15 days
  - Subgroup analysis of non-fermenting GNB
    - Recurrence OR 1.42 (95% CI: 0.66-3.04)
    - Mortality OR 0.94 (95% CI: 0.56-1.59)

Pugh et al. *Cochrane Database of Systematic Reviews*. 2015
Kalil et al. *Clin Infect Dis*. 2016

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HAP/VAP: Takeaways

- 7 days of antimicrobial therapy is sufficient for VAP
  - Applies to non-fermenting GNB
  - Applies to patients with high severity of illness
- 7 days of antimicrobial therapy extrapolated to HAP
- These data did not include immunosuppressed patients
  - ANC < 500 cells/mcL, AIDS, immunosuppressants, steroids >0.5mg/kg/day for > 1 month

Kalil et al. Clin Infect Dis. 2016

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Community Acquired Pneumonia (CAP)

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For Pharmacists:
What is the shortest evidence based treatment for CAP?

A. 1 day

B. 3 days

C. 5 days

D. 7 days

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CAP: Guidelines

- IDSA CAP guidelines recommendations
- Minimum of 5 days of therapy (moderate recommendation; level II evidence)
  - Afebrile 48-72 hours
  - No more than 1 sign of clinical instability
    - Temp ≥ 37.8°C
    - 100 beats/min
    - 24 breaths/min
    - SBP ≥ 90mmHg
    - O_2 ≥ 90% on room air
    - PO intake and normal mental status

Mandell et al. Clin Infect Dis 2007

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CAP: Fluoroquinolones

- RCT levofloxacin 750mg x 5 days vs. 500mg x10 days for CAP
  - 528 patients; 60% pneumonia severity index (PSI) class I/II; 40% class III; IV
  - No difference in clinical success 14 days post-therapy 92.4% vs. 91.1% (95%CI: -7.0 to 4.4)
- RCT of hospitalized CAP patients; 5 days vs. 10 days
  - 312 patients; 60% PSI class I/II/III; 40% class IV/V
  - ~80% receiving fluoroquinolones
  - No difference in clinical success at 30 days: 91.9% vs. 88.6% (*P* = 0.33)
  - Higher clinical success at 30 days for PSI class IV/V 93.1% vs. 80.3% (*P* = 0.04)

Dunbar et al. *Clin Infect Dis* 2003
Uranga et al. *JAMA Intern Med* 2016

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CAP: Beta-lactams

- ''Efficacité comparée de la ceftriaxone dans un traitement de dix jours versus un traitement raccourci de cinq jours des pneumonies aigues communautaires de l'adulte hospitalisé avec facteur de risque''
- RCT ceftriaxone 1g/day x 10 days vs. 5 days
  - 246 inpatients;
  - No difference in cure rates 81.9% vs. 82.6%
- RCT of hospitalized CAP patients; 3 days vs. 8 days
  - 119 patients; 60% PSI class I/II; 40% class III/IV
  - Initially IV amoxicillin, transition to placebo or amoxicillin PO 750mg TID
  - No difference in clinical cure 90% vs. 88% (95% CI: -9 to 15)

Leophonte et al. *Med Mal Infect* 2002
el Moussaoui et al. *BMJ* 2006.

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CAP: Short Duration Therapy

- PTC Trial: 3 days vs. 8 days of beta-lactams for CAP
  - 310 patients; receiving amox/clav or 3rd generation cephalosporin
  - Comorbid patients: COPD (35%), DM (20%)
  - Median PSI was 82
  - Randomized if afebrile, normal HR and RR, SBP>90mmHg, and O_2 saturation >90% at day 3
  - Randomized to continue same agent for 5 days or placebo for 5 days
  - No difference in clinical cure at 15 days: 69.9% vs. 61.2% (*P* > 0.05)

Dinh et al. Data presented at ECCMID 2018

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CAP: Ultra Short Duration??

