

Infection Control and Antimicrobial Stewardship: Our only two strategies to combat antimicrobial resistance

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Learning Objectives

- Optimize clinical outcomes through appropriate infection control and antimicrobial use
- Minimize unintended consequences of antimicrobial use
- Understand the importance of appropriate antimicrobials for patient safety
- Facilitate appropriate antimicrobial use through stewardship and infection control programs

Faculty Disclosures

Dr. Rapp:

Consultant—Ortho-McNeil, Wyeth
Pharmaceuticals;

Scientific advisor—Ortho-McNeil, Wyeth
Pharmaceuticals;

Promotional speakers bureau—Astellas Pharma
US, Inc, Ortho-McNeil, Wyeth Pharmaceuticals

Overview

- Morbidity and mortality of nosocomial infection
- Economics of nosocomial infections
- Impact of infection control strategies
 - Recognizing colonization a priori and treatment
 - Protocols and prevention guidelines
 - Hand washing
 - Contact precautions
 - Isolation
 - Environmental decontamination
 - Antibiotic stewardship
- Contemporary examples
 - HA-MRSA and CA-MRSA
 - Detection & management of colonized patients
 - *C difficile* pseudomembraneous colitis
 - BI/NAP1
 - SHEA Annual Meeting

HA-MRSA = hospital-acquired methicillin-resistant *Staphylococcus aureus*; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; *C difficile* = *Clostridium difficile*; SHEA = Society for Healthcare Epidemiology of America.

MDR Pathogens & Healthcare Economics

- Medicare will not reimburse hospitals when infection acquired after admission in 2008
 - 1.7M patients acquire an infection in the hospital each year
 - 100,000 patients die of these infections
 - Estimated annual cost \$6.5B
 - Dickema DJ, et al. *JAMA*. 2008;299(10):1190-1192.
- Consumer reporting of infection rates
 - Being used as a marketing tool
 - 19 states require hospitals to report infection rate
 - 4 states publish rates for individual hospitals

MDR = multidrug resistant.

Dickema DJ, et al. *JAMA*. 2008;299(10):1190-1192. US Department of Health and Human Services. www.hospitalcompare.hhs.gov. Accessed March 18, 2009.

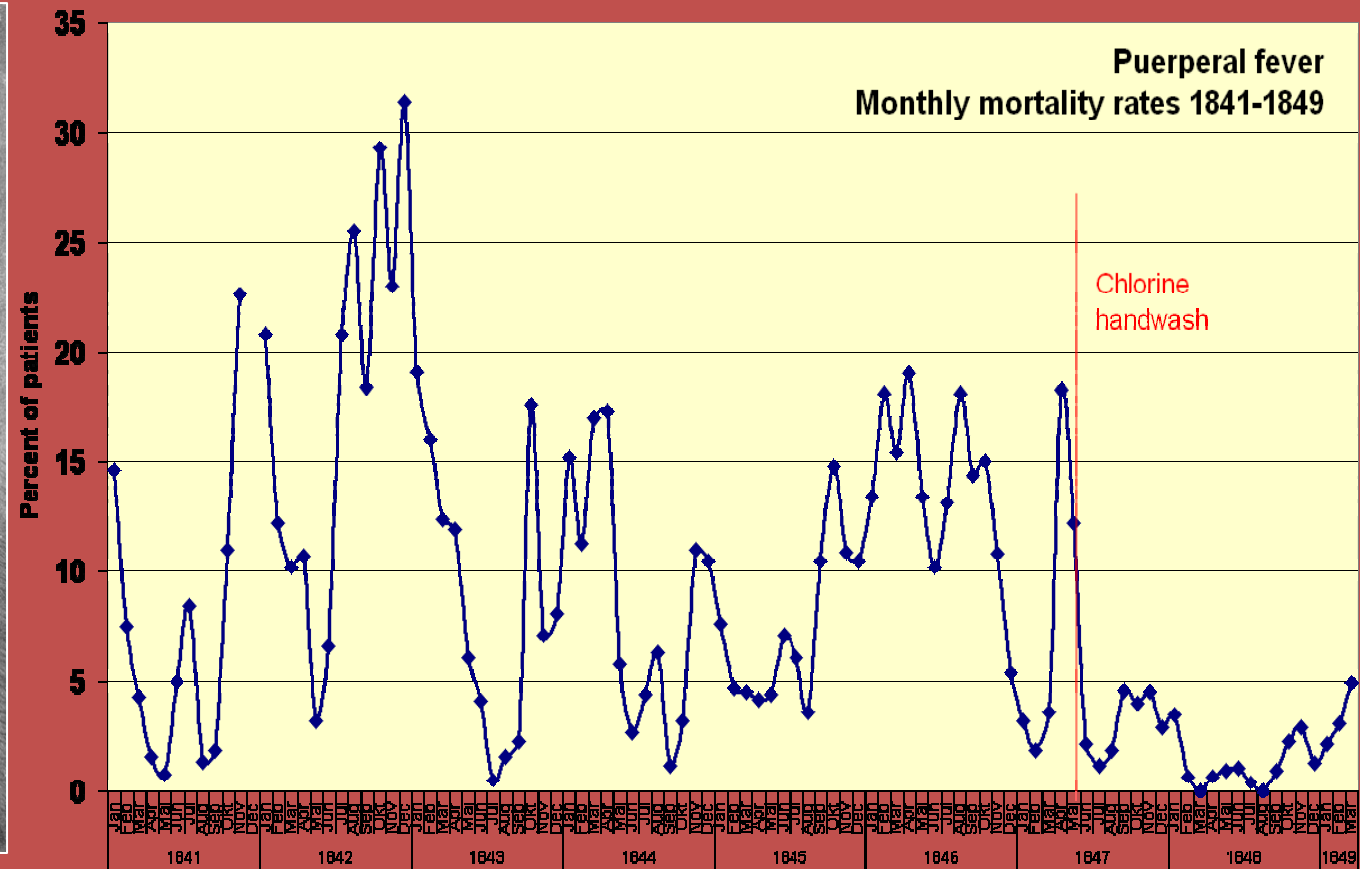
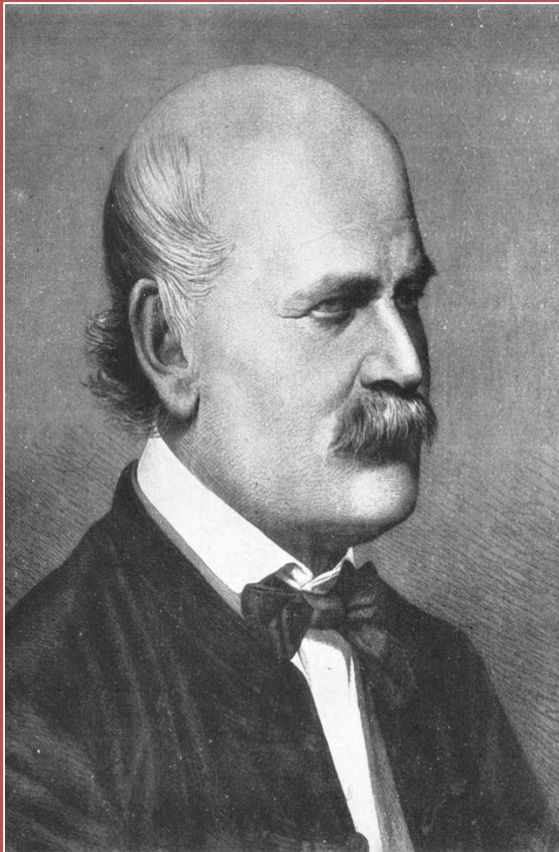
Consumers Union. <http://www.stophospitalinfections.org/learn.html>.

