HOW LOW CAN YOU GO?
DURATIONS OF ANTIBIOTIC THERAPY FOR COMMON INFECTIONS

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I have no financial disclosures
OUTLINE

General Principles
UTI
Gram-negative bacteremia
Intra-abdominal infections
Skin and soft tissue infections
Pneumonia
GENERAL PRINCIPLES

- UNNECESSARY antibiotics are bad
- “Standard of care”
- Medical myths
- Source control is probably as, if not more, important than antibiotics
UNNECESSARY ANTIBIOTICS ARE BAD

- Resistance
- Adverse effects
- Drug Interactions
- Infections
- Length of stay
- Cost
UNNECESSARY ANTIBIOTICS

**Hospital**
- About half of hospitalized patients receive an antimicrobial.
- Up to 50% of those antibiotics are inappropriate.

**Outpatient**
- At least 30% of antibiotic courses are unnecessary.
- 50% are inappropriate.

**Nursing Homes**
- Up to 70% of residents receive one antimicrobial course in a year.
- Up to 75% are inappropriate.
GENERAL PRINCIPLES

- **UNNECESSARY** antibiotics are bad
- "Standard of care"
- Medical myths
- Source control is probably as, if not more important than antibiotics
“STANDARD OF CARE”


Late-career Physicians Prescribe Longer Courses of Antibiotics.
Fernandez-Lazaro C1,2, Brown K1, Langford B1, Daneman N1,4, Garber G1,8, Schwartz K1,3,7.

Author information
1 Infection Prevention and Control, Public Health Ontario, Toronto, Canada.
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3 Dalla Lana School of Public Health, University of Toronto, Canada.
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.
7 Department of Medicine, St. Joseph’s Health Centre, Toronto, Canada.
“STANDARD OF CARE”

N=10,616
family physicians

<table>
<thead>
<tr>
<th>Variables</th>
<th>Proportion of Prolonged Antibiotic Courses (Mean ± Standard Deviation)</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Physician variables (N = 10 616)</td>
<td></td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36.7% ± 19.3%</td>
<td>1.13</td>
<td>(1.09–1.16)</td>
<td>1.02</td>
<td>(0.96–1.08)</td>
</tr>
<tr>
<td>Female</td>
<td>34.0% ± 16.5%</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Career stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late career (&gt;24 years)</td>
<td>38.6% ± 19.8%</td>
<td>1.44</td>
<td>(1.39–1.49)</td>
<td>1.48</td>
<td>(1.38–1.58)</td>
</tr>
<tr>
<td>Mid-career (11–24 years)</td>
<td>34.4% ± 17.2%</td>
<td>1.19</td>
<td>(1.15–1.24)</td>
<td>1.25</td>
<td>(1.16–1.34)</td>
</tr>
<tr>
<td>Early career (&lt;11 years)</td>
<td>30.5% ± 13.9%</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
</tbody>
</table>
GENERAL PRINCIPLES

- **UNNECESSARY** antibiotics are bad
- “Standard of care”
- Medical myths
- Source control is probably as, if not more important than antibiotics
MEDICAL MYTHS

What are you supposed to be?

An unfinished course of antibiotics.

I can lead to antibiotic resistance. Aren't I terrifying?!

And Beatrice was never invited to a Halloween party ever again.

Beatrice the Biologist
MEDICAL MYTHS

- Pneumonia used to be treated for 4 days or less
- Penicillin was first discovered in 1928
- Clinicians first started using penicillin in 1942

MEDICAL MYTHS

Treatment of Pneumococcal Pneumonia with Penicillin

Manson Meads, M.D.†, H. William Harris, M.D.‡, Maxwell Finland, M.D.§, and Clare Wilcox

44 survivors, 3 recurrences
Authors suggested extending by 2-3 days and completing course
1 patient received <12 hours of therapy
1 developed pneumonia with a different serotype
1 developed recurrence a month later
GENERAL PRINCIPLES

- **UNNECESSARY** antibiotics are bad
- **“Standard of care”**
- Medical myths
- **Source control is probably as, if not more important than antibiotics**
URINARY TRACT INFECTIONS

OMG!!!

