The Pharmacist’s Role in Preventing Antimicrobial Resistance
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Program Agenda
Monday and Tuesday, December 5–6

6:15 a.m. – 6:45 a.m. Registration and Breakfast Buffet

6:45 a.m. – 6:50 a.m. Introductory Remarks
Stephen F. Eckel, Pharm.D., BCPS, Program Moderator

6:50 a.m. – 7:40 a.m. The Pharmacist's Role in Preventing Antimicrobial Resistance
Debra A. Goff, Pharm.D.

7:40 a.m. – 7:45 a.m. Question and Answer Discussion

Program Agenda
Wednesday and Thursday, December 7–8

6:15 a.m. – 6:45 a.m. Registration and Breakfast Buffet

6:45 a.m. – 6:50 a.m. Introductory Remarks
Jerry Siegel, Pharm.D., FASHP, Program Moderator

6:50 a.m. – 7:40 a.m. The Pharmacist's Role in Preventing Antimicrobial Resistance
Debra A. Goff, Pharm.D.

7:40 a.m. – 7:45 a.m. Question and Answer Discussion
The Pharmacist’s Role in Preventing Antimicrobial Resistance

Program Faculty

Stephen F. Eckel, Pharm.D., BCPS, *Program Moderator*
Assistant Director of Pharmacy
University of North Carolina Hospitals
Chapel Hill, North Carolina

Jerry Siegel, Pharm.D., FASHP, *Program Moderator*
Senior Director, Pharmaceutical Services
The Ohio State University Medical Center
Assistant Dean
The Ohio State University College of Pharmacy
Columbus, Ohio

Debra A. Goff, Pharm.D.
Clinical Associate Professor
The Ohio State University College of Pharmacy
Infectious Diseases Specialist
The Ohio State University Medical Center
Columbus, Ohio
The Pharmacist’s Role in Preventing Antimicrobial Resistance

Program Description

Antimicrobial resistance is a serious public health threat not only in the United States, but also globally. In addition to an ever-increasing number of patients acquiring bacterial infections in hospitals each year, the majority of these infections are resistant to at least one drug and mortality rates attributed to these infections continue to rise. In 2005, public reporting of hospital-acquired infections became mandatory in some states. Eventually all states will be required to release this information and pharmacists must now anticipate and prepare for the role they will play in this public reporting database.

Various factors contribute to antimicrobial resistance, most notably improper antibiotic use and inappropriate empiric therapy selection. Immunocompromised patients and patients in intensive care units are particularly vulnerable to infections caused by resistant microorganisms, but such infections also can affect otherwise healthy persons of all ages. Efforts to reduce the emergence of antimicrobial resistance and the spread of infections caused by resistant microorganisms include the Centers for Disease Control and Prevention (CDC) Campaign to Prevent Antimicrobial Resistance, which is designed to prevent antimicrobial resistance in health-care settings. The CDC campaign focuses on four main strategies: prevent infection, diagnose and treat infection, use antimicrobials wisely, and prevent disease transmission. By working collaboratively with hospital epidemiologists, microbiologists, and infectious disease physicians, pharmacists can play an integral role in implementing these strategies, especially in special patient populations, including surgical and intensive care unit patients and those with chronic diseases such as diabetes. This program will describe the role of the pharmacist in that team and provide drug formulary management strategies that can be implemented to address a facility’s specific resistance patterns.

