Antimicrobial Stewardship:
Opportunities & Challenges In the Era of Increasing Resistance

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Disclosures

- I am a consultant or member of the speakers bureau for AstraZeneca, Cerexa, Cubist, Forest, Merck, Optimer, Pfizer, Tetraphase and Trius.
- I have received research grant funding from AstraZeneca, Cerexa, Cubist, Forest, Merck, Optimer, Pfizer, Rib-X, Tetraphase and Trius.

Improving the Probability of Positive Outcomes
IMPROVING THE ODDS

- **Assessing Host Compromise:**
  - Chronologic versus physiologic age
  - Presence of co-morbidities (i.e., malnutrition, DM, renal / hepatic Dx
  - Concomitant disease entities (i.e., HIV, transplant, rheumatologic)
  - Medical and / or surgical interventions (i.e., Blood products, medicines, recent surgery, intubation)
- **Alterations in Drug Handling:**
  - Hyper dynamic clearance, Volume of Distribution, Renal Dx (i.e., CRRT)

Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

Improving the Probability of Positive Outcomes

IMPROVING THE ODDS

- **Organisms of Concern:**
  - *Staphylococcus aureus*
  - Enterococci
  - Enterobacteriaceae
  - Pseudomonas
  - Acinetobacter

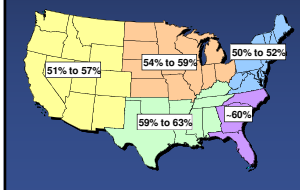
Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

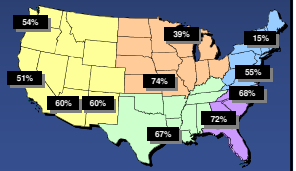
Epidemiology of Infection

Historic		Now
• Skin and Skin Structure – *S. aureus* – *Streptococcus* sp.	→	- MRSA
• CAP – *S. pneumoniae* – *H. influenzae* – Atypicals	→	- PRSP, Mac^R, Tet^R - β-lactamase producing
• HAP / VAP – *S. aureus* – *P. aeruginosa /A. baumannii* – Enterobacteriaceae	→	- MRSA, VISA, VRSA - MDR, XDR - ESBL, CRE
• Urinary Tract Infection – Enterobacteriaceae – *Enterococcus* sp.	→	- ESBL, CRE - VRE

MRSA in the Hospital & Community

- Close to 60% of *S. aureus* isolates from hospitalized patients are methicillin-resistant.[1]
- MRSA is isolated from 59% of patients with community-acquired skin and skin structure infections.[2]





1. Styers D, et al. *Ann Clin Microbiol Antimicrob.* 2006;5:2.
2. Moran GJ, et al. *N Engl J Med.* 2006;355:666-674.

Characteristics of Infections due to ESBL-producing Bacteria Risk Factors

Community-onset

- Repeat UTIs with underlying renal pathology
- Previous antibiotics (cephalosporins, fluoroquinolones)
- Previous hospitalization
- Nursing-home residents
- Older men and women
- Diabetes mellitus
- Underlying liver pathology

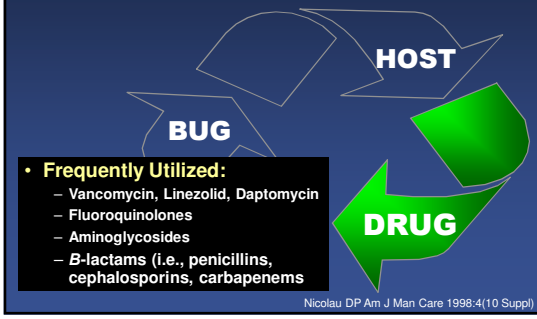
Hospital-onset

- Longer length of hospital stay
- Severity of illness (more severe, the higher the risk)
- Longer time in the ICUs
- Intubations and mechanical ventilation
- Urinary or arterial catheterization
- Previous exposure to antibiotics (cephalosporins, FQ)

Pitout JD and Laupland KB. *Lancet Infect Dis* 2008;8:159-66.

Improving the Probability of Positive Outcomes

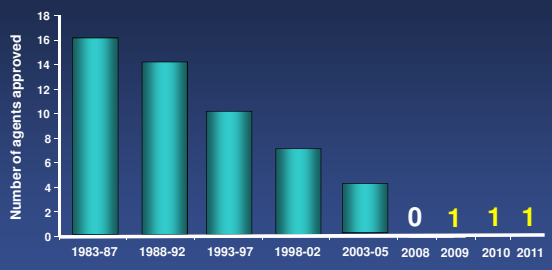
IMPROVING THE ODDS



- Frequently Utilized:
  - Vancomycin, Linezolid, Daptomycin
  - Fluoroquinolones
  - Aminoglycosides
  - *B*-lactams (i.e., penicillins, cephalosporins, carbapenems

Nicolau DP Am J Man Care 1998:4(10 Suppl) S525-30

Changing Landscape for Numbers of Approved Antibacterial Agents



Bars represent number of new antimicrobial agents approved by the FDA during the period listed.

Infectious Diseases Society of America. *Bad Bugs, No Drugs.* July 2004.
Spellberg B et al. *Clin Infect Dis.* 2004;38:1279-1286.
New antimicrobial agents. *Antimicrob Agents Chemother.* 2006;50:1912

Antimicrobial Stewardship: Part of the Solution?

