Defining Failure: 360° Approach

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Hospital-Acquired Infections

- **1.7 million infections in 2002[1]**
- **99,000 deaths per year[1]**
- **Costs to healthcare industry estimated at $20 billion per year[2]**
  - **Healthcare charges for *S. aureus* bloodstream infections for Medicare patients exceeded $2.5 billion in 2005[2]**

[1]Klevens RM, et al. *Pub Health Rep.* 2007;122:160-166.
[2]HHS Action Plan to Prevent HAIs. Accessed at : http://www.hhs.gov/ophs/initiatives/hai/introduction.html.

Attributable Costs of Hospital-Acquired Infections

Infection Type	Attributable cost, mean (range), 2005 US$	Excess LOS, mean (range), days
Ventilator-associated pneumonia	22,875 (9,986–54,503)	9.6 (7.4–11.5)
Catheter-associated bloodstream infection	18,432 (3,592–34,410)	12 (4.5–19.6)
CABG-associated surgical site infection	17,944 (7,874–26,668)	25.7 (20–35)
Catheter-associated urinary tract infection	1,257 (804–1,710)	-

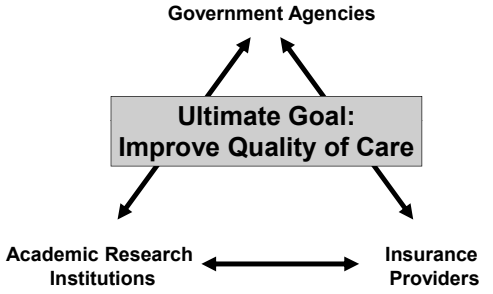
CABG, coronary artery bypass graft.
Perencevich EN, et al. *Infect Control Hosp Epidemiol*. 2007;28:1121-1133.

The Burden of Hospital-Acquired Infections

Infection Type	Total Infections	Hospital Cost per Infection	Total annual hospital cost (in Millions)	Deaths per Year
SSI	290,485	$25,546	$7,421	13,088
CLABSI	248,678	$36,441	$9,062	30,665
VAP	250,205	$9,969	$2,494	35,967
Catheter-associated UTI	561,667	$1,006	$565	8,205

SSI, surgical site infection; CLABSI, central line-associated bloodstream infection; VAP, ventilator-associated pneumonia; UTI, urinary tract infection.
Klevins RM, et al. *Public Health Rep*. 2007;122:160-166.
HHS Action Plan to Prevent HAIs. Accessed at: http://www.hhs.gov/ophs/initiatives/hai/introduction.html.

Mandates to Reduce HAIs: Greater Accountability and Transparency

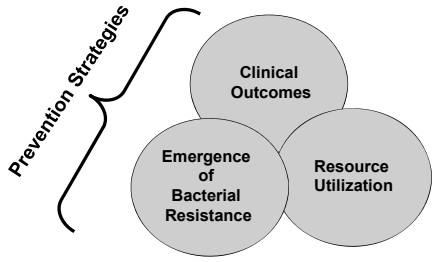


Greater Emphasis on Prevention Initiatives

- **Institute of Medicine** (2002)
  - Prevention of HAIs identified as priority area for transforming health care
- **Deficit Reduction Act** (2005)
  - Promotes greater reporting of prevention measures by hospitals
- **National Quality Forum** (2006)
  - 5 safe practices endorsed to prevent HAIs
- **Institute for Healthcare Improvement** (2006)
  - 5 million lives campaign
- **IDSA/SHEA: Compendium of strategies to prevent HAIs in acute care hospitals** (2008)
- **HHS Action Plan to Prevent Healthcare-Associated Infections** (2009)

Yokoe DS and Classen D. *Infect Control Hosp Epidemiol*. 2008;29:S3-11.
HHS Action Plan to Prevent HAIs. Accessed at: http://www.hhs.gov/ophs/initiatives/hai/introduction.html.

360° Approach to Success in HAIs



Success in HAI management involves taking all aspects into consideration

Program Agenda

Know Your Enemies: Many Faces of HAIs
Thomas M. File, Jr. MD

Know Your Armamentarium and How to Use It: Individualize Therapy Through Optimized Dosing
Robert P. Rapp, PharmD

Clinical Skills and Competencies Workshop
All Faculty and Audience

Know Your Enemies: Many Faces of HAIs

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Associate Professor of Medicine
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Burden of HAIs in the US

Infection Type	No. in ICU	No. in non-ICU	No. of Deaths
Urinary tract	102,200	424,060	13,088
Bloodstream	81,942	133,368	30,665
Pneumonia	100,689	129,519	35,967
Surgical site	28,725	244,385	8,205
Other	80,732	263,810	11,062
Total	394,288	1,195,142	98,987

Klevins RM, et al. *Public Health Rep*. 2007;122:160-166.