Learning Objectives

At the conclusion of this program, participants should be able to:

- Describe the role of the pharmacist in combatting antibiotic resistance, including the implementation of drug formulary management strategies that combat hospital-specific antibiotic resistance patterns.
- Given a patient profile, recommend antimicrobial therapy appropriate to the known or probable pathogen in special patient populations, including surgical and intensive care unit patients and those with chronic diseases such as diabetes.
- Describe recent trends in antimicrobial resistance in the United States and the factors that contribute to these trends.
- Compare and contrast the new and existing broad-spectrum antibiotics that are used for the treatment of multidrug-resistant infections.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 1 hour (0.1 CEU) of continuing education credit (program number 204-000-05-474-L01). Attendees must complete a Continuing Pharmacy Education Request online and may immediately print their official ASHP CE statements at the ASHP Advantage CE Processing Center at www.ashpadvantage.com.
Stephen F. Eckel, Pharm.D., BCPS
Assistant Director of Pharmacy
University of North Carolina Hospitals
Chapel Hill, North Carolina

Dr. Stephen Eckel received his Bachelor of Science in pharmacy from the University of North Carolina (UNC) at Chapel Hill in 1995 and his Doctor of Pharmacy degree in 1997, also from UNC. Following completion of a pharmacy practice residency at Duke University Medical Center in 1998, he accepted a position as a clinical pharmacist at the University of North Carolina Hospitals. Dr. Eckel currently serves as Assistant Director of Pharmacy and Residency Program Director at UNC Hospitals. He is also board certified as a pharmacotherapy specialist and Clinical Assistant Professor at the University of North Carolina School of Pharmacy.
The Pharmacist’s Role in Preventing Antimicrobial Resistance

Jerry Siegel, Pharm.D., FASHP
Senior Director, Pharmaceutical Services
The Ohio State University Medical Center
Assistant Dean
The Ohio State University College of Pharmacy
Columbus, Ohio

Dr. Jerry Siegel is Senior Director of Pharmaceutical Services at The Ohio State University Medical Center in Columbus, Ohio. He is also Clinical Associate Professor and Assistant Dean of the Ohio State University College of Pharmacy.

Dr. Siegel received his B.S in microbiology, B.S. Pharmacy, and Pharm.D. from The Ohio State University. He practiced as a pharmacist in transplant and hematology/oncology prior to his administrative responsibilities. In addition, he was a recognized as a fellow by the American Society of Health-Systems Pharmacists (ASHP) in 1996 for his work in immunology.

Dr. Siegel is a member of many professional societies including ASHP and the Ohio Society of Health-System Pharmacists, for which he served as president. Throughout his career, Dr. Siegel has been honored with several awards such as the Walter Frazier Award and the Latiolais Leadership Award presented at ASHP in 2003.

Dr. Siegel has published in numerous journals and textbooks and has presented nationally and internationally on a broad range of pharmacy topics from immunology to management issues.
The Pharmacist’s Role in Preventing Antimicrobial Resistance

Debra A. Goff, Pharm.D.
Clinical Associate Professor
The Ohio State University College of Pharmacy
Infectious Diseases Specialist
The Ohio State University Medical Center
Columbus, Ohio

Dr. Debra A. Goff is Infectious Disease Specialist and Antibiotic Utilization Review Coordinator at The Ohio State University Medical Center (OSUMC) in Columbus, Ohio. She is also an Associate Professor at OSU College of Pharmacy.

Dr. Goff serves as a preceptor in the infectious diseases residency program at OSUMC and she is Chairperson for the OSUMC Robert J. Fass Memorial Infectious Disease Fund. She received her B.S. and Doctor of Pharmacy degrees and completed a pharmacy residency at the University of Illinois at Chicago.

Dr. Goff serves as an abstract reviewer for the American College of Clinical Pharmacy and was honored in 2002 by the OSUMC Leadership Council for Clinical Value Enhancement for developing clinical practice guidelines entitled “Community-Acquired Pneumonia in Immunocompetent Adult Patients.” She has received over 100 research grants and presented over 200 lectures nationally and internationally. She has published in several journals, including Pharmacotherapy, Current Opinion in Infectious Diseases, Archives of Internal Medicine, and Clinical Infectious Diseases. Dr. Goff is a member of the American College of Clinical Pharmacy, the Infectious Disease Society of America, the American Society for Microbiology, and the Society of Infectious Diseases Pharmacists.

