Session 3: Infectious Disease
A: Resistance: A Four Letter Word
3:00pm - 4:00pm

ACPE UAN 107-000-12-019-L01-P 0.1 CEU/1.0 Hr
Activity Type: Application-Based

Program Objectives for Pharmacists: Upon completion of this CPE activity participants should be able to:
1. Identify recent trends in antibiotic resistance
2. Discuss the epidemiology of antibiotic resistance
3. Illustrate the clinical implications of antibiotic resistance
4. Propose strategies pharmacists can utilize to help curb the emergence of resistance
5. Demonstrate and appraise clinical situations where strategies are applicable

Speaker: Sarah Johnson, PharmD, BCPS, is a Clinical Pharmacy Specialist at the University of Iowa Hospitals and Clinics and is a Clinical Assistant Professor at the University of Iowa College of Pharmacy. She received her Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the University of Iowa College of Pharmacy and completed a Pharmacy Practice Residency at the University of Iowa Hospitals and Clinics (UIHC). She has held positions in Solid Organ Transplantation, Medication Use Evaluation, and is currently the Antimicrobial Stewardship Program Clinical Pharmacy Specialist at UIHC. She is a preceptor for pharmacy students and pharmacy residents on the Infectious Diseases rotation at UIHC and also teaches at the College of Pharmacy. Her areas of interest are antimicrobial stewardship, dose optimization, outcomes research, and teaching.

Speaker Disclosure: Sarah Johnson does not report any actual or potential conflicts of interest in relation to this CPE activity. Off-label use of medications will not be discussed during this presentation.
Resistance: A Four Letter Word

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University of Iowa College of Pharmacy

Faculty Disclosure
- Sarah Johnson reports she has no actual or potential conflicts of interest associated with this presentation.
- Sarah Johnson has indicated that off-label use of medication will be discussed during this presentation.

Learning Objectives
Upon completion of this activity pharmacists will be able to:
1. Identify trends in antibiotic resistance.
2. Discuss the epidemiology of antibiotic resistance.
3. Discuss the clinical implications of antibiotic resistance.
4. Propose strategies pharmacists can utilize to help curb the emergence of resistance.
5. Appraise clinical situations where strategies are applicable.

ESKAPE Pathogens
- Enterococcus
- Staphylococcus aureus
- Klebsiella pneumoniae
- Acinetobacter baumanii
- Pseudomonas aeruginosa
- Enterobacter spp.

Spread of Resistance

Beta-lactamases
- Penicillinase - first enzyme capable of destroying penicillin
- Extended spectrum beta-lactamases (ESBLs)
  - E. coli, K. pneumoniae
  - Inactivate sulbactam, clavulanate, tazobactam
- Amp C
  - Resistant to third generation B-lactamase and cephalosporins
- Carbapenemases
  - New Delhi metallo-beta-lactamases (NDM -1)
  - Enterobacteraeae, K. pneumoniae (KPC), E. coli, Citrobacter freundii, Enterobacter cloacae, and Morganella morganii
- In U.S. – isolated in Klebsiella, E. coli, and Enterobacter
U.S. Resistance Trends

Geographical distribution of extreme-drug resistant Klebsiella bacteria

Current

Global Resistance

Worldwide Resistance 2009

Since 2000:
- 10 new antibiotics launched in the U.S. market
- 21 launched worldwide

CID 2008; 46, J Antivir 2011; 44: 413.
Antibiotic Pipeline
- 12 in Phase I trials – one with gram-negative activity and potentially new mechanism of action
  - It takes ~ 10 yrs and 1 billion $ to bring to the market
- 22 in Phase II studies – 5 quinolones
- 5 in Phase III studies

ESKAPE Pathogens
- Enterococcus
- Staphylococcus aureus
- Klebsiella pneumoniae
- Acinetobacter baumanii
- Pseudomonas aeruginosa
- Enterobacter spp.

