Golden Nuggets: Bugs, Drugs and Antibiotic Stewardship

Please logon to: www.ascp.com/ga and find the session title to submit your questions.

Pharmacist Learning Objectives

• Discuss methods for prevention, treatment of infection with best in class/new therapies, and prevention of drug resistance for use in the older adult.
• Identify novel strategies for therapeutics for infectious conditions and antibiotic stewardship.
• Describe medication strategies for prevention of bacterial resistance and best practices in antibiotic stewardship.
• List practice models for antibiotic stewardship and prevention of drug resistance in senior care practice settings.
Pharmacy Technician Learning Objectives

• List best in class and new therapies for use in the older adult.
• Identify novel therapeutic strategies for infectious conditions.
• Describe best practices in antibiotic stewardship for older adults.

Chair and Moderator

• Dr. Deborah Milito

• Disclosure: I have no actual or potential conflict of interest to this presentation. I have no financial relationships with regard to this presentation to disclose.
10/18/19

Topics and Speakers (Each talk is 15 minutes)

1. Bugs & Drugs for the Older Adult—Spencer Durham
2. Antibiotic Adverse Drug Events: Improving Patient Assessment and Management—Joshua Chou
3. New and Future Antibiotics in the Pipeline—Jonathan Cho

15 minute Q&A Session with first 3 speakers

4. Optimizing The Use Of Clinical Laboratory Values In Antimicrobial Stewardship—Nicholas Ladikos
5. Clostridioides difficile Infection in the Older Adult—Elias B. Chahine
6. Multi-Drug Resistant Organisms—Eddie Grace

15 minute Q&A Session with second 3 speakers

2019 ASCP Annual Meeting & Exhibition
Aged to Perfection
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Bugs & Drugs for the Older Adult

Spencer H. Durham, Pharm.D., BCPS, BCIDP
Associate Clinical Professor of Pharmacy Practice
Director, Alumni & Professional Affairs
Auburn University Harrison School of Pharmacy

2019 ASCP Annual Meeting & Exhibition
Aged to Perfection
November 7-10, 2019 | Grapevine, Texas
#ASCP50
Disclosure

I have no conflicts of interest to disclose.

Introduction

• “The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

  - Sir Alexander Fleming
Introduction

- Multidrug-resistant organisms (MDROs) are increasing at an alarming rate
- 2 million illnesses and 23,000 deaths associated with antibiotic-resistant bacteria annually
- Misuse of antimicrobial agents is the major contributing factor to disseminated resistance
- Up to 50% of antimicrobials prescribed in the outpatient, emergency, and acute care settings are unnecessary or inappropriate
- Up to 75% of antimicrobials in the long-term care setting are prescribed inappropriately

Introduction

- Older adults are at a high risk of infection with MDROs
- Immune system naturally weakens over time
  - Immunosenescence
- Have likely been exposed to many courses of antibiotics over time
- Comorbidities may predispose to acquiring certain infections
  - Examples: diabetes, COPD
- May be at higher risk for adverse effects associated with antimicrobial treatment
  - *C. difficile* infection
Introduction

• Antimicrobial therapy crosses into most, if not all, areas of pharmacy practice
• Many antibiotics are either unnecessary, or prescribed inappropriately, all of which may contribute to antimicrobial resistance
  • No indication for antibiotic therapy
  • Incorrect antibiotic for the disease
  • Incorrect dose, frequency or duration
• Limited development of new antibiotics, particularly novel antibiotics

Goals of Antimicrobial Therapy

• In general, ultimate goal is to eradicate the causative organism of infection
• Treat infection appropriately
  • Empiric therapy: target most likely pathogens for the disease state
  • Definitive therapy: use the least broad-spectrum, yet most appropriate, therapy to target the known pathogen
• Minimize the development of antimicrobial resistance
  • Use most narrow-spectrum, effective agent possible
  • Judicious overall use of antimicrobials
    • Example: Abx use for infections likely due to viral causes
Antimicrobial Considerations

- **Empiric therapy**
  - Broad-spectrum agent(s) with reliable coverage against the most likely causative pathogens

- **Definitive therapy**
  - Can generally only be done after obtaining culture and sensitivity results
  - May use other tests to guide therapy, such as PCRs

- **Duration of treatment**
  - Not well-defined, usually based on experience rather than evidence
  - Generally, 7-14 days for most infections

Antimicrobial Stewardship

- **SNAP approach to antimicrobial stewardship**
  - Safety, Need, Adequacy, Prudence

- **Step-by-step process to assess antimicrobial therapy** when antibiotics have already been prescribed

- If initially recommending an antibiotic, change to the NAPS approach
Antimicrobial Stewardship

• “S” – Safety
• Ask “is it safe for this patient to be receiving this antimicrobial?”
• Assessment of allergies
• Assess for likelihood of potential adverse drug reactions

Antimicrobial Stewardship

• “N” – Need
• Ask “Does this patient need antimicrobial therapy?”
  • Does the patient actually have an infection?
  • Is the infection likely to be:
    • Bacterial?
    • Viral?
    • Fungal?
Antimicrobial Stewardship

• “A” – Adequacy
  • Ask “Is the prescribed antimicrobial treating, or likely to treat, the infection?”
    • Is the antimicrobial a guideline recommended therapy?
    • Does the antimicrobial provide appropriate coverage against the pathogens most likely causing the infection?
    • Will the antimicrobial reach the site of infection?