Her research interests include antimicrobial resistance, clinical outcomes research, and antifungals.
The Pharmacist’s Role in Preventing Antimicrobial Resistance

Debra Goff, Pharm.D.
Associate Professor
Infectious Disease Specialist
The Ohio State University Medical Center
Columbus, Ohio

Objectives
• Describe the prevalence of antimicrobial resistance
• List the consequences of inappropriate antibiotic prescribing
• Describe strategies to improve antibiotic use
• Discuss how pharmacists can be proactive
• The Ohio State University specific data
  – Implementation of physician computer order entry (CPOE) ID Web site
• Resistance problems with ESBLs and strategies to resolve them

Resistance is Global

Canada 30-52%
USA 40%
Taiwan 59%
Switzerland 45%

Resistant Pathogens

- **Gram negatives**
  - *Pseudomonas aeruginosa*
  - ESBL: extended spectrum B-lactamase
  - *Klebsiella pneumoniae*
  - *Klebsiella oxytoca*
  - *E. coli*
  - *Acinetobacter*

- **Gram Positives**
  - *CA-MRSA*: community associated methicillin resistant staph aureus
  - *PRSP*: penicillin resistant strep pneumoniae (and macrolide)
  - *VRE*: vancomycin resistant enterococci

The "Superbugs" Aren't Waiting!

- Industry is getting out of the anti-infective business
- No new Gram-negative class of antibiotics in the pipeline
- From discovery to FDA approval is 10 years

Infectious Disease Society of America (IDSA). Press release, 9/04.

Consequences of Inappropriate Antibiotics

- **Myth**
  There is time to start with one antibiotic and then switch to an alternative if the 1st therapy is found to be inadequate.

- **Fact**
  Inadequate initial therapy increases mortality in patients with VAP.

• "Hospitals, as the primary incubators of antimicrobial resistant pathogens, carry the highest responsibility for proper stewardship of antimicrobials."


Antimicrobial Management Team

Every hospital has at least one person from each category

One can’t function without the others

Don’t try to do it all by yourself

That’s a recipe for failure
Information You Must Gather to Become Proactive in the Fight against Resistant Pathogens

- What are the problem pathogens?
- How can I find out if my hospital has them?
- What do I do with the information?
- What has been shown to work?

Decide What Strategy to Use

- Size of hospital
  - 1125 beds
- Intensity of antibiotic use
  - >$3 million/year
- Sophistication of hospital information systems
  - CPOE 2000
- Personnel available
  - ID Pharm.D. 50%
  - ID resident

Strategies That Have Worked

- Create a list of inappropriate combinations
- Daily queries to IS to identify patients
- Over a 3-month period 134/137 inappropriate combinations modified by the pharmacist
- $48,000 cost savings

Strategies That Have Worked

• CPOE hospital vancomycin project
  • Half the MDs had to indicate a rationale for vanco from one of the categories provided on CPOE, the others just ordered vanco
  • If prescribed, an additional screen displayed at 72 hours to indicate reason for continuing vanco
  • MDs in intervention group wrote significantly fewer orders for vancomycin


Strategies That Have Worked

• 275-bed community hospital
  • 1 ID physician, 1 clinical pharmacist
  • Patients on inappropriate antimicrobials randomized to standard care vs ID team
  • Suggestions for therapy via chart note
  • 89% acceptance
  • LOS shorter by 3 days
  • Cost reduction of $2,642/intervention
  • Outcomes similar


Strategies That Have Worked

• 731-bed teaching hospital
  • Review and feedback strategy
  • Restricted antibiotics required ID approval
  • Others dispensed but reviewed by pharmacists within 48 hours
  • Recommendation via chart note
  • If no action (accept/reject) within 24 hours pharmacist wrote recommendation as ordered
  • 92% of recommendations accepted
  • Significant reduction in total and targeted antibiotics

The Ohio State University Medical Center

- James Cancer Center 165 beds
  bone marrow transplants
- Ross Heart Hospital 110 beds
  Heart and lung transplants
- The Ohio State University Hospital 850 beds
  solid organ transplant
  SICU, MICU, NICU, burn unit