Accessed March 18, 2009.

Comparison of Hospital Costs and Charges for MRSA versus MSSA Infections

Type of Infection	End Point	Hospital Costs and Charges	
		MRSA (\$)	MSSA (\$)
Nosocomial bloodstream infection	Median total cost of hospitalization attributable to bloodstream infection	27,083	9661
Infections in an LTCF	Median infection cost	2607	1332
Nosocomial bloodstream infection	Median hospital charges after onset of bloodstream infection	26,212	19,212
Surgical site infection	Median hospital charges attributable to surgical site infection	92,363	52,791
Nosocomial bloodstream infection	Adjusted mean cost after onset of bloodstream infection	21,577	13,978
Nosocomial bloodstream infection	Mean cost/patient-day of hospitalization	5878	2073
Bloodstream infection in patients undergoing dialysis	Adjusted mean cost of first hospitalization	21,251	13,978
	Adjusted mean cost 12 weeks after first hospitalization	25,518	17,354
All infections	Attributable mean cost	34,000	31,500
Nosocomial infections	Attributable mean cost	31,400	27,700
Nosocomial infections	Mean total cost of hospitalization directly attributable to infection	7481	2377

**MSSA = methicillin-susceptible *Staphylococcus aureus*; LTCF = long-term care facility.
Lodise TP, et al. *Pharmacotherapy*. 2007;27(7):1001-1012.**



Ignaz Philipp Semmelweis (July 1, 1818, to August 13, 1865)

- Assistant to the professor of the maternity clinic at Vienna General Hospital
- Introduced hand washing with chlorinated lime for interns
- Reduced puerperal fever (childbed fever) from about 10% to 1%-2%
- His hand-washing theory was ridiculed and rejected by his colleagues

SHEA Guidelines

- Antimicrobial stewardship—2007
- Preventing antibiotic resistance—1997
- Surveillance of *C difficile*—2007
- *C difficile* in LTCFs—2002
- *C difficile* diarrhea and colitis—1995

The Society for Healthcare Epidemiology of America. SHEA Guidelines and position papers. <http://www.shea-online.org/evidence-based-guidelines.cfm>. Accessed April 22, 2009.

STOP SUPERBUGS



SCRUB
EM!

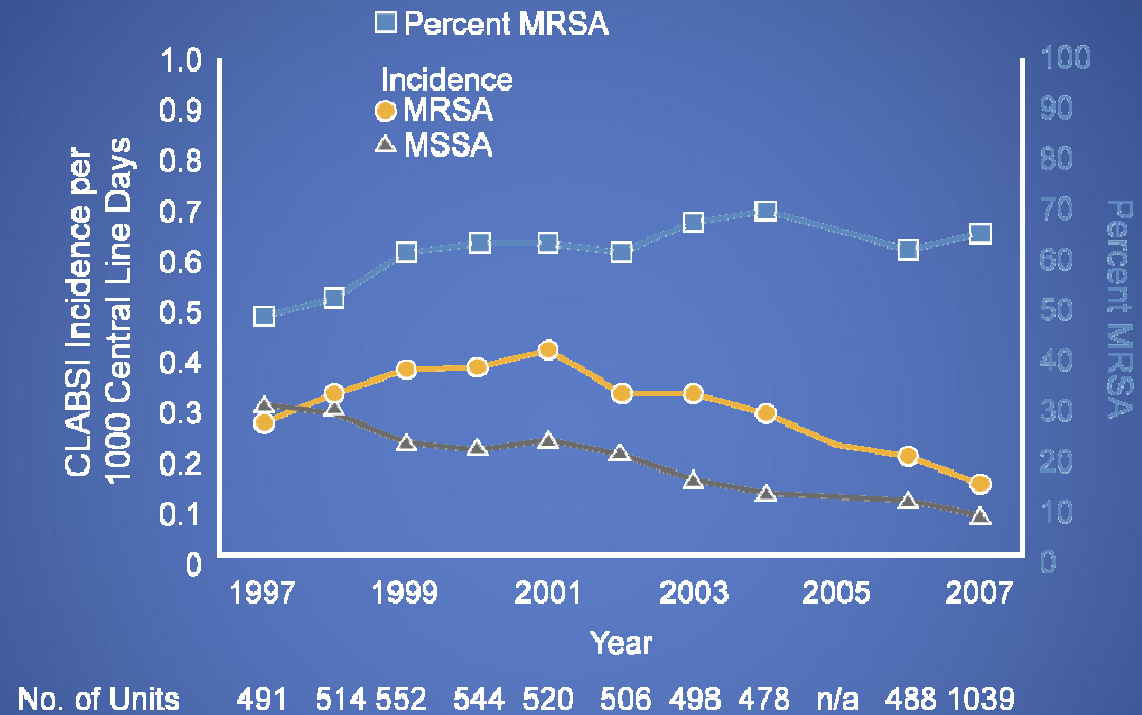
Proper hand washing is
the single most effective
measure to prevent
infection