- Pertel el al.
  - Combination of 2 phase 3, double-blind, RCTs
  - 834 adults with CAP requiring hospitalization
  - Ceftriaxone 2g IV q24h vs. daptomycin 4mg/kg IV q24h for 5-14 days
  - Cure rate at 7-14 days post-treatment: 87.9% vs. 79.4% (*P* < 0.05)

	Daptomycin cure rate	Ceftriaxone cure rate	Difference (95% CI)
Treated with 1 day of ceftriaxone			
Yes	90.7%	88.0%	2.7 (-6.1 to 11.5)
No	75.4%	87.8%	-12.4 (-18.8 to -6.0)

Pertel et al. *Clin Infect Dis.* 2008

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CAP: Takeaways

- Patients with clinical improvement by day 3 are appropriate to stop antibiotic therapy
- Patients with more severe presentation or without improvement by day 3 may need 5 days of therapy
- CAP is sufficiently treated by 5 days of antibiotics
  - Alternative diagnoses?
  - Source control?

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For Pharmacists:
Which of these PNA patients are not receiving evidence based regimens?

A. 75 yo male with T2DM develops VAP after being intubated for CHF exacerbation. He is started on IV vancomycin and IV cefepime. Vancomycin is stopped after negative MRSA nasal swab, and he finishes 7 days on IV cefepime.

B. 68 yo female with CHF, HTN, and Afib is admitted with CAP. She receives IV ceftriaxone for 3 days and feels greatly improved. All her symptoms have resolved, and she is discharged home without any antibiotics.

C. 47 yo male with HLD, CAD, and CABG x2 is admitted with CAP. He receives IV levofloxacin for one day and feels vastly improved. He is sent home with 2 more days of PO levofloxacin.

D. 70 yo female with COPD admitted for acute exacerbation and started on 40mg prednisone. However, she declines into respiratory failure, is intubated, and develops VAP after 48 hours. She is started on IV vancomycin and IV pip/tazo. BAL cultures grow *P. aeruginosa*. She completes 7 days of IV pip/tazo.

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For Technicians:
True or false: patients who get pneumonia while mechanically ventilated require longer treatment courses?

A: True

B: False

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Intra-abdominal Infections (IAI)

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IAI: Guidelines

- IDSA guidelines
- Complicated intra-abdominal infections
  - Disruption of hollow viscus
  - Abscess or peritonitis
- 4-7 days of antimicrobial therapy unless uncontrolled source (moderate strength; low-quality evidence)

Solomkin et al. Clin Infect Dis. 2010

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IAI: Observational Studies

- Lennard et al.
  - Retrospective cohort study of 65 patients with IAI
  - Evaluated for persistent leukocytosis when antibiotics were stopped
    - Leukocytosis present: 33% developed recurrent IAI
    - Leukocytosis absent: 0% developed recurrent IAI
- Hedrick et al.
  - Retrospective cohort of 5,561 patients, with any infection admitted to surgery unit
    - ~20% abdominal source; performed subgroup analysis of only IAI
  - Analyzed rates of recurrence based on duration of therapy
    - Less recurrence in 0-7 days vs. 13-17 days; aOR= 1.81 (95% CI=1.12-2.92)
    - Less Recurrence in 0-7 days vs. >17 days (aOR= 2.79 (95% CI=1.25-4.67

Lennard et al. *Ann Surg* 1982
Hedrick et al. *Surg Infect* 2006

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IAI: STOP-IT Trial

- Design
  - Prospective RCT
- Patients
  - Adults with cIAI
  - Excluded: Patients without source control procedure
- Intervention
  - Control: therapy for 2 days after resolution of fever, WBC, and ileus for maximum of 10 days
  - Intervention: fixed course of 4 days of antibiotics
- Outcomes
  - Surgical site infection, recurrent IAI, or mortality at 30 days

Sawyer et al. *N Engl J Med* 2015

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IAI: STOP-IT Trial

Characteristic	Control Group (N=260)	Experimental Group (N=258)
Age (yr)	52.2	52.2
APACHE II score	9.9	10.3
Colon/rectum origin	30.8%	37.6%
Appendix origin	13.1%	15.1%
Small bowel origin	11.9%	16.3%
Percutaneous drainage	33.1%	33.3%
Resection and anastomosis or closure	26.5%	24.8%
Surgical drainage	21.2%	20.9%

