Duration of antibiotic therapy:
How low can you go?
Disclosures

• **Consulting**: The Medicines Company, Basilea Pharmaceutica

• **Adjudication committee**: Achaogen

• **Grant support**: NIH, FDA

• **Royalties**: UpToDate

• **Employment**: Duke University
Overview

• A very ill man with CAP

• A tale of daptomycin and Noah’s ark

• Examine the basis for duration of therapy for some common bacterial infections
  – Pneumonia
  – Complicated UTI
  – Diverticulitis
  – Bacteremia
A very ill man

- 70yo Vietnamese male p/w severe sepsis due to CAP, with hypoxic respiratory failure requiring intubation in the ED.
Case, continued

• Initially given ceftriaxone/azithro but as he decompensated in the ED, broadened to vanc/zosyn*

• Blood and sputum cultures grow pan-sensitive *S. pneumoniae*, and therapy is narrowed to ceftriaxone

• He is extubated on HD #3 and transferred to gen med on HD #5, doing well

• What do you do with his antibiotics?
The inconvenient truth

• We don’t really know the optimal duration of antibiotics for most of the common infectious syndromes we treat every day
Competing motivations

• **Factors driving increased antibiotic use:**
  – Mortality benefits of early appropriate therapy for septic patients
  – Uncertain diagnoses
  – Human psychology – better to overtreat unnecessarily than undertreat and be wrong?
  – Concern for relapse
  – Lack of data and knowledge

• **Factors driving decreased antibiotic use:**
  – Public health concerns – a very weak motivating force
  – Growing recognition of harms of antibiotics
  – Cost – also a weak driver, at least from the provider side
Too short

Too long

Relapse

Treatment failure

Resistance

Compliance

AE & Collateral Damage
LESS IS MORE

Less Is More

How Less Health Care Can Result in Better Health
### IDSA Guidance: HISTORICAL PERSPECTIVE

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Date</th>
<th>Duration</th>
<th>Authors Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTI: Cellulitis</td>
<td>2005</td>
<td>??</td>
<td>No mention of duration</td>
</tr>
<tr>
<td>Bacterial Meningitis</td>
<td>2004</td>
<td>7-21 days</td>
<td>based more on tradition than evidence</td>
</tr>
<tr>
<td>Intra-Abdominal Infection</td>
<td>2003</td>
<td>??</td>
<td>“continued until resolution of clinical signs of infection occurs including normalization of temperature and WBC count and return of GI function”</td>
</tr>
<tr>
<td>Diabetic Foot Infection</td>
<td>2006</td>
<td>1-6 weeks</td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td>1998</td>
<td>??</td>
<td>“We are not aware of any controlled trials that have specifically address the questions of how long pneumonia should be treated”</td>
</tr>
</tbody>
</table>

**CAP Treatment Duration**

- **Keefer et al**
  - 500 patients
  - PCN
  - Duration for cure: 2-3 d

- **Meads & Finland**
  - 54 patients
  - PCN
  - Duration for cure: 2-3 days after fever resolution

- **Dawson & Hobby**
  - 100 patients
  - PCN
  - Duration for cure: 1.5-2 d

- **El Moussaui et al**
  - RCT N=121 hospitalized
  - Amoxicillin
  - Duration for cure: 3d

- **Uranga et al**
  - RCT N= 312 hospitalized
  - Fluoroquinolone (80%)
  - Duration for cure: 5d

**“Relapse” (N=3)**

1) Same pneumococcal species after receiving only ttl of 10hrs treatment
2/3) Different species 10 days – 1 month post tx

**Conclusion:** Relapses suggest tx even after fever and symptoms resolve is needed

**CAP Treatment in Practice**

- **10 – 14 Days**

---

• Review of 1195 CAP and 544 HCAP cases

• 13.6% received guideline-concordant therapy duration
  – 6.9% with CAP (≤5d), 29% with HCAP (≤8d)
  – >97% were stable by day 4, but >50% remained on IV abx
    • The average treatment course was 4 days IV, then 1 week PO, with more than half post-discharge
  – 17.3% had antibiotic therapy stopped prior to discharge

• Therapy duration was not associated with readmission or mortality rate
The untold story?