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

[1]Harborview Medical Center and the University of Washington, Seattle; [2]Maine Medical Center, Portland; [3]Emory University, Atlanta, Georgia; [4]Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and [5]Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; [6]University of Utah, Salt Lake City; [7]Mayo Clinic College of Medicine, Rochester, Minnesota; [8]University of Pittsburgh Medical Center, Pittsburgh, and [9]University of Pennsylvania, Philadelphia, Pennsylvania; [10]William Beaumont Hospital, Royal Oak, Michigan; [11]Ochsner Health System, New Orleans, Louisiana; and [12]University of Miami, Miami, Florida

The Primary Goal of Antimicrobial Stewardship:
"Optimize clinical outcomes while minimizing unintended consequences of antimicrobial use"

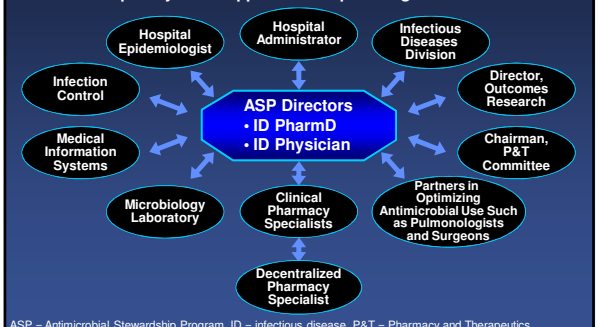
Dellit T, et al. *Clin Infect Dis*. 2007;44:159-177.

Antimicrobial Stewardship: Consideration Across the Continuum of Care

- **Hospital Setting**
- **Community Setting**
  - **"The Other Community"**
    - » **Transitions of Care**: Increased introduction of resistant organisms from the nursing home / rehabilitation facilities
  - **Non-institutionalized "The True Community"**
    - » Increased introduction of resistant organisms from the community "home" setting [Shlaes *et al. Clin Infect Dis* 1997; 25: 584-599

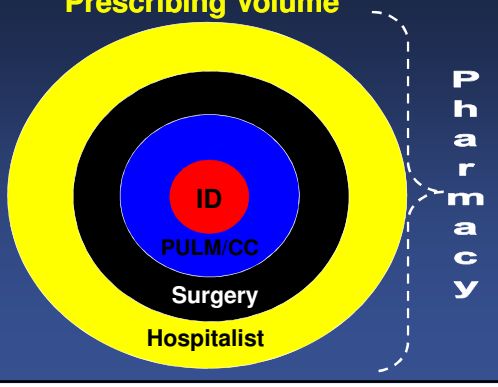
Antimicrobial Stewardship Team: Hospital Setting

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;44:159-177 and Fishman N. *Am J Med*. 2006;119:S53-S61.

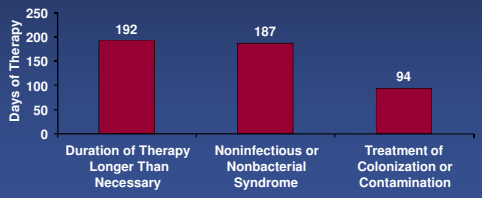
Antimicrobial Expertise vs. Prescribing Volume



Unnecessary Use of Antimicrobials in Hospitalized Patients

- Prospective observational study in ICU
- 576 of 1941 days (30%) of antimicrobial therapy deemed unnecessary

Most Common Reasons for Unnecessary Days of Therapy



Hecker MT et al. *Arch Intern Med.* 2003;163:972-978.

Appropriate Antimicrobial Therapy

- Matches antibiotic susceptibilities of the organism to the antibiotic used

"S" = Success

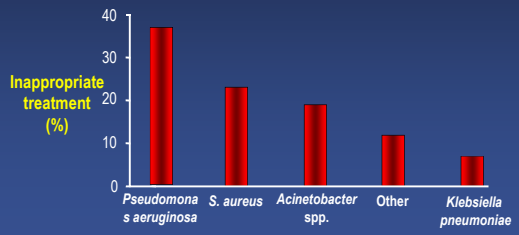
Improved Outcomes = Reductions in:

- Hospital and infection-related mortality
- Infection-related morbidity
- Length of hospital stay
- Days of antimicrobial therapy
- Cost of hospitalization

Kollef, et al. *Chest.* 1999; 115:462-474.
Engemann, et al. *Clin Infect Dis.* 2003; 36:592-598.
Lodise, et al. *Clin Infect Dis.* 2002; 34:922-929.
Toubes, et al. *Clin Infect Dis.* 2003; 36:724-730.
Pelz, et al. *Intensive Care Med.* 2002. 28:692-697.
Song, et al. *Infect Control Hosp Epidemiol.* 2003; 24:251-256.

Inappropriate Therapy Often Due to Antibiotic Resistance

- Inappropriate therapy more likely if antibiotic resistance is present
- Antibiotic-resistant organisms are more commonly associated with inappropriate therapy



Adapted from Kollef MH. *Clin Infect Dis.* 2000;31(suppl 4):S131–S138.

