Improving Antimicrobial Therapy in Elders

Margo Schilling MD
April 2, 2014
41st
Annual Family Physician Refresher Course
Objectives

- Distinguish between symptomatic UTI and asymptomatic bacteriuria in older adults, and apply this distinction to reduce unnecessary antibiotic use.
- Estimate risk of antibiotic resistant pathogens in pneumonia in nursing home residents and identify prescribing practices for pneumonia that may contribute to unnecessary antibiotic exposure.
- Describe measures to prevent outbreaks and reduce risk of C. difficile infection in LCTFs.
- Discuss criteria to reduce the risk of antibiotic associated adverse events in elders.
### Urinalysis Chemistry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Yellow</td>
</tr>
<tr>
<td>Appearance</td>
<td>Nary</td>
</tr>
<tr>
<td>Glucose</td>
<td>Negative</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Negative</td>
</tr>
<tr>
<td>Ketones</td>
<td>Negative</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.026</td>
</tr>
<tr>
<td>Blood</td>
<td>Trace</td>
</tr>
<tr>
<td>pH</td>
<td>5.5</td>
</tr>
<tr>
<td>Protein</td>
<td>Trace</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>0.2</td>
</tr>
<tr>
<td>Nitrites</td>
<td>Negative</td>
</tr>
<tr>
<td>Leuk Est</td>
<td></td>
</tr>
</tbody>
</table>

### Urine Microscopic

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>None</td>
</tr>
<tr>
<td>Bacteria</td>
<td>None</td>
</tr>
<tr>
<td>RBC</td>
<td>None</td>
</tr>
<tr>
<td>RBC Cells</td>
<td>Rare</td>
</tr>
<tr>
<td>Mucous</td>
<td>None</td>
</tr>
<tr>
<td>Cytokines Cast</td>
<td>0 to 2</td>
</tr>
<tr>
<td>Yeast</td>
<td>2+</td>
</tr>
</tbody>
</table>

### Urine Culture

- **Set Up:** 03/28/2009 1040
- **Signature:** Description
- **Special Requests:**
  - Colony Count
  - Culture

**Report Status:** Pending
American Geriatrics Society Identifies Five Things That Healthcare Providers and Patients Should Question

#4. Do not use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.

- AGS Choosing Wisely Workgroup

## Prevalence of Asymptomatic Bacteriuria in Older Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community</td>
<td>9-33</td>
<td>2.4-13</td>
</tr>
<tr>
<td>Institutionalized</td>
<td>17-55</td>
<td>15-37</td>
</tr>
</tbody>
</table>

Yoshikawa, 1996
Reasons to avoid antibiotic treatment of asymptomatic bacteriuria

- Doesn’t reduce mortality
- NNH=3\(^1\)
- Increased antibiotic resistance

## Prospective randomized studies of treatment of asymptomatic bacteriuria

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicolle et al, NEJM 1983</td>
<td>36 Men &gt; 80 yr NH residents</td>
<td>Randomized to abx vs none. Duration 2 years</td>
<td>No difference in: Mortality Infectious morbidity</td>
</tr>
<tr>
<td>Nicolle et al, Am J Med 1987</td>
<td>50 women 83 yr NH residents</td>
<td>Randomized to abx vs none Duration 1 year</td>
<td>No difference in: Mortality GU morbidity Increased AE and resistance in treated group</td>
</tr>
<tr>
<td>Abrutyn et al, Ann Intern Med 1994</td>
<td>358 women, 82 yr Apartment and NH</td>
<td>Randomized to abx vs none Duration 8 years</td>
<td>No survival benefit in treatment group</td>
</tr>
<tr>
<td>Ouslander et al, Ann Intern Med 1995</td>
<td>71 women and men 85 yr NH</td>
<td>Randomized to abx vs placebo 4 weeks</td>
<td>No difference in chronic urinary inc symptoms</td>
</tr>
</tbody>
</table>

Juthani-Mehta M. *Clin Geriatr Med, 2007*
Clinical symptoms of UTI

- Frequency
- Urgency
- Dysuria
- New incontinence
- CVA or suprapubic tenderness
Altered clinical presentation of infection in older persons