OSUMC Hospital-wide
Antibiogram 1998 - 1999

<table>
<thead>
<tr>
<th></th>
<th>Pip</th>
<th>Celfo</th>
<th>Imip</th>
<th>Gmr</th>
<th>Tobram</th>
<th>Telomycin</th>
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OSUMC - MICU Antibiogram
July 1999 - Dec. 1999 First isolates only

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<td>E. cloacae</td>
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Targeted Coverage

- Ertapenem
- Ampicillin/sulbactam
- Piperacillin/tazobactam
- Imipenem

Historical Data for Imipenem

- Was restricted (from routine use) in 1996 and reserved for documented MDR Gram-negative infections
- All orders were reviewed for appropriate use
- Interventions were made if the guidelines were not followed
OSU-specific Data

- Hospital-wide antibiograms
  no resistance problems identified
- Unit-specific antibiograms
  *Klebsiella pneumoniae*
  ESBL resistance
- Implemented antibiotic cycling x 1 year

**MICU First Isolates: Pre and Post Data**

<table>
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<tr>
<th>Year</th>
<th>K. pneumoniae</th>
<th>P. aeruginosa</th>
<th>S. maltophilia</th>
<th>A. baumannii</th>
<th>E. coli</th>
<th>E. cloacae</th>
<th>S. marcescens</th>
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<td>40</td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>20</td>
<td>30</td>
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<td>1/00-6/00</td>
<td>12</td>
<td>30</td>
<td>3</td>
<td>4</td>
<td>10</td>
<td>15</td>
<td>20</td>
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<td>7/00-12/00</td>
<td>12</td>
<td>20</td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>10</td>
<td>15</td>
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*p<0.05

**Klebsiella pneumoniae**

MICU data: first isolates decrease from 32 to 12
Hospital-wide Use of Imipenem-cilastatin
(# of doses)

Take Home Message

• A hospital-wide antibiogram can mask resistance issues
• Individual ICU antibiograms can be useful in guiding the selection of empiric antibiotics
• Know if your micro lab is reporting ESBL-producing Klebsiella isolates
• The price of antibiotic resistance is much greater than the price of the antibiotic

Microbiology Issues

• The results of this study clarified the need to have ESBL-producing Klebsiella identified by our micro lab
• The new antibiogram identifies ESBL-producing Klebsiella
Evaluation of Clinical Outcomes of Patients with ESBL *K. pneumoniae*

Methods:
- Patients with ESBL *Kp* from Oct 00–Dec 02 were identified from the micro database
- Micro data: antibiotic susceptibility, site of infection (blood, urine, sputum, other)
- Patient data: community or nosocomially acquired, antibiotic exposure, risk factors for ESBL *Kp*, mortality

OSUMC Hospital-wide Data
2000-2002 ESBL-*KP*  n=96

Acquisition of Infection
Patient Location at OSU  \( n=64 \)

ESBL-\textit{Klebsiella pneumoniae} Patients

- Patients were located in many different areas
- This was NOT just an ICU problem

Patient Outcome Data

62/64 had empiric antibiotics started at OSU
- The empiric choice was ineffective (resistant to the ESBL-\textit{Kp}) in 41/64 (64%)
- Overall mortality = 19% (12/64)

12 deaths
- All died while on antibiotics
- 10 received ineffective empiric antibiotics
- 7 died before drug susceptibility results
Conclusions

• ESBL-Kp is not just an ICU problem
• Mortality is associated with initial antibiotic choice
• Carbapenems are the most appropriate choice for patients with nosocomial or community-acquired ESBL-Kp
• Recent literature indicates ESBL-Kp is increasing in frequency (up to 40%)
• Can OSU improve antibiotic prescribing?