IT BUUUURRRNNNNSSSS!!!
68-year-old woman presents with 2 days of dysuria. UA showed 600 white cells, cultures are growing pan-sensitive E. coli. You pick nitrofurantoin for…

A) 3 days
B) 5 days
C) 7 days
SIMPLE UTI

- Randomized, double-blind, placebo-controlled
- n=327
- Excluded patients with pyelonephritis and immunosuppressed (including diabetics)
- TMP/SMX for 3 days vs. 7 days
- No recurrence at 1, 2, and 6 weeks
SIMPLE UTI

- Iravani et al 1999
  - Randomized, double-blind
  - n=521
  - 3 days ciprofloxacin vs 7 days TMP/SMX or 7 days nitrofurantoin
    - no recurrence at 4-6 weeks
  - ciprofloxacin = 91%, TMP/SMX = 79%, nitrofurantoin = 82%
- Gupta et al 2007
  - Randomized, open-label
  - n=338
  - 3 days TMP/SMX vs 5 days nitrofurantoin
    - clinical cure at 30 days

Table 3. Treatment Outcomes by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients, No./Total No. (%)</th>
<th>Difference (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMP-SMX Group (n = 148)</td>
<td>Nitrofurantoin Group (n = 160)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall clinical cure</td>
<td>117/148 (79)</td>
<td>134/160 (84)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early clinical cure</td>
<td>133/148 (90)</td>
<td>144/160 (90)</td>
</tr>
<tr>
<td>Early microbiological cure</td>
<td>131/144 (91)</td>
<td>141/154 (92)</td>
</tr>
</tbody>
</table>

Iravani J Antimicrob Chemother 1999
Gupta Arch Intern Med 2007
BETA-LACTAMS?

- Two studies compared ciprofloxacin and a beta-lactam for 3 days in women with acute uncomplicated cystitis.
- In the 2005 study, 58% of women treated with amoxicillin-clavulanate had clinical cure compared with 77% treated with ciprofloxacin (p <0.001).
- In the 2012 study, favorable outcome at day 30 was 93% for ciprofloxacin and 82% for cefpodoxime (95% CI, 3 to 18)
- The data on beta-lactams are mostly limited to studies comparing older antibiotics

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

Kalpana Gupta,1 Thomas M. Hooton,2 Kurt G. Naber,9 Björn Wullt,10 Richard Colgan,2 Loren G. Miller,4 Gregory J. Moran,5 Lindsay E. Nicelle,8 Raul Raz,11 Anthony J. Schaeffer,6 and David E. Soper7
SIMPLE UTI

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)
SIMPLE UTI

Fluoroquinolones
(resistance prevalence high in some areas)

OR

β-lactams
.avoid ampicillin or amoxicillin alone; lower efficacy than other available agents; requires close follow-up)
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). For these reasons, β-lactams other than pivmecillinam should be used with caution for uncomplicated cystitis.
SIMPLE UTI

- Answer: 5 days
- How low can you go? 3 days
PYELONEPHRITIS

Background Studies

• Talan 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

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
    - Obstruction
    - eGFR <50
    - Known resistance
  - 5d levofloxacin 750mg PO daily vs 10d ciprofloxacin 500mg PO BID

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

<table>
<thead>
<tr>
<th></th>
<th>Levofoxacin (10–14 days after end of active therapy)</th>
<th>Ciprofoxacin (5–9 days after end of active therapy)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=94</td>
<td>n=98</td>
<td></td>
</tr>
<tr>
<td>Microbiologic outcome</td>
<td>Eradicated</td>
<td>Persisted</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>78 (83.0)</td>
<td>6 (6.4)</td>
<td>10 (10.6)</td>
</tr>
<tr>
<td>Success</td>
<td>Eradicated</td>
<td>Persisted</td>
<td>Unable to evaluate</td>
</tr>
<tr>
<td></td>
<td>81 (86.2)</td>
<td>6 (6.4)</td>
<td>7 (7.4)</td>
</tr>
</tbody>
</table>

Klausner Curr Med Res Opin 2007
PYELONEPHRITIS

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

Torsten Sandberg, Gunilla Skoog, Anna Bornefalk Hermansson, Gunnar Kahlmeter, Nils Kuylenstierna, Anders Lannergård, Gisela Otto, Bo Settergren, Gunilla Stridh Ekman