*Daptomycin vs Ceftriaxone for CAP*

• Daptomycin worked fine for *S. aureus* pneumonia in a hamster model

• In 2000-2002, Cubist conducted 2 trials of daptomycin versus ceftriaxone among hospitalized adults with CAP
  – One of the exclusion criteria was >24h of potentially effective therapy

• Daptomycin did not meet noninferiority criteria
The untold story?

*Daptomycin vs Ceftriaxone for CAP*

- A closer look:

<table>
<thead>
<tr>
<th>Prior effective therapy</th>
<th>Daptomycin arm</th>
<th>Ceftriaxone arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cured patients/total no. of patients</td>
<td>Cure rate, %</td>
</tr>
<tr>
<td>Yes</td>
<td>88/97</td>
<td>90.7</td>
</tr>
<tr>
<td>No</td>
<td>205/272</td>
<td>75.4</td>
</tr>
</tbody>
</table>

*For the difference in cure rates.*

- A single day of therapy was enough to influence outcomes

• So let’s keep doing less and less…. And less…. And less
• How much less can we possibly have?

“Other than tuberculosis—which is caused by a very slowly replicative organism that spends much of its time in a nonreplicating state—for every bacterial infection for which trials have compared short-course with longer course antibiotic therapy, short-course therapy has been just as effective…”

Spellberg, JAMA Intern Med. 2016;176(9):1254-1255
### Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia$^{1-3}$</td>
<td>3-5</td>
</tr>
<tr>
<td>Nosocomial pneumonia$^{6,7}$</td>
<td>≤8</td>
</tr>
<tr>
<td>Pyelonephritis$^{10}$</td>
<td>5-7</td>
</tr>
<tr>
<td>Intraabdominal infection$^{11}$</td>
<td>4</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis and COPD$^{12}$</td>
<td>≤5, ≥7</td>
</tr>
<tr>
<td>Acute bacterial sinusitis$^{13}$</td>
<td>5</td>
</tr>
<tr>
<td>Cellulitis$^{14}$</td>
<td>5-6</td>
</tr>
<tr>
<td>Chronic osteomyelitis$^{15}$</td>
<td>42</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>84</td>
</tr>
</tbody>
</table>

**Abbreviation:** COPD, chronic obstructive pulmonary disease.
Pyelonephritis: Cipro 7 vs 14 days

**Study Design**
- Multicenter (21), prospective non-inferiority RCT
- Open label (D1-7), double blind placebo controlled (D8-14)
- Cipro 500mg PO BID; Option for first dose 400mg IV

**Patients**
- Non-pregnant women ≥ 18yrs with acute pyelonephritis

**Endpoint**
- Primary objective: clinical and bacteriological efficacy 10-14d after treatment with cipro
- Secondary outcome: Long term (42-63d) cumulative efficacy

*Lancet* 2012; 380: 484–90
<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin for 7 days (n=73)</th>
<th>Ciprofloxacin for 14 days (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46 (27–62)</td>
<td>41 (23–58)</td>
</tr>
<tr>
<td>Recurrent urinary tract infections</td>
<td>11 (15%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Complicated urinary tract infections</td>
<td>4 (5%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (3%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>39·2 (38·7–39·7)</td>
<td>39·0 (38·5–39·6)</td>
</tr>
<tr>
<td>Flank pain or costovertebral angle tenderness</td>
<td>69 (95%)</td>
<td>79 (95%)</td>
</tr>
<tr>
<td>Serum CRP concentrations (mg/L)</td>
<td>100 (56–199)</td>
<td>125 (68–227)</td>
</tr>
<tr>
<td>Pyuria</td>
<td>70 (96%)</td>
<td>78 (94%)</td>
</tr>
<tr>
<td>Bacteria isolated from pretreatment urine cultures</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>64 (88%)</td>
<td>79 (95%)</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>3 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>3 (4%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>16 (22%)</td>
<td>26 (32%)*</td>
</tr>
<tr>
<td>Initial intravenous dose(s) of ciprofloxacin</td>
<td>14 (19%)</td>
<td>11 (13%)</td>
</tr>
</tbody>
</table>

Data are number (%) or median (IQR). All blood cultures grew *Escherichia coli*. *Blood cultures missing for one patient.