- Blunted fever response (1/3 without fever)
- Mental status changes (acute)
- Anorexia, malaise, weakness (new)
- Falls (acute)
- Incontinence (new)
- Functional decline (change)
Clinical features in NH residents attributed to “suspected UTI”

- Prospective cohort study in women and men
- 5 Connecticut nursing homes
- Clinically “suspected UTI”
  - Staff responses (symptoms)
  - Urinalysis/urine culture
- Multivariable regression model

Clinical features in NH residents attributed to “suspected UTI”

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in mental status</td>
<td>156 (39.1%)</td>
</tr>
<tr>
<td>Change in behavior</td>
<td>76 (19.0%)</td>
</tr>
<tr>
<td>Change in character of urine</td>
<td>62 (15.5%)</td>
</tr>
<tr>
<td>Fever or chills</td>
<td>51 (12.8%)</td>
</tr>
<tr>
<td>Change in gait or fall</td>
<td>35 (8.8%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>31 (7.8%)</td>
</tr>
<tr>
<td>Change in voiding pattern</td>
<td>28 (7.0%)</td>
</tr>
<tr>
<td>Flank pain</td>
<td>23 (5.8%)</td>
</tr>
<tr>
<td>Patient or family request</td>
<td>15 (3.8%)</td>
</tr>
<tr>
<td>Change in functional status</td>
<td>10 (2.5%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>5 (1.3%)</td>
</tr>
</tbody>
</table>

Clinical features in NH residents attributed to “suspected UTI”

- 399 “suspected UTI” episodes
  - 240/551 subjects with at least one “suspected UTI”
- Majority had negative UA ($<10$ WBC, $<10^5$ cfu)
  - 252/399 (63%)
- Absence of dysuria identified subjects at low risk for abnormal UA
Clinical features in NH residents attributed to “suspected UTI”

- Conclusions
  - Staff are indiscriminant in diagnosing UTI when clinical deterioration is identified in NH residents.
  - A wide spectrum of nonspecific clinical symptoms are misinterpreted as UTI.
  - Alternate diagnoses are likely overlooked.

Minimum criteria for initiation of empiric antibiotics for UTI in LTCF

- **UTI with no catheter**
  - Acute dysuria or
  - Fever and one GU symptom
    - New urgency, frequency, suprapubic pain, gross hematuria, CVA tenderness or urinary incontinence

- **UTI with catheter**
  - One symptom of:
    - Fever
    - CVA tenderness
    - Rigors
    - Delirium

Loeb M et al. *Infect Control Hosp Epidemiol*, 2001
Multifaceted intervention to reduce antimicrobial use for “suspected UTI” in LTCF


* Respiratory symptoms include increased shortness of breath, increased cough, increased sputum production, new pleuritic chest pain.
Gastrointestinal symptoms include nausea or vomiting, new abdominal pain, new onset of diarrhoea
Skin and soft tissue symptoms include new redness, warmth, swelling, purulent drainage
Multifaceted intervention to reduce antimicrobial use for “suspected UTI” in LTCF

Summary: UTI overdiagnosis and overtreatment

- UTI incorrectly diagnosed in 40% of hospitalized older adults\(^1\)
- “UTIs” account for 30-56% of antibiotic scripts written in nursing homes\(^2\)
- Adverse outcomes of overtreatment
  - Emerging antibiotic resistance
  - Increased prevalence of health-care associated \textit{C. difficile} infections

\(^1\)Woodford HJ et al. \textit{J Am Geriatr Soc.} 2009
\(^2\)Loeb et al. \textit{BMC Health Services Research.} 2002
Case 2
--83 year old NH resident with dementia.

--2 day history of fever, lethargy and recent fall in room.

--IPOST: IV antibiotics acceptable. May transfer to improve comfort.

--VS: 97.7-16-76-105/72. O2 sat 92% RA.
4. Use severity-of-illness scores:
CURB-65 criteria
(confusion, uremia, respiratory rate, low blood pressure, age >65 years)

or prognostic models:
Pneumonia Severity Index (PSI)

to identify patients with CAP who may be candidates for outpatient treatment. (Strong recommendation; level I evidence.)

Criteria for severe community-acquired pneumonia.

