Antimicrobial Stewardship in Ambulatory Care
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Dr. Suntharam indicated no potential conflict of interest to this presentation. She does not intend to discuss any unapproved/investigative use of a commercial product/device.

What is Antimicrobial Stewardship?
Antimicrobial Stewardship

• “Stewardship is a commitment to always use antibiotics only when they are necessary to treat, and in some cases prevent, disease; to choose the right antibiotics; and to administer them in the right way in every case. Effective stewardship ensures that every patient gets the maximum benefit from the antibiotics, avoids unnecessary harm from allergic reactions and side effects, and helps preserve the life-saving potential of these drugs for the future.”

• CDC.gov

“The public will demand (the drug and ). then will begin an era of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed on to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin resistant organism. I hope the evil can be averted.”

Alexander Fleming 1946 - in reference to PCN, the drug he discovered
Operational Goals of Antimicrobial Therapy and Stewardship? The 5 (6?) Ds

• **Right Diagnosis**
  – First, is this even an infection? Infiltrates on CXR do not immediately mean a pneumonia, erythematous legs do not automatically mean cellulitis
  – Have you collected necessary cultures?

• **Right Drug**
  – Effective, narrow spectrum, minimal side effects
  – Least costly

3. **Right Dose**
   - Dose appropriately for renal function

4. **Right Duration:**
   – Minimal duration - undefined for many indications but recent evidence supports shorter courses

5. **Right De-escalation:** change to narrowest-spectrum/safest/least expensive regimen when:
   – Justified by culture results (positive or negative)
   – Clinical improvement (e.g., IV to PO switch)

6. **Right Debridement or source control**

Slides courtesy of Rebecca Pegelow MD. Healthpartners
## What are the Goals of Antimicrobial Stewardship? Why do we care?

1. Reduce antibiotic consumption and inappropriate use
2. Reduce Clostridium difficile infections
3. Improve patient outcomes
4. Increase the utilization of treatment guidelines
5. Reduce adverse drug events
6. Decrease or limit antimicrobial resistance
7. Reducing cost without adversely affecting patient outcome

Cosgrove S. Inf Dis Clinics N.America 2011 p 245

## Antimicrobial Overuse

- 30% of outpatient antimicrobial therapy is unnecessary
- 20-50% of inpatient antimicrobial therapy is either unnecessary or inappropriate
- Much of the antimicrobial use in animals is inappropriate.

[cdc.gov/get smart](https://www.cdc.gov/getsmart)
Pharmaceutical Companies and Antimicrobials

- Development of new antimicrobials have stalled due to economic and regulatory issues
- A majority of pharmaceutical companies have left the antibiotic field
- Bartlett, J. Clin Infect Dis 2013 p 1445  Seven Ways to Preserve the Miracle of Antibiotics
WHO today published its first ever list of antibiotic-resistant "priority pathogens" – a catalogue of 12 families of bacteria that pose the greatest threat to human health.

The list was drawn up in a bid to guide and promote research and development (R&D) of new antibiotics, as part of WHO’s efforts to address growing global resistance to antimicrobial medicines.

Top reasons for antimicrobial prescriptions in ambulatory settings (including ER)

- URI (40%)
- Skin/soft tissue infections (20%)
- UTI (10%)
- Antibiotics were prescribed in 10% of visits
- Quinolones (25%), macrolides (20%), pcn (12%)


AMS in Ambulatory Care

1. Where to start with treatment of pneumonia?
2. Quinolone use in the outpatient setting
3. Appropriate use of azithromycin in the outpatient setting
Pneumonia

- Published studies indicate that viral etiologies account for 11-55% of Community Acquired Pneumonia (CAP)
- 50% of antibiotics given in ER for acute RTIs (Respiratory Tract Infections) are for nonbacterial cases.
- Ghazi, Infection Control and Hospital Epi 2016

Treatment of CAP (Community Acquired Pneumonia)

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

EXECUTIVE SUMMARY

Intensive care is a cornerstone of hospital care, and substantial overlap exists among the patients whom
Definitions

- CAP - Community Acquired Pneumonia
- HCAP - Healthcare Associated Pneumonia

Patients from community potentially at higher risk for MDR (multidrug resistant organisms). Patients have been from nursing home, on hemodialysis, visiting outpatient infusion center. **HCAP is a term no longer used in the recently updated guidelines**