Medicare's New Reimbursement Rule: Nonpayment for Performance

- **CMS will disallow incremental payments associated with eight secondary conditions considered preventable complications of medical care**
- **If not present at the time of admission, these will no longer be taken into account in calculating reimbursement after October 1, 2008**

Conditions for Which Medicare Will No Longer Pay More If Acquired during an Inpatient Stay.*

Condition	No. of Medicare Cases in Fiscal Year 2006	Average Medicare Payment for Admissions in Which Condition Was Present
Object left in patient during surgery	764	$61,962
Air embolism	45	$66,007
Blood incompatibility	33	$46,492
Catheter-associated urinary tract infection	12,780	$40,347
Pressure ulcer	322,946	$40,381
Vascular-catheter–associated infection†	Unknown	Unknown
Mediastinitis after coronary-artery bypass grafting	108	$304,747
Fall from bed	2,591	$24,962

* Data are from the *Federal Register*.[2]
† Data are unknown because a unique code for this condition was introduced for fiscal year 2008.

Rosenthal MB. *N Engl J Med*. 2007;357:1573-1575.

Multidrug-Resistant Pathogens: ESKAPE

E: ***E. faecium*** **(vancomycin-resistant enterococci)**

S: ***S. aureus*** **(MRSA)**

K: **ESBL-producing *E. coli* and *K. pneumoniae***

(K: K. pneumoniae **carbapenemase-hydrolyzing β-lactamases)**

A: ***A. baumannii***

P: ***P. aeruginosa***

E: ***Enterobacter*** **species**

Boucher HW, et al. *Clin Infect Dis*. 2009;48:1-12.

Healthcare-Associated Infections: 2006-2007 Drug-Resistant Pathogens

Pathogen	CLABSI %	CAUTI %	VAP %
S. aureus	**9.9**	**2.2**	**24.4**
MRSA*	**56.8**	**65.2**	**54.4**
***Enterococcus* spp.**	**16.0**	**14.9**	**1.3**
VRE*	**36.4**	**29.1**	**32.8**
P. aeruginosa	**3.1**	**10.0**	**16.3**
CIPRO-R*	**30.5**	**33.8**	**27.8**
IMI or MERO-R*	**23.0**	**25.1**	**26.4**
K. pneumoniae	**4.9**	**7.7**	**7.5**
CTR or TAZ-R	**27.1**	**21.2**	**23.7**
A. baumannii	**2.2**	**1.2**	**8.4**
IMI or MERO-R*	**29.2**	**25.6**	**36.8**

*Percent of total pathogen
CIPRO, ciprofloxacin; IMI, imipenem; MERO, meropenem; CTR, ceftriaxone; TAZ, ceftazidime.
Hidron AI et al. *Infect Control Hosp Epidemiol*. 2008;29:996-1011. (data from National Healthcare Safety Network)

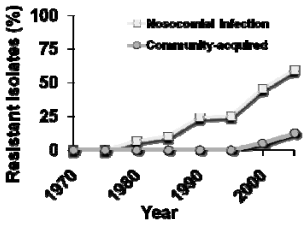
Impact of ESKAPE Pathogens: Bacteremia Treatment Outcomes

Pathogen		p value, OR	Ref.
VRE	**VSE**		**1**
n=683	**n=931**	**OR, 2.52**	
MRSA	**MSSA**		**2**
11.8% (n=382)	**5.1% (n=433)**	**P<.001**	
KPN-ESBL*	**KPN-ESBL-**		**3**
52% (n=48)	**29% (n=99)**	**P=0.007**	
AB (IMP-R)	**AB (IMP-S)**		**4**
57.5% (n=40)	**27.5% (n=40)**	**P=0.007**	
MDR-Pae	**No-MDR-Pae**		**5**
21% (n=40)	**12% (n=40)**	**P=0.08**	

*95% CI, 1.9–3.4
VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci; MRSA, methicillin-resistant *S.aureus;* MSSA, methicillin-susceptible *S.aureus;* KPN, *K.pneumoniae;* ESBL, extended-spectrum β-lactamase; AB, *A.baumannii;* IMP, imipenem; Pae, *P.aeruginosa;* EB, *Enterobacter spp.*
[1]DiazGranados CA, et al. *Clin Infect Dis*. 2005; 41:327–333.
[2]Melzer M, et al. *Clin Infect Dis*. 2003;37:1453-1460.
[3]Tumbarello M, et al. *Antimicrob Agents Chemother*. 2006;50:498-504.
[4]Kwon K. et al. *J Antimicrob Chemother* 2007;59:525–530.
[5]Aloush V. et al. *Antimicrob Agents Chemother* 2006;50: 43–48.

Epidemiology of HA- and CA-MRSA Infection

Prevalence of MRSA increasing in hospitals and in the community.[1]

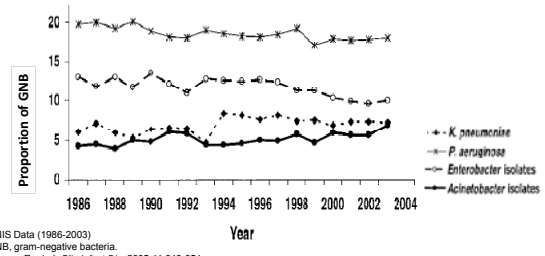


Type of Infection	Infections associated with CA-MRSA (n=131)[2]	HA-MRSA (n=937)[2]
Skin/ Soft Tissue	75%	37%
Otitis media/ Externa	7%	1%
Respiratory Tract	6%	22%
BSI	4%	9%
UTI	1%	20%
Other	8%	12%

1. McDonald LC. *Clin Infect Dis*. 2006;42:S65-71.
2. Naimi TS et al. *JAMA*. 2003;290:2976-2984.

Nosocomial Pneumonia due to Multidrug-resistant Gram-Negative Bacilli:

- **Increasing among *P. aeruginosa* and *Acinetobacter* spp. (incl. to carbapenems)**



NNIS Data (1986-2003)
GNB, gram-negative bacteria.
Gaynes R, et al. *Clin Infect Dis*. 2005;41:848-854.