• “P” – Prudence
  • Ask “Is this the most prudent drug to use for this infection?”
    • Is the drug the most-narrow spectrum agent that will adequately treat this infection?
  • This often cannot be fully assessed unless culture and susceptibility results are available
Self-Assessment Question #1

- D.B. is a 67-year-old male, permanent resident of a LTCF, who is admitted to the hospital for evaluation of difficulty breathing, 3 day history of fever, productive cough, night sweats, and chills
- Allergies: NKDA
- PMH: T2DM, HTN, dyslipidemia
- Meds: Metformin, glypizide, atorvastatin, lisinopril, HCTZ
- PE: BP-130/82; HR-90; RR-28; Temp 103.5°F
- Chest x-ray reveals bilateral infiltrates

What is the best recommendation for D.B. at this time?

A. Begin oral azithromycin 500 mg PO on day 1, then 250 mg on days 2-5
B. Do not begin antibiotics, infection is likely viral; supportive care only
C. Begin ciprofloxacin 500 mg IV BID
D. Begin ceftriaxone 2 grams IV once daily plus azithromycin 500 mg IV once daily
Self-Assessment Question #1

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Antibiotic Adverse Drug Events: Improving Patient Assessment and Management

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Geriatric Pharmacotherapy Fellow
Peter Lamy Center on Drug Therapy and Aging
University of Maryland School of Pharmacy
Disclosure

• I have no actual or potentially relevant financial relationship to disclose and no conflict of interest in relation to this activity.

• This work was supported by a Cooperative Agreement funded by the Centers for Disease Control and Prevention in collaboration with the Maryland Department of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the Centers for Disease Control and Prevention of the Department of Health and Human Services.

Why Focus on Antibiotic Adverse Drug Events (AADEs)?

• Protect the resident from future exposure to the AADEs
• Communicate findings with other health care clinicians to avoid future occurrences
• Comply with standards of practice
• Adhere to regulatory and accreditation guidance
  • Centers for Disease Control (CDC) Core Principles of Antibiotic Stewardship
  • State Operations Manual: Appendix PP
Tracking: Monitoring Antibiotic Prescribing, Use, and Resistance

Does your facility monitor one or more outcomes of antibiotic use?

- Rates of *C. difficile* infection
- Rates of antibiotic resistant organisms
- Rates of adverse drug events due to antibiotics

Adverse events due to use of medications in skilled nursing homes accounted for nearly 40% of harms identified in a recent report.\(^1\) Antibiotics are among the most frequently prescribed medications in LTCFs and have a high rate of adverse drug events.\(^2,3\)

Antibiotic Adverse Drug Events\(^4\)

- **Rate**: 20% of hospitalized adults have at least 1 adverse drug event (ADE)
- **Risk**: Every 10 days of antibiotic therapy confers a 3% increased risk of ADE
- **Type**: GI (42%), Renal (24%), Blood (15%), Liver (7%), Neurologic (7%)
Antibiotic ADE: GI Event

- Diarrhea: > 3 loose stools per day; absence of laxatives
- Nausea and/or vomiting; nausea and vomiting associated with antibiotic; no other explanation
- Prevalence: 42%
- Median time to occurrence: 5 days (2 – 9)

Possible Gastrointestinal Adverse Event

Contact Prescriber. Evaluate whether antibiotic can be taken with food to decrease nausea/vomiting.

Possible Renal Event

Contact Prescriber. Evaluate other possible causes of renal impairment, i.e. sepsis, contrast dye

Antibiotics Implicated

- Ampicillin
- Amoxicillin-clavulanate
- Ampicillin-sulbactam
- Oxacillin
- Piperacillin-tazobactam
- Ceftriaxone
- Cefpodoxime
- Cefepime
- Trimethoprim-Sulfamethoxazole

- Ertapenem
- Meropenem
- Azithromycin
- Clindamycin
- Doxycycline
- Fluoroquinolones
- Metronidazole
- Vancomycin

ADE: Renal Event

- Increase in SCr to > 1.5 times baseline; absence of precipitating renal factors (i.e. sepsis, other nephrotoxic drugs)
- Prevalence: 24%
- Median time to occurrence: 5 days (2 – 10)
ADE: Blood Disorder

- Anemia (hgb < 10 g/dL); Leukopenia (WBC < 4500 cells/µL); thrombocytopenia (platelets < 150 x 10⁳/µL; no bleeding or myelosuppressive therapy
- Prevalence: 15%
- Median time to occurrence: 12 days (6 – 24)

Most Likely Antibiotics Implicated
- Ampicillin
- Oxacillin
- Piperacillin-tazobactam
- Ceftriaxone
- Macrolides
- Fluoroquinolones
- Trimethoprim-Sulfamethoxazole

ADE: Cardiac Event - Arrhythmia

- QTc > 440 ms in females
- QTc > 460 ms in males on two or more EKGs; absence of pre-existing arrhythmias
- Prevalence: 1%
- Median time to occurrence: 11 days (4-18)

Most Likely Antibiotics Implicated
- Azithromycin
- Ciprofloxacin
- Erythromycin
- Fluconazole
- Levofoxacin
- Moxifloxacin
- Ketoconazole
- Itraconazole;
  Determine if other risk factors for Torsades de Pointes exist