- Multicenter study in Sweden in non-pregnant women
- n=248
- Randomized to receive 7 or 14 days of ciprofloxacin
- Patient characteristics
  - Median age was 41 and 46 years respectively
  - 12 to 15% had recurrent UTI
  - 22 and 32% had positive blood cultures
### Table 3: Clinical outcomes in the per-protocol population

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin for 7 days</th>
<th>Ciprofloxacin for 14 days</th>
<th>Difference (90% CI)</th>
<th>Non-inferiority test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>73 (97%)</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure or recurrent</td>
<td>71 (97%)</td>
<td>80 (96%)</td>
<td>-0.9% (-6.5 to 4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>symptomatic urinary tract infections</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>73 (97%)</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure or recurrent</td>
<td>68 (93%)</td>
<td>78 (93%)</td>
<td>-0.3% (-7.4 to 7.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>symptomatic urinary tract infections</td>
<td>5 (7%)</td>
<td>6 (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated.
Included 8 trials that evaluated 7 days or less vs longer treatment

Study characteristics

- Most of the studies included hospitalized patients, men (0 to 33%), and patients with urogenital abnormalities (not specified to 50%)
- Positive blood culture rate ranged from 3 to 29%

No difference in clinical failure at end of treatment (RR 0.63, 95% CI 0.33-1.18) or end of follow-up (RR 0.79, 95% CI 0.56-1.12)

- In a subgroup analysis of bacteremia, there was no advantage to longer therapy (RR 0.54, 95% CI 0.15 to 1.92)
PYELONEPHRITIS

IDSA Guidelines

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

- Answer: 5-7 days
  - Women
  - Even in bacteremia
  - Maybe not with beta lactams
WHAT ABOUT MEN?
WHAT ABOUT MEN?

- n=1102; 427 were male
- Levofloxacin 750 mg once daily x 5 days vs. ciprofloxacin 400 mg IV/500 mg PO twice daily for 10 days in patients with complicated cystitis and acute pyelonephritis
- Clinical success rate of 82.6% and 78.5%, respectively (95% CI -10.4 to 2.1).
WHAT ABOUT MEN?

Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women

Cees van Nieuwkoop1,2*, Willize E. van der Starre*, Janneke E. Stalenhoef3, Anna M. van Aartrijk2, Tanny J. K. van der Reijden2, Albert M. Vollaard6, Nathalie M. Delfos4, Jan W. van ’t Wout2,4, Jeanet W. Blom5, Ida C. Spelt6, Eliane M. S. Leyten7, Ted Koster8, Hans C. Ablij9, Martha T. van der Beek10, Mirjam J. Knol10 and Jaap T. van Dissel2,11

- Multicenter study of outpatients and inpatients in the Netherlands
- N=200; 86 were male
- Patients randomized to receive 7 vs 14 days (the 2nd week being a fluoroquinolone)
- **7 days was non-inferior** to 14 days in women
- **7 days was inferior** to 14 days in men (86 vs 98%, 90% CI -20.6 to -1.8)
MEN

- Answer: 7-14 days
SIDE NOTE

- Odor, cloudy urine, etc. ARE NOT UTI
- Don’t treat if asymptomatic unless pregnant, getting an invasive urology procedure, or neutropenic
- There is NO test of cure
GRAM-NEGATIVE BACTEREMIA
68-year-old woman presents with 2 days of dysuria. UA showed 600 white cells, urine and blood cultures grew pan-sensitive E. coli. She is afebrile, cultures cleared the next day. You pick ciprofloxacin for...