Minor criteria:
- Respiratory rate $\geq 30$ breaths/min
- $\text{PaO}_2/\text{FiO}_2$ ratio $\leq 250$
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level, $\geq 20$ mg/dL)
- Leukopenia (WBC count, $< 4000$ cells/mm$^3$)
- Thrombocytopenia (platelet count, $< 100,000$ cells/mm$^3$)
- Hypothermia (core temperature, $< 36^\circ\text{C}$)
- Hypotension requiring aggressive fluid resuscitation

Major criteria:
- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

**NOTE.** BUN, blood urea nitrogen; $\text{PaO}_2/\text{FiO}_2$, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

* Other criteria to consider include hypoglycemia (in non-diabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

* A need for noninvasive ventilation can substitute for a respiratory rate $>30$ breaths/min or a $\text{PaO}_2/\text{FiO}_2$ ratio $<250$.

* As a result of infection alone.

16. Presence of comorbidities
   chronic heart, lung, liver, renal disease, diabetes mellitus;
   immunosuppressing conditions or use of immunosuppressing drugs;
   use of antimicrobials within the previous 3 months
   other risks for drug resistant infection then treat with:

   A. Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)

   B. β-lactam **plus** a macrolide
      - High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-
        clavulanate [2 g 2 times daily] or
      - Ceftriaxone, cefpodoxime, and cefuroxime [500 mg 2 times daily];
      - Doxycycline [level II evidence] is an alternative to the macrolide.

Health care-associated pneumonia (HCAP) risk factors

- Hospitalization for more than 2 days in an acute care hospital in the last 90 days
- Residence in a skilled nursing facility
- Recent IV antibiotic therapy, chemotherapy, or wound care in the last 30 days
- Attending a hospital or hemodialysis clinic
- Immunosuppression

Antibiotics for empiric therapy of healthcare-associated pneumonia in patients with risk factors for multidrug-resistant pathogens

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipseudomonal cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1–2 g every 8–12 h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g every 8 h</td>
</tr>
<tr>
<td>Carabepenems</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg every 6 h or 1 g every 8 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g every 8 h</td>
</tr>
<tr>
<td>β-Lactam/β-lactamase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>4.5 g every 6 h</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7 mg/kg per d†</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7 mg/kg per d†</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20 mg/kg per d†</td>
</tr>
<tr>
<td>Antipseudomonal quinolones</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg every d</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg every 8 h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg every 12 h‡</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 h</td>
</tr>
</tbody>
</table>

Mean mortality rate is patients with pneumonia.
## Microbiology of pneumonia

<table>
<thead>
<tr>
<th>Pathogen, %</th>
<th>CAP</th>
<th>HCAP</th>
<th>HAP</th>
<th>VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>S aureus</td>
<td>25.5</td>
<td>46.7</td>
<td>47.1</td>
<td>42.5</td>
</tr>
<tr>
<td>MRSA</td>
<td>8.9</td>
<td>26.5</td>
<td>22.9</td>
<td>14.6</td>
</tr>
<tr>
<td>S pneumoniae</td>
<td>16.6</td>
<td>5.5</td>
<td>3.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>17.1</td>
<td>25.3</td>
<td>L18.4</td>
<td>21.2</td>
</tr>
</tbody>
</table>

From: Effect of a Clinical Pathway to Reduce Hospitalizations in Nursing Home Residents With Pneumonia: A Randomized Controlled Trial

Resident of Nursing Home With ≥2 of the Following Symptoms or Signs of Lower Respiratory Tract Infection:
- New or Increased Cough
- New or Increased Sputum Production
- Temperature >38°C
- Pleuritic Chest Pain
- New or Increased Abnormal Findings on Chest Examination

Obtain Mobile Chest Radiograph

Does the Resident Meet the Following Criteria?
- Ability to Eat and Drink
- Pulse ≤100/min
- Respiratory Rate <30/min
- Systolic Blood Pressure ≥90 mm Hg*
- Oxygen Saturation ≥92%†

Yes
- Treatment On-site in the Nursing Home
  - Levofloxacin 500 mg Orally for 10 Days
  - Hypodermoclysis to Treat Dehydration if Needed
  - Transfer to Hospital if No Longer Meets Criteria for Nursing Home Treatment