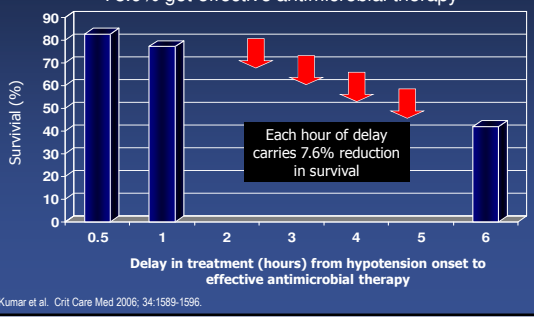
Appropriate Antimicrobial Therapy An Increasing Challenge

- Impact of previous ABX therapy on outcomes of Gram-negative sepsis
  - ABX therapy in previous 90 days, patients = 310
  - Organisms
    - *E. coli* 31%
    - *Klebsiella pneumoniae* 23%
    - *Pseudomonas aeruginosa* 18%
  - ABX use: Cefepime > Cipro > imipenem
  - Patients with prior ABX higher RESISTANCE to cefepime, Pip/tazo, carbapenems, Cipro & gentamicin
  - Patients with prior ABX higher INAPPROPRIATE THERAPY and MORTALITY compared with patients without ABX exposure

Johnson MT, et al. Crit Care Med 2011;39(8):1859-1865

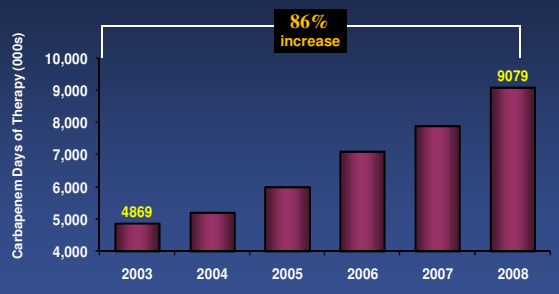
Not Just Appropriate Therapy: RAPID Therapy in Septic Shock

2154 patients with septic shock
78.9% got effective antimicrobial therapy



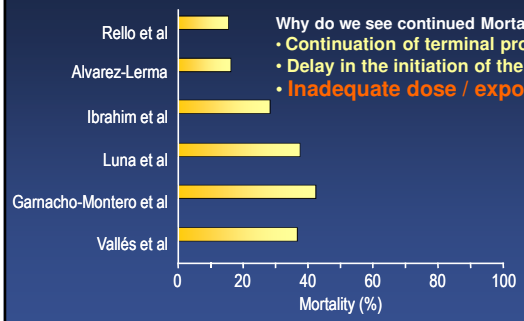
Kumar et al. Crit Care Med 2006; 34:1589-1596.

Carbapenem Usage Continues to Rise Dramatically in the US (2003-2008)



National Sales Perspective (NSP) Audit. IMS. December 2008.

Mortality Associated with Appropriate Therapy in Patients with Serious Infections



Why do we see continued Mortality?
- Continuation of terminal process
- Delay in the initiation of therapy
- Inadequate dose / exposure

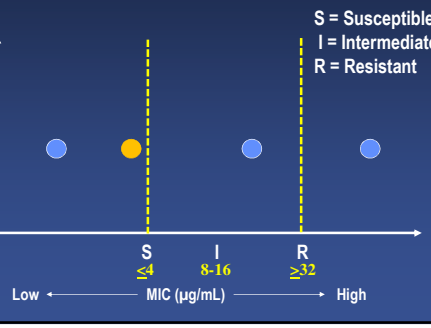
Rello et al. Am J Respir Crit Care Med 1997;156:196–200; Alvarez-Lerma. Intensive Care Med 1996;22:387–394
Ibrahim et al. Chest 2000;118:146–155; Luna et al. Chest 1997;111:676–685
Garnacho-Montero et al. Crit Care Med 2003;31:2742–2751; Vallés et al. Chest 2003;123:1615–1624

Do We Deliver Effective Doses in Critically Ill Patients: Empiric Therapy

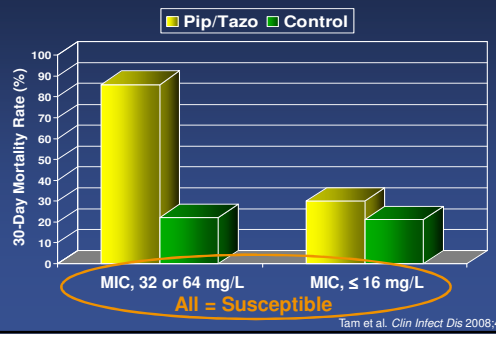
- Pharmacodynamic goal (i.e., optimal exposure) not achieved in 16/19 (84%)
  - 8/16 (50%): organism resistant to empiric therapy
- 8/16 (50%): organism susceptible..but therapy not optimal
  - 6/8 organisms had MIC's at the breakpoint
  - 2/8 organisms had MIC's 1 dilution below the breakpoint

Mohr JF, et al. Diagn Micro Infect Dis 2004;48:125-30.