- A) 7 days
- B) 10 days
- C) 14 days
GRAM NEGATIVE BACTEREMIA

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

Darunee Chotiprasitsakul, Jennifer H. Han, Sara E. Cosgrove, Anthony D. Harris, Ebbing Lautenbach, Anna T. Conley, Pam Tolomeo, Jacquleen Wise, and Pramit D. Tamma; for the Antibacterial Resistance Leadership Group

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

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

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

*Adjusted for immunocompromised status and variables with P < .10 in univariable analysis.
### SECONDARY OUTCOMES

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Short-Course</th>
<th>Long-Course</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent BSI (same organism)</td>
<td>5 (1.3%)</td>
<td>9 (2.3%)</td>
<td>1.32 (0.48-3.41)</td>
</tr>
<tr>
<td>CDI</td>
<td>7 (1.8%)</td>
<td>6 (1.6%)</td>
<td>1.16 (0.39-3.51)</td>
</tr>
<tr>
<td>MDRGN resistance</td>
<td>17 (4.4%)</td>
<td>28 (7.3%)</td>
<td>0.59 (0.32-1.09; p=0.09)</td>
</tr>
</tbody>
</table>

- Post-hoc power calculation: Only 40% powered to detect difference in emergence of MDRGNs
- <1% had inadequate source control
Randomized, multicenter, open-label, noninferiority trial

Patients who were afebrile and hemodynamically stable for at least 48 hours

7d vs 14d

No source control – excluded

N=604

90-day composite all-cause mortality, clinical failure including relapse, local suppurative complications, distal complications, readmission, or extended hospital stay >14 days
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Short Arm (7 d) (n = 306)</th>
<th>Long Arm (14 d) (n = 298)</th>
<th>Risk Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>140 (45.8)</td>
<td>144 (48.3)</td>
<td>-2.6 (-10.5 to 5.3)</td>
<td>.527</td>
</tr>
<tr>
<td>90-d all-cause mortality</td>
<td>36 (11.8)</td>
<td>32 (10.7)</td>
<td>1.0 (-4.0 to 6.1)</td>
<td>.702</td>
</tr>
<tr>
<td>Readmissions</td>
<td>119 (38.9)</td>
<td>127 (42.6)</td>
<td>-3.7 (-11.5 to 4.1)</td>
<td>.363</td>
</tr>
<tr>
<td>Extended hospitalization beyond 14 d</td>
<td>15 (4.9)</td>
<td>19 (6.4)</td>
<td>-1.5 (-5.1 to 2.2)</td>
<td>.483</td>
</tr>
<tr>
<td>Distant complications</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
<td>...</td>
<td>1.0</td>
</tr>
<tr>
<td>Relapse of bacteremia</td>
<td>8 (2.6)</td>
<td>8 (2.7)</td>
<td>-0.07 (-2.6 to 2.5)</td>
<td>.957</td>
</tr>
<tr>
<td>Suppurative complications</td>
<td>16 (5.2)</td>
<td>10 (3.4)</td>
<td>1.8 (-1.4 to 5.1)</td>
<td>.257</td>
</tr>
<tr>
<td>Time to return to baseline activity, wk (90 d)</td>
<td></td>
<td></td>
<td></td>
<td>.010</td>
</tr>
</tbody>
</table>
GRAM-NEGATIVE BACTEREMIA

- Answer: 7 days
INTRA-ABDOMINAL ABSCESS

It’s okay, I get irritable sometimes, too.
68-year-old woman presents with 2 days of abdominal pain. Abdominal CT scan showed appendicitis with abscess. She underwent laparoscopic appendectomy with washout. You recommend antibiotics for...

- A) 0 days
- B) 4 days
- C) 7 days
- D) 10-14 days
INTRA-ABDOMINAL ABSCESS

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

Robert G. Sawyer, M.D., Jeffrey A. Claridge, M.D., Avery B. Nathens, M.D., Ori D. Rotstein, M.D., Therese M. Duane, M.D., Heather L. Evans, M.D., Charles H. Cook, M.D., Patrick J. O’Neill, M.D., Ph.D., John E. Mazuski, M.D., Ph.D., Reza Askari, M.D., Mark A. Wilson, M.D., Lena M. Napolitano, M.D., et al., for the STOP-IT Trial Investigators

- Study to Optimize Peritoneal Infection Therapy (STOP-IT)
- Prospective, randomized, open-label multi-center study in adult patients with complicated intra-abdominal infection with adequate source control
STOP-IT