Device to Monitor Hand Washing: Big Brother Is Watching

- Pager-sized device is worn by healthcare professional
- User badge read automatically logging in time, date, and dispenser
 - Data downloaded to a server
- Sensor can detect using signal strength to determine location of healthcare professional
- Can measure compliance with hand hygiene
- With a 30-second room presence sensitivity 91% and specificity 100%

Trends in Percent MRSA and Incidence of *S aureus* CLABSI in ICUs—National Nosocomial Infections Surveillance System, 1997-2004; National Healthcare Safety Network, 2006-2007



Data are aggregated for the 7 ICU types evaluated. Pooled mean percent MRSA is calculated as the MRSA CLABSI incidence divided by the sum of the MRSA CLABSI incidence and the MSSA CLABSI incidence. CLABSI incidence for 2005 is estimated from log-linear models of the annual CLABSI trend. (No 2005 data are available from either surveillance system.) Error bars indicate 95% confidence intervals.

S aureus = *Staphylococcus aureus*; ICUs = intensive care units; CLABSI = central line-associated bloodstream infection.

Burton DC, et al. *JAMA*. 2009;301:727-736.

MRSA CLABSIs in US ICUs 1997-2007

- Examined rates of central line infections from 1684 ICUs (7 types of adult and non-neonatal pediatric)
- Examined rate of overall and MRSA central line–induced BSIs/1000 central line days
- 33,587 CLABSIs reported over 16M+ days of surveillance
 - 7.4% MRSA and 4.7% MSSA
- Incidence of MRSA-induced central line infections decreased in all major adult ICUs and remained stable in pediatrics

MRSA CLABSIs in US ICUs 1997-2007 (continued)

- Possible cause:
 - Improved central line insertion and care practices
 - Dissemination of prevention guidelines
 - Preventing transmission of MRSA patient to patient
 - PCR improves detection time for MRSA but may not reduce transmission or infection rates
- Limitations (accompanying editorial)
 - <6% of ICUs participated in the NNIS/NHSN for the entire 11-year interval
 - Cannot identify a specific intervention as the reduction cause
 - Authors cannot confirm whether targeted MRSA interventions were in place at participating hospitals

PCR = polymerase chain reaction; NNIS/NHSN = National Nosocomial Infection Surveillance/National Healthcare Safety Network.

Burton DC, et al. *JAMA*. 2009;301(7):727-736. Climo MW. *JAMA*. 2009;301(7):772-773.

Audience Response Question

Patient is a 62-year-old male who will undergo elective open heart surgery. What action(s) might be considered?

1. Nasal swab for detection of *S aureus*
2. Decolonization if patient is positive for *S aureus*
3. Screening of his primary healthcare professionals for *S aureus*
4. Appropriate contact precautions
5. All of the above

What to Do for CA-MRSA Colonization

- Patients
 - Active surveillance cultures
 - Isolation or cohorting
- Healthcare workers
 - No uniformly accepted policy
- Hospital
 - Good hand hygiene policies and environmental cleaning
 - Soap and water for 20-30 seconds
 - Use 60%-plus alcohol-based product
- Home
 - No sharing towels, razors, etc
 - Showering with soap and hand washing
 - Laundering or disinfecting sports equipment
 - Pets

Evaluation of CDC Hospital Environmental Hospital Room Cleaning Guidelines

- Room cleaning procedures guided by CDC and Healthcare Infection Control Practices Advisory Committee guidelines
- A more intensive cleaning effort could reduce risks for MRSA and VRE
 - Cleaning products used and procedures
 - Use of internal controls
 - Education
 - Attention to high-touch surface areas
 - Light switches, touch pads, bedrails, window ledges, door knobs, etc
- Using the authors' previous developed modeling techniques and OR, the authors suggest that cleaning standard guidelines may need to be changed

CDC = Centers for Disease Control and Prevention; VRE = vancomycin-resistant enterococci; OR = odds ratio.

Datta R. Society for Healthcare Epidemiology of America (SHEA) 19th Annual Scientific Meeting: Abstract 273. Presented March 20, 2009.

What to Do for CA-MRSA Colonization

- Topical agents
 - 4% Chlorhexidine gluconate wash every 24 hours X 5 days
 - 2% Calcium mupirocin 1-gram single-use tube every 12 hours for 10 days
 - Resistance already noted
 - Neomycin/triple antibiotic ointment (Neosporin)
 - Bacitracin
 - Retapamulin (Altabax)
 - Approved for impetigo but not MRSA
 - Tea tree oil (nares-10% cream or 5% body wash)
 - Povidone-iodine (shampoo, nasal and oral options)
 - Hexachlorophane
 - Triclosan

Diekema DJ, et al. *JAMA*. 2008;299(10):1190-1192. Harbarth S, et al. *JAMA*. 2008;299(10):1149-1157. Owens RC. *Pharmacotherapy*. 2006;26(3):299-311. McConeghy KW, et al. *Pharmacotherapy*. 2009;29(3):263-280.