Sawyer et al. *N Engl J Med* 2015

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IAI: STOP-IT Trial

Outcome	Control Group (N=260)	Experimental Group (N=257)	*P* value
Composite: SSI, recurrent IAI, or mortality	22.3%	21.8%	0.92
SSI	8.8%	6.6%	0.43
Recurrent IAI	13.8%	15.6%	0.67
Mortality	0.8%	1.2%	0.99

Time To Event	Control Group (N=260)	Experimental Group (N=257)	*P* value
Diagnosis of SSI	15.1 days	8.8 days	<0.001
Diagnosis of recurrent IAI	15.1 days	10.8 days	<0.001

Sawyer et al. *N Engl J Med* 2015

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IAI: Takeaways

- Source control is the essential first intervention in cIAI
- 4 days of antibiotics is sufficient to treat cIAI

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For Pharmacists:

True or False: IDSA guidelines for IAI recommend short course therapy in concordance with RCT data.

A. True

B. False

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Pyelonephritis (PN)

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For Pharmacists:

True or False: Short courses (≤7 days) have only been proven effective for pyelonephritis with fluoroquinolones.

A. True

B. False

PN: Guidelines

- PN presentation: Piccoli et al.
  - Retrospective study of PN confirmed by CT/MR
  - Fever 93%; Flank pain 82%; Lower UTI symptoms 52.9%
- IDSA guidelines: 7-14 days
  - Ciprofloxacin x7 days (Strong recommendation; high-quality evidence)
  - Levofloxacin x5 days (Moderate recommendation; moderate-quality evidence)
  - TMP-SMX 14 days (Strong recommendation; high-quality evidence)
  - Oral beta-lactam 10-14 days (based on previous guideline; lack of evidence)
    - Use initial parenteral beta-lactam (moderate recommendation; moderate-quality of evidence)

Piccoli et al. *BMC Nephrology* 2011
Gupta et al. *Clin Infec Dis* 2011

PN: Fluoroquinolones

- Sandberg et al.
  - RCT of 156 patients with PN
  - Ciprofloxacin 500mg BID x7 days vs. 14 days
  - No difference in 42-63 day clinical cure 93% vs. 93%
- Klausner et al.
  - RCT of 198 patients with PN
  - Levofloxacin 750mg daily x5 days vs. ciprofloxacin 500mg BID x10 days
  - No significant difference in 15-19 day clinical cure 86.2% vs. 80.6% (difference= -5.6; 95% CI=-16 to 4.9)

Sandberg et al. *Lancet* 2012
Klausner et al. *Curr Med Res Opin* 2007

PN: TMP-SMX

- Talan et al.
  - RCT of 255 women with PN
  - Ciprofloxacin 500mg BID x7 days vs. TMP-SMX 160/800mg BID x14 days
  - Ciprofloxacin showed higher clinical cure on day 29-55 89% vs. 78% (95% CI 3 to 23; *P* = 0.02)
  - 18.4% of isolates resistant to TMP-SMX
    - Clinical cure if S= 92%; clinical cure if R=35%
- Fox et al.
  - Retrospective cohort of 272 women with PN
  - 7 days of ciprofloxacin vs. 7 days of TMP-SMX
  - Cipro: 55% initial oral treatment; TMP-SMX: 70% initial oral treatment
  - No significant difference in recurrence of any UTI at 30 days 6% vs. 7%
    - aOR remained non-significant after adjustments

Talan et al. *JAMA* 2000
Fox et al. *Am J Med.* 2017

PN: Beta-lactams

- IDSA Guidelines: "Oral beta-lactam agents are less effective than other available agents for treatment of pyelonephritis" (moderate recommendation; low-quality evidence)
- Cronberg et al.
  - RCT 158 patients with PN
  - Cefuroxime 750mg-1,500mg IV TID x2-4 days
    - Randomized to ceftibuten 200mg BID or norfloxacin 400mg BID x10 days
  - Clinical cure lower on day 17-24 with ceftibuten 89% vs. 96% (OR 0.92; 95% CI: 0.85-0.99)

Cronberg et al. *Scand J Infect Dis* 2001
Gupta et al. *Clin Infec Dis* 2011.