Multidrug-resistant *Pseudomonas* and *Acinetobacter*: Treatment Options

- ***Pseudomonas***
  - **Anti-pseudomonal β-lactam + aminoglycoside**
    - **Carbapenem, cephalosporin, penicillin, or β-lactam/β-lactamase inhibitor**
- ***Acinetobacter***
  - **Carbapenems**
    - **Increasing rates of resistance**
  - **Colistin + β-lactam, rifampicin, doxycycline**
    - **Monotherapy with colistin leads to colistin-resistant organisms**
  - **Sulbactam-based regimens**
  - **Tigecycline**

KNOW YOUR LOCAL ANTIBIOGRAM!!!

Matthaiou DK, et al. *Crit Care Med*. 2008;36:807-811.

Evolution of β-Lactamases

Wild-Type

↘ **Penicillins**

β-lactamase (TEM-1, TEM-2, SHV-1)

↘ **β-lactam/β-lactamase inhibitors; Cephalosporins**

AmpC; ESBL (TEM, SHV, CTX-M)

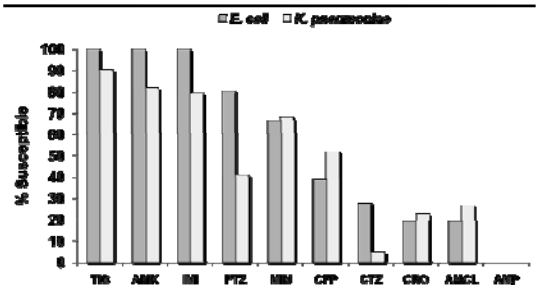
KPC, *klebsiella pneumonia* carbapenemase; MBL, metallo-β-lactamase; TEM-1,TEM-2, SHV-1, TEM, SHV, CTX-M=types of β-lactamases.
Adapted from Burgess DS, et al. *Am J Health Syst Pharm*. 2008;65:S4-S15.

Prevalence of ESBL-EK and Multidrug-Resistant *A. baumannii*

US Census Region	ESBL *E. coli* n/N (%)	ESBL *K. pneumoniae* n/N (%)	MDR* *A. baumannii* n/N (%)
New England	3/143 (2.1)	10/102 (9.8)	6/69 (8.7)
Middle Atlantic	13/519 (2.5)	76/401 (19.0)	104/236 (44.1)
East North Central	2/353 (0.6)	19/274 (6.9)	41/165 (24.8)
West North Central	1/171 (0.6)	4/120 (3.3)	6/60 (10.0)
South Atlantic	9/401 (2.2)	23/326 (7.1)	60/214 (28.0)
East South Central	2/176 (1.1)	5/136 (3.7)	28/74 (37.8)
West South Central	3/197 (1.5)	3/153 (2.0)	14/82 (17.1)
Mountain	0/83 (0)	2/66 (3.0)	2/38 (5.3)
Pacific	3/186 (1.6)	4/152 (2.6)	21/88 (23.9)
TOTAL US	36/2229 (1.6)	146/1730 (8.4)	282/1026 (27.5)

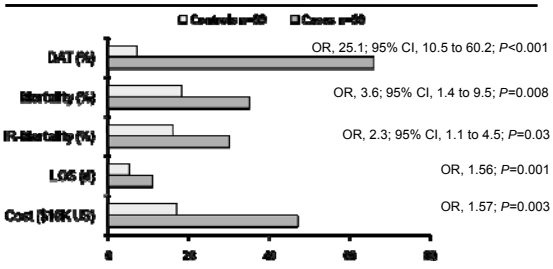
*MDR = resistance to ≥3 antimicrobial classes including penicillins ± b-lactamase inhibitor, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, and tetracyclines.
Hoban DJ, et al. *Diagn Microbiol Infect Dis*. 2007;57:423-428.

Susceptibility of ESBL-Producing *E. coli* and *K. pneumoniae* in the US



TIG, tigecycline; AMK, amikacin; IMI, imipenem; PTZ, piperacillin-tazobactam; MIN, minocycline; CFP, cefepime; CTZ, ceftazidime; CRO, ceftriaxone; AMCL, amoxicillin-clavulanate; AMP, ampicillin
Adapted from Hoban DJ et al. *Diagn Microbiol Infect Dis*. 2007;57:423-428.

Impact of ESBL-Producing *Escherichia coli*, *Klebsiella* spp., or *Proteus* spp.



