MAKING THE CASE:
LIMITING ANTIBIOTIC TREATMENT DURATIONS

Disclosure
I do not have any relevant financial relationships with any commercial interests.

Learning Objectives
Discuss the potential benefit of reducing the length of antibiotic courses on antimicrobial resistance
Review clinical data and/or treatment guidelines that support shorter courses of antibiotic therapy
Identify opportunities for antimicrobial stewardship intervention to optimize durations of therapy
Explore potential outcomes and benefits of shorter antibiotic durations on the healthcare system

Antimicrobial Resistance
The ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive
A serious global threat that affects almost every bacterial species
Dynamics of antibiotic resistance are dependent on the host, environment, drug, and disease

How does antimicrobial use drive resistance development?

a. Reduces the rate of bacteria eradication
b. Selects for resistant mutant subpopulations
c. Induces enzymes that degrade antibiotics
d. A and B
e. B and C

Resistance Development
Antibiotic resistance can arise in several ways:
- Selection of pre-existing, resistant mutants occurring as minority subpopulations
- Selection of random or induced mutations
- Acquisition of resistant determinants (i.e. plasmids, phages, mosaic genes, transposons, transformation)
- Clonal spread of a pre-existing transmissible, resistant isolate
- Induction in the presence of an inducer (i.e. β-lactams)

Misuse and overuse of antimicrobials can accelerate this process
**Target: Antimicrobial Exposure**

Reduces selective pressure and rate of resistance development

Antimicrobial selective pressure can be reduced at three points:

- Before therapy begins – optimizing empiric prescribing
- During therapy – reducing the number and spectrum of antimicrobials
- At the end of therapy – limiting treatment durations

Timely initiation of antimicrobial therapy and encouragement of broad spectrum empiric coverage limits intervention

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**Community Acquired Pneumonia**

IDSA/ATS Guidelines recommend that patients with CAP should be treated for a minimum of 5 days.

Recommendations largely based on empiric therapy

Most patients clinically stable by 3 – 7 days

Longer durations of therapy rarely necessary

Exceptions:

- Pseudomonas aeruginosa
- Burkholderia pseudomallei
- Endemic fungi

Criteria for clinical stability defined as temperature ≤ 99.5°F, heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, arterial oxygen saturation ≥90% or PaO2 ≥ 60 mm Hg on room air, ability to maintain oral intake, and normal mental status

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**High-Dose, Short-Course Levofloxacin for CAP**

**Study Design:** Randomized, double-blind, active treatment-controlled, noninferiority study

**Study Population:** ≥18 years of age with mild to severe CAP and radiographic evidence of acute PNA

**Intervention:** Levofloxacin 750 mg/day IV/PO for 5 days versus levofloxacin 500 mg/day IV/PO for 10 days

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**Additional RCTs on Antimicrobial Duration in CAP**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Dose, Short-Course Levofloxacin</td>
<td>≥18 years of age with mild to severe CAP and radiographic evidence of acute PNA</td>
<td>Noninferiority demonstrated for high-dose, short-course levofloxacin compared to standard-dose, extended-duration regimen.</td>
</tr>
<tr>
<td>A more recent look...</td>
<td>Enrolled 312 patients age ≥18 years diagnosed with CAP at 4 teaching hospitals in Spain</td>
<td>Randomized at day 5 to intervention or control group</td>
</tr>
</tbody>
</table>
If recommended treatment durations are evidence-based and guideline driven they should not be modified to extend the duration of use.

a. True  
b. False

Extending Treatment Durations - CAP

6% - 15% of hospitalized patients with CAP do not respond to initial antibiotic therapy

Treatment failure should be considered with failure to improve, clinical deterioration or pneumonia progression, and/or nonresponse