4 days of antimicrobial therapy after source control

260 patients in intention to treat analysis
Median DOT: 4 days

189 patients in per protocol analysis

VS

Antimicrobial therapy until 2 days after the resolution of SIRS

257 patients in intention to treat analysis
Median DOT: 8 days

211 patients in the per protocol analysis
## STOP-IT

### Duration of outcome — days

<table>
<thead>
<tr>
<th>Antimicrobial therapy for index infection</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>8</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>5–10</td>
</tr>
</tbody>
</table>

### Table 2. Primary and Major Secondary Outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (N = 260)</th>
<th>Experimental Group (N = 257)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)</td>
<td>58 (22.3)</td>
<td>56 (21.8)</td>
<td>0.92</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>23 (8.8)</td>
<td>17 (6.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent intraabdominal infection</td>
<td>36 (13.8)</td>
<td>40 (15.6)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td>2 (0.8)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
No difference in the primary outcome of composite surgical site infection, recurrent intra-abdominal infection, and death

- Approximately 20% had an event regardless of treatment group

Major differences:

- Increased time to event with longer antibiotic therapy (10 vs 15 days)
- Infection with a resistant infection trended toward an increase with longer antibiotic therapy
SUBGROUP ANALYSES

- Surgical intervention vs percutaneous drainage
  - No difference in primary outcomes
  - Time to recurrent IAI (12.7 days with short course vs 21.3 with long course, P = 0.015)

- No difference in primary outcomes regardless of risk factor
  - Obesity, diabetes, obesity and diabetes, APACHE II ≥ 15, corticosteroid use, hospital-acquired infection, and/or colonic source
COMPLICATED INTRA-ABDOMINAL INFECTIONS

- There will be failures (~20%) regardless of the duration of antibiotic therapy
- Failures are likely from inadequate source control rather than insufficient antibiotics
- Longer durations appear to delay the inevitable failures
INTRA-ABDOMINAL ABSCESS

IDSA GUIDELINES

• 4-7d after “adequate source control”

• 24h for perforation controlled within 24hrs

• ≤24hrs for penetrating injury repaired in under 12hrs

• Only pre-operative for simple appendicitis (no perforation, no abscess)
INTRA-ABDOMINAL ABSCESS

- Answer: 4 days
SKIN AND SOFT TISSUE INFECTIONS
SKIN AND SOFT TISSUE INFECTIONS

68-year-old woman presents with 2 days of non-purulent swelling, pain and redness of R leg. She was started on IV ceftriaxone with good improvement by day 2, now afebrile, blood cultures are negative. On discharge, you pick levofloxacin for:

- A) 5 days
- B) 7 days
- C) 10 days
Median duration of antibiotics: 13 days
Pediatric study, randomized, non-inferiority (n=249)

Excluded
- no drainage (only abscesses)
- immune compromised
- inpatient

TMP/SMX 3d vs TMP/SMX 10d
<table>
<thead>
<tr>
<th></th>
<th>3-day therapy, no. failures/no. cultures (%)</th>
<th>10-day therapy, no. failures/no. cultures (%)</th>
<th>P value</th>
<th>Difference, % (95% CI)</th>
<th>OR value (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with culture obtained</td>
<td>9/125 (7)</td>
<td>4/124 (3)</td>
<td>.25</td>
<td>4.0 (-1.5 to 9.5)</td>
<td>2.6 (.13)</td>
</tr>
<tr>
<td>All patients with <em>Staphylococcus aureus</em></td>
<td>9/108 (8)</td>
<td>2/109 (2)</td>
<td>.03</td>
<td>6.5 (0.7-12.3)</td>
<td>5.2 (.04)</td>
</tr>
<tr>
<td>Patients with MRSA</td>
<td>8/69 (12)</td>
<td>1/69 (1)</td>
<td>.03</td>
<td>10.1 (2.1-18.2)</td>
<td>10.4 (.03)</td>
</tr>
<tr>
<td>Patients with MSSA</td>
<td>1/39 (3)</td>
<td>1/40 (3)</td>
<td>ns</td>
<td>0.1 (-6.9 to 7.0)</td>
<td></td>
</tr>
<tr>
<td>Patients with non-<em>Staphylococcus aureus</em></td>
<td>0/14 (0)</td>
<td>1/14 (7)</td>
<td>ns</td>
<td>-7.1 (-20.6 to 6.4)</td>
<td></td>
</tr>
</tbody>
</table>