Assessment of *In Vitro* Potency
MIC Breakpoints

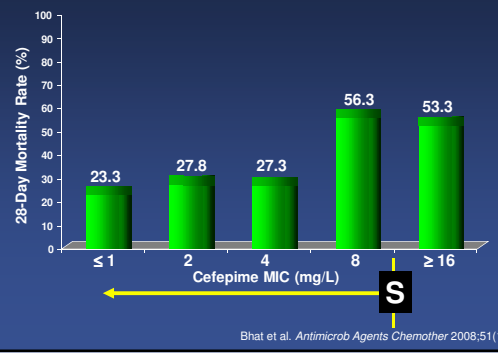


Outcomes of Bacteremia Due to *P. aeruginosa* Based on the Susceptibility of Piperacillin/Tazobactam



Tam et al. *Clin Infect Dis* 2008;46:862-7

Failure of Current Cefepime Breakpoints to Predict Clinical Outcomes in Gram-Negatives



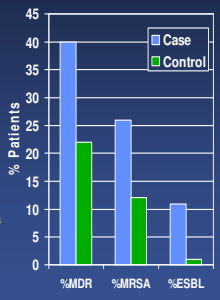
Bhat et al. *Antimicrob Agents Chemother* 2008;51(12):4390-5

Fluoroquinolone Pharmacodynamics

- **What's the problem?**
  - What's your % of FQ-R PSA?
  - What's your % of FQ-R *E. coli*?
  - When original studies done, vast majority of organism MICs ≤ 0.5 µg/ml
    - » Now majority of susceptible isolates just below the breakpoint
    - » Conventional FQ doses don't optimize PD profile for many TARGET Gram Negative pathogens
      - Poor microbiologic eradication → promotes resistance
      - Collateral Damage → MRSA, *Clostridium difficile*

Should we NOT Use Quinolones for a First ICU Infection?

- 239 ICU patients with no prior antibiotic exposure
  - Screen for MDR pathogens on admit
- Multivariate analysis of risks for acquiring MDR pathogens
  - 77 patients with ICU acquired MDR organisms (50 were infection)
    - » Multivariate risks for MDR acquisition: FQ use (OR 3.3), duration antibiotics (OR 1.1).
- 135 got a quinolone (ofloxacin or ciprofloxacin). Case-control matching for 72 of 135 rx with FQ
  - Cases with more antibiotics/pt, more BL/BLI use, more aminoglycoside use
  - Cases with more ICU-acquired MRSA (26% vs 12%, p=0.015), ICU- acquired ESBL (11% vs. 1%, p=0.017) than controls
- Maybe reserve quinolones for a second course of ICU infection



Nseir S, et al. *Crit Care Med*. 2005;33:283-9.
Niederman MS. *Crit Care Med*. 2005;33:443-4.

Stewardship: Supplemental Strategies

- ***Education*** **is essential for any program**
- ***Guidelines and clinical pathways*** **can improve antimicrobial utilization**
- ***Combination therapy*** **– insufficient data to recommend routine use...to prevent resistance**
- ***Streamlining or de-escalation*** **– can decrease antimicrobial exposure and save costs**
- ***Dose optimization*** **– an important part of stewardship**
- ***IV-to-PO switch*** **– can decrease LOS and health care costs**

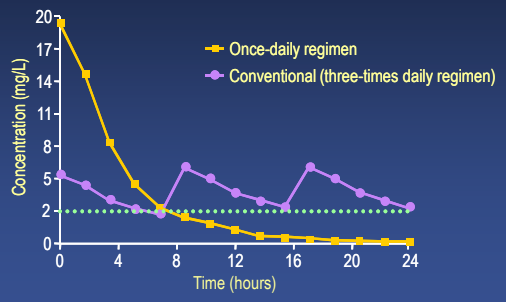
LOS = Length of stay

Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship: *Clin Infect Dis*. 2007;44:159-77.

Optimizing Antimicrobial Exposures: Pharmacodynamics

- **Considerations:**
  - ***In vitro potency***
  - ***In vivo exposure***: pharmacokinetics
    - » High drug clearance (young trauma patient)
    - » Increased volume of distribution (sepsis / septic shock)
  - ***In vivo killing profile***: pharmacodynamics
- **Pharmacodynamic Dosing Interventions:**
  - Escalated dosing: vancomycin, daptomycin
  - Once-daily aminoglycosides
  - Prolonged or continuous infusion of β-lactams

Once-daily vs. Conventional Three-times Daily Aminoglycoside Regimens

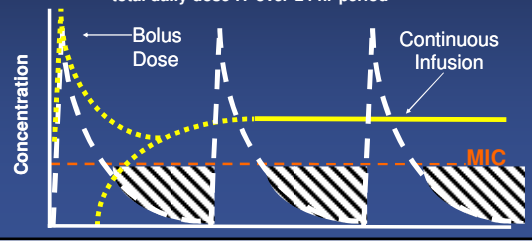


Nicolau DP, et al. *Antimicrob Agents Chemother* 1995;39:650–5.

Strategies to Improve Efficacy and Limit Resistance for β-Lactams

Increase duration of infusion

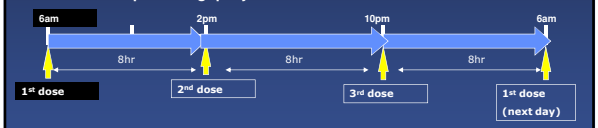
- **Continuous infusion**
  - » **Administer loading dose, then use pump to give total daily dose IV over 24 hr period**



Treatment of *Bla*$_{kpc-2}$-Positive *Klebsiella pneumoniae* Blood Stream Infection With Continuous Infusion Meropenem

58 yo hospitalized for aortic dissection complicated by intra-abdominal catastrophe and acute kidney injury → developed bacteremia

- MDR KPC (**MICs:** AMK 16, TAZ ≥ 64, P/T ≥ 128, Tige ≥ 8, PMX B 32, Mer 8)
- Cl cr ~45 ml/min
- Meropenem 2 g q8 by continuous infusion