Longer durations of therapy warranted in the following cases:
- Initial therapy not active against the isolated pathogen
- Extrapulmonary infection identified (e.g., meningitis or endocarditis).
- Pneumonia caused by *P. aeruginosa*, *S. aureus*, or *Legionella* spp or pneumonia caused by some unusual and less common pathogens (e.g. *B. bronchiseptica*, *fungus*).
- Necrotizing pneumonia, empyema, or lung abscess

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

IDSA/ATS guidelines recommend a 7 day treatment course for patients with HAP/VAP

Conventional treatment typically 14 – 21 days and is largely empirical

Concern for MDR pathogens and increased risk of relapse with shorter treatment courses

Comparison of 8 vs 15 days in VAP

Study Design:
Randomized, double-blind trial among two parallel groups in 51 ICUs in France conducted between May 1999 and June 2002

Study population:
≥18 years with clinical suspicion for VAP and positive quantitative cultures initiated on appropriate empiric antibiotics therapy within 24 hours of bronchoscopy (N=402)

Intervention:
Treatment duration of 8 vs 15 days with antibiotic selection at prescribers discretion

Primary Outcomes

<table>
<thead>
<tr>
<th>Treatment Duration</th>
<th>Probability of Survival</th>
<th>Days After Bronchoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-Day Antibiotic Regimen</td>
<td>0.03</td>
<td>0</td>
</tr>
<tr>
<td>15-Day Antibiotic Regimen</td>
<td>0.02</td>
<td>5</td>
</tr>
</tbody>
</table>

Probability of Survival

No. at Risk | 8-Day Antibiotic Regimen | 197 | 190 | 183 | 176 | 169 | 162 |
| 15-Day Antibiotic Regimen | 204 | 197 | 190 | 183 | 176 | 169 |
Short-course versus prolonged-course antibiotic therapy in HAP

Meta-analysis of RCTs assessing a fixed 'short' duration of antibiotic therapy with a 'prolonged' course for HAP (including patients with VAP) in critically ill adults

Six relevant studies involving 1088 participants

Primary outcomes:
- 28-day mortality
- Recurrence of pneumonia (diagnosed on the basis of clinical and/or microbiological criteria)
- 28-day antibiotic-free days.

Recurrence of Pneumonia

Uncomplicated Cystitis

One of the most common indications for antimicrobial use

Numerous clinical studies supporting limited durations of therapy

Optimal agent and treatment duration dependent on multiple factors (i.e. allergy history, local resistance patterns, availability)

Treatment Regimens and Expected Early Efficacy Rates:

<table>
<thead>
<tr>
<th>Drug (dose)</th>
<th>Estimated clinical efficacy</th>
<th>Estimated microbiological efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin monohydrate/macrocystals (100 mg twice daily for 5–7 days)</td>
<td>93 (84-95)</td>
<td>88 (86-92)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (160/800 mg twice daily for 3 days)</td>
<td>93 (90-100)</td>
<td>94 (91-100)</td>
</tr>
<tr>
<td>Fosfomycin trometamol (3 g single-dose sachet)</td>
<td>91</td>
<td>80 (78-83)</td>
</tr>
<tr>
<td>Fluoroquinolones (dose varies by agent; 3-day regimen)</td>
<td>90 (85-98)</td>
<td>91 (81-98)</td>
</tr>
<tr>
<td>β-lactams (dose varies by agent; 3 – 5 day regimen)</td>
<td>89 (79-98)</td>
<td>82 (74-98)</td>
</tr>
</tbody>
</table>

Acute Uncomplicated Pyelonephritis – 7 Days vs 14 Days

Study Design:
Randomized, double-blind comparative trial of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days)

Patient Population:
Women aged ≥18 years with clinical diagnosis of acute uncomplicated pyelonephritis

Primary Outcomes:
Study drug efficacy based on continued bacteriologic and clinical cure
**Continued Bacteriologic and Clinical Cure Rates**

[Graph showing cure rates over time for different antibiotics.]