**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).*
Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess


- Randomized, double-blind, superiority (n=1265)
- Excluded
  - <12 years of age
  - <2cm fluctuant lesion (only abscesses) for < 1 week
  - inpatient
- TMP/SMX 7d vs placebo
• Median age: 35
• 45.3% of patients: MRSA
Comparison of Short-Course (5 Days) and Standard (10 Days) Treatment for Uncomplicated Cellulitis

Matthew J. Hepburn, MC, USA; David P. Dooley, MC, USA; Peter J. Skidmore, MC, USA; et al

- Randomized, double-blind, placebo controlled; n=121
- Excluded: no source control, worsening cellulitis, lack of improvement, abscess formation, immunocompromised
- Levofloxacin 5d vs 10d
- 43 (98%) of 44 patients in 5d arm had resolution; 42 (98%) of 43 patients in the 10d arm had resolution by 14 days (p>0.05)
- No relapse by 28 days

Hepburn et al JAMA 2004
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).
SKIN AND SOFT TISSUE INFECTIONS

- Answer: 5 days
PNEUMONIA

How far have we gone? Ten miles? Ten kilometers? 20 klicks?

Almost to the end of the driveway!

Lung distance running

theAwkwardYeti.com
68-year-old woman presents with 2 days of fever and cough. White count was 12k. CXR showed a new RLL opacity. She was initiated on IV ceftriaxone and her fever and leukocytosis resolved in 48 hours. You complete a total antibiotic course of...

- A) 5 days
- B) 7 days
- C) 14 days
COMMUNITY ACQUIRED PNEUMONIA


Dunbar LM¹, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, Kahn JB.

- Randomized, double-blind, non-inferiority (n=528)
- Excluded
  - Known resistance or high risk for Pseudomonas
  - Aspiration or empyema
  - Neutropenia or HIV
  - Meningitis
- Levofloxacin 750mg daily x 5d vs 500mg daily x 10d
Clinical success rates:

- 92.4% (183 of 198) in the 750 mg group
- 91.1% (175 of 192) in the 500 mg group (95% CI, -7.0 to 4.4).

Li JZ¹, Winston LG, Moore DH, Bent S.