DAT, delayed appropriate therapy; IR, infection-related; LOS, length of stay.
Bacteremic patients. Comparisons via multivariable analysis.
Schwaber MJ, et al. *Antimicrob Agents Chemother*. 2006;50(4):1257-1262.

Infection by ESBL Producers: Treatment Options

- **3rd-generation cephalosporins**
  - **Avoid as monotherapy, especially against *Enterobacter* spp.**
- **Aminoglycosides and fluoroquinolones**
  - **Higher likelihood of resistance with ESBL-producing Enterobacteriaceae**
- **Carbapenems**
  - **Preferred agents (almost uniform in vitro susceptibility)**
  - **Extensive clinical experience**
  - **Resistance in ESBL-producing bacteria**
    - **Rare, though multiple mechanisms have been identified**

ATS/IDSA. *Am J Respir Crit Care Med*. 2005;171:388-416.
Paterson DL and Bonomo RA. *Clin Microbiol Rev*. 2005;18:657-686.

AmpC β-lactamases

- **AmpC β-lactamases are different from ESBLs[1]**
  - AmpC enzymes are not inhibited by clavulanate
  - The phenotypes of the 2 classes of β-lactamases overlap
  - Distinguishing between ESBL- and AmpC-producing strains is important because of differing susceptibilities
- **AmpC β-lactamases are usually chromosomally encoded[1]**
  - Migration of AmpC β-lactamase–encoding genes to plasmids has been observed
  - Some AmpC β-lactamases are now seen in organisms that did not previously have chromosome-encoded versions of these enzymes
- **AmpC expression generally confers resistance to a wide range of antibiotics such as[1,2]**
  - 1st-, 2nd-, and 3rd-generation cephalosporins and aztreonam[1]
  - Broad-spectrum penicillins associated with β-lactamase inhibitors[1,2]

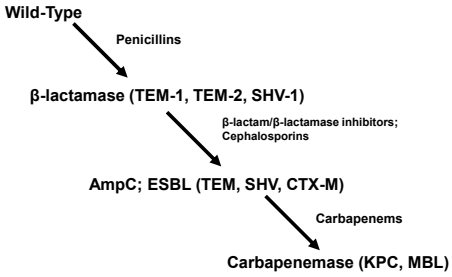
1. Pfaller MA, et al. *Clin Infect Dis*. 2006;42(suppl 4):S153-S163.
2. Rupp ME, et al. *Drugs*. 2003;63:353-365.

'Appropriate' Therapy for HAP/VAP: ATS/IDSA Guidelines

Organism	Treatment Regimen
***P. aeruginosa* /**	**Anti-pseudomonal cephalosporin OR**
***Acinetobacter* spp. /**	**Anti-pseudomonal carbapenem OR**
K. pneumoniae*	**β-lactam/β-lactamase inhibitor PLUS**
	Anti-pseudomonal fluoroquinolone OR
	Aminoglycoside
MRSA	**Linezolid or vancomycin**
Legionella	**Any fluoroquinolone or macrolide**

*If an ESBL+ strain, a carbapenem is a reliable choice.
ATS/IDSA. *Am J Respir Crit Care Med*. 2005;171:388-416.

Evolution of β-Lactamases



Adapted from Burgess DS, et al. *Am J Health Syst Pharm.* 2008;65:S4-S15.

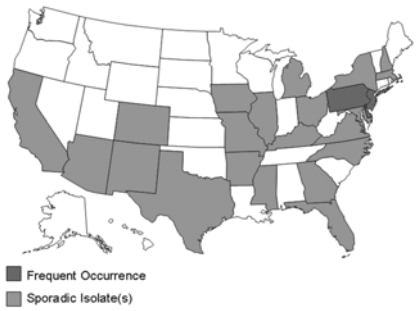
Carbapenem-Resistant Enterobacteriaceae

- **Unique among Class A β-lactamases [1]**
  - **Hydrolyze carbapenems, cephalosporins, penicillins, aztreonam[2]**
  - **Inhibited by clavulanic acid, tazobactam[3]**
  - **Found on transferable plasmids, increasing the risk of spread[2]**
- **Most frequently observed in *K. pneumoniae (CRKP)***
  - **(2007) 8% of *K. pneumoniae* nosocomial infections due to CRKP compared to <1% in 2000 (CDC)**
- **MICs often elevated but within susceptible range**
  - **Automated systems unreliable at detecting**
  - **Requires modified Hodge test for detection**
- **Virtually all CRKP concurrently produce an ESBL**

CRKP, carbapenem-resistant *K. pneumoniae.*

1. Ke W, et al. *Biochemistry.* 2007;46:5732-5740.
2. Anderson KF, et al. *J Clin Microbiol.* 2007;45:2723-2725.
3. Yigit H, et al. *Antimicrob Agents Chemother.* 2001;45:1151-1161.

Klebsiella pneumoniae Carbapenemase–producing Organisms in the United States



Srinivasan P, et al. *Infect Control Hosp Epidemiol.* 2008;29(12):1107-1109.