Audience Response Question

As a member of your hospital pharmacy and therapeutics committee, you are probing a recent outbreak of *C difficile* colitis. Items that should be included in your evaluation might be:

1. Individual antibiotic use within the last 3-12 months and changes in patterns of antibiotic use within the hospital itself
2. Mapping the geography of the outbreak and care personnel involved
3. Compliance with infection control policies
4. Hand-washing products currently being used
5. All of the above

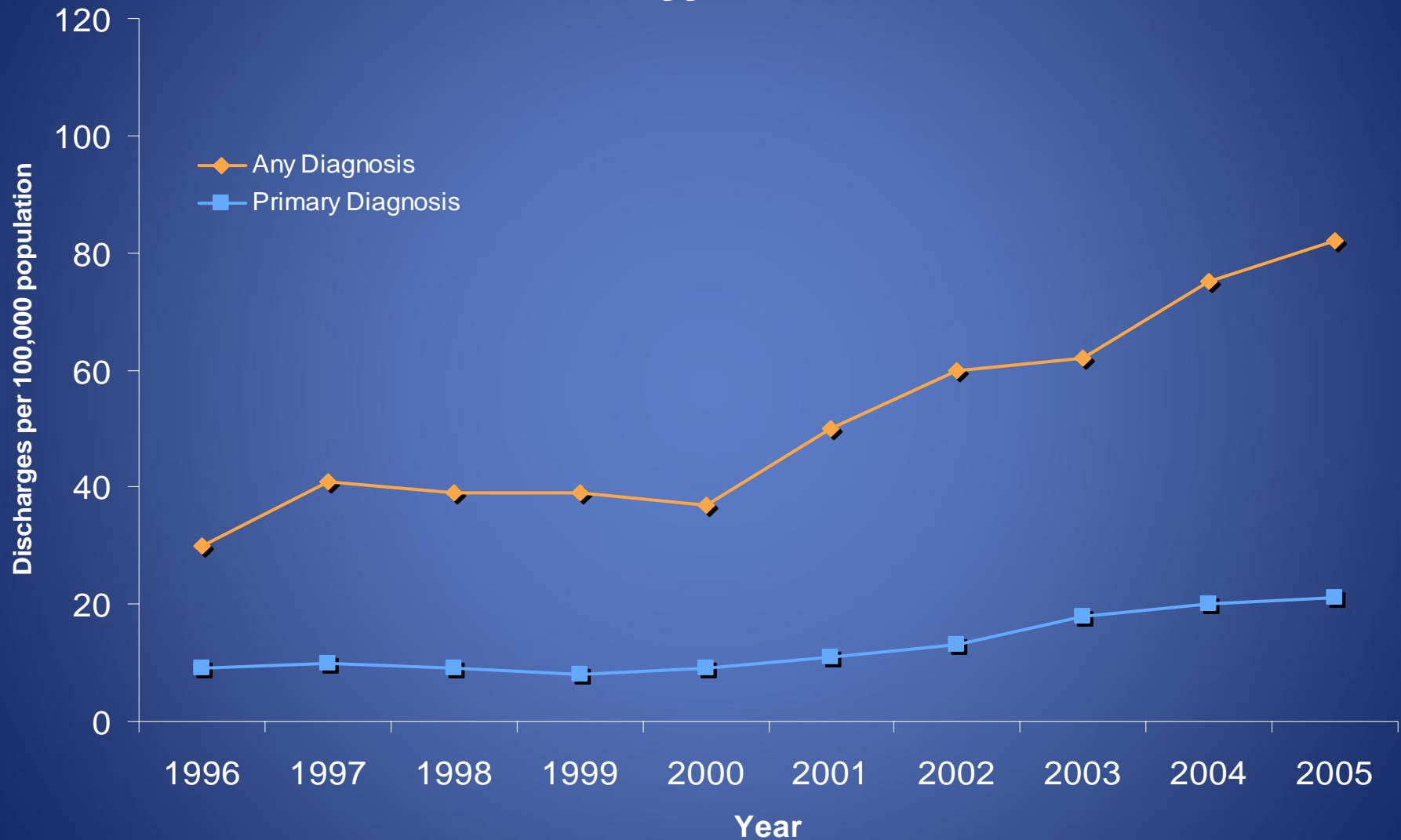
C difficile (CDAD) Outbreak

- Rates of pseudomembraneous colitis on the rise
 - BI/NAP1
 - Linked to patients' recent use of antibiotics, PPIs, etc
 - Possible link to patterns of antibiotic utilization
 - Fluoroquinolones
- Great concern over binary toxin producing strain and increasing incidence and higher morbidity and mortality
- Outbreaks the result of:
 - New and more virulent strain
 - Alteration of environment
 - Index case with infection control failure

CDAD = *C difficile*-associated disease; PPIs = proton pump inhibitors.

Owens R. *Pharmacotherapy*. 2006;26:299-311. McMaster-Baxter NL, et al. *Pharmacotherapy*. 2007;27:1029-1039. Miller M. *Clin Infect Dis*. 2007;45:S122-S128. Adams DA. *Antimicrob Agents Chemother*. 2007;51:2674-2678.