Evaluate need for emergency triage, and potassium and magnesium replacement.
Longer Term Antibiotic ADEs – up to 90 days

**C. Difficile Infection – Infectious Diarrhea**
- Prevalence:
  - 3.9 cases per 10,000 person days
  - 4% of study patients
- Median time to occurrence: 15 days (4 – 34)
- Implicated antibiotics:
  - 3rd generation cephalosporins,
  - cefepime, and fluoroquinolones

**Infection with Multi-drug Resistant Organisms (MDROs)**
- Prevalence:
  - 6.1 cases per 10,000 person days
  - 6% of study patients
- Median time to occurrence: within 90 days
- Gram positive resistance (4.8/10,000 person days): VRE (67%)
- Gram negative resistance (1.7/10,000 person days): extended spectrum β-lactamase production

C. difficile and MDROs infections comprised 43% of all antibiotic-associated ADEs

### Proposed Workflow

1. **Antibiotic Started**
   - Trigger ADE Assessment

2. **48 – 72 hour ADE Assessment**

3. **Signs and Symptoms of Possible ADE Detected**
   - Nurse provides ADE signs and symptoms in EHR
   - MD/NP evaluates and intervenes as is appropriate
   - Pharmacist evaluates and documents outcome
   - Infection Control Specialist evaluates and reports

4. **No Signs and Symptoms of ADE Detected**
   - Usual Care Continued

Where: EHR=electronic health record
Self-Assessment Question

Which of the following are reasons why documenting antibiotic adverse drug events are important?

A. Avoid future exposure to the antibiotic that caused the antibiotic adverse drug event
B. Communicate findings with other healthcare professionals to reduce future occurrences
C. To increase Medicare reimbursement
D. A and B
Golden Nuggets

• Monitoring and documenting antibiotic adverse drug events (AADEs) is critical in reducing future AADEs.
• Increasing ongoing surveillance of potential and actual AADEs needs to be integrated into workflow.
• Reducing AADEs requires an interprofessional collaborative effort championed by the pharmacy team.

References

Antibiotic Adverse Drug Events: Improving Patient Assessment and Management

Joshua Chou, PharmD
Geriatric Pharmacotherapy Fellow
Peter Lamy Center on Drug Therapy and Aging
University of Maryland School of Pharmacy

New and Future Antibiotics in the Pipeline

Jonathan Cho, PharmD, MBA, BCIDP, BCPS
Clinical Associate Professor
The University of Texas at Tyler Fisch College of Pharmacy
Disclosure

Jonathan Cho serves on the speakers’ bureau for Allergan.

Antimicrobial Drug Approval

Self-Assessment Question #1

Which of the following antimicrobials works against vancomycin-resistant *Enterococcus* sp.?

A. Meropenem/vaborbactam  
B. Plazomicin  
C. Omadacycline  
D. None of the above
Delafloxacin (Baxdela®)

• Studies compared delafloxacin vs. vancomycin/aztreonam (V/A)
  • IV delafloxacin to V/A: 78.2% vs. 80.9% in intent-to-treat (ITT) analysis
  • PO delafloxacin to V/A: 83.7% vs. 80.6% in ITT analysis
• Pooled safety analysis showed no association of adverse reactions seen with other fluoroquinolones

Meropenem/vaborbactam (Vabomere®)

• Phase 3 study compared meropenem/vaborbactam vs. piperacillin/tazobactam with optional PO levofloxacin switch
  • Overall success: 98.4% vs. 94%
  • Microbial eradication in ITT population: 66.7% vs. 57.7%
• What about CRE? → evaluated against best available therapy
  • Associated with ↑ clinical cure, ↓ mortality, and ↓ nephrotoxicity
Plazomicin (Zemdri™)

<table>
<thead>
<tr>
<th>Approval Date</th>
<th>Indications</th>
<th>Spectrum of Activity</th>
<th>Dosing</th>
<th>Clinical Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2018</td>
<td>cUTI</td>
<td>ESBL, CRE, MRSA</td>
<td>15mg/kg IV daily</td>
<td>- Same adverse reactions seen with other aminoglycosides</td>
</tr>
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</table>

- Phase 3 study compared plazomicin vs. meropenem
  - Composite cure rate at day 5: 88% vs. 91.4%
  - Composite cure rate at test-of-cure (TOC): 81.7% vs. 70.1%
  - Fewer recurrence: 3.7% vs. 8.1%
  - Fewer clinical relapse: 1.6% vs. 7.1%
  - Increase in serum creatinine levels ≥0.5mg/dL: 7% vs 4%

Eravacycline (Xerava™)

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<tr>
<td>August 2018</td>
<td>cIAI</td>
<td>MRSA, VRE, ESBL, CRE, A. baumannii</td>
<td>1mg/kg IV q12h</td>
<td>- Same adverse reactions seen with other tetracyclines</td>
</tr>
</tbody>
</table>

- Phase 3 study compared eravacycline vs. meropenem
  - Clinical cure rates at TOC: 90.8% vs. 91.2%
  - Clinical cure rates in modified-ITT: 92.4% vs. 91.6%
  - Clinical cure rates in clinically evaluable population: 96.9% vs. 96.1%
  - Clinical cure in patients with ESBL-producing Enterobacteriaceae: 87.5% (14/16) vs. 84.6% (11/13)
Omadacycline (Nuzyra™)