- Meta analysis of 15 RCTs (n=2796)
- Excluded
  - Children
  - Aspiration
  - Pneumocystis
- Short course (<7d) vs long course (>7d)
<table>
<thead>
<tr>
<th>Study</th>
<th>Short-Course</th>
<th>Extended-Course</th>
<th>n</th>
<th>Mean Age*</th>
<th>Time to Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohste et al, 1995</td>
<td>Azithromycin, 5 d</td>
<td>Erythromycin, 10 d</td>
<td>42</td>
<td>61</td>
<td>Within 21 days of discharge</td>
</tr>
<tr>
<td>Brion et al, 1990</td>
<td>Azithromycin, 5 d</td>
<td>Erythromycin, 10 d</td>
<td>97</td>
<td>53</td>
<td>30 days</td>
</tr>
<tr>
<td>Dunbar et al, 2003</td>
<td>Levofloxacin, 5 d</td>
<td>Levofloxacin, 10 d</td>
<td>528</td>
<td>54</td>
<td>7-14 days after last dose of antibiotic</td>
</tr>
<tr>
<td>Kinasewitz &amp; Wood, 1991</td>
<td>Azithromycin, 5 d</td>
<td>Cefaclor, 10 d</td>
<td>119</td>
<td>42</td>
<td>10-13 days</td>
</tr>
<tr>
<td>Kobayashi et al, 1995</td>
<td>Azithromycin, 3 d</td>
<td>Clarithromycin, 14 d</td>
<td>163</td>
<td>Not reported</td>
<td>14 days</td>
</tr>
<tr>
<td>Leophonte et al, 2004</td>
<td>Gemifloxacin, 7 d</td>
<td>Amoxicillin/clav, 10 d</td>
<td>320</td>
<td>54</td>
<td>24-30 days</td>
</tr>
<tr>
<td>Leophonte et al, 2002</td>
<td>Ceftriaxone, 5 d</td>
<td>Ceftriaxone, 10 d</td>
<td>244</td>
<td>64</td>
<td>10 days</td>
</tr>
<tr>
<td>O'Doherty &amp; Muller, 1998</td>
<td>Azithromycin, 3 d</td>
<td>Clarithromycin, 10 d</td>
<td>203</td>
<td>51</td>
<td>12-16 days</td>
</tr>
<tr>
<td>Rahav et al, 2004</td>
<td>Azithromycin, 3 d</td>
<td>Multiple abx, 10 d</td>
<td>108</td>
<td>50</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Rizzato et al, 1995</td>
<td>Azithromycin, 3 d</td>
<td>Clarithromycin, 10 d</td>
<td>40</td>
<td>46</td>
<td>30 days</td>
</tr>
<tr>
<td>Schonwald et al, 1994</td>
<td>Azithromycin, 3 d</td>
<td>Roxithromycin, 10 d</td>
<td>150</td>
<td>40</td>
<td>14 days</td>
</tr>
<tr>
<td>Schonwald et al, 1990</td>
<td>Azithromycin, 5 d</td>
<td>Erythromycin, 10 d</td>
<td>101</td>
<td>Not reported</td>
<td>15-21 days</td>
</tr>
<tr>
<td>Siegel et al, 1999</td>
<td>Cefuroxime, 7 d</td>
<td>Cefuroxime, 10 d</td>
<td>52</td>
<td>61</td>
<td>42 days</td>
</tr>
<tr>
<td>Sopena et al, 2004</td>
<td>Azithromycin, 3 d</td>
<td>Clarithromycin, 10 d</td>
<td>70</td>
<td>43</td>
<td>25-30 days</td>
</tr>
<tr>
<td>Tellier et al, 2004</td>
<td>Telithromycin, 5 or 7 d</td>
<td>Clarithromycin, 10 d</td>
<td>559</td>
<td>42</td>
<td>17-21 days</td>
</tr>
</tbody>
</table>

*Mean age (years) is estimated to be the average age of the 2 arms if reported separately.
Figure 2  Relative risk of clinical failure with short-course versus extended course antibiotic regimens.
Multicenter, randomized, noninferiority clinical trial in 4 teaching hospitals in Spain

312 hospitalized patients with CAP randomized into two groups at 5 days of therapy

- Intervention: Duration by CAP guideline
- Control: Duration determined by physician

Patients excluded if admitted to ICU prior to randomization; however 40% of patients with PSI class IV/V (severe pneumonia)

Median duration of therapy: 5 vs 10 days
Outcome: Clinical success rate at 10 and 30 days since admission and CAP symptoms at 5 and 10 days

- **No difference in clinical cure** at 10 and 30 days in the intent-to-treat or per-protocol analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Group</th>
<th>Intervention Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intent-to-Treat Analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of participants</td>
<td>150</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Clinical success, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 10</td>
<td>71 (48.6)</td>
<td>90 (56.3)</td>
<td>.18</td>
</tr>
<tr>
<td>At day 30</td>
<td>132 (88.6)</td>
<td>147 (91.9)</td>
<td>.33</td>
</tr>
<tr>
<td>CAP symptom questionnaire score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At day 5</td>
<td>24.7 (11.4)</td>
<td>27.2 (12.5)</td>
<td>.10</td>
</tr>
<tr>
<td>At day 10</td>
<td>18.6 (9.0)</td>
<td>17.9 (7.6)</td>
<td>.69</td>
</tr>
</tbody>
</table>
- Severe subgroup: **Improved 30-day clinical outcome in the intervention group** in the intent to treat population

<table>
<thead>
<tr>
<th>Table 3. Clinical Success Rates at Days 10 and 30 Among Different Severity Groups Defined by PSI Class*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSI Class</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Clinical Success at Day 10</strong></td>
</tr>
<tr>
<td>PSI classes IV-V</td>
</tr>
<tr>
<td>Intent to treat</td>
</tr>
<tr>
<td>Per protocol</td>
</tr>
<tr>
<td><strong>Clinical Success at Day 30</strong></td>
</tr>
<tr>
<td>PSI classes IV-V</td>
</tr>
<tr>
<td><strong>Intent to treat</strong></td>
</tr>
<tr>
<td>Per protocol</td>
</tr>
</tbody>
</table>
No difference in mortality, radiographic resolution, time to clinical improvement, time to return to normal activity, recurrence by day 30, or in-hospital complications.