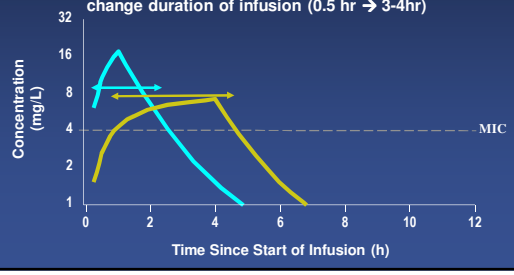
- Meropenem serum concentrations 22 mcg/mL (range 20-29)
- 6 wks of the therapy
- Microbiologic and clinical cure

Ho V, et al. *Surgical Infect* 2011;12(4):325-327

Optimizing β-lactam Therapy: Maximizing Percent T>MIC

Increased duration of infusion

- Prolonged infusion
  - » Same dose and dosing interval, 100-250ml, however, change duration of infusion (0.5 hr → 3-4hr)



Intravenous Antibiotic Pharmacodynamics against *Pseudomonas aeruginosa* from TRUST 12

- Benefits of Prolonged Infusion

1,533 *P. aeruginosa* from 56 US hospitals

Antibiotic	Dosing Regimen	CFR (%) Standard Infusions (0.5 – 1 hour)	CFR (%) Prolonged Infusions (3 – 4 hours)
Cefepime	2g q12h	84	-
	2g q8h	90	**93**
Doripenem	0.5g q8h	83	**94**
	1g q8h	89	**97**
Imipenem	1g q8h	78	**86**
Meropenem	1g q8h	88	**94**
	2g q8h	93	**97**
Pip/tazo	3.375g q8h	-	**81**
	4.5g q6h	77	**86**

Koomanachai P, et al. *Clin Ther* 2010;32(4):766-779

Cumulative Fraction of Response in Pediatric Patients with Pseudomonas

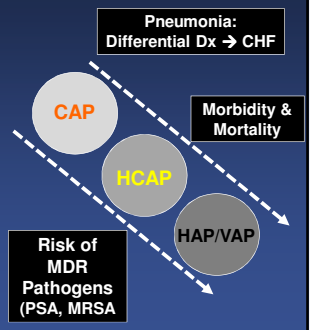
LOW Dose Regimens	Infusion Duration	% S	CFR
Ceftazidime 30 q8h	0.5 h	95	87
	3.0 h		95
	Continuous		95
Piperacillin /Tazobactam 75 Q6h	0.5 h	95	54
	3.0 h		89
	Continuous		92
Meropenem 20 q8h	0.5 h	98	84
	3.0 h		98

Doses in mg/kg per dose. Bactericidal exposures = 40% for carbapenems; 50% for other β-lactams

Courter JD, et al. Pediatr Blood Cancer 2009;53:379-385.

Pneumonia: The Continuum of Pulmonary Disease

- Community-acquire (CAP)
- Healthcare-associated (HCAP) is a relatively new clinical entity that includes a spectrum of adult patients who have a close association with acute care hospitals or reside in chronic care settings that increase their risk for pneumonia caused by multidrug-resistant pathogens.
- Hospital-acquired / Ventilator Associated (HAP / VAP)



Craven DE. *Curr Opinion Infect Dis.* 2006;19:153-160.

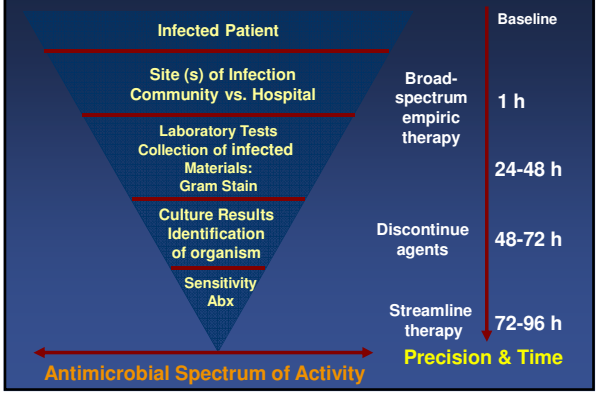
Frequency of Pathogens between VAP and HAP

Pathogen, by class	No. (%) of isolates			
	VAP		HAP	
	ICU (n=365)	Non-ICU (n=35)	ICU (n=101)	Non-ICU (n=169)
Gram-positive cocci				
MSSA	35 (9.6)	2 (5.7)	13 (12.9)	23 (13.6)
MRSA	69 (18.9)	2 (5.7)	13 (12.9)	42 (24.9)
Streptococcus pneumoniae	7 (1.92)	1 (2.9)	7 (6.9)	8 (4.7)
Gram-negative bacilli				
Enterobacter species	9 (2.5)	0	2 (2.0)	6 (3.6)
Escherichia coli	10 (2.7)	5 (14.3)	3 (3.0)	5 (3.0)
Klebsiella pneumoniae	6 (1.6)	2 (5.7)	5 (5.0)	8 (4.7)
Acinetobacter species	29 (8.0)	2 (5.7)	4 (4.0)	5 (3.0)
Stenotrophomonas maltophilia	25 (6.9)	2 (5.7)	2 (2.0)	1 (0.6)
Pseudomonas aeruginosa	60 (16.4)	10 (28.6)	11 (10.9)	14 (8.3)
Other	32 (8.8)	2 (5.7)	9 (8.9)	9 (5.3)

Single Center: UNC. Period 2000 through 2003, infection control surveillance.
Specimens isolated by BAL, expectorated sputum, or tracheal aspiration.