Special Problem Assessment

- **MRSA**
- **ESBLs**
- **CDI**
- **VRE**

Infection control + Antibiotic control

- **MDR-*Acinetobacter baumannii***
- **MDR-*Pseudomonas***
- ***Stenotrophomonas maltophilia***
- **Carbapenemases**

Mainly infection control

CDI, *C. difficile* infection; VRE, vancomycin-resistant entrococci ; MDR, multidrug-resistant.

Know Your Armamentarium and How to Use It: Individualize Therapy Through Optimized Dosing

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Paradigm "Shifts" in Antibiotic Use

	Traditional
Timing	Whenever possible
Empiric Therapy	Room for error
Dosing	Standard dosing
Spectrum	Narrow-spectrum "workhorse"
De-escalation	Discouraged
Potency	Reserve potent drugs
Duration	Longer durations

Antimicrobial Resistance: Risk Factors

- Immunosuppressive therapy
- Prior (prolonged) antibiotic therapy
- High rates of resistance in the hospital/community
- Antibiotics for non-human use
- Prolonged hospitalization
- Invasive devices
- Hemodialysis
- Residence in long-term care facilities
- Inadequate infection control practices

1. Tenover FC. *Clin Infect Dis*. 2001;33:S108-115.
2. Levy SB. *Clin Infect Dis*. 2001;33:S124-129.
3. Niederman MS. *Clin Infect Dis*. 2006;42:S72-81.

Multiple Mechanisms of Antimicrobial Resistance: Gram-Negative Pathogens

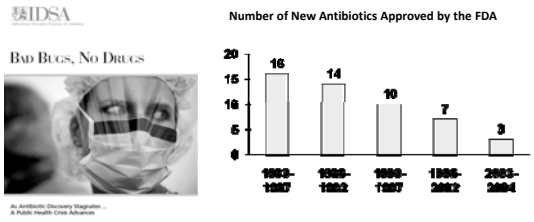
Antibiotic Class	Mechanisms of Resistance
Cephalosporins	• ESBLs • Chromosomal cephalosporinases
β-lactam/ β-lactamase inhibitors	• Hyper production of β-lactamases • β-lactamase not affected by inhibitor
Carbapenems	• Porin mutations • Efflux pump overproduction • *K. pneumoniae* carbapenemases (KPC) and other β-lactamases
Fluoroquinolones	• Alterations in topoisomerase, DNA gyrase • Efflux pumps • Permeability changes

ESBL, extended-spectrum b-lactamase.

Strategies to Combat Antimicrobial Resistance

- **Paradigms**
  - Avoid unnecessary use
  - Surveillance
  - Education programs
  - Vaccination
  - Improved diagnostics
  - Infection control
  - Guidelines /consultation/ restrictions
  - Risk stratification
  - "Targeted" antimicrobial control
  - Benchmarking
- **Pills**
  - Pharmacodynamic dosing
  - Combination therapy
  - Old drugs made new again
  - New antimicrobials
  - New vaccines
  - De-escalation
  - Antimicrobial cycling
  - IV-to-PO programs
  - Short-course therapy

Lack of New Options



"Bad Bugs, No Drugs". Infectious Diseases Society of America. July 2004.
Slama G. *Crit Care*. 2008;12:S4.

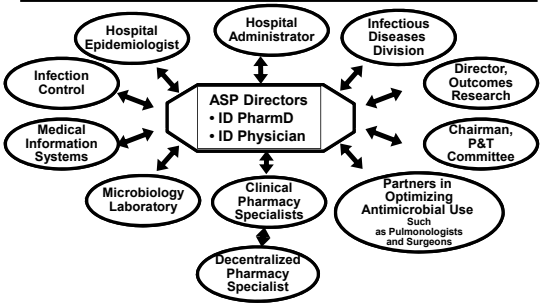
Antibiotic Stewardship: Fundamentals

- **Definition**
  - *"An ongoing effort . . . to optimize antimicrobial use in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae of antimicrobial use (including antimicrobial resistance)."*
- **Axioms/Assumptions**
  - Antibiotic prescribing behaviors can be changed or regulated
  - Antibiotic use is primary driving force in development of antibiotic resistance
  - Reduction in antibiotic use will reduce prevalence of resistance or slow its increase
  - Appropriate antibiotic use can improve patient outcomes and reduce costs

MacDougall C and Polk RE. *Clin Microbiol Rev.* 2005;18:638-656.

Antimicrobial Stewardship Teams

Multidisciplinary Team Approach to Optimizing Clinical Outcomes



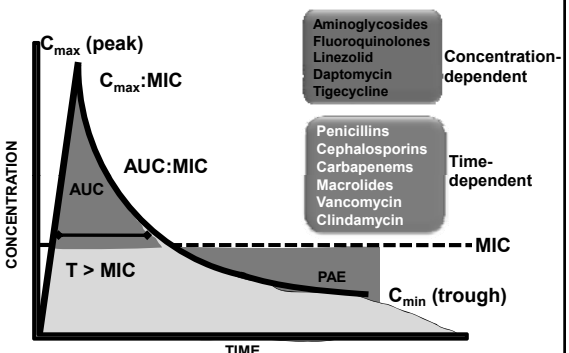
ASP, antimicrobial stewardship program; ID, infectious disease; P&T, Pharmacy and Therapeutics.
1. Dellit TH, et al. *Clin Infect Dis*. 2007;44:159-177.
2. Fishman N. *Am J Med.* 2006;119:S53-S61.