Rates of *C difficile* Infection



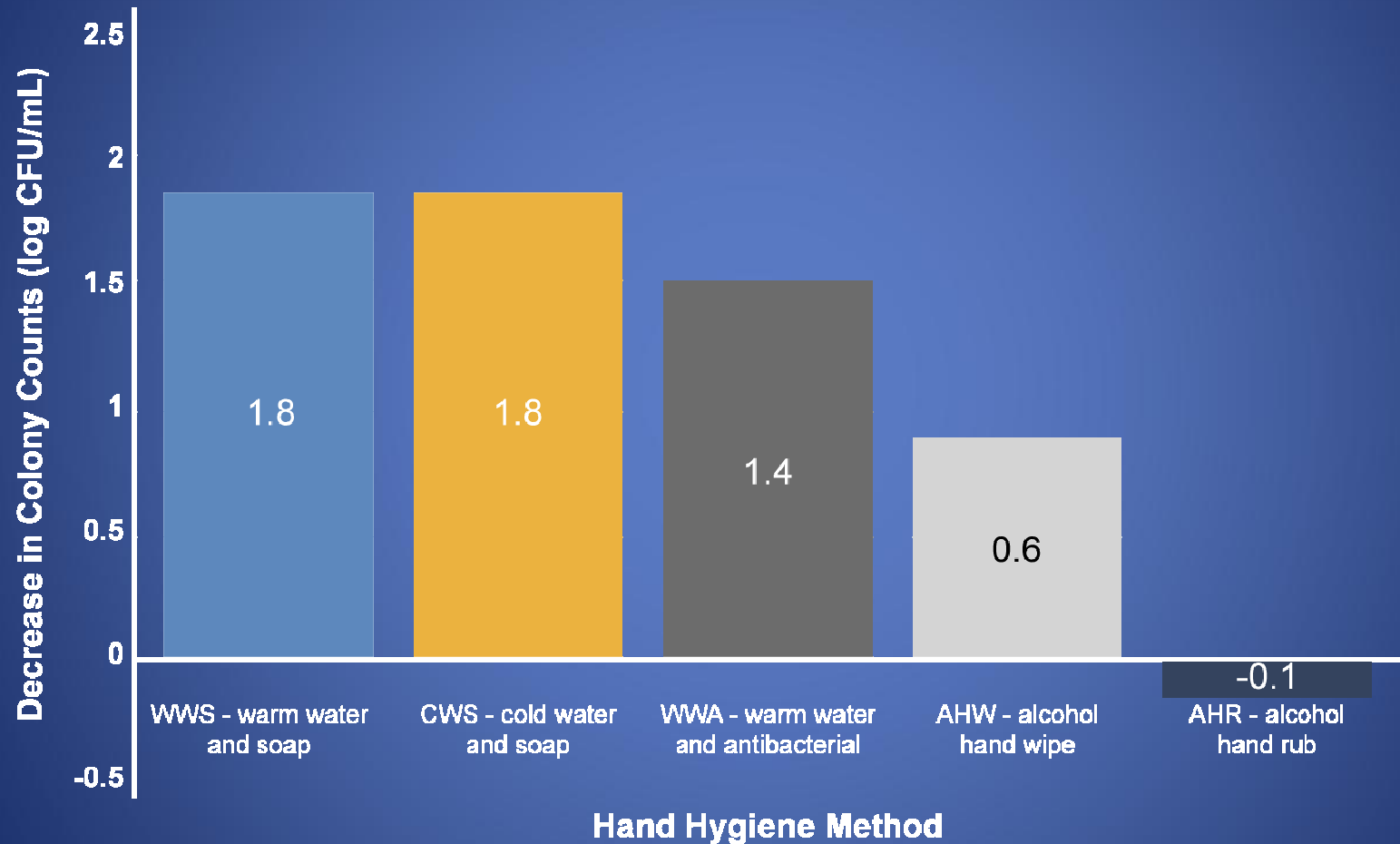
McDonald LC, et al. *Emerg Infect Dis.* 2006;12:409-415.

C difficile and Infection Control

- Effective intervention equates with preventing organism and spore transmission
 - Hand washing
 - After each patient contact and throughout the day
 - Agent used for hand washing
 - Soap and water vs alcohol-based hand gel/foams vs quaternary ammonium products
 - Isolation and contact precautions
 - Dedicated equipment
 - Decontamination of the environment
 - 10% bleach solution or commercial hypochlorite product
 - Antibiotic stewardship

Owens R. *Pharmacotherapy* 2006;26:299-311. McMaster-Baxter NL, et al. *Pharmacotherapy*. 2007;27:1029-1039. Miller, M. *Clin Infect Dis*. 2007;45:S122-S128. Adams DA. *Antimicrob Agents Chemother*. 2007;51:2674-2678.

Hand-washing Methods and *C difficile* Colony Count Reduction



CFU = colony-forming unit.

Oughton M, et al. Interscience Conference on Antimicrobial Agents and Chemotherapy. 2007.

Effectiveness of Hand-Washing Agent for *C difficile* Spores

- ~10⁶ nontoxigenic spores placed on the palms of the hands of volunteers
 - 15-second wash followed by a 15-second rinse for each product
 - Modified American Society for Testing Materials E1174 method used to evaluate spore removal
 - Products tested
 - 4% Chlorhexidine gluconate hand wash
 - 0.3% Triclosan hand wash
 - Nonantimicrobial hand wash
 - Nonantimicrobial body wash
 - Heavy-duty hand cleaner used by printers
 - Tap water
 - Most products reduced counts by 1 log
 - Heavy-duty hand cleaner best with a 1.2 log reduction

C difficile Lessons Learned

- Fixing the problem is multifactorial
 - Patient environment often complex and interwoven
 - Antibiotic stewardship must extend beyond the hospital
- Epidemic vs index case with bad infection control
 - What can be changed
 - Compliance with infection control policies
 - Antibiotic formulary changes or changes in patterns of utilization
- You can wash your hands or be cleaning the environment but you need to be using the right agent