Pre-assessment Question #1
Which is a true statement regarding antibiotic resistance?
A. Antibiotic resistance in the U.S. is less compared to other regions of the world.
B. Several novel antibiotics with mechanisms against gram-negative pathogens are in the antibiotic pipeline.
C. ESKAPE is the acronym for gram-negative bacteria with exquisite antibacterial susceptibility.
D. We are relying on infection control and antibiotic stewardship to preserve current antibacterial agents as treatment for infectious diseases.

Mechanisms of resistance
- Resistance genes are often associated with transposons – these are genes that easily move from one bacteria to another
- Bacteria can pass on to other stains or OTHER SPECIES
- Bacteria can carry several resistance genes = MULTIPLE DRUG RESISTANCE
Factors that Promote Resistance

- Poor infection control
- Alteration of normal bacterial flora
- Antibiotic misuse
  - Inappropriate specimen selection and collection
  - Inappropriate clinical tests
  - Failure to use culture and susceptibility tests
  - Use of antibiotics with no clinical indication
  - Use of unnecessary broad spectrum antibiotics
  - Incorrect dosing, route, and duration

“Much needless expense, untoward effect, harm, and disappointment can be prevented by better judgment in the use of antimicrobials for prophylaxis and therapy” HA Reimann, 1961

Articles on Resistance from NEJM in 1960:

Historical Perspective

<table>
<thead>
<tr>
<th>Antibiotic or herbicide</th>
<th>Year deployed</th>
<th>Resistance observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamide</td>
<td>1930s</td>
<td>1940s</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1943</td>
<td>1946</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1943</td>
<td>1959</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1947</td>
<td>1959</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1948</td>
<td>1953</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1952</td>
<td>1968</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1956</td>
<td>1968</td>
</tr>
<tr>
<td>Methicillin</td>
<td>1960</td>
<td>1961</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1961</td>
<td>1973</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1960s</td>
<td>late 1960s</td>
</tr>
</tbody>
</table>

Antibiotic Consumption Map

Antibiotic Resistance Map

Resistant Acinetobacter sp. in the United States
Resistant *Escherichia Coli* in the United States

Fluoroquinolone Use versus Susceptibility

Pre-Assessment Question #2
Which of the following is true?
A. Bacteria can only pass resistance genes within their species.
B. Resistance in bacteria is primarily due to one resistance mechanism.
C. Antibiotic use facilitates emergence of resistance.

Clinical Implications of Resistance
- Increased use of broad spectrum antibiotics leading to multiple drug resistance
- Collateral damage
- Increased adverse effects related to increasing doses of antibiotics
- Increased morbidity and mortality
- Increased costs

Respiratory FQ Use and Influenza

C. *Difficile* vs Influenza
Pennsylvania Health Care Cost Containment Report
Hospital acquired infections 2005

- Increased morbidity, mortality, length of stay, and cost.

<table>
<thead>
<tr>
<th>Type</th>
<th>Increased LOS (days)</th>
<th>Increased Cost ($)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLABSI</td>
<td>10 to 20</td>
<td>1,700 to 29,000</td>
<td>35%</td>
</tr>
<tr>
<td>CA-UTI</td>
<td>10</td>
<td>500 to 1,000</td>
<td></td>
</tr>
<tr>
<td>VAP</td>
<td>4.3</td>
<td>40,000</td>
<td>10 to 50%</td>
</tr>
<tr>
<td>HAP/HCAP</td>
<td>40,000</td>
<td>10 to 50%</td>
<td></td>
</tr>
<tr>
<td>SSI</td>
<td>2 to 10</td>
<td>3,000 to 29,000</td>
<td>75%</td>
</tr>
</tbody>
</table>

Cost to the U.S. health care system of antibiotic resistant infections is $21 billion to $34 billion each year and more than 8 million additional hospital days.