Microbiology of CAP

- Majority of time, no pathogen is identified
- If patient is being treated as outpatient, it is considered optional to obtain further testing such as sputum, blood cultures and urinary antigen testing (legionella and streptococcus pneumonia antigen)
Microbiology of CAP

- Ask about travel (within the US and abroad)
- Be aware of local outbreaks (for example, there was a legionella outbreak in the Hopkins area in 2015)
- Is it influenza season? S. pneumoniae and S. aureus infections can occur post influenza as well

### Table 6. Most common etiologies of community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Respiratory viruses</em></td>
</tr>
</tbody>
</table>

Viruses: Influenza A and B, adenovirus, Respiratory syncytial virus and parainfluenza
Microbiology of CAP

### Empiric Therapy

**Table 7. Recommended empirical antibiotics for community-acquired pneumonia.**

- **Outpatient treatment**
  1. Previously healthy and no use of antimicrobials within the previous 3 months
     - A macrolide (strong recommendation; level I evidence)
     - Doxycycline (weak recommendation; level III evidence)
  2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
     - A respiratory fluoroquinolone (ofloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
     - A β-lactam plus a macrolide (strong recommendation; level I evidence)
  3. In regions with a high rate (>25%) of infection with high-level (MIC >16 μg/mL) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation; level III evidence)
CAP Treatment

• Duration of Therapy for CAP: 5 to 7 days of therapy. 5 days should be adequate in most cases of outpatient therapy. 3 days an option if using azithromycin 500mg po daily.
• Be aware of S.pneumoniae macrolide drug resistance which is over 25% in the US

CAP Treatment

• Minnesota Department of Health antibiogram
• S.pneumoniae
tetracycline (doxycycline) – 90% sensitive
erythromycin (azithromycin) -65% sensitive
levofloxacin- 100% sensitive
AMS in Ambulatory Care

- Where to start with treatment of pneumonia?
- Quinolone use in the outpatient setting
- Appropriate use of azithromycin in the outpatient setting
Quinolones in the Outpatient Setting

• FDA warning 2016

Safety Announcement
• [05-12-2016] The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.
  • https://www.fda.gov/Drugs/DrugSafety/ucm500143.htm

Quinolones in the Outpatient Setting

• QT prolongation
• Association with Clostridium difficile
• Tendonitis/tendon rupture
• CNS: HA, confusion, dizziness
Quinolone Use in the Outpatient Setting

Urinary Tract

- UTI. Nitrofurantoin 100mg po bid for 5 days, cephalexin 500mg po bid for 7 days, trimethoprim-sulfa (Bactrim DS )for 3 days, Cipro 250 bid for 3 days
- Prostatitis. Quinolones and Trimethoprim with good prostate penetration
- IDSA Cystitis Guidelines

Respiratory

- Sinusitis. Most etiologies are viral.
- Bronchitis. Most etiologies are viral
- Pneumonia. Alternative options available

Skin/Soft Tissue

- Cellulitis. Most cases due to S.aureus or Streptococcus. Would not use quinolones as beta lactams and clindamycin would provide better coverage.
What are the organisms involved with rhinosinusitis?

<table>
<thead>
<tr>
<th>Microbial Agent</th>
<th>Publications Before 2000</th>
<th>Publications in 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults (%)</td>
<td>Children (%)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2-3</td>
<td>13</td>
</tr>
<tr>
<td>Staphylococcus pyogenes</td>
<td>2-7</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>2-7</td>
<td>2</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>2-3</td>
<td>13</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2-10</td>
<td>16</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>2-10</td>
<td>16</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>31-35</td>
<td>36</td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>31-35</td>
<td>36</td>
</tr>
<tr>
<td>Staphylococcus pneumonia</td>
<td>30-43</td>
<td>44</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2-3</td>
<td>13</td>
</tr>
<tr>
<td>Gram-negative bacilli (includes</td>
<td>6-24</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacteriaceae spp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes ( Fusobacterium,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus spp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>3-15</td>
<td>30</td>
</tr>
<tr>
<td>No growth</td>
<td>40-50</td>
<td>30</td>
</tr>
</tbody>
</table>

* Data compiled from [87-89].
* Data compiled from [81, 90].
* Data from [46].
* Data extrapolated from middle ear fluid of children with acute otitis media [81, 90].
Recommended Therapy for Sinusitis