PN: Beta-lactams

- ASPECT-cUTI trial
  - 800 patients with cUTI; 82% had PN present
  - 1,500mg ceftolozane-tazobactam IV q8h vs. levofloxacin 750mg IV q8h
  - Non-significantly higher clinical cure with cef-tazo at 12-16 days 92% vs. 88.6%
    - diff=3.4 (95% CI: -0.7 to 7.6)
- Mensa et al.
  - RCT 304 patients with PN
  - Ceftriaxone 1g IV daily x1 day
    - Randomized to cefixime 400mg PO daily x7 days vs. 14 days.
  - No difference in clinical cure at 22-63 days 90.2% vs. 90.3%

Wagenlehner et al. *Lancet* 2015
Mensa et al. *Abstracts of the Thirty-ninth Interscience Conference on Antimicrobial Agents and Chemotherapy* 1999

PN: Takeaways

- 5 days of levofloxacin is sufficient to treat PN
- 7 days of TMP/SMX is sufficient to treat PN
- 7 days of beta-lactams with initial IV therapy is sufficient to treat PN

Gram Negative Bacteremia (GNB)

GNB: Guidelines

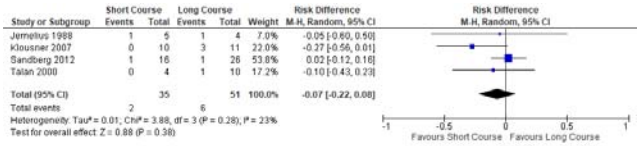
- IDSA CLABSI Guidelines
  - Duration of therapy for GNB: 7-14 days
- Citation: "Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis"

"Since most studies in our analysis **did not provide details of dosing regimens and duration**, we are not able to correlated these factors with survival."

Mermel et al. *Clin Infec Dis* 2009
Safdar et al. *Lancet Inf Dis* 2004

GNB: Urinary source

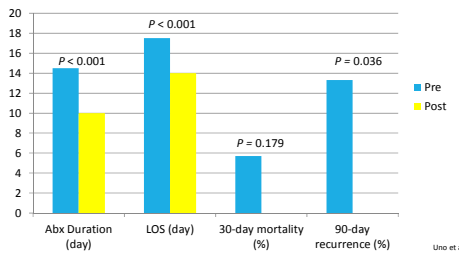
- Meta-analysis of RCT for ≤7 days of therapy vs. longer
  - Subgroup analysis of bacteremic patients
  - Found no significant difference in treatment failure RR=0.54 (95% CI: 0.15 to 1.92)



Eliakim-Raz et al. *J Antimicrob Chemother* 2013

GNB: Biliary Source

Observational pre/post study of bacteremic cholangitis patients



Uno et al. *Int J Infect Dis* 2017

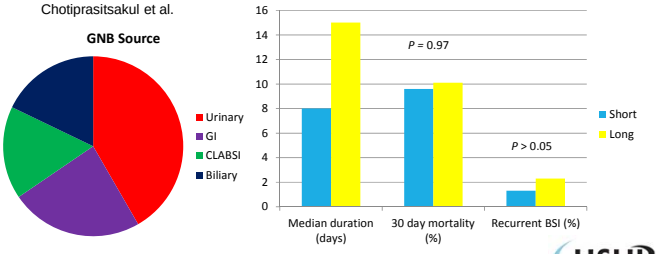
GNB: Observational Studies

- Nelson et al
  - Retrospective cohort of 411 patients with GNB
  - ~70% from urinary source, 65% *E. coli*
  - Short 7-10 days (median 8.5) vs. long >10 days (median 13.3)
  - Cox regression with propensity score adjustment
  - Increased risk of failure at 90 days with short course; HR=2.6 (95% CI: 1.2-5.53)
    - 121 patients lost to follow up
    - 90 day treatment failure with levofloxacin was 2%

Nelson et al. *Infection* 2017

GNB: Observational Studies

Chotiprasitsakul et al.