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</thead>
<tbody>
<tr>
<td>October 2018</td>
<td>CABP, ABSSSI</td>
<td>MRSA, VRE, ESBL, ±CRE, A. baumannii</td>
<td>LD then 100mg IV or 300mg PO daily</td>
<td>- Same adverse reactions seen with other tetracyclines</td>
</tr>
</tbody>
</table>

- Two phase 3 studies compared omadacycline vs. linezolid
  - Oasis-1: initiated on IV with option to transition to PO after day 3
    - Modified-ITT early clinical response: 84.8% vs. 85.5%
  - Oasis-2: PO only study
    - Modified-ITT early clinical response: 88% vs. 83%
  - Gastrointestinal adverse events were most common

Imipenem/cilastatin/relebactam (Recarbrio™)

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</thead>
<tbody>
<tr>
<td>July 2019</td>
<td>cUTI, cIAI</td>
<td>ESBL, CRE, P. aeruginosa</td>
<td>1.25g (500 / 500 / 250mg) IV q6h</td>
<td>- Similar adverse effect profile as imipenem/cilastatin</td>
</tr>
</tbody>
</table>

- Phase 3 study compared imipenem/cilastatin/relebactam vs. colistin + imipenem/cilastatin for HAP/VAP, cIAI, or cUTI due to imipenem non-susceptible pathogens
  - Favorable overall response: 71% vs. 70%
  - Day 28 clinical response: 71% vs. 40%
  - 28-day mortality: 10% vs. 30%
  - Serious adverse events: 10% vs. 31%; drug-related: 16% vs. 31%
Lefamulin (Xenleta\textsuperscript{TM})

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<tr>
<td>August 2019</td>
<td>CABP</td>
<td>MRSA, VRE, Atypicals, MDR-N. gonorrhoeae</td>
<td>150mg IV BID or 600mg PO BID</td>
<td>- First pleuromutilin systemically - Potential for QTc prolongation and fetal harm</td>
</tr>
</tbody>
</table>

- LEAP-1: 7 days of IV to PO lefamulin vs. moxifloxacin (±) linezolid for moderate-severe CABP
  - Early clinical response: 87.3% vs. 90.2%
  - Modified-ITT clinical response: 81.7% vs. 84.2%
  - Clinically evaluable: 86.9% vs. 89.4%
- LEAP-2: 5 days of PO lefamulin vs. 7 days of moxifloxacin for moderate CABP
  - Similar results were found

Summary of Approved Antibiotics

<table>
<thead>
<tr>
<th>MRSA</th>
<th>VRE</th>
<th>ESBL</th>
<th>CRE</th>
<th>CR-Pseudomonas</th>
<th>MDR-Acinetobacter</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Delafloxacin</td>
<td>Green</td>
<td>Red</td>
<td>Yellow</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td>● Meropenem / vaborbactam</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
</tr>
<tr>
<td>● Plazomicin</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>● Eravacycline</td>
<td>Green</td>
<td>Red</td>
<td>Green</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>● Omadacycline</td>
<td>Green</td>
<td>Red</td>
<td>Green</td>
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<td>Red</td>
</tr>
<tr>
<td>● Imipenem / relebactam</td>
<td>Red</td>
<td>Green</td>
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Great activity: Green
Moderate activity: Red
Low/no activity: Yellow
Cefiderocol

• Siderophore cephalosporin
  • Enhanced stability to β-lactamases (AmpC, ESBL, carbapenemases)
• Currently being studied in phase 3 trials as 2g IV q8h as 3-hr infusion
• Spectrum of activity is mainly targeted against gram-negatives
  • ESBL, CRE, MDR-\textit{A. baumannii}, MDR-\textit{P. aeruginosa}, S. maltophilia
• Phase 2 study compared cefiderocol vs. imipenem/cilastatin for cUTI
  • Clinical response and microbiological response at TOC: 73% vs. 55%
  • Adverse events: 41% vs. 51% with gastrointestinal being the most common

Iclaprim

• Dihydrofolate reductase inhibitor
  • Designed to overcome trimethoprim resistance without sulphonamide use
• Spectrum of activity is mainly targeted against gram-positives
  • MRSA, vancomycin-resistant strains
• Two phase 3 trials were conducted (REVIVE-1 and REVIVE-2)
  comparing iclaprim vs. vancomycin for ABSSSI
  • ≥20% reduction in lesion size: 79.6% vs. 78.8%
  • Adverse reactions were same except for ↑ incidence of SCr with vancomycin
• FDA requested additional data to evaluate risk for liver toxicity
Zoliflodacin

- Spiropyrimidinetrione against bacterial type II topoisomerases
- FDA awarded fast track status as PO option for gonococcal infections
- Phase 2 study compared zoliflodacin 2g or 3g PO x1 dose vs. ceftriaxone 500mg IM x1 dose for uncomplicated or untreated urogenital gonorrhea
  - Microbiologic cure in the micro-ITT: 96% vs. 96% vs. 100%
  - All rectal patients were cured in all 3 groups
  - Pharyngeal infections: 50% vs. 82% vs. 100%
  - Most adverse reactions with zoliflodacin were gastrointestinal

Ridinilazole

- Demonstrates rapid bactericidal activity for *C. difficile* infection (CDI)
  - Diminish production of *C. difficile* toxins
- Preclinical studies show negligible systemic exposure
- Phase 2 study compared ridinilazole vs. vancomycin x 10 days
  - Sustained clinical response: 66.7% vs. 42.4%, showing superiority
    - Largely due to reduced CDI 30-day recurrence rates
  - Adverse effect profile was similar to vancomycin, most being gastrointestinal
  - Lower propensity for collateral damage to gut microbiome compared with vancomycin
Fosfomycin