Clin Microbiol Rev 2011; www.CDC.gov

Pre-assessment Question #3
Which of the following is true?
A. Fluoroquinolones have the highest association with development of C. difficile associated disease.
B. Treatment of resistant infections costs significantly more compared to treatment of antibiotic susceptible infections.
C. Emergence of resistance has lead to increased use of broad spectrum antibiotics.
D. All of the above.

Strategies to Curb Emergence of Resistance
- Assess the need for antibiotic therapy!!!
- Antibiotic optimization
  - Empiric choice
  - Direct therapy based on culture and susceptibility information
  - Use of guidelines or pathways
  - Antibiotic allergy assessment
  - Streamlining or de-escalating broad spectrum antibiotics
- Optimization of the antibiotic dose
- Duration of antibiotic

Importance of Broad Spectrum Antibiotic Therapy
- Inappropriate initial antibiotic therapy is associated with higher mortality, longer hospital stay, increased costs
- Key pathogens – Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter baumannii

Case #1
32 year old 80 kg male with normal renal function is transferred to the medicine floor after 3 days in the ICU. One day later, he spikes a fever and has leukocytosis. Blood cultures are drawn and he is initiated on vancomycin and piperacillin/tazobactam therapy.

Is the antibiotic choice appropriate for the patient?
What dose of vancomycin is appropriate for this patient?

A. 1500 mg q8h
B. 1000 mg q12h
C. 1000 mg q24h
D. 500 mg q12h

Dose Optimization

- Strategies
  - Increase the dose to achieve the desired peak/MIC ratio (concentration-dependent antibiotics)
  - Maintain concentration over the MIC (T>MIC) is the best predictor of bacterial killing and microbiologic response (time-dependent antibiotics)

Vancomycin Dose Optimization

- 15 mg/kg/dose based on actual body weight
- 25 to 30 mg/Kg loading dose
- Younger patients consider Q8h
- MRSA aim for serum trough level 15 to 20 mcg/ml for AUC/MIC 400
  - Exception – skin/soft tissue infection with MIC < 1
  - 10 mcg/ml needed for prevention of resistance

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists
UIHC Guidelines for Vancomycin Dose Optimization

Pharmacist pharmacokinetic dosing guideline:
- Loading dose 20 to 35 mg/kg based on ABW
- 15 mg/kg based on ABW
- Interval calculated at 1.5 x estimated half-life

Empiric Adult Vancomycin Dosing Recommendations in Physician Order Entry
- Vancomycin 15 mg/kg based on total body weight
- Age < 40 years and Scr is < 1.4, interval = Q8h
- Age 40 to 65 years Scr < 1.4, interval = Q12h
- Age > 65 or Scr is > 1.4 (regardless of age), interval = Q24h

What dose of vancomycin is appropriate for this patient?
A. 1500 mg q8h
B. 1000 mg q12h
C. 1000 mg q24h
D. 500 mg q12h

Piperacillin-tazobactam Dose Optimization


Piperacillin/tazobactam


UIHC Guidelines

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Piperacillin-tazobactam dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 20 mL/min</td>
<td>3.375 gm q8h over 4 hours</td>
</tr>
<tr>
<td>CrCl &lt; 20 mL/min</td>
<td>3.375 gm IV q12h over 4 hours</td>
</tr>
<tr>
<td>Peritoneal/hemodialysis</td>
<td>3.375 gm IV q12h over 4 hours</td>
</tr>
<tr>
<td>Continuous renal</td>
<td>3.375 gm IV q8h over 4 hours</td>
</tr>
<tr>
<td>replacement therapy</td>
<td></td>
</tr>
</tbody>
</table>

Question #4
Which of the following is a strategy a pharmacist could use to facilitate appropriate antibiotic use?
A. Encourage the use of antihistamines and decongestants for treatment of cough symptoms
B. Develop an extended-infusion beta-lactam protocol for use in their health-system
C. Work with the local microbiology lab to develop an Antibiogram
D. All of the above
Case #2

Young female patient presents to the outpatient clinic with urinary symptoms. UA consistent with UTI. The physician wants to know how she can treat this patient in line with good antimicrobial stewardship principles.