No
- Transfer to Hospital
  - Levofloxacin 500 mg Orally or Intravenously for 10 Days
  - Transfer Back to Nursing Home When Criteria for Nursing Home Treatment Met
Table 2. Summary of Weighted Outcome Variables and the Differences in 10 Clinical Pathway and 9 Usual Care Nursing Homes*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Weighted Mean (95% CI)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations, %†</td>
<td>8 (4 to 12)</td>
<td>20 (15 to 26)</td>
<td>12 (5 to 18)</td>
</tr>
<tr>
<td>Hospital days per resident</td>
<td>0.79 (0.45 to 1.13)</td>
<td>1.74 (1.17 to 2.3)</td>
<td>0.95 (0.34 to 1.55)</td>
</tr>
<tr>
<td>Visits to emergency department without admission, %</td>
<td>1.2 (−0.2 to 2.5)</td>
<td>1.6 (−0.6 to 3.8)</td>
<td>0.4 (−1.9 to 2.8)</td>
</tr>
<tr>
<td>Death, %</td>
<td>3.1 (−0.2 to 6.4)</td>
<td>6.0 (1.8 to 10.3)</td>
<td>2.9 (−2.0 to 7.9)</td>
</tr>
<tr>
<td>Change in quality of life from baseline</td>
<td>−0.032 (−0.044 to −0.019)</td>
<td>−0.037 (−0.050 to 0.023)</td>
<td>−0.005 (−0.022 to 0.012)</td>
</tr>
<tr>
<td>Change in functional status from baseline</td>
<td>−0.105 (−0.188 to −0.022)</td>
<td>−0.175 (−0.389 to 0.040)</td>
<td>−0.069 (−0.263 to 0.124)</td>
</tr>
<tr>
<td>Falls, %</td>
<td>10.9 (6.4 to 15.3)</td>
<td>9.5 (5.9 to 1.3)</td>
<td>−1.3 (−6.6 to 3.9)</td>
</tr>
<tr>
<td>Time to normalization of vital signs, d‡</td>
<td>2.55 (1.60 to 3.48)</td>
<td>2.66 (2.24 to 3.08)</td>
<td>0.12 (−0.78 to 1.02)</td>
</tr>
</tbody>
</table>

*No residents met eligibility criteria for enrollment in 1 usual care nursing home. Differences may not be exact due to rounding.
†Based on residents in whom complete 30-day follow-up was obtained (314 [96%] of the 327 residents in the clinical pathway group and 347 [98%] of the 353 residents in the usual care group). Rates of hospitalization in the clinical pathway group were 6 of 43 (14%), 4 of 26 (15%), 6 of 50 (12%), 1 of 21 (5%), 3 of 20 (15%), 1 of 33 (3%), 2 of 5 (40%), 6 of 37 (16%), 2 of 43 (5%), and 3 of 36 (8%) for residents in each of the 10 nursing homes; and in the usual care group, rates were 6 of 43 (14%), 14 of 43 (33%), 11 of 43 (26%), 7 of 36 (19%), 10 of 53 (19%), 2 of 24 (8%), 7 of 23 (30%), 8 of 30 (27%), and 11 of 52 (21%) for residents in each of the 9 nursing homes.
‡Defined as heart rate of 100/min or less, systolic blood pressure of at least 90 mm Hg, respiratory rate of 24/min or less, and temperature of 37.2°C or less.
Summary: Nursing home acquired pneumonia may be treated without hospitalization according to a clinical pathway.

- Broad-spectrum antibiotic therapy
  - Hospitalization within 90 days
  - Recent antibiotic therapy within the last 30 days
  - Severity of pneumonia
  - Immunosuppression
  - Poor functional status

- Appropriate monotherapy
  - Not seriously ill
  - No risk factors
Case 3
--90 year old NH resident with dementia complicated by behavior changes on 3rd course of quinolone for “UTI”

--Watery diarrhea, anorexia and recurrent fever

--VS 100.7-30-120-88/60.
C. difficile in LTCFs

- Prevalence 14.7%
- Incidence 0.2-2.6 per 1000 resident days
- Major risk for acquisition
  - Preceding antibiotic use
  - Functional disability
  - Gastrostomy feeding tube
  - Acid suppressant medications