Weber DJ et al. Infect Control Hosp Epidemiol 2007;28:825-31.

Start Broad, Then Streamline Therapy



Hartford Hospital: VAP Pathway – EMPIRIC Therapy

1st Line Regimen:	Dosage (CrCl ≥ 50ml/min)	Adjustment for Renal Dysfunction (CrCL in ml/min) 30 - 49	< 30	CRRT
Vancomycin (Linezolid) *plus*	Dosing per Pharmacy Protocol (High Dose)			
Tobramycin *plus*	Dosing per Once Daily Aminoglycoside Protocol			
High Dose β-lactam				
Medical Intensive Care Unit: Meropenem	2g q 8 hr (3 hr infusion)			
Surgical and Neurosurgical Intensive Care Unit: Cefepime	2g q 8 hr (3 hr infusion)			
Piperacillin / Tazobactam	18g continuous inf			

- Target entire MIC distribution → focus on 4, 8 &16 µg/ml
- Anticipate variable PK → Cl & Vd
- Target PD profile → 40% *f*T>MIC

CI = continuous infusion; CRRT = continuous renal replacement therapy

Nicasio AM, et al. *J Crit Care* 2010;25:69-77; Kuti & Nicolau *J Crit Care* 2010;25:152-153

Improved Outcomes: VAP Pathway

Outcome	Historic n = 74	Pathway n = 94	P-value

The Pathway Statistically Decreased:

- Infection Related Mortality
- Infection Related Length of Stay
- Time to Appropriate Therapy
- Number of Super-infections

IR = Infection Related, MDR = Multi-Drug Resistant

Nicasio AM, et al. *J Crit Care* 2010;25:69-77

De-escalation of Antibiotic Therapy

- **Approach to de-escalation / streamlining**
  - Initial treatment with broad-spectrum antibiotics to cover most probable pathogens[1,2]
  - Discontinue antibiotic therapy if no evidence of infection (bronchoalveolar lavage samples negative)[3]
  - Narrow the spectrum of activity when possible, based on culture findings[1,2]
  - Shorten course of therapy, based on culture findings and clinical course[4]

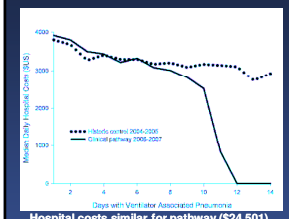
1. Weber DJ. *Int J Infect Dis.* 2006;10(suppl 2):S17-S24. **2.** Höffken G, Niederman MS. *Chest.* 2002;122:2183-2196. **3.** American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA). *Am J Respir Crit Care Med.* 2005;171:388-416. **4.** Singh N et al. *Am J Respir Crit Care Med.* 2000;162:505-511.

De-escalation of Antibiotic Therapy

- **Approach to de-escalation / streamlining**
  - Initial treatment with broad-spectrum antibiotics to cover most probable pathogens[1,2]
  - Discontinue antibiotic therapy if no evidence of infection (bronchoalveolar lavage samples negative)[3]
  - Narrow the spectrum of activity when possible, based on culture findings[1,2]
  - Shorten course of therapy, based on culture findings and clinical course[4]
- **Exceptions to general approach**
  - **Do not discontinue antibiotics in a patient who is decompensating**
  - **Patients may be ill and require therapy, notwithstanding negative culture results**

1. Weber DJ. *Int J Infect Dis.* 2006;10(suppl 2):S17-S24. **2.** Höffken G, Niederman MS. *Chest.* 2002;122:2183-2196. **3.** American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA). *Am J Respir Crit Care Med.* 2005;171:388-416. **4.** Singh N et al. *Am J Respir Crit Care Med.* 2000;162:505-511.

Economics of the VAP Pathway



Hospital costs similar for pathway ($24,501) and control ($28,817) over first week of VAP, but significantly lower for clinical pathway during week 2 ($12,231 vs $20,947, p<0.001).

Variable	Control (n=73)	Pathway (n=93)	P-value
LOTVAP	27.1±18.5	12.7±8.1	<0.001
LOS	35.0±22.0	28.9±17.3	0.076*
COSTVAP	$75K	$35K	<0.001
COSTafter	$95K	$76K	0.077*
Antibiotic Cost	$934±1533	$766±755	0.45

* Treatment on Clinical Pathway was independently associated with lower total LOS after VAP (p=0.012) and lower total hospital costs after VAP (p=0.033) in multivariable models.

LOTVAP – length of VAP treatment; LOS – total length of hospital stay after identification of VAP; COSTVAP – hospital costs (2007$) of treating VAP; COSTafter – total hospital costs (2007$) of treating VAP after VAP identification; Antibiotic Cost – acquisition cost of antibiotics used to treat VAP

Nicasio AM, et al. *Pharmacother* 2009;30:453-62

What is "Collateral Damage"?

- *"Collateral Damage"*
  - a term used to refer to ecological adverse effects of antibiotic therapy; namely, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug resistant organisms (i.e., *Clostridium Difficile* Infection)
- Two antibiotic classes commonly linked to collateral damage:
  - Cephalosporins & Fluoroquinolones

Paterson DL. *Clin Infect Dis.* 2004;38(suppl 4):S341-S345.