However, readmission by day 30 was higher in the control group:
- 9 (6.6%) control group vs 2 (1.4%) intervention group, p < 0.02
IDSA/ATS GUIDELINES - 2019

- “No less than 5 days” in patients who are improving
- “We believe that the duration of therapy for CAP due to suspected or proven MRSA or P. aeruginosa should be 7 days”
CAP

- Answer: 5 days
Pugh et al, 2015

Systematic review, 6 randomized trials\(^1\)-\(^6\)

508 patients with HAP/VAP

Compared fixed durations of antibiotic therapy

Nearly all had VAP
Short courses of antibiotics (7–8 days) increased **28-day antibiotic-free days** (mean difference, 4.02 days; 95% CI, 2.26–5.78 days) and reduced recurrent VAP due to MDR pathogens (42.1% vs 62.3%; OR, 0.44; 95% CI, .21–.95) compared with long courses of antibiotics (10–15 days).

No differences in mortality, recurrent pneumonia, treatment failure, hospital length of stay, or duration of mechanical ventilation.

In the subgroup of patients with VAP due to a **non-glucose-fermenting gram-negative bacillus** including *Pseudomonas* and *Acinetobacter* (33%), short courses of antibiotics were associated with recurrent infection (OR, 2.18; 95% CI, 1.14–4.16)
“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.”
The panel agreed that a different recommendation was not indicated because, even if there is a small increased recurrence rate, mortality and clinical cure do not appear to be affected.

In addition, the evidence for recurrence is from subgroup analyses with important limitations [...] potential bias in favor of long-course therapy due to the differential time period during which recurrence was assessed; there was the possibility that the second episode of VAP is incorrectly being considered a recurrence because of persistent colonizing organisms; many studies reported superinfections from both lung and other organ sites (e.g., UTI) as recurrence; pulmonary infiltrates are known to persist on imaging studies and lag behind clinical resolution, leading to false identification of a new or recurrent pneumonia.
**Observational study**

**Patients with VAP due to non-glucose-fermenting gram-negative bacilli**

**27 patients treated for 3–8 days and 127 patients treated for ≥9 days. There were no differences in mortality or recurrence rate**
**IDSA/ATS GUIDELINES**

- "**We conducted our own meta-analyses** using the trials that were included in the published systematic reviews, as well as data provided by these trials' authors. We also found **no differences** between short-course antibiotic regimens (i.e., 7–8 days) and long-course regimens (i.e., 10–15 days) in terms of **mortality, clinical cure, and recurrent pneumonia**.

- Of note, the specific subpopulation with VAP due to **non-glucose-fermenting gram-negative bacilli** was analyzed, and **no differences were observed for pneumonia recurrence** (OR, 1.42; 95% CI, 0.66–3.04; \( P = .37 \)) or mortality (OR, 0.94; 95% CI, 0.56–1.59; \( P = .83 \))."
The panel agreed that a different recommendation was not indicated because, even if there is a small increased recurrence rate, **mortality and clinical cure do not appear to be affected**

In addition, the evidence for recurrence is from subgroup analyses with important limitations […] potential bias in favor of long-course therapy due to the **differential time period during which recurrence was assessed**; there was the possibility that the second episode of VAP is incorrectly being considered a recurrence because of **persistent colonizing organisms**; many studies **reported superinfections from both lung and other organ sites (e.g., UTI) as recurrence**; pulmonary infiltrates are known to persist on imaging studies and lag behind clinical resolution, leading to **false identification of a new or recurrent pneumonia**
HAP/VAP

- Answer: 7 days
ACKNOWLEDGMENTS

- Jessica Thompson, PharmD
  - ID Pharmacist, University of Nevada, Reno
- Matt Greene, MD
  - Division of ID, Vanderbilt University Medical Center
THANK YOU!

Antibiotics don’t treat viruses
Don’t forget your flu shot
Wash your hands.
QUESTIONS?