- Works against many gram-positive and gram-negatives
  - MRSA, VRE, ESBL, CRE
  - Does not work against *Pseudomonas* and *Acinetobacter* sp.
- Phase 2/3 study evaluated IV fosfomycin vs. piperacillin/tazobactam for treatment of cUTI
  - Overall success: 64.7% vs. 54.5%
  - Clinical cure at TOC: 90.8% vs. 91.6%
  - Adverse reactions include hypokalemia, hypernatremia, ↑ AST/ALT
- FDA rejected approval due to manufacturing issues
Q&A Session 1 – 15 min

Please logon to: www.ascp.com/qa and find the session title to submit your questions.

Moderated by Dr. Milito

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Golden Nuggets: Bugs, Drugs and Antibiotic Stewardship: 2nd Hour

Optimizing The Use of Clinical Laboratory Values in Antimicrobial Stewardship

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Clinical Coordinator
Antimicrobial Stewardship Program Lead Pharmacist
Investigational Drug Program Lead Pharmacist
Johns Hopkins Medicine | Suburban Hospital
Speaker Information—Bio

• Committee member for ASCP, SIDP, ACCP, SHEA, and MSHP
• Additional degrees in Biochemistry, Finance, and International Business
• LEAN/Six Sigma Certification
• Recipient of The Johns Hopkins Patient Safety Award (twice)

Disclosure – Nicholas Ladikos, PharmD BCPS, BCGP, BCIDP

• I have no actual or potentially relevant financial relationship to disclose and no conflict of interest in relation to this activity
Learning Objectives

At the end of this presentation, attendees will be able to understand:

• The effects of immunosenescence on laboratory values
• The complexities of penicillin allergy skin testing and procalcitonin values
• The limitations of current clinical laboratory instrumentation

Historical Context: Hippocrates (c. 425 BC)

• Separated medicine from superstition and religion and made it a science
• The original uroscopist: Advocated examination of urine to diagnose disease
• “Understand the patient as an individual”
Clinical Laboratory Values

• 13 billion tests performed annually in the U.S.
• Acute (baseline) and chronic changes (trends)
• Initiate medication regimens, then adjust based on new information
• Order tests only when necessary
  • Will you take action on the results?

Is a Laboratory Value “WNL” Really Normal?

• Population norms can be established for any physiologic parameter and its laboratory measurement

• Normal lab value = Mean ± 2 SD of healthy people
  - i.e., 95% of results

• Thus, 5% of results are classified as "abnormal," even though they represent variability within a normal population
Immunosenescence

- Multifactorial, progressive decline in immune function with increasing age
  - Low-grade chronic inflammation ("inflamm-aging")
  - Increased incidence and severity of infections
  - Attenuates the host’s capacity to respond to infections
  - Difference in clinical presentation of infections

"All that is gold does not glitter, not all who wander are lost, and not all laboratory values are legitimate."
Microbiology Laboratory—Your [New] BFF!

- Institutional/Facility antibiograms
  - Feeder hospital’s antibiograms
- Rapid/POC tests
- Turnaround time from preliminary/final cultures and susceptibilities to regimen change
- Strategic suppression and/or displaying of susceptibilities

Medical Team: “Patient is fine, but the urine...”
Urinalysis in Asymptomatic Bacteriuria (ASB)

**Screen/Treat**
- Patients undergoing endo-urologic surgery (1 or 2 doses)
- Renal transplant patients within one month of transplant
- Pregnant women (4-7 days)

**Do NOT Screen/Treat**
- Elderly persons living independently or in a long-term care facility
- Patients with indwelling urinary catheters of any duration
- Patients with diabetes
- Patients with spinal cord injury
- Healthy non-pregnant women of any age
Patient: “I’m Allergic to Penicillin...”

- ~10% of US population self-identifies as allergic to penicillin
  - <0.05%-1% have an IgE-mediated penicillin allergy
    - 1/100,000 experience anaphylaxis
  - 1%-2% cross-allergy to carbapenems/select cephalosporins
- Do your due diligence—Investigate, interpret, ask questions!
  - Beta-lactams often first-line therapy
  - Penicillin allergy skin testing (NPV ~98%)

Which is the Penicillin Allergy?
Procalcitonin

**The Good...**
- Serum biomarker that rises in response to bacterial infections
- Approved for CAP and sepsis
  - Bacterial versus viral/atypical
  - 95% NPV
- Known kinetics (follow trends)

**The Bad...**
- Not for viral/atypical infections
- Many other causes of systemic inflammation
- Not perfect

**The Future...**
- Cell-free DNA
- 16s (bacteria)
- 18s (fungi)
Self-Assessment Question

Which of the following is true?

A. The normal value for a laboratory measurement is usually defined as its mean value ± 3 SD.
B. Infections manifest with typical signs or symptoms characterizing disease the same for adults of all ages.
C. ~1% of the U.S. population self-identifies as having an allergy to penicillin.
D. Patients with indwelling catheters should always be treated with antibiotics.
E. Hippocrates advocated to understand the patient as an individual.
Golden Nuggets

- Don’t interpret the patient based on the test
  - Interpret the test based on the patient
- Understand the limitations and timing of tests
- Partner with your clinical laboratory staff and other infection prevention specialists!