Conclusion – Infection Control

- Always better to prevent rather than treat an infection
- Proper hand washing is the single most effective measure in preventing infection but needs to be part of an overall effort
 - Should wash frequently and after each patient contact
 - There is a right and wrong way
 - Use the right agent
 - Not just something you do in the hospital
- Infection control is a 24/7 job and only as good as the weakest element

Audience Response Question

The 2 core members of the Antimicrobial Stewardship Team include:

1. An infectious diseases–trained physician and a clinical microbiologist
2. An infection control practitioner and an infectious diseases–trained physician
3. An infectious diseases–trained pharmacist and an infectious diseases physician
4. A clinical microbiologist and an infection control practitioner

Factors Encouraging the Development of Antimicrobial-resistant Pathogens

- High severity of illness in patients once hospitalized
- Inappropriate antibiotic use
 - Prolonged use or inadequate antimicrobial exposure
- Institutional factors
- Agricultural use of antimicrobials

Stein GE. *Pharmacotherapy*. 2005;25(10 pt 2):44S-54S. South M, et al. *Med J Aust*. 2003;178(5):207-209. McGowan JE Jr. *Clin Infect Dis*. 2004;38(7):939-942. Levy SB. *J Antimicrob Chemother*. 2002;49(1):25-30.

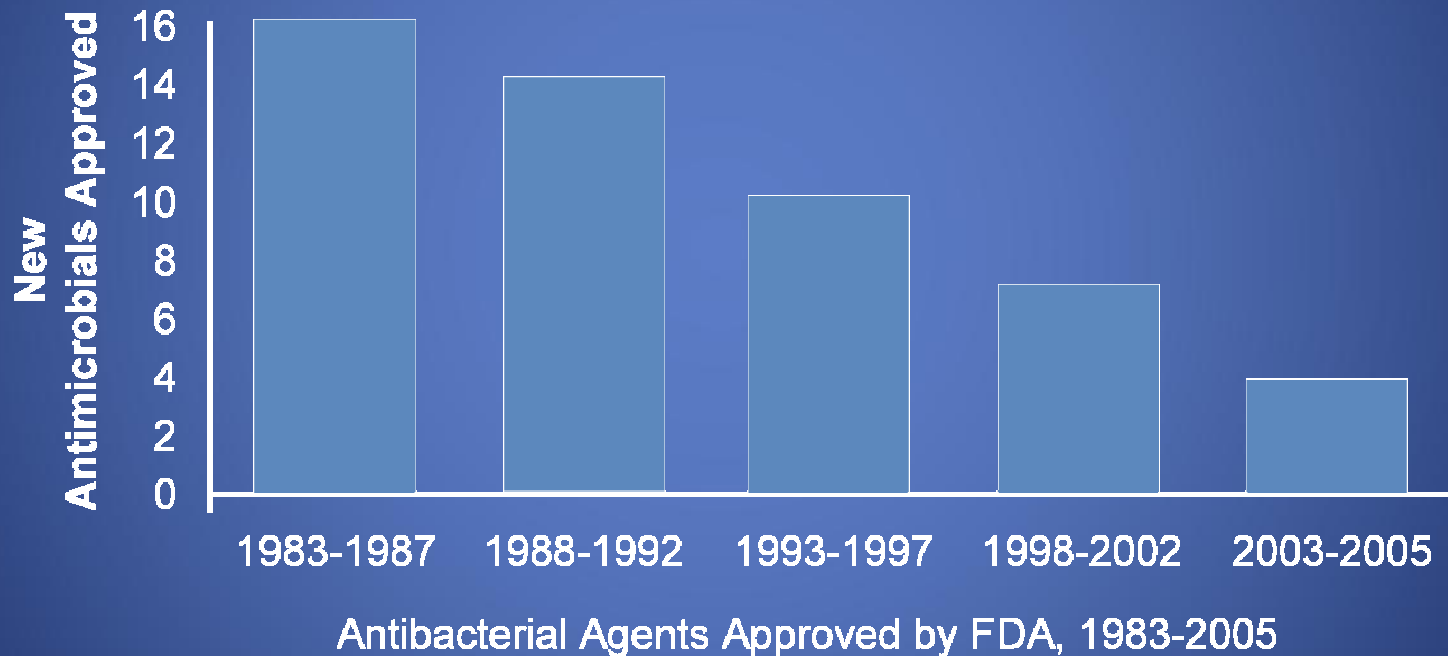
Mortality Rates Correlate with Presence of Multidrug-resistant Organisms

- Association between development of antimicrobial resistance in *S aureus*, enterococci, and gram-negative bacilli and mortality
- *Pseudomonas aeruginosa* is increasingly resistant to fluoroquinolones, with a number of consequences, including infection-related mortality
- Enterococcal infections have been associated with mortality rates exceeding 30%
- A meta-analysis of published studies found that patients with MRSA bacteremia had an increased risk of mortality compared with patients who had MSSA bacteremia (OR = 1.93; $P < .001$)

Cosgrove SE. *Clin Infect Dis*. 2006;42(suppl 2):S82-S89. McGowan JE Jr. *Am J Infect Contr*. 2006;34(5 suppl 1):S29-S37. Lautenbach E, et al. *Clin Infect Dis*. 2003;36(4):440-446. Cosgrove SE, et al. *Clin Infect Dis*. 2003;36(1):53-59.

Fewer Antibiotics to Address Increased Resistance

Fewer New Antibiotics Are Being Brought to Market as More Companies Leave the Anti-Infectives Business



FDA = US Food and Drug Administration.

Laxminarayan R, et al. Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance. http://www.extendingthecure.org/sites/default/files/ETC_FULL.pdf. Accessed March 19, 2009.

Antimicrobial Stewardship

- The optimal selection, dose, and duration of an antimicrobial that results in the best clinical outcome for the treatment of infection, with minimal toxicity to the patient and minimal impact on subsequent development of resistance.