Chotiprasitsakul et al. *Clin Infec Dis* 2018

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GNB: Observational Studies

Mercuro et al.

- Retrospective cohort study of 240 adults with GNB
- 43% DM; 10% h/o transplant; 40% urinary abnormality
- 70% urinary source; 20% IAI
- No difference in 30 day clinical success 86.9% BL vs. 87.1% FQ (*P* = 0.96)
- Free from adverse effects: 90.5% BL vs. 79.3% FQ (*P* = 0.03)
- No difference in success short vs. long course: 88.2% vs. 86.7% (*P* > 0.05)
- No difference in success early vs. late step-down: 86.7% vs. 87.5% (*P* > 0.05)

Mercuro et al. *Int J Antimicrob Agents* 2018

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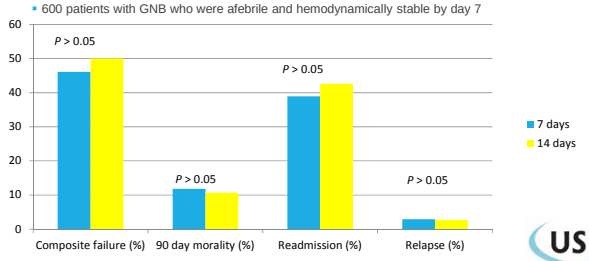
GNB: RCT Data

- 7 versus 14 days of therapy for GNB
  - 600 patients with GNB who were afebrile and hemodynamically stable by day 7



Yahav et al. *European Conf Clin Micro and Inf Dis* 2018

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GNB: Upcoming RCTs

- Yahav et al.; ClinicalTrials.gov Identifier: NCT01737320
  - Data presented at ECCMID 2018
- BALANCE trial; Daneman et al.; ClinicalTrials.gov Identifier: NCT03005145
  - ICU patients; pilot available in *J of Trials*
- BALANCE-Wards trial; Daneman et al.; ClinicalTrials.gov Identifier: NCT02917551
- SHORTEN trial; Gil-Bermejo et al.; ClinicalTrials.gov Identifier: NCT02400268
- PIRATE study; Huttner et al.; ClinicalTrials.gov Identifier: NCT03101072

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GNB: Takeaways

- GNB is likely sufficiently treated with 7 days of antibiotics with source control
- Follow up on RCT data in progress
- Guideline support: 2017 Surgical Infection Society Guidelines on Management of IAI
  - Consider limiting therapy to 7 days in bacteremia secondary to IAI with source control (moderate strength; moderate-quality evidence)

Mazuski et al. *Surg Infec* 2017

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Febrile Neutropenia (FN)

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FN: Defined

- Definition
  - Tmax ≥ 38.3°C
  - Less than 500 neutrophils/mcL
- Management
  - Low risk may be appropriate for outpatient management
    - MASCC ≥ 21
    - IV or PO antibiotics
    - Close follow up and monitoring
  - High risk should be admitted
    - MASCC < 21
    - Organ dysfunction
    - Allo HCT
    - Severe mucositis

Baden et al. *J Natl Compr Canc Netw* 2017
Freifeld et al. *Clin Infect Dis* 2011
Klastersky et al. *Ann Oncol* 2016

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FN: Guidelines

- IDSA/NCCN
  - Stop gram-positive coverage at 48 hours (strong recommendation; moderate level evidence)
  - IV to oral switch at clinical stability (strong recommendation; high level evidence)
  - Unexplained, resolving fever: continue until ANC exceeds 500 cells/mcL (moderate recommendation; moderate level evidence)
- ESMO
  - Unexplained, resolving fever: continue until afebrile 5-7 days (strong recommendation; moderate level of evidence)

Baden et al. *J Natl Compr Canc Netw* 2017
Freifeld et al. *Clin Infect Dis* 2011
Klastersky et al. *Ann Oncol* 2016

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FN: Why Prolonged Therapy?