Optimizing The Use of Clinical Laboratory Values in Antimicrobial Stewardship

Nicholas Ladikos
PharmD, BCPS, BCGP, BCIDP

Thank you!
Clostridioides difficile
Infection in the Older Adult

Elias B. Chahine, PharmD, FCCP, FFSHP, BCPS, BCIDP
Professor of Pharmacy Practice
Gregory School of Pharmacy
Palm Beach Atlantic University

Conflicts of Interest

- Speakers’ bureau of Merck & Co, Inc.
- Speaker’s bureau of Paratek Pharmaceuticals, Inc.
Outline

- Epidemiology
- Clinical presentation
- Risk factors
- Treatment
- Prevention

Epidemiology

Epidemiology

Epidemiology

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www.cdc.gov/vitalsigns/HAI/index.html
Epidemiology

Question

• Which statement is true?

  • A) CDI cases are decreasing in frequency and severity.
  • B) *C. difficile* is more likely to cause disease in children than older adults.
  • C) More than 50% of healthy adults are carriers of *C. difficile* in their stool.
  • D) The NAP1/BI/027 and 078 ribotypes of *C. difficile* are very virulent.
Clinical Presentation

- Asymptomatic carrier
- Offensive-smelling acute watery diarrhea and fever
- Pseudomembranous colitis with adherent plaques
- Toxic megacolon and systemic toxicity
- Fulminant colitis, sepsis, and paralytic ileus
- Recurrent infections

Clinical Presentation

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Supportive data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>WBC count &lt;15,000 cells/mL AND Scr &lt;1.5 mg/dL</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC count ≥15,000 cells/mL OR Scr ≥1.5 mg/dL</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
</tr>
</tbody>
</table>

Grace E et al. Sr Care Pharm. 2019;34:29-42

Question

• Which patient would be classified under the category of severe infection according to the IDSA/SHEA guidelines?

  • A) A 65-year-old man with a WBC count of 10,100 cells/mL and a SCr of 1.1 mg/dL
  • B) A 70-year-old man with a WBC count of 12,200 cells/mL and a SCr of 1.2 mg/dL
  • C) A 75-year-old woman with a WBC count of 16,300 cells/mL and a SCr of 1.6 mg/dL
  • D) A 79-year-old woman with a WBC count of 10,000 cells/mL and a SCr of 1.4 mg/dL

Risk Factors

• Drug-induced:
  • Antibiotic exposure
  • Broad-spectrum antibiotics
  • Multiple antibiotics
  • Long-term antibiotics
  • Proton pump inhibitors
  • Histamine-2 receptor blockers
  • Chemotherapy agents

• Non drug-induced:
  • Advanced age
  • Female gender
  • Caucasian ethnicity
  • Severe underlying disease
  • Immunocompromising conditions
  • Manipulation of the GI tract
  • Hospitalization or ICU admission
Risk Factors

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Medium risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Penicillins</td>
<td>Clindamycin</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Trimethoprim/</td>
<td>Ampicillin</td>
</tr>
<tr>
<td></td>
<td>sulfamethoxazole</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Macrolides</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td>Fluoroquinolones</td>
</tr>
</tbody>
</table>

Question

• Which antibiotic is the **LEAST** likely to cause CDI?

  • A) Ampicillin
  • B) Ceftriaxone
  • C) Gentamicin
  • D) Levofloxacin
Treatment

• Stop offending antibiotics when possible

• Replace fluid and electrolytes

• Avoid antimotility agents

• Consider surgical interventions in severe cases

• Treat for 10 days

**Definitions**

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Supportive data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>WBC &lt;15,000 cells/mL AND Scr &lt;1.5 mg/dL</td>
<td>Vancomycin 125 mg PO every 6 hrs for 10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fidaxomicin 200 mg PO every 12 hrs for 10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metronidazole 500 mg PO every 8 hrs for days if no access to first-line options</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC ≥15,000 cells/mL OR Scr ≥1.5 mg/dL</td>
<td>Vancomycin 125 mg PO every 6 hrs for 10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fidaxomicin 200 mg PO every 12 hrs for 10 days</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin 500 mg PO/NG every 6 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Metronidazole 500 mg IV every 8 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>± Vancomycin via rectal instillation</td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Recommended treatment</th>
</tr>
</thead>
</table>
| **First recurrence**            | Vancomycin 125 mg PO every 6 hrs for 10 days if metronidazole was used initially  
                                | Vancomycin 125 mg PO every 6 hrs for 10 to 14 days, every 12 hrs for a week, every 24 hrs for a week, and then every 2 or 3 days for 2 to 8 weeks (tapered and pulsed regimen)  
                                | Fidaxomicin 200 mg PO every 12 hours for 10 days if vancomycin was used initially                                                                   |
| **Second or subsequent recurrence** | Vancomycin 125 mg PO every 6 hrs for 10 to 14 days, every 12 hrs for a week, every 24 hrs for a week, and then every 2 or 3 days for 2 to 8 weeks (tapered and pulsed regimen)  
                                | Vancomycin 125 mg PO every 6 hrs for 10 days followed by rifaximin 400 mg PO every 8 hours for 20 days (rifaximin chaser)  
                                | Fidaxomicin 200 mg PO every 12 hours for 10 days  
                                | Fecal microbiota transplantation                                                                                                                      |

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### Bezlotoxumab

![Bezlotoxumab Graph](image)

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Bezlotoxumab

Bezlotoxumab  
Case Vignette

- M.F., a 71-year-old man, was transferred from the nursing home to the hospital for the management of HAP.
- He is receiving cefepime and ciprofloxacin.
- On day 8, his lungs are clear, and he is no longer complaining of shortness of breath.
- However, he is now complaining of foul-smelling diarrhea and is diagnosed with CDI.
- WBC 22,000 cells/mm$^3$; SCr 2 mg/dL; Alb 2.4 g/dL.
- All: penicillin (itching).