C. difficile clinical features and complications

- Onset during or within 8 weeks of antibiotics
- Watery diarrhea, abdominal cramps, fever
- Fulminant pseudomembranous colitis may be life-threatening.
- 15-35% recurrence rate within 2 months
  - Relapse (same strain)
  - Recurrence (new strain)
C. difficile diagnosis and treatment

- Test for *C. diff* toxin only on diarrheal stool
- Do not test for cure
- Discontinue inciting antimicrobial agent as soon as possible
- Avoid use of antiperistaltic agents
- Metronidazole is the drug of choice for initial episode of mild-to-moderate CDI.
  - Metronidazole 500 mg TID for 10-14 days (mild, moderate disease)
  - Vancomycin 500 mg QID with or without IV metronidazole 500 mg q 8 hrs (severe, complicated CDI)
- Same regimen as for initial episode for first recurrence
  - Do not use metronidazole beyond first recurrence or for long-term chronic therapy
  - Vancomycin taper or pulse regimen (Second or later recurrence)

Measures to reduce Risk of C. difficile acquisition and transmission in LTCFs

- **Surveillance**
  - Test for toxin only on diarrheal specimens
  - Test should not be performed to identify asymptomatic carriers

- **Barrier precautions**
  - Private room/commode/dedicated patient care equipment
  - Hand hygiene with soap and water after glove removal

- **Environmental cleaning/disinfection**
  - Clean with diluted hypochlorite solution

- **Antimicrobial use and other measures**
  - Antibiotic stewardship programs
CDI and interventions to improve antibiotic prescribing

  - Restriction of clindamycin in hospital
  - 11.5 CDI cases/month vs. 3.33 cases/month P < .001
  - Incidence of CDI was increasing by 2.9 cases per quarter before restriction protocol.

CDI and interventions to improve antibiotic prescribing

  - Antimicrobial management team
    - Targeted 3rd gen cephalosporins and aztreonam
    - Stopped therapy after 2-3 days if no confirmed infection
    - Switched from IV to oral formulations
  - No impact on prevalence of VRE
  - No impact on prevalence of MRSA
  - Significant reduction in rate of CDI (P=.002)
  - Significant reduction in rate of antibiotic resistant GNRs

Fluoroquinolone resistant NAP1/BI/027 C. diff

- More severe disease, higher 14 day mortality.
- Two genetically distinct lineages
  - Identical mutation (Thr82Ile) in the DNA gyrase subunit A gene *gyrA*
  - High-level fluoroquinolone resistance
- Possible control with fluoroquinolone restriction

Figure 1. Rate of hospital-onset *Clostridium difficile* infection (CDI; dashed line), rate of hospital-onset CDI predicted from an interrupted time-series model (solid line), and percentage of *C. difficile* isolates recovered that were the epidemic strain (asterisks), January 2005-March 2007. A total of 61 isolates were tested during the outbreak period (June 2005-May 2006); 33, during the FQ-restriction period (June-Oct 2006); and 24, during the FQ-reinstitution period (Nov 2006-Mar 2007). FQ, fluoroquinolone.

<table>
<thead>
<tr>
<th>Anti-infective</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl &lt; 60 mL/min due to inadequate drug concentration in the urine</td>
<td>Avoid for long-term suppression; avoid in patients with CrCl &lt; 60 mL/min</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Azithromycin and the risk of cardiovascular death

2013 FDA warning

- Consider the risk of torsades de pointes and fatal arrhythmia when prescribing azithromycin or alternative antibacterial drugs. Groups at higher risk include:
  - Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure
  - Patients on drugs known to prolong the QT interval
  - Patients with hypokalemia or hypomagnesemia, clinically significant bradycardia, or receiving Class IA or Class III antiarrhythmic agents.
  - Elderly patients and patients with cardiac disease may be more susceptible to the effects of arrhythmogenic drugs on the QT interval.

- The potential risk of QT prolongation should be placed in appropriate context when choosing an antibacterial drug: Alternative drugs in the macrolide or fluoroquinolone drug classes also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.