Antimicrobial Stewardship: Overview

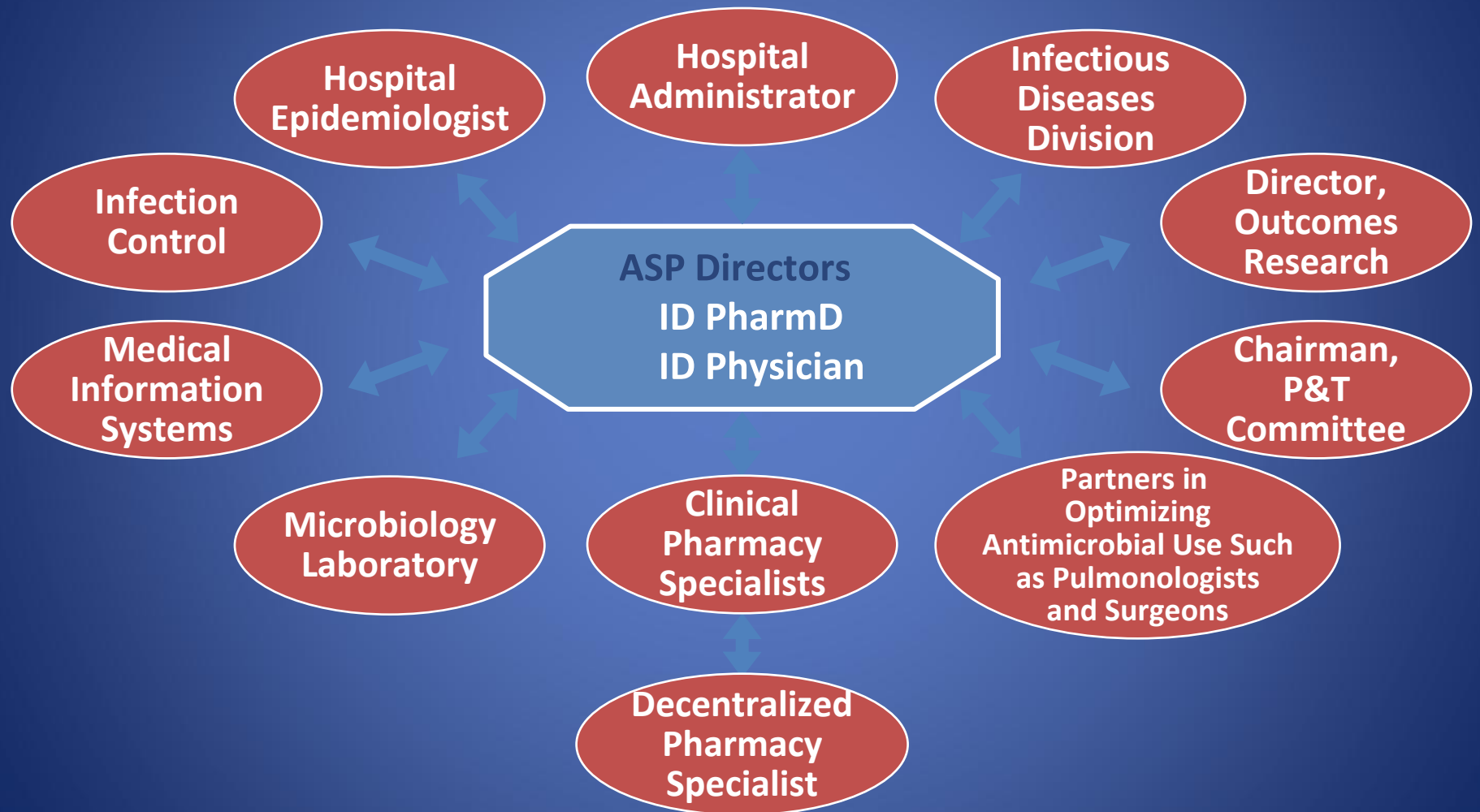
- Updated guidelines for developing programs to enhance antimicrobial stewardship published in 2007
- IDSA/SHEA consensus guidelines endorsed by
 - American Academy of Pediatrics
 - American Society of Health-System Pharmacists
 - Infectious Diseases Society for Obstetrics and Gynecology
 - Pediatric Infectious Diseases Society
 - Society for Hospital Medicine
 - Society of Infectious Diseases Pharmacists
- Primary goal
 - Optimize clinical outcomes while minimizing unintended consequences of antibiotic use
 - Toxicity
 - Selection of pathogenic bacteria (eg, *C difficile*)
 - Emerging resistance
- Secondary goal
 - Reduce healthcare cost without compromising quality of care

IDSA = Infectious Diseases Society of America.

Dellit TH, et al. *Clin Infect Dis*. 2007;44(2):159-177.

Antimicrobial Stewardship Teams

Multidisciplinary Team Approach to Optimizing Clinical Outcomes



ASP = Antimicrobial Stewardship Program; ID = infectious disease; P&T = pharmacy and therapeutics. Dellit TH, et al. *Clin Infect Dis*. 2007;44(2):159-177. Fishman N. *Am J Med*. 2006;119(6 suppl 1):S53-S61.

Qualifications of the Infectious Disease Pharmacist Specialist

- PharmD degree
- Pharmacy Practice Residency
- Infectious Disease Specialty Residency
(preferred)
- Maintains competency in infectious diseases
and microbiology

Responsibilities of the Infectious Disease Pharmacist Specialist

- Provides cost-effective pharmaceutical care to patients receiving select/targeted antimicrobial therapy
- Discuss antimicrobial order changes with infectious disease physician or prescriber
- Document changes and inform others of those changes
- Monitor antimicrobial therapy to evaluate appropriateness of use
- Provide PK/PD services as required
- Facilitate discharge planning
- Provide in-service programs to all hospital staff
- Review yearly antibiogram with appropriate individuals on a regular basis

Responsibilities of the Infectious Disease Pharmacist Specialist (continued)

- Provide financial forecasts for the infectious disease physician and the Department of Pharmacy Services for new and investigational antimicrobials and related pharmaceuticals
- Precept College of Pharmacy students
- Precept and mentor pharmacy practice and infectious disease specialty residents
- Provide presentations and publications at the local, state, regional, and national levels
- Conduct collaborative research to test the effectiveness of new methods of antimicrobial control/restriction/ reporting that may increase the effectiveness of antimicrobial stewardship

Audience Response Question

Which of the following PK/PD parameters best predicts killing with beta-lactam antibiotics?