Table 2: Baseline characteristics of the per-protocol population
<table>
<thead>
<tr>
<th>Results</th>
<th>Cipro 7d</th>
<th>Cipro 14d</th>
<th>Difference (90% CI)</th>
<th>Non-inferiority p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure</td>
<td>N=73</td>
<td>N=83</td>
<td>-0.9% (-6.5 to 4.8)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>71 (97%)</td>
<td>80 (96%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>2 (3%)</td>
<td>3 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal Candida</td>
<td>0</td>
<td>5 (5%)</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4 (5%)</td>
<td>6 (6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis

L. Daniels¹, Ç. Ünlü¹, N. de Korte⁵, S. van Dieren², H. B. Stockmann⁶, B. C. Vrouwenraets³, E. C. Consten⁷, J. A. van der Hoeven⁸, Q. A. Eijsbouts⁵, I. F. Faneyte⁹, W. A. Bemelman¹, M. G. Dijkgraaf² and M. A. Boermeester¹, for the Dutch Diverticular Disease (3D) Collaborative Study Group

- 528 patients with left-sided uncomplicated acute diverticulitis at 22 sites in the Netherlands
- Could have up to 5cm abscess
- Randomized to antibiotics (amox/clav) vs observation
- Primary endpoint was time to recovery

Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis
Randomized clinical trial of observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis

![Graph showing proportion of participants without recovery over time after randomization (months).](image)

No. at risk
- Observation: 262, 70, 41, 27, 24, 22, 19
- Antibiotics: 266, 65, 39, 24, 22, 19, 14

**a** All patients

No. at risk
- Observation: 236, 64, 39, 25, 22, 20, 17
- Antibiotics: 250, 60, 35, 20, 18, 16, 11

**b** Patients with Hinchey 1a disease
Acute diverticulitis

- That study may be not be applicable to a US inpatient population, few of whom likely would have met study entry criteria.

- But traditional durations of 7-10 days aren’t supported either.
A cautionary tale

• 520 kids with AOM received 10 days amox/clav vs 5 days (with additional 5 days of placebo)

• In children 6 to 23 months of age with otitis media, 5 days of antibiotic therapy was associated with less-favorable outcomes than standard 10-day treatment.

• The shorter course did not result in a lower rate of adverse events or of emergence of antimicrobial resistance.

## IDSA Guidance: UPDATED

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Date</th>
<th>Duration</th>
<th>Authors Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTI: Cellulitis</td>
<td>2005</td>
<td>??</td>
<td>No mention of duration</td>
</tr>
<tr>
<td></td>
<td>2014</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>Bacterial Meningitis</td>
<td>2004</td>
<td>7-21 days</td>
<td>based more on tradition than evidence</td>
</tr>
<tr>
<td>IAI</td>
<td>2003</td>
<td>??</td>
<td>“continued until resolution of clinical signs of infection occurs including normalization of temperature and WBC count and return of GI function”</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>4-7 days</td>
<td>“unless it is difficult to achieve source control”</td>
</tr>
<tr>
<td>Diabetic Foot Infection</td>
<td>2006</td>
<td>1-6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2012</td>
<td></td>
<td>“can usually be discontinued once the clinical signs and symptoms of infection have resolved”</td>
</tr>
<tr>
<td>CAP</td>
<td>2000</td>
<td>??</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2007</td>
<td>5 days</td>
<td></td>
</tr>
</tbody>
</table>