Table 10. Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Adults

<table>
<thead>
<tr>
<th>Indication</th>
<th>First-line (Daily Dose)</th>
<th>Second-line (Daily Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial empirical therapy</td>
<td>Amoxicillin-clavulanate (500 mg/125 mg PO tid, or 875 mg/125 mg PO bid)</td>
<td>Amoxicillin-clavulanate (2000 mg/125 mg PO bid)</td>
</tr>
<tr>
<td>Ectomycorrhizal allergy</td>
<td>Doxycycline (100 mg PO bid or 200 mg PO qd)</td>
<td>Doxycycline (100 mg PO bid or 200 mg PO qd)</td>
</tr>
<tr>
<td>Risk for antibiotic resistance or failed initial therapy</td>
<td>Levofloxacin (500 mg PO qd)</td>
<td>Levofloxacin (500 mg PO qd)</td>
</tr>
<tr>
<td>Severe infection requiring hospitalization</td>
<td>Ampicillin-sulbactam (1.5-3 g IV every 6 h)</td>
<td>Ampicillin-sulbactam (1.5-3 g IV every 6 h)</td>
</tr>
<tr>
<td>Abbreviations: bid, twice daily; IV, intravenously; PO, orally; qd, daily; tid, 3 times a day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IDSA guidelines Sinusitis 2012

Bronchitis

- Self limited bronchial inflammation. Majority caused by viruses
- 60-90% who seek medical care are given antibiotics
- Etiology: influenza, parainfluenza, coronavirus, rhinovirus, RSV, metapneumovirus
- Bacterial (rare): mycoplasma, chlamydia pneumonia, bordetella pertussis
  - JAMA 1997 Gonzalez
AMS in Ambulatory Care

• Where to start with treatment of pneumonia?
• Quinolone use in the outpatient setting
• Appropriate use of azithromycin in the outpatient setting

Azithromycin

• Macrolide. Derivative of erythromycin
• Azithromycin, Clarithromycin
• Bind to 50s ribosomal unit of bacteria and inhibit protein synthesis
• Macrolides do have anti-inflammatory effects
• QT prolongation
Azithromycin- CAP

• Despite high rates in vitro of *S*. *pneumoniae* resistance, combination therapy with macrolide has been shown to be of benefit in CAP due to *S*. *pneumoniae*
• Provides atypical pneumonia coverage

Azithromycin- Sinusitis

• Not recommended for sinusitis due to resistance noted with *S*. *pneumoniae* (30% in 2006, 5% in 1993) Highest resistance noted among children

• IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults 2012
Azithromycin – Group A Streptococcal Pharyngitis

- Azithromycin
  500mg once and 250mg on day 2-5
  500mg day 1-5
  500mg day 1-3
- MDH Antibiogram – erythromycin 90% susceptible

Azithromycin - COPD exacerbation

- Antibiotics indication if moderate or severe exacerbation of COPD (2/3 symptoms of increased sputum volume and purulence, DOE)
- Uncomplicated COPD - <65 years, FEV1 >50% predicted, <2 exacerbations/year, no cardiac disease
- Azithromycin 500mg for 3 days
### Adult Treatment Recommendations