Antimicrobial Cross-Resistance Among Selected Gram-Negative Bacilli

	Pseudomonas aeruginosa		*Enterobacter* Species	
Antimicrobial Resistance	Ciprofloxacin Resistant (n = 1946)	Ciprofloxacin Susceptible (n= 6298)	Ciprofloxacin Resistant (n = 486)	Ciprofloxacin Susceptible (n= 4513)
Gentamicin	66.0	21.7	48.8	3.9
Ceftazidime	39.8	14.0	81.5	31.8
Imipenem	37.6	10.9	3.9	1.0
Amikacin	26.0	5.6	10.9	0.8

Data are presented as percentages of strains exhibiting cross-resistance, 1994-2000.

Neuhauser MM, Weinstein RA, Rydman R, et al. *JAMA.* 2003;289:885-888.

Carbapenems: Saving the Best for Last

- Broad spectrum of activity including Pseudomonas
  - Imipenem
  - Meropenem
  - Doripenem
- Broad spectrum but lacking Pseudomonas activity
  - Ertapenem

Ertapenem

- **US experience: Sustained efficacy & safety over more than 10 years**
  - Complicated urinary tract infection
  - Complicated Intra-abdominal infection
  - Complicated skin & skin structure including diabetic foot infections
- **Active against ESBL-producing *Enterobacteriaceae organisms***
  - *2005 -2010: 261 patients with ESBL bloodstream infections*
  - Outcomes equivalent between ertapenem and group 2 carbapenems (e.g., imipenem & meropenem)

Collins VL, et al. *Antimicrob Agents Chemother.* 2012;56(4):2173-7.

What is the concern with Ertapenem?

- ***Alteration in Gut Flora***
  - *Selection of resistant Enterobacteriaceae*
  - *Selection of resistant Pseudomonas aeruginosa*
- ***Alteration of Institutional Ecology***
  - *Selection of G*roup 2 carbapenem (e.g., imipenem, meropenem, doripenem) *resistant Pseudomonas aeruginosa*

ABC study

ABC study : examine effect of ertapenem on gut flora employing selective media

ABC = antibacterial R in the colon

- Rectal swabs in all pts enrolled in two IAI studies
  - ertapenem vs piperacillin/tazobactam
  - ertapenem vs ceftriaxone / flagyl

Dinubile MJ, et al. *Eur J Clin Micro Infect Dis.* 2005;24(7):443-9.

Resistant Gram-negative Bacilli Isolated from Rectal Swabs

Organism	Ertapenem (N=196) N (%)			Ceftriaxone/Metronidazole (N=193) N (%)		
	Baseline	DCOT	DCOT/TOC	Baseline	DCOT	DCOT/TOC
CRO-R Enteric	9 (4.6)	3 (1.5)*	6 (3.1)†	4 (2.1)	31 (16.1)*	50 (25.9)†
ETP-R Enteric	1 (0.5)	1 (0.5)	1 (0.5)	0 (0)	0 (0)	0 (0)
ESBL-Enteric	8 (4.0)	1 (0.5)**	5 (2.6)††	4 (2.0)	18 (9.3)**	39 (20.2)††
IPM-R Ps	0 (0)	2 (1.0)‡	2 (1.0)	0 (0)	0 (0)‡	0 (0)

*, †, **, †† P<0.001 for between-treatment comparison ‡p=0.5 for between-treatment comparison

Emergent Ceftriaxone-resistant Enterobacteriaceae: 19 *E coli*, 20 *Enterobacter cloacae*, 10 *K pneumoniae*, 3 *Enterobacter aerogenes*, 3 *Citrobacter freundii*, 2 *K oxytoca*

Friedland I, *et al.* ACCP, Portofino, Italy, October 16-19, 2003 (Poster # 30).
Dinubile MJ, et al. *Eur J Clin Micro Infect Dis.* 2005;24(7):443-9.

Resistant Gram-negative Bacilli Isolated from Rectal Swabs

Organism	Ertapenem (N=155) N (%)			Piperacillin-Tazobactam (N=156) N (%)		
	Baseline	DCOT	DCOT/TOC	Baseline	DCOT	DCOT/TOC
P/T-R Enteric	1 (0.6)	1 (0.6)*	4 (2.6)†	1 (0.6)	18 (11.5)*	21 (13.5)†
ETP-R Enteric	0 (0)	1 (0.6)	1 (0.6)	0 (0)	2 (1.3)	2 (1.3)
ESBL-Enteric	1 (0.6)	0 (0)	1 (0.6)	1 (0.6)	4 (2.6)	5 (3.2)
IPM-R Ps	0 (0)	0 (0)	0 (0)	1 (0.6)	2 (1.3)	2 (1.3)

* P<0.05 for between-treatment comparison †p<0.001 for between-treatment comparison

P/T R; 8 E Coli, 8 Klebsiella, 6 Enterobacter

Friedland I, *et al.* Presented at 13th ECCMID, Glasgow, UK, May 10-13, 2003
Dinubile MJ, et al. *Eur J Clin Micro Infect Dis.*,2005;24(7):443-9.