**Acute Uncomplicated Pyelonephritis**

RCTs on Antimicrobial Duration in Acute Pyelonephritis:

CID 2011; 52: 1232 - 1240

**Intra-abdominal Infection**

Previous guidelines recommended a duration of therapy no greater than 1 week with adequate source control.

Typical durations of 7 – 14 days observed in clinical practice.

Ability to shorten therapy limited by 20% rate of clinically significant infectious complications after treatment.

SIS-IDSA guidelines recommendation that antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control.

**Short-Course Antimicrobial Therapy for Intra-abdominal Infection**

Study design:
Open-label, multi-center trial comparing fixed-duration antibiotic therapy (4 days) after source control to antimicrobial therapy until 2 days after the resolution of SIRS.

Study population:
≥16 years old with complicated intra-abdominal infection and adequate source control.

Primary outcome:
A composite of surgical-site infection, recurrent intra-abdominal infection, or death within 30 days after the index source-control procedure.

**Primary Outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n=240)</th>
<th>Experimental Group (n=247)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: surgical-site infection, recurrent intra-abdominal infection, or death</td>
<td>Name of values</td>
<td>Name of values</td>
<td>0.12</td>
</tr>
<tr>
<td>Surgical-site infection</td>
<td>23 (9.6)</td>
<td>17 (6.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>Recurrent intra-abdominal infection</td>
<td>24 (10.4)</td>
<td>49 (19.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>Death</td>
<td>3 (0.8)</td>
<td>3 (1.2)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Time to event — rel. of days after index source-control procedure:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Rel. Number of Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical-site infection</td>
<td>103 (4.2)</td>
</tr>
<tr>
<td>Recurrent intra-abdominal infection</td>
<td>103 (4.2)</td>
</tr>
<tr>
<td>Death</td>
<td>190 (7.8)</td>
</tr>
</tbody>
</table>

**Kaplan-Meier Time-to-Event Curves for Composite Primary Outcome**

[Graph showing Kaplan-Meier curves for control and experimental groups.]
Limiting Antimicrobial Treatment Durations in Clinical Practice

Direct Feedback

Education
- Increases knowledge of evidence-based guideline recommendations
- Supports multi-disciplinary antimicrobial stewardship initiatives

Post-prescription antibiotic review
- Opportunity to provide real-time, case specific recommendations
- One-on-one education of prescribers

Antibiotic time out
- Opportunity to reassess antimicrobial therapy at 48 – 72 hours
- Ability to establish treatment durations and order stop dates for active antimicrobial therapy

Treatment Duration Guidelines

An educational tool used to summarize treatment duration recommendations for key indications
Serves as a quick reference and guide for prescribers and pharmacists; format varies
Should present recommendations which are evidence-based and developed with consensus from Infectious Disease Specialists (if possible)

Incorporation Into the EMR

Ability in multiple EMR platforms to pre-select or pre-specify treatment durations based on indication

Outcome Measures

Clinical
- Length of stay
- Clinical cure/failure rates
- Hospital readmission rates
- Infection-related mortality

Process
- Dose optimization
- Adherence to hospital specific guidelines
- Appropriate de-escalation/streamlining
- Appropriateness of therapy

Humanistic
- Adverse drug events avoided
- Time to receipt of appropriate antimicrobials
- Duration of intravenous therapy
- IV/PO conversion rates
- Outpatient intravenous therapy rates

Economic
- Antibiotic utilization
- Hospital-wide antibiotic expenditures
- Hospitalization rates
- Rate of intravenous antimicrobial use
- Antibiotic use avoided
Summary

Misuse and overuse of antimicrobials can increase antimicrobial resistance development.
Antimicrobial treatment duration is a feasible target to reduce overall antimicrobial exposure.
Clinical evidence supports shorter antimicrobial treatment courses for a number of common infectious diseases.
Limiting treatment durations in clinical practice can potentially improve key outcome measures.

Questions?

“Antibiotic resistance: no action today, no cure tomorrow.”