Antibiotic prescribing guidelines establish standards of care and focus quality improvement efforts. The table below summarizes the most recent recommendations for appropriate antibiotic prescribing for adults seeking care in an outpatient setting.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
</table>
| Acute rhinosinusitis | • About 1 in 40 adults (12%) in 2012 reported receiving a diagnosis of rhinosinusitis in the previous 12 months, resulting in more than 30 million diagnoses.  
• Ninety-nine percent of rhinosinusitis cases are viral, and antibiotics are not recommended to help even if the causative agent is bacterial. | • Diagnose acute bacterial rhinosinusitis based on symptoms that are:  
  - Severe (>3-4 days), such as a fever >39°C (102°F) and purulent nasal discharge or facial pain;  
  - Persistent (>10 days) without improvement, such as nasal discharge or daytime cough; or  
  - Worsening (3-4 days) such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement of a viral upper respiratory infection (URI) lasting 3-4 days.  
• Sinus radiographs are not routinely recommended. | • If a bacterial infection is established:  
  - Watchful waiting is encouraged for uncomplicated cases for which reliable follow-up is available.  
  - Amoxicillin or amoxicillin/clavulanate is the recommended first-line therapy.  
  - Macrolides such as azithromycin are not recommended due to high levels of Streptococcus pneumoniae antibiotic resistance (>40%).  
  - For penicillin-allergic patients, doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) are recommended as alternative agents. |
| Acute uncomplicated bronchitis | • Cough is the most common symptom for which adult patients visit their primary care providers, and acute bronchitis is the most common diagnosis in these patients. | • Evaluation should focus on ruling out pneumonia, which is rare among otherwise healthy adults in the absence of abnormal vital signs (heart rate ≥ 100 beats/min, respiratory rate ≥ 24 breaths/min, or oral temperature ≥ 38°C) and abnormal lung examination findings (focal consolidation, egophony, fremitus).  
• Cough sounds do not indicate bacterial infection.  
• For most cases, chest radiography is not indicated.  
• Premature cold symptoms include fever, cough, rhinorrhea, nasal congestion, postnasal drip, sore throat, headache, and myalgias. | • Routine treatment of uncomplicated acute bronchitis with antibiotics is not recommended, regardless of cough duration.  
• Options for symptomatic therapy include:  
  - Cough suppressants (codeine, dextromethorphan);  
  - Fast-acting antitussives (diphenhydramine);  
  - Decongestants (phenylephrine); and  
  - Beta agonists (salbutamol).  
• Decongestants (pseudoephedrine and phenylephrine) combined with a first-generation antihistamine may provide short-term symptom relief of nasal symptoms and cough.  
• Non-stEROidal anti-inflammatory drugs can be given to relieve symptoms.  
• Evidence is lacking to support antibiotics (as monotherapy), steroids, intranasal corticosteroids, and nasal saline irrigation as effective treatments for cold symptom relief.  
• Providers and patients must weigh the benefits and harms of symptomatic therapy. |
| Common cold or non-specific upper respiratory tract infection (URI) | • The common cold is the third most frequent diagnosis in office visits, and most adults experience two to four colds annually.  
• At least 200 viruses can cause the common cold. | • Clinical features alone do not distinguish between GAS and viral pharyngitis; a rapid antigen detection test (RADT) is necessary to establish a GAS pharyngitis diagnosis.  
• Those who meet two or more Centers criteria (e.g., fever, tender lymph nodes, tender cervical lymphadenopathy, absence of cough) should receive a RADT.  
• Throat cultures are not routinely recommended for adults. | • Antibiotic treatment is NOT recommended for patients with negative RADT results.  
• Amoxicillin and penicillin V remain first-line therapy due to their reliable antibiotic activity against GAS.  
• For penicillin-allergic patients, erythromycin, azithromycin, and clarithromycin are recommended.  
• GAS antibiotic resistance to azithromycin and clarithromycin is increasingly common.  
• Recommended treatment course for all oral beta lactams is 10 days. |
| Pharyngitis | • Group A beta hemolytic streptococcal (GAS) infection is the only common indication for antibiotic therapy for sore throat cases.  
• Only 5–10% of adult sore throat cases are caused by GAS. | • Antibiotic treatment is NOT recommended for patients with negative RADT results.  
• Amoxicillin and penicillin V remain first-line therapy due to their reliable antibiotic activity against GAS.  
• For penicillin-allergic patients, erythromycin, azithromycin, and clarithromycin are recommended.  
• GAS antibiotic resistance to azithromycin and clarithromycin is increasingly common.  
• Recommended treatment course for all oral beta lactams is 10 days. |

### Acute uncomplicated cystitis

| Cystitis is among the most common infections in women and is usually caused by E. coli. | Classic symptoms include dysuria, frequent voiding of small volume, and urinary urgency. Hematuria and suprapubic discomfort are less common.  
• Nitrites and leukocyte esterase are the most accurate indicators of acute uncomplicated cystitis | For acute uncomplicated cystitis in healthy adult non-pregnant, premenopausal women:  
• Nitrofurantoin, trimethoprim/sulfamethoxazole (TMP-SMX, where local resistance is <20%), and fosfomycin are appropriate first-line agents.  
• Fluoroquinolones (e.g., ciprofloxacin) should be reserved for situations in which other agents are not appropriate. |