What antibiotic therapy would be appropriate?

Guidelines

- IDSA guidelines
- Development of local guidelines based on local culture and susceptibility data

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Antibiogram

UIHC E. coli Susceptibility

Nitrofurantoin versus TMP/SMX for Uncomplicated Cystitis

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>85</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Duration of Therapy CAP

<table>
<thead>
<tr>
<th></th>
<th>Ciprofloxacin</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Duration</td>
<td>5 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Length of stay</td>
<td>9 days</td>
<td>15 days</td>
</tr>
<tr>
<td>Resistance</td>
<td>14%</td>
<td>18%</td>
</tr>
</tbody>
</table>
Case #3

Patient case number # had blood cultures that grew *Staphylococcus aureus*. The patient is currently on vancomycin and piperacillin/tazobactam.

What is the appropriate course of action?

MIC

Oxacillin ≤ 0.5 S
Vancomycin 1 S

De-escalation

- Broad-spectrum to a narrower spectrum agent after culture and susceptibility data are available
- Vancomycin to nafcillin for MSSA
- Caspofungin to fluconazole
- Data suggest that de-escalation happens in < 50% of situations where it would be appropriate
- Antibiotic “time out” – 48 to 72 hours after initiation of therapy

CID 2011:52

Question #5

Which of the following is not an antimicrobial stewardship strategy?

A. De-escalation
B. Dose optimization
C. Shorten the antibiotic duration
D. Decreasing fluoroquinolone use
E. All of the above are strategies

Take Home Messages

- Antibiotic use contributes to the growing problems of *Clostridium difficile* infection and antibiotic resistance.
- The antibiotic pipeline is dry.
- Patients are dying from multiple-drug resistant infections.
- Improving antibiotic use through stewardship interventions and programs is important in slowing further emergence of antibiotic resistance, decreasing mortality and health care costs.
- Interventions to improve antibiotic use can be implemented by pharmacists in any healthcare setting.

Continuing Pharmacy Education

- Go to [www.GoToCEI.org](http://www.GoToCEI.org) click on My Portfolio
- Scroll down to Take Exam – Enter Access Code: (case sensitive)

Pharmacists - __________
Technicians - __________
For serious infections caused by *P. aeruginosa*, the susceptible category for piperacillin/tazobactam implies the need for combination therapy with an aminoglycoside with *in vitro* activity against *P. aeruginosa*. High-dose or extended infusions of piperacillin/tazobactam and other beta-lactam antibiotics should also be considered. Clinical failures have been associated with aminoglycoside monotherapy.

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### Appendix

#### UIHC Antibiogram

<table>
<thead>
<tr>
<th>Gram Negative Bacilli (number of isolates tested)</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefazolin</td>
</tr>
<tr>
<td><em>Citrobacter freundii (74)</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Citrobacter koseri (44)</em></td>
<td>93</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes (87)</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Enterobacter cloacae (211)</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Escherichia coli (2275)</em></td>
<td>87</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca (131)</em></td>
<td>49</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae (533)</em></td>
<td>91</td>
</tr>
<tr>
<td><em>Morganella morganii (44)</em></td>
<td>0</td>
</tr>
<tr>
<td><em>Proteus mirabilis (241)</em></td>
<td>88</td>
</tr>
<tr>
<td><em>Serratia marcescens (98)</em></td>
<td>0</td>
</tr>
</tbody>
</table>