Goal of Antimicrobial Therapy

- **"The objective of antimicrobial therapy . . . is to provide an effective drug, in sufficient concentration, [started] and maintained for sufficient time at the infection site(s), to kill all microbial organisms and achieve clinical cure of infection . . ."**
- **"The questions . . . which drug, how much, how often, and how long . . ."**

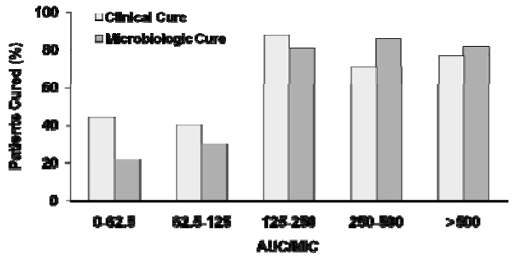
[Modified] from Lees P, et al. *Int J Antimicrob Agents*. 2002;19:269-284.

Optimizing Drug Exposure



AUC, area under the concentration–time curve; PAE, post-antibiotic effect.
Slide (modified) courtesy of Shannon Holt, PharmD.
Rybak MJ. *Am J Med*. 2006;119:S37-S44.

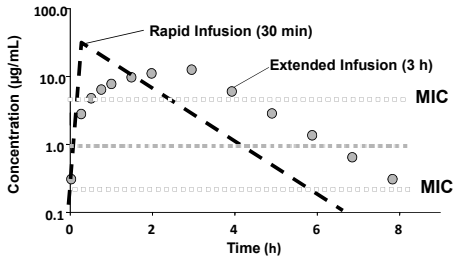
Nosocomial Pneumonia: Quinolone Exposure and Outcome



Forrest A, et al. *Antimicrob Agents Chemother*. 1993;37:1073-1081.

Extended Infusions Overcome Carbapenem Instability while Increasing % T>MIC

Meropenem 500 mg administered as a 30-minute or 3-hour infusion



Dandekar PK, et al. *Pharmacother.* 2003;23:988-991.

Extended Infusion of Piperacillin-Tazobactam for Susceptible *P. aeruginosa* Infections

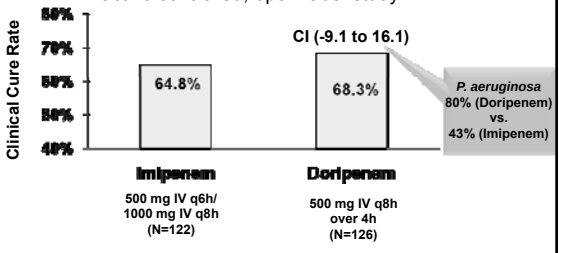
3.375 g IV for 30 min every 4 h or 6 h (N=92) vs.
3.375 g IV for 4 h every 8 h (N=102)

	Extended Infusion	Intermittent Infusion	*P*
APACHE II<17			
14-day Mortality, %	**6.6**	**3.7**	**.5**
Median LOS (Range), days	**18 (4–159)**	**18 (3–144)**	**.5**
APACHE II≥17			
14-day Mortality, %	**12.2**	**31.6**	**.04**
Median LOS (Range), days	**21 (3–98)**	**38 (6–131)**	**.02**

Lodise TP, et al. *Clin Infect Dis.* 2007;44:357-363.

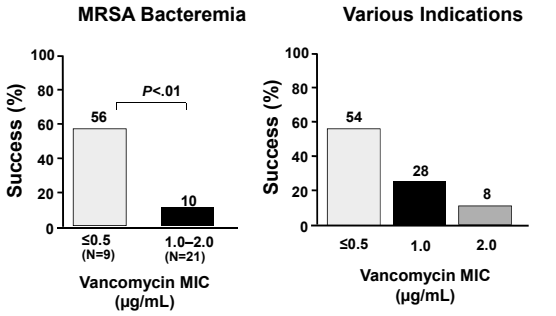
Prolonged Infusion: Doripenem vs. Imipenem for VAP

Prospective, multicenter, parallel, randomized, active controlled, open-label study*



VAP, ventilator-associated pneumonia; *Adjunctive vancomycin or aminoglycoside therapy allowed in both groups.
Chastre J, et al. *Crit Care Med.* 2008;36:1089-1096.

Vancomycin MIC and MRSA Treatment Outcome

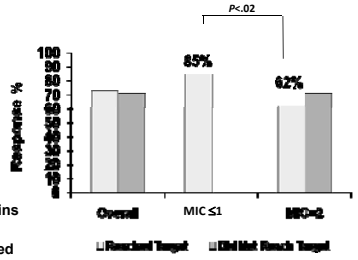


Sakoulas G, et al. *J Clin Microbiol*. 2004;42:2398-2402.

Moise-Broder PA, et al. *Clin Infect Dis*. 2004;38:1700-1705.