Question

- What is the best recommendation for M.F.?
  - A) Start vancomycin 125 mg PO every 6 hours and continue cefepime and ciprofloxacin
  - B) Start vancomycin 125 mg PO every 6 hours and discontinue cefepime and ciprofloxacin
  - C) Start vancomycin 1000 mg IV every 12 hours and continue cefepime and ciprofloxacin
  - D) Start vancomycin 1000 mg IV every 12 hours and discontinue cefepime and ciprofloxacin
Prevention

- Implement institution-based infection control programs
- Isolate affected patients in single rooms
- Use barrier precautions such as gloves and gowns
- Emphasize hygiene particularly hand washing
- Implement antimicrobial stewardship programs
- Discontinue unnecessary gastric acid suppression

Key References and Readings


- Grace E, Chahine EB. Updates on Clostridioides (Clostridium) difficile infection with emphasis on long-term care. Sr Care Pharm. 2019;34:29-42.
Clostridioides difficile
Infection in the Older Adult

Elias B. Chahine, PharmD, FCCP, FFSHP, BCPS, BCIDP
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Multi-Drug Resistant Organisms

Eddie Grace, Pharm.D., BCIDP, AAHIVP, FIDSA
President & Chief Infectious Diseases Consultant
Sovereign Medical Consulting, LLC
Speaker Information – Bio

- Board-Certified Infectious Diseases Pharmacist
- Fellow of the Infectious Diseases Society of America (IDSA)
- American Academy of HIV Medicine Certified HIV Pharmacist
- ASCP Antimicrobial Stewardship and Infection Control Committee
- Current Chair of ACCP HIV PRN (2018-19)

Disclosure – Eddie Grace, Pharm.D., BCIDP, AAHIVP, FIDSA

- None to disclose
Gram-negative MDROs
Evolution of Resistance

- **Extended-Spectrum Beta-Lactamase (ESBL):**
  - Enzymes able to hydrolyze third and fourth generation cephalosporins and monobactams.
  - Inhibited by CLA, TZB, and SLB
  - Resistance genes acquired through plasmids (not chromosomally present)

- **Carbapenem-Resistant Enterobacteraeaceae (CRE)/ Carbapenemase Producing Enterobacteraeaceae (CPE):**
  - Enzymes able to hydrolyze penicillins, cephalosporins, most β-lactams, most β-lactamase inhibitors (±TZB), and carbapenems

---

**Timeline of Resistance Evolution**

- 1940: Penicillin introduced
- 1941: Penicillinase identified in E. coli
- 1946: TEM-1 identified in E. coli
- 1965: SHV-1 identified
- 1981: 3rd generation cephalosporins introduced
- 1985: Imipenem introduced
- 1989: AmpC (CMY-1) & ESBL (CTX-M) identified
- 1991: CRE identified (MBL and OXA-1)
- 2001: KPC-1 identified (NC, USA)
Gram-Negative MDROs
Evolution of Resistance

• CTX-M has become the dominant ESBL with a prevalence of 35-45% of all E. coli related UTIs and BSIs
• Currently >5 subtypes have been identified
• E. coli CTX-M has been identified as E. coli Sequence Type 131 (ST131)
  • Also known as phylogenetic type B2 or serotype 025:H4
  • Resistance to CLA and TZB
  • Resistance to fluoroquinolones (especially ciprofloxacin) is common
  • Co-resistance to aminoglycosides and TMP/SMX also common
Gram-negative MDROs
Evolution of Resistance

Gram-negative MDROs
E. coli
- Gram-negative rod
- Facultative anaerobe
- Lactose and D-glucose fermenter
- Member of the Enterobacteriaceae family
- Most common organism in the small intestines
- Wild-type E. coli is typically susceptible to most antibiotic classes:
  - penicillins, aminopenicillins, cephalosporins, fluoroquinolones, sulfonamides, carbapenems, aminoglycosides, nitrofurantoin, fosfomycin, β-lactam/β-lactamase inhibitors
Gram-negative MDROs
E. Coli – Resistance

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>98.8%</td>
<td>64.2%</td>
<td>98.8%</td>
<td>63%</td>
<td>2.5%</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>100%</td>
<td>1.6%</td>
<td>98.4%</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

E. coli resistance patterns:
- 
- ESBL E. coli
  - Resistance to one or more of the following:
    - Penicillins
    - Cephalosporins
    - β-lactam β-lactamase inhibitor combinations
    - Fluoroquinolones
    - Aminoglycosides
    - TMP/SMX
    - Monobactams
    - Carbapenems (≥1 agent)
- CR-E. coli
  - Resistance to all the following:
    - Carbapenems (ALL)
    - Cephalosporins (ALL)
Gram-negative MDROs
E. Coli –CipREc