BACTEREMIA
Factors Influencing Antibiotic Duration in Bacteremia

- Organism characteristics
  - Metastatic infection potential
  - Attachment behaviours
  - Biofilm formation
  - Kinetics of growth
- Patient characteristics
  - Immune status (e.g. age, cirrhosis)
  - Foreign material
- Place of acquisition
  - Community vs. nosocomial
- Infection characteristics
  - Duration of infection
  - Site of infection (e.g. immunologically privileged, inadequate blood flow)
  - Severity (e.g. shock)
  - Consequences of treatment failure
  - Response to therapy
- Antibiotic characteristics
  - Sensitivity of organism
  - Bactericidal vs. bacteriostatic
  - Bioavailability at infection site
  - Monotherapy vs. combination therapy
- Other therapeutic factors
  - Source control or eradication – surgical vs. non-surgical (e.g. removal of catheter, drainage)
Antibiotic treatment duration for bloodstream infections in critically ill patients: a national survey of Canadian infectious diseases and critical care specialists

Nick Daneman, Kevin Shore, Ruxandra Pinto, Rob Fowler

CONCLUSIONS:
1) Significant variation in treatment duration
2) Equipoise
3) S. aureus is different

S. aureus ~ 3/4
Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis

Thomas C Havey¹, Robert A Fowler¹,² and Nick Daneman¹,³*

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Short Duration</th>
<th>Long Duration</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudhry</td>
<td>5 Events</td>
<td>6 Total</td>
<td>0.95 [0.61, 1.48]</td>
</tr>
<tr>
<td>Runyon</td>
<td>9 Events</td>
<td>9 Total</td>
<td>1.10 [0.87, 1.39]</td>
</tr>
<tr>
<td>Siegel</td>
<td>1 Event</td>
<td>2 Total</td>
<td>0.56 [0.17, 1.79]</td>
</tr>
</tbody>
</table>

Total (95% CI): 17 Events, 29 Total, 0.97 [0.76, 1.23]

CONCLUSIONS: No difference in short vs. longer duration
Definitive trial needed
Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE): study protocol for a pilot randomized controlled trial

- Multicenter pilot randomized controlled trial in ICU patients with bacteremia
- Randomized to 7 v. 14d abx
- Outcome: 90 day mortality as determined by blinded outcome adjudicators
- Excludes S. aureus bacteremia
- Other Exclusions: Candidemia; Prosthetic valve; immunocompromised; complicated infection
So, How Much Treatment **IS** Enough for Bacteremia?

**Uncomplicated**

- Defervesce promptly
- Follow up blood cultures negative
- Source control
- No cardiac devices

**Gram-negative Bacteria**

- **5-14 days**
  - Streptococci
  - Enterococci*
    - 7-14d

**Coagulase negative Staphylococci***

- **5-10 days**
  - S. aureus
    - Echo Negative
    - At least 14d

*Worry about community acquisition
Case resolution
Combination therapy for pneumococcal bacteremia

- 844 consecutive cases of pneumococcal bacteremia
- Combination therapy with no overall survival benefit but in a subgroup analysis, better among the critically ill
- No specific combo was better but β-lactam/macrolide was most common
  - Adding a macrolide also appeared helpful in another observational study

1 Baddour et al, Am J Respir Crit Care Med. 2004;170(4):440-4
2 Martinez et al, CID 2003; 36(4):389-95
Case resolution - pneumococcal pneumonia

• Expert opinion-based recs:
  – 5 days for most CAP
  – For critically ill bacteremic patients, initial combo therapy, until patient is improving and susceptibilities are known?
  – 10-14 days total therapy for bacteremic patients
    • Not supported by high quality evidence
Case resolution

• 70yo male with bacteremic pneumococcal CAP
• Converted to moxifloxacin to complete a 14-day antibiotic course
Conclusions

• We know less than we would like to regarding optimal duration of antibiotic therapy, even for common bacterial infections

• In general, shorter durations of antibiotic therapy are as effective as longer ones

• Once your patient is doing better, it may be time to stop