OSUMC Hospital-wide
Antibiogram 2003

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<th>Pathogen</th>
<th>01</th>
<th>02</th>
<th>03</th>
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<td>K. pneumonia (557)</td>
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<td>98</td>
<td>99</td>
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<td>K. pneumonia ESBL (40)</td>
<td>5</td>
<td>16</td>
<td>100</td>
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<td>E. cloacae (211)</td>
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<td>E. coli (1648)</td>
<td>93</td>
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<td>P. aeruginosa (741)</td>
<td>82</td>
<td>76</td>
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<tr>
<td>A. baumannii (58)</td>
<td>39</td>
<td>42</td>
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What’s the Urgency to Improve Antibiotic Use?
OSUMC Antibioticgrams: 2001-2003

• Antibiotic resistant pathogens are increasing
  
<table>
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<th>Pathogen</th>
<th>MICU</th>
<th>01</th>
<th>02</th>
<th>03</th>
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<tr>
<td>MRSA</td>
<td></td>
<td>50%</td>
<td>54%</td>
<td>59%</td>
</tr>
<tr>
<td>VRE (E. faecium)</td>
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<td>52%</td>
<td>75%</td>
<td>75%</td>
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<tr>
<td>K. pneumoniae ESBL</td>
<td></td>
<td>0%</td>
<td>4%</td>
<td>9%</td>
</tr>
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</table>

• Antibiotic susceptibility for Pseudomonas aeruginosa (most prevalent Gram-negative pathogen) is decreasing

<table>
<thead>
<tr>
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<th>MICU</th>
<th>01</th>
<th>02</th>
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<tbody>
<tr>
<td>Ciprofloxacin</td>
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<td>72%</td>
<td>62%</td>
<td>60%</td>
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<td>Imipenem</td>
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<td>85%</td>
<td>71%</td>
<td>73%</td>
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<td>Piperacillin/tazo</td>
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<td>87%</td>
<td>82%</td>
<td>83%</td>
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<tr>
<td>Cefepime</td>
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<td>84%</td>
<td>72%</td>
<td>76%</td>
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<tr>
<td>Gentamicin</td>
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<td>87%</td>
<td>65%</td>
<td>68%</td>
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OSU Formulary Decision

- The incidence of multi-drug resistant ESBL K. pneumoniae at OSU increased from 4% to 7% in 2003
- Over 50% of ESBL infections were community acquired
- The only class of antibiotics that had susceptibilities over 70% to the ESBL K. pneumoniae were the carbapenems
- Ertapenem was added to the formulary on May 27, 2003

Ertapenem

- New IV carbapenem 1 gram daily
- Approved in the USA for:
  - complicated intra-abdominal
  - skin and skin structure
  - complicated urinary tract and pelvic infections
  - Community-acquired pneumonia
  - diabetic foot infections
- Spectrum of activity is similar to cefoxitin
  - It’s NOT a cephalosporin it’s a carbapenem
  - It’s DOSED once daily not 4 times a day

Ertapenem

- Gram-positive
  - MSSA, Strep pyogenes, S. pneumonia, S. agalactiae
- Gram-negatives (aerobes)
  - E. coli, K. pneumoniae
  - H. influenzae and oxytoca, M. catarrhalis
- Anaerobes
  - Bacteroides fragilis
  - B dot group
  - Peptostreptococcus
  - Clostridium perfringes, clostridioforme
  - Eubacterium lentum
Targeted Coverage

**Ertapenem**

**Ampicillin/sulbactam**

**Piperacillin/tazobactam**

**Imipenem**

Collateral Damage

Empiric coverage

Non-Pseudomonas gram-

negatives

Gram-

positives

Resistant

ESBL's

Anaerobes

Gram-

positives

Resistant

ESBL's

Why Add Ertapenem?