- Pizzo et al.
  - Open-label RCT
  - 33 FN patients who defervesced on therapy
  - Randomized to continue cephalothin, gentamicin, carbenicillin or stop after 7 days
  - More recurrent fever in discontinuation group 7/17 (41%) vs. 0/16 (0%); *P* = 0.007
  - Fever recurred within 48 hours
  - Bacteremia and PNA within 48 hours
  - Followed until recovery of ANC

Pizzo et al. *Am J Med* 1979

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FN: Slobbe et al.

- Single-center, prospective, observational study
- 137 patients who experienced one or more episodes of FN
  - 39% AML/MDS; 28% MM; 22% Non-Hodgkin lymphoma
  - 66% HD chemotherapy; 31% auto HSCT; 3% allo HSCT
  - PO FQ and fluconazole prophylaxis
- Started on imipenem
- Discontinued after 72h if afebrile
- 30 day mortality: 6 days
  - 2 from infection, both related to aspergillus

Slobbe et al. *Eur J Cancer* 2009

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FN: How Long study

- Design
  - Multi-center, prospective, open-label RCT
- Patients
  - Adults with FN
    - Treatment for hematological malignancy or HSCT
  - Excluded: microbiologic diagnosis, antibiotics prior to fever
- Intervention
  - Discontinuation of antibiotics after 72 hours
    - Apyrexia, normal vital signs, resolution of symptoms
- Outcomes: assessed at 28 days
  - Empiric antibiotic therapy free days
  - All cause mortality
  - Number of febrile days
  - Recurrent fevers

Aguilar-Guisadeo et al. *Lancet Haematol* 2017

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FN: How Long study

Characteristic	Experimental (n=78)	Control (n=79)
Acute leukemia	51%	39%
Lymphoma	29%	37%
Multiple myeloma	9%	18%
Treatment		
Chemotherapy	50%	39%
Auto HSCT	37%	54%
Allo HSCT	12%	6%
Source		
Unknown	40%	41%
Oral mucositis	18%	22%
Abdominal	19%	19%
Pulmonary	9%	3%

Aguilar-Guisadeo et al. *Lancet Haematol* 2017

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FN: How Long study

Outcome	Experimental (n=78)	Control (n=79)	*P* value
EAT-free days	16.1	13.6	0.026
Mortality	1.3%	3.8%	0.62
Febrile days	5.7	6.3	0.53
Recurrent fever	14%	18%	0.54
Median duration neutropenia (days)	14	11	0.13
Infections (n)	36	35	0.17
Bacteremia (n)	9	14	0.29
Fungal (n)	4	10	0.12
Adverse effects (n)	341	295	0.057
Serious adverse effects (n)	11	27	0.0087

Aguilar-Guisadeo et al. *Lancet Haematol* 2017

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FN: Takeaways

- FN patients with fever of unknown origin who respond to EAT are appropriate to discontinue therapy after 72 hours of apyrexia, normal VS, resolution of symptoms
  - Supported by How Long trial
  - Similar strategy (5-7 days) supported by ESMO guidelines
  - Supported by European Conference on Infections in Leukemia
- FN patients with fever from clinically documented infection may be appropriate for this strategy
  - Supported by How Long trial
  - Limited numbers of each infection; majority were FUO

Aguilar-Guisadeo et al. *Lancet Haematol* 2017
Averbuch et al. *Haematologica* 2013
Klastersky et al. *Ann Oncol* 2016

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For Pharmacists:

Which of these disease states are <u>lacking</u> RCT data for shorter durations of treatment?

A. Febrile Neutropenia

B. Pyelonephritis

C. Gram Negative Bacteremia

D. None of the above

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Evidence Based Durations of Therapy

Infection	Duration	Caveat
HAP/VAP	7 days	Data from VAP patients
CAP	3 days	Only beta-lactams studied
IAI	4 days	If source control achieved
PN	5-7 days	5 days for FQ; 7 days for TMP-SMX or beta-lactams
GNB	7 days	More RCTs coming soon
FN	72 hours after resolution of fever and symptoms	Limited data for clinically documented infections

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