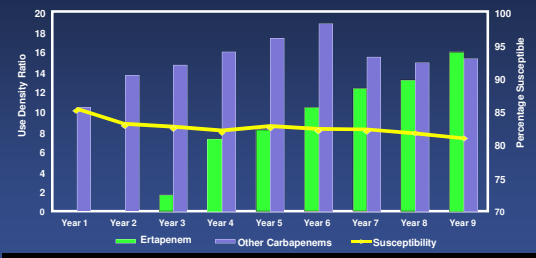
Ertapenem Does NOT Adversely Effect the Hospital Ecology → *P. aeruginosa* Susceptibility to Group 2 Agents

Clinical Studies

- **Crank, 44th IDSA Annual Meeting,** Toronto, CA 2006. Abst. 285
- **Goff & Mangino,** ***J Infection*** 2008;57:123-126
- **Lima A, et al.,** ***Brazilian J Infect Dis*** 2008;12:105-106
- **Goldstein et al.,** ***Antimicrob Agents Chemother*** 2009;53:5122-5126
- **Carmeli et al.,** ***Diagn Microbiol Infect Dis*** 2011;70:367-372
- **Cook et al.,** ***Antimicrob Agents Chemother*** 2011;55(12):5597-5601
- **Graber et al.,** ***Epidemiology Infection*** 2012;140(1):115-25
- **Sousa et al (SPAIN)., ECCMID,** London, UK 2012 Abst. P1204
- **Eagye & Nicolau,** ***Infect Control Hosp Epidemiol*** 2010;31:485-490
- **Eagye & Nicolau,** ***J Antimicrob Chemother*** 2011;66:1392-1395

Nicolau DP, et al. International Journal of Antimicrobial Agents, 39 (2012) 11– 15

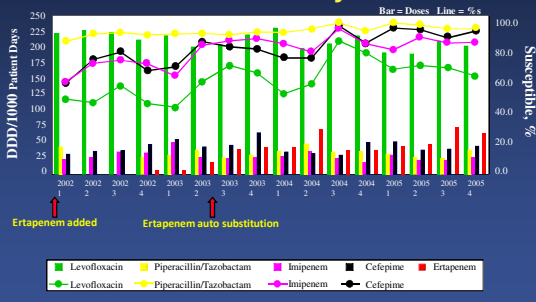
Mean Carbapenem Use and *Pseudomonas aeruginosa* Susceptibility at 25 Hospitals during the 9 Years Surrounding Adoption of Ertapenem



- No relationship found between rate of ertapenem use and change in *Pseudomonas aeruginosa* carbapenem susceptibility over 6 years

Eagye KJ & Nicolau DP *Journal Antimicrobial Chemotherapy* 2011;66:1392-1395.

Collateral Damage v. Collateral Benefit
Susceptibility of *P. aeruginosa:* 3 Years of Formulary Inclusion

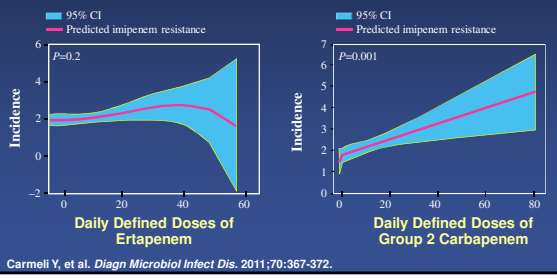


Goldstein EJ, et al. *Antimicrob Agents Chemother.* 2009;53:5122-5126.

Collateral Damage v. Collateral Benefit
Minimal Risk of Imipenem-Resistant *P. aeruginosa* with Ertapenem: 4-Year Retrospective Study: Israel

Ertapenem - Not Associated With Imipenem-Resistant *P. aeruginosa*

Imipenem and Meropenem-Direct Correlation With Imipenem-Resistant *P. aeruginosa*



Carmeli Y, et al. *Diagn Microbiol Infect Dis.* 2011;70:367-372.

Strategies to Optimize Clinical & Microbiologic Outcomes & Slow the Development of Resistance

- **Antimicrobial Stewardship Efforts**
  - Appropriate Initial Therapy
    - » Right DRUG(s)
    - » Optimize Exposures (PD profile)
  - De-escalation / Streamlining
    - » <50% of nosocomial sepsis cases b/c susceptibility & previous ABX [Heenen et al., CCM 2012;40(5):1404-9]
  - Reduce Duration of Therapy

Unintended Consequences of Poor Antimicrobial Practices

- Development of resistance in the target pathogen
- Development of superinfection @ original infection site
- Development of new infection (i.e., *Clostridium difficile*)
- Increased cost of care

Societal and Hospital Costs of Antimicrobial-Resistant Infections

	All Patients	Patients with ARI	Patients without ARI
n (%)	1391	188 (13.5)	1203 (86.5)
APACHE III Score*	42.1	54.8	40.1
Duration of Stay* (days)	10.2	24.2	8.0
HAI* (n)	260	135	125
Cost per Day* (US$)	1651	2098	1581
Total Cost* (US$)	$19,267	$58,029	$13,210
Death* [n (%)]	70	34 (18.1)	36 (3.0)

* *P*<.001. Mean values shown in table
APACHE=Acute Physiology and Chronic Health Evaluation; ARI=antimicrobial-resistant infections; HAI=healthcare–acquired infection

Roberts RR, et al. *Clin Infect Dis.* 2009;49:1175-1184.

Hospital and Societal Costs of Antimicrobial-Resistant Infections

Organism	Mean Cost Per Patient N=1391 ($)	Mean Cost Per Patient Healthcare-