• Ciprofloxacin-Resistant E. coli (CipREc)
  • 2011 study 34% of NH-residents colonized with CipREc
    • Risk factor for colonization was use of medical devices (HR 1.93)
  • 2014 study showed a prevalence among colonized NH-residents of 47.5% (57 of 120)
    • Time to colonization positive averaged 46 days (IQR 21-296 days)
    • Risk factors for CR-EC acquisition included:
      • Fecal incontinence (HR 1.78, 95%CI 1.04-3.06, p=0.04)
      • Amoxicillin-clavulanate receipt within 12-months (HR 6.48, 95%CI 1.43-29.4, p=0.02)
      • Urinary catheter use (HR 3.81, 95%CI 1.06-13.8, p=0.04)

• 2016 study in high-risk NH-residents (urinary-catheter or enteral nutrition tubes or both)
  • 15% of all NH-residents were colonized with CipREc with an increase of 7.7%/year
  • 62.2% of CipREc were identified as ST131 (ESBL+)
  • All residents with CipREc had urinary-catheters
  • 63.2% of non-colonized residents had urinary-catheters
    • Risk of CipREc was higher with suprapubic-catheter vs ureteral- catheters (22.6% vs 12.3%, respectively)
    • Interestingly, residents with enteral nutrition tubes were less likely to have CipREc colonization (28.3% vs 49.2%)
Gram-negative MDROs
E. Coli –ESBL/ST131

• Nosocomial colonization rate in the US:
  • 7.8% in 2010 and 18.3% in 2014
• In NH-residents the mean ESBL colonization rate is ~17% (data from 2016) with a range from 8-28%
• Risk factors for colonization:
  • MDRO history (OR 4.1, 95%CI 1.6-10.4, p=0.003)
  • Bed-bound status (OR 2.6, 95%CI 1.3-5.4, p=0.008)
  • Urinary/fecal incontinence (OR 8.86, p<0.001)
  • Presence of urinary catheter (OR 8.57, P<0.001)

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Gram-negative MDROs
E. Coli –ESBL/ST131

• NH-residents are at increased risk of E.coli ST131 infections and resulting bacteremia
  • 2014 study showed that being a resident of a LTCF increased the risk of hospital-onset ESBL bacteremia by 5.1-fold (95%CI 2.2-11.9, p<0.01) in residents without antibiotic use in the past 30 days and without history of ESBL
    • Odds ratio increased to 6.9 with antibiotic use in prior 30 days
    • Odds ratio increased by 1.8 if resident had history of ESBL infections (95%CI 1.3-2.7, p<0.01)
    • The risk remained elevated even after 48-hours of hospitalization (OR 3.4, 95%CI 1.3-9.0, p=0.01)
**Gram-negative MDROs**

**ESBL E. Coli – Treatment**

<table>
<thead>
<tr>
<th>Antibiotic/Class</th>
<th>Place in therapy</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyxin E/B</td>
<td>Drugs of choice</td>
<td>All</td>
<td>Use in combination with other agents (never use monotherapy)</td>
</tr>
<tr>
<td></td>
<td>for severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>with evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>of resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>to carbapenems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Alternative</td>
<td>UTI</td>
<td>Can be used in the treatment of UTIs is shown susceptible. Do not use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>monotherapy for severe invasive infections</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>AVOID</td>
<td></td>
<td>High likelihood of resistance</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>AVOID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>AVOID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CRE (including E. coli) infections account for 4.2% of all infections in the US (2011)**

- Increase from 1.2% of infections in 2001
- E. coli accounts for 10% of all CRE-related infections

- Carbapenem-Resistant Enterobacteriaceae are resistant to carbapenems and most other antibiotic classes previously mentioned
- CRE are encoded by one or more of the following genes: NDM, OXA, VIM, and IMP
- 4.6% of NH-residents admitted to hospitals are colonized with a carbapenem-resistant GN
  - Approximately 25% are colonized with CR-E. coli
- CRE (including E. coli) infections account for 4.2% of all infections in the US (2011)
  - Increase from 1.2% of infections in 2001
  - E. coli accounts for 10% of all CRE-related infections
Self-Assessment Question

Which of the following antibiotics would be considered an appropriate agent for the empiric treatment of a suspected ESBL E. coli (ST131) bacteremia secondary to a UTI of the same organism?

A. Tobramycin  
B. Colistin  
C. Ertapenem  
D. Levofloxacin
References

- Chea N, Bulens SN, Kongphet T, et al. Improved Phenotype-Based Definition for Identifying Carbapenemase Producers among Carbapenem-Resistant Enterobacteriaceae. Emerg Infect Dis. 2015 Sep;21(9):1611-6
Multi-Drug Resistant Organisms

Eddie Grace, Pharm.D., BCIDP, AAHIVP, FIDSA
President & Chief Infectious Diseases Consultant
Sovereign Medical Consulting, LLC

Q&A Session 2 – 15 min

Please logon to: www.ascp.com/ga and find the session title to submit your questions.

Moderated by Dr. Milito

4. Optimizing The Use Of Clinical Laboratory Values In Antimicrobial Stewardship—Nicholas Ladikos
5. Clostridioides difficile Infection in the Older Adult—Elias B. Chahine
6. Multi-Drug Resistant Organisms—Eddie Grace