#### Non-Enterobacteriaceae

|                                               | Cefazolin | Ceftaxone | Ampicillin | Ampicillin - | Piperacillin - | Cefepime | Ceftazidine | Tobramycin | Gentamicin | Meropenem | Erlapepem | Aztreonam | Trimethoprim - | Ciprofloxacin | Nitrofurantoin |
|-----------------------------------------------|-----------|-----------|------------|--------------|---------------|-----------|-------------|------------|------------|-----------|-----------|-----------|-----------|----------------|--------------|----------------|
| *Acinetobacter species (65)*                  | -         | 83        | -          | 95           | 94            | 92        | 89          | 92         | 91         | 97        | -         | -         | -         | 85             | -            |                |
| *Pseudomonas aeruginosa*                       | -         | -         | -          | -            | 96            | 92        | 93          | 94         | 88         | 94        | -         | 84        | -         | 82             | -            |                |
| *Stenotrophomonas maltophila* (105)*           | -         | -         | -          | -            | -             | 38        | -           | -          | -          | -         | -         | -         | -         | 99             | -            |                |

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* For serious infections caused by *P. aeruginosa*, the susceptible category for piperacillin/tazobactam implies the need for combination therapy with an aminoglycoside with *in vitro* activity against *P. aeruginosa*. High-dose or extended infusions of piperacillin/tazobactam and other beta-lactam antibiotics should also be considered. Clinical failures have been associated with aminoglycoside monotherapy.
2012 Educational Expo
Resistance: A Four Letter Word
Sarah Johnson, PharmD, BCPS

Post-Assessment Questions

1. Which of the following statements is true regarding antibiotic resistance?
   A. Pathogens producing carbapenemases are easy to identify.
   B. NDM-1 is a type of beta-lactamase that has been associated with resistance to all antibiotics.
   C. The current antibiotic pipeline is primarily aimed at drugs with activity against key gram-negative pathogens.
   D. Antibiotic resistance has stabilized in most areas of the world.

2. What antibiotic would be a useful addition to the market?
   A. An antibiotic with a novel mechanism of action against MRSA.
   B. An oral antibiotic with novel activity against ESBL-producing bacteria.
   C. None of the above.
   D. All of the above

3. Antibiograms are most useful for all of the following except:
   A. Determining appropriate choice of empiric antibiotic therapy.
   B. De-escalation of antibiotic therapy based on the patient’s specific culture and susceptibility data.
   C. Identifying organisms exhibiting multidrug resistance.
   D. Identifying annual trends in antibiotic resistance.

4. The antibacterial activity of which of the following antibiotics can be optimized by administering as a prolonged infusion?
   A. Gentamicin
   B. Trimethoprim/sulfamethoxazole
   C. Piperacillin/tazobactam
   D. Levofloxacin

5. Which of the following is an antibiotic stewardship strategy that pharmacists can initiate?
   A. Recommending cultures prior to beginning antibiotic therapy.
   B. Counseling patients on non-antibiotic treatment of viral symptoms.
   C. Facilitating use of treatment guidelines by prescribers at their health care facility.
   D. All of the above are appropriate stewardship strategies for pharmacists to initiate.
62 year old female with history of hypertension, depression, and high cholesterol, was admitted to the hospital for monitoring s/p surgery. No significant issues were noted while she was in the hospital, other than vague urinary tract symptom and an abnormal urine analysis for which levofloxacin was initiated, and on day 2 she was discharged. Cross covering resident physician ordered the following medications on discharge:

Ibuprofen 600 mg q6h as needed for headache
Simvastatin 20 mg daily
Hydrochlorothiazide 25 mg daily
Multiple vitamin once daily
Levofloxacin 500 mg daily x 14 days

One week post discharge she presented to the clinic complaining of loose stools, and abdominal pain. She reports that she has been taking her scheduled medications as prescribed. Labs are all normal except for an elevated WBC of 20,000. Her C. difficile toxin assay was positive.

What went wrong? (Assessment)

Patient problems:
Uncomplicated UTI.
Levofloxacin x 3 days is adequate for UTI.
Patient has developed an adverse event due to prolonged, unnecessary therapy.

System problems:
Physician was cross covering and may have assumed that the levofloxacin was for surgical site infection.
The actual indication for levofloxacin was not addressed when the patient was discharged or when prescription was filled.

Intervention: (Plan)
Discontinue levofloxacin.
Treat C. difficile colitis.