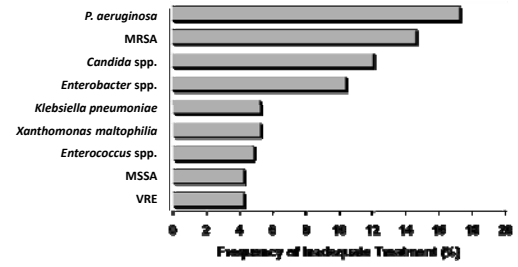
Targeting Higher Troughs for Vancomycin Outcomes for Invasive Disease

- Prospective study of MRSA infections treated with vancomycin (n=86)
- Indications included pneumonia and bacteremia
- "Target troughs" of 15-20 µg/mL
- Results
  - 54% of nosocomial strains had MIC=2 µg/mL
  - Overall response reduced with MIC ≥2 µg/mL regardless of trough



Hidayat, LK. et al. *Arch Intern Med.* 2006;166:2138-2144.

Pathogens Most Often Associated with Inappropriate Initial Antimicrobial Treatment*



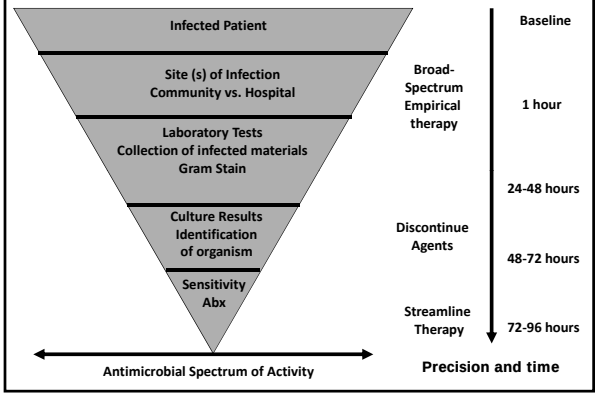
*For patients requiring ICU admission for nosocomial or community-acquired infections.
Kollef MH, et al. *Chest.* 1999;115:462-474.

Combination *P. aeruginosa* Therapy

- **Meta-analysis of β-lactam monotherapy vs. β-lactam plus an aminoglycoside for severe infection**
- **64 randomized trials: 7,586 patients**
  - No difference in mortality or resistance
  - Greater clinical and bacteriologic failure with combination therapy
  - Greater nephrotoxicity with combination therapy
  - Less superinfections with monotherapy

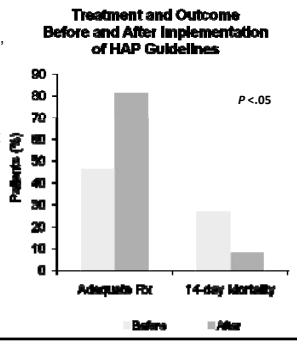
Paul M, et al. *Brit Med J.* 2004;328:668.

Start Broad, Then Streamline Therapy



De-escalation Therapy: Outcomes and Resistance

- Compared severe ICU HAP management before (n=48) and after (n=56) 'de-escalation'
  - Guideline Rx for severe HAP: imipenem + amikacin/quinolone ± vancomycin. Adjust therapy to cultures within 5 days.
- MRSA and *P. aeruginosa* most common and similar in both groups
- 100% after guideline received imipenem, only 26% not adjusted per cultures
  - No increased imipenem resistance observed

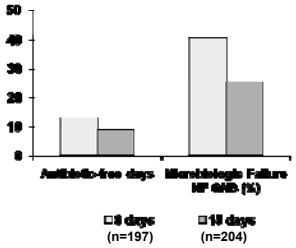


ETA, endotracheal aspirate.
Soo Hoo GW, et al. *Chest*. 2005;128:2778-2787.

Short-Course Therapy for VAP

- **At 28 days**
  - **Similar mortality**
  - **Similar recurrence rates**
- **Short-course therapy**
  - **More antibiotic-free days (*P*<.001)**
  - **More microbiologic failure for NF GNB, 40.6% vs. 25.4% (*P*=.06)**
  - **Higher rates of recurrence for *P. aeruginosa* (41% vs 25%)**

Prospective, multicenter, randomized trial: 8-day vs. 15-day therapy for VAP* and appropriate initial therapy



* Quantitative confirmation.
NF GNB, non-fermenting gram-negative bacteria.
Chastre J, et al. *JAMA*. 2003;290:2588-2598.

Duration of Therapy for HAP: ATS Guidelines

"If patients receive an initially appropriate antibiotic regimen, efforts should be made to shorten the duration of therapy from the traditional 14 to 21 days to periods as short as 7 days, provided that the etiologic pathogen is not *P. aeruginosa*, and that the patient has a good clinical response with resolution of clinical features of infection."

ATS. *Am J Resp Crit Care Med*. 2005;171:388-416.