- Provides an effective antibiotic for ESBL-producing pathogens, without resortsing to imipenem
- Provide an alternative to ampicillin/sulbactam for the post-operative surgical patient
- Does not contribute to “collateral damage”
- Not for empiric therapy of nosocomial infections
- Ertapenem does NOT COVER:
  - *Pseudomonas aeruginosa*
  - *Enterococcus species*
  - *Acinetobacter spp.*

OSU Changed the Method of Ordering Antibiotics

- Why?
  - Inappropriate use contributes to antibiotic resistance
  - Patients infected with antibiotic resistant bacteria have an increased length of stay and higher mortality
  - Increased length of stay increases hospital costs
- How?
  - CPOE (computer physician order entry)
  - Must select an indication


Antibiotic Prescribing Committee
Winter 2002
• CPOE was introduced at OSU in May 2000
• Can we change antibiotic prescribing via CPOE?
• Can we establish indications for ALL antibiotics?
• Start with piperacillin-tazobactam (old antibiotic)
• Introduce ertapenem (new antibiotic)
• Goals: Improve antibiotic utilization and preserve anti-pseudomonal antibiotics for patients with documented or suspected P. aeruginosa infections

Ertapenem Specific Goals
• Evaluate the effectiveness of using CPOE to identify the utilization of ertapenem
• Monitor the susceptibility of ESBL isolates and other Gram-negative pathogens to ertapenem

Enter an Indication or Select an Alternative Treatment

Indications screen for piperacillin-tazobactam
Screen for alternative selection, requires an indication

Indications screen for Ertapenem (5/03)

Discussion

- The CPOE method provided insight into many issues
- What has improved because of this?
  1. Cultures are being ordered
  2. Underdosing has been identified
  3. Prescribing was altered for amp/sulbactam by removing 3 g option
  4. Ertapenem was introduced and prescribed appropriately

Discussion

- **What needs to improve?**
  Little change takes place after the culture results are back. In order to preserve broad-spectrum antibiotics we MUST streamline if *P. aeruginosa* is not confirmed.

- New antibiotics
  Ertapenem was successfully introduced and used appropriately. All new antimicrobials will be introduced by this method.
Objective

- Monitor the effect of ertapenem on the susceptibility of Gram-negative aerobes to other formulary antibiotics including:
  - Imipenem
  - Piperacillin/tazobactam
  - Cefepime
  - Ampicillin/sulbactam
  - Ciprofloxacin
  - Tobramycin

Methods

- Hospital antibiograms reflecting the year prior to ertapenem and 19 months post-ertapenem were compared
  - Antibiotic % susceptible were compared using Fisher’s exact test
- Susceptibilities were determined by microdilution using Microscan panels for all but ertapenem
- Ertapenem testing was performed by Etest for all ESBL K pneumonia, K oxytoca, E.coli
- Antibiotic DDD/1000 patient days from 2002 was compared to 2004
Results

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Discussion Pseudomonas aeruginosa

- Decreasing susceptibility of PA to ciprofloxacin has been occurring since 1999
- A slight improvement (51-55%) was observed the year following ertapenem’s addition

Ertapenem/Imipenem and ESBL Klebsiella pneumoniae

- CPOE initiated for ertapenem
Conclusion

• The formulary addition of ertapenem did NOT negatively effect the susceptibilities of Gram-negative aerobes to imipenem
• The percent of ESBL pathogens has decreased as total carbapenem use increased
• Pharmacists have an important role in the management of antibiotic therapy and resistance prevention

Questions and Discussion

• We welcome your questions.
• Staff will collect all written question cards.
• Please approach the standing microphones in the aisle.
• Please complete the program evaluation and hand to staff as you exit.
• Thank you for your attention.
• Join us again for CE in the Mornings.
The Pharmacist’s Role in Preventing Antimicrobial Resistance

References


Goff DA, Sierawski SJ. Clinical experience of quinupristin-dalfopristin for the treatment of antimicrobial-resistant Gram-positive infections.


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Dr. Goff reports that she has received grants and serves as a speaker for Merck and Enzon Pharmaceuticals and that she serves as a speaker for Pfizer, Inc.