1. Peak to MIC ratio
2. AUC to MIC ratio
3. Peak to AUC ratio
4. Time >MIC

MIC = minimum inhibitory concentration; AUC = area under the curve.

Core Strategies for Antimicrobial Stewardship

Core Strategy 1: Prospective Audit with Intervention and Feedback

- Involves concurrent review of patients receiving antimicrobials
- Inappropriate orders initiate interaction between antimicrobial team members and the prescriber
- Goal is to enhance antimicrobial stewardship (optimize selection, dose, duration, route)
- Advantages
 - Avoids loss of autonomy for prescribers
 - Creates incentives for physicians to improve performance
- Disadvantages
 - Compliance is voluntary
 - Less effective unless it distinguishes between appropriate and inappropriate prescribing

MacDougall C, et al. *Clin Microbiol Rev.* 2005;18(4):638-656. Laxminarayan R, et al. Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance. http://www.extendingthecure.org/sites/default/files/ETC_FULL.pdf. Accessed March 19, 2009.

Efficacy of Prospective Audit with Intervention and Feedback

- A randomized trial in a 600-bed teaching hospital evaluated clinical and microbiologic response to antimicrobials
- Intervention group—chart review by clinical pharmacists and infectious disease fellow
- No significant difference in clinical or microbiologic outcomes between intervention and nonintervention group
- Cost savings for intervention group was \$390,000 per year
- Additional studies have found decreased length of stay and reductions in duration of inappropriate therapy

Fraser GL, et al. *Arch Intern Med.* 1997;157(15):1689-1694. Gums JG, et al. *Pharmacotherapy.* 1999;19(12):1369-1377. Solomon DH, et al. *Arch Intern Med.* 2001;161(15):1897-1902.

Core Strategy 2: Formulary Restriction/Preauthorization

- Effective method to control antibiotic use and cost; conflicting results on decreasing antimicrobial resistance
- Advantages
 - Provides the most direct control over antimicrobial use
- Disadvantages
 - Prescribers may feel loss of autonomy
 - Team members must have contingency plans for off-hour approvals
 - May discourage appropriate antibiotic use
 - May delay receiving appropriate therapy initially

Dellit TH, et al. *Clin Infect Dis*. 2007;44(2):159-177. MacDougall C, et al. *Clin Microbiol Rev*. 2005;18(4):638-656. Laxminarayan R, et al. Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance. http://www.extendingthecure.org/sites/default/files/ETC_FULL.pdf. Accessed March 19, 2009.

Efficacy of Formulary Restriction/Preauthorization

- A 2003 study found that when requests for restricted antimicrobials were referred to a clinical pharmacist specialist, resulting cost savings exceeded \$68,000, despite 83% of all requests receiving pharmacist approval
- Additional studies found that restriction of antimicrobials such as third-generation cephalosporins, vancomycin, and clindamycin resulted in significant decreases of resistant pathogens such as methicillin-resistant *S aureus* and *C difficile*

Supplemental Strategies for Antimicrobial Stewardship

- Supplemental strategies
 - Clinical pathways and guidelines
 - Streamlining/de-escalation
 - Dose optimization
 - Combination therapy
 - Switch from parenteral to oral therapy
 - Education
 - Antimicrobial order forms
 - Antibiotic cycling/switch
- Other recommendations
 - Working closely with microbiologists
 - Physician order entry

Evaluation of the Antibigram from ABC Medical Center (2005-2008)

- MRSA
- VRE
- Stable derepression
- ESBLs
- KPCs

ESBLs = extended-spectrum beta-lactamases; KPCs = *K pneumoniae* carbapenemase.

ABC Community Medical Center Antibiogram* 2008

Percent (%) Susceptible

Bacteria	n	Ampicillin	Cefazolin	Ceftaz	Cipro	Meropenem	Oxacillin	P/T	Vanco	Tigecycline
<i>E cloacae</i>	231	2	3	59	81	94		68		96
<i>E coli</i>	1472	52	84	91	77	96		91		100
<i>K pneumoniae</i>	383	1	81	85	83	94		85		98
<i>P aeruginosa</i>	1017			85	61	67		81		
<i>A baumannii</i>	121			67	70	61		67		78
<i>S aureus</i>	1219	8	37		44	37	37	37	100	100
<i>E faecalis</i>	585	98			42				99	100
<i>E faecium</i>	203	5			5				42	99

*Hypothetical case study.

Bad Bugs, No Drugs: No ESCAPE!

- Antimicrobial Drug-Development Needs
 - E: *E faecium* (VRE)
 - S: *S aureus* (MRSA)
 - C: *Clostridium difficile* Infection
 - (K: KPC-hydrolyzing beta-lactamases)
 - A: *A baumannii*
 - P: *P aeruginosa*
 - E: Enterobacteriaceae

Summary and Conclusions

- Antimicrobial stewardship and improved infection control are the best hopes for preserving the effectiveness of presently available antimicrobial agents
- There are no new antimicrobials in phase 3 clinical trials that appear promising for the treatment of patients infected with multidrug-resistant gram-negative infections
- The Antimicrobial Stewardship Practice Guidelines offer clinical pharmacists an opportunity our profession cannot afford to pass up