Antimicrobial Guidelines: Use of Local Antibiogram Data

Retrospective analysis of in vitro susceptibility of pathogens

	Regimens	HAP Episodes (N=76) N (%)	HAP Isolates (N=120) N (%)
ATS guideline	Piperacillin-tazobactam, vancomycin, ciprofloxacin	53 (70)	95 (79)
	Cefepime, vancomycin, ciprofloxacin	53 (70)	96 (80)
Local guideline	Piperacillin-tazobactam, vancomycin, amikacin	71 (93)	115 (96)
	Cefepime, vancomycin, amikacin	71 (93)	115 (96)

HAP, hospital-acquired pneumonia.
Beardsley J, et al. *Chest*. 2006;130:787-793.

Paradigm "Shifts" in Antibiotic Use

	Traditional	New
Timing	Whenever possible	As soon as possible
Empiric Therapy	Room for Error	Get it right the first time
Dosing	Standard dosing	Pharmacodynamics dosing
Spectrum	Narrow-spectrum "workhorse"	Broad-spectrum OK in sick patient
De-escalation	Discouraged	Encouraged
Potency	Reserve potent drugs	Potent drugs may prevent resistance
Duration	Longer Durations	Hit 'um hard and stop

Clinical Skills and Competencies Workshop

About the Hospital . . .

- 500-bed tertiary care center
- Location: Northeastern US
- ↑ problem with MDR *P. aeruginosa* in ICUs over past several years
  - Both polyclonal and clonal outbreaks
- Hospital antibiogram is available

Hospital Antibiogram 2009*
Percent (%) Susceptible

Bacteria	n	Genta	Tobra	Ceftaz	Cipro	Mero	Oxacil	P/T	Vanco	Linezo
E. cloacae	231	52	54	59	81	94		68		
E. coli	1472	76	81	91	77	99		91		
K. pneumoniae	383	68	74	80	76	98		81		
P. aeruginosa	1017	57	66	62	41	67		81		
A. baumannii	121	46	52	67	70	61		67		
S. aureus	1219				44	37	37	37	100	100
E. faecalis	585				42				99	100
E. faecium	203				5				42	97

*Genta, gentamicin; Tobra, tobramycin; Ceftaz, ceftazidime; Cipro, ciprofloxacin; Mero, meropenem; Oxacil, Oxacillin; P/T, piperacillin/tazobactam; Vanco, vancomycin; Linezo, linezolid

*Chart shows a subset of all antimicrobials tested at the hospital

About "Mr. Jones" . . .

- **72-year-old male (weight = 70 kg)**
- **Admitted directly to medical ICU**
  - **Transferred from nursing home where he resides with an acute congestive heart failure exacerbation**
  - **Multiple comorbidities: diabetes mellitus, dementia, hypertension, hypercholesterolemia, and peripheral vascular disease**
  - **Treated for UTI with ciprofloxacin 3 weeks ago**
- **After 4 days in ICU, develops altered mental status, has worsening tachypnea, becomes hypotensive, and requires intubation**
  - **Portable CXR: new infiltrate in the left lung**
  - **Pertinent labs/findings**
    WBC: 17,000 cells/mm^3, Temperature: 101.4°F, SCr: 1.1 mg/dL

Clinical Considerations

- **What pathogen(s) do you suspect?**
- **What are your suggestions for initial antimicrobial therapy?**

Patient Update

Action Taken

- **Vancomycin 1 g IV q12h + tobramycin 550 mg IV q24h + piperacillin/tazobactam 4.5 g IV q6h**

Clinical Presentation

- **Continues to require vasopressor support**
- **Respiratory function not improving**
- **Gram stain of a deep tracheal aspirate reveals**
  - **Multiple WBCs**
  - **Many gram-negative rods**
  - **Moderate number of gram-positive cocci in clusters**

Clinical Considerations

- **Would you alter therapy?**

Patient Update

Action Taken

- **Previous regimen (vancomycin + tobramycin + piperacillin/tazobactam) continued**

Clinical Presentation: Laboratory reports after 48 h

- **Respiratory cultures: *K. pneumoniae* and MRSA**
  - **MRSA susceptible to vancomycin (MIC=2 µg/mL), clindamycin, doxycycline, TMP/SMX, and linezolid**
  - ***K. pneumoniae* (ESBL-positive) resistant to all antibiotics tested except meropenem, gentamicin, and amikacin**
- **All other cultures: negative**

Clinical Considerations

- At this point, would you discuss these results with any other members of the healthcare team?
- Would you suggest altering therapy? If so, how?

Patient Update

Action Taken

- Therapy changed to meropenem 1 g IV q8h (over 30 min) + linezolid 600 mg IV q12h

Clinical Considerations

- Do you agree with these changes?

Patient Update

Scenario 1

- Continued deterioration and subsequent death
- Further workup of *K. pneumoniae* isolate reveals
  - KPC-2 enzyme production (via PCR analysis by reference lab)
  - Meropenem MIC: 4.0 µg/mL (susceptible)

Clinical Considerations

- What would you have done differently?

Scenario 2

- Marked improvement over next several days
- KPC screen on *K. pneumoniae* isolate (via Modified Hodge Test): negative
- New lab result:
  - Meropenem MIC: 0.25 µg/mL
  - Ertapenem MIC: 0.5 µg/mL

Clinical Considerations

- How long would you continue this therapy?

Learning by Sharing:
Interactive Q&A with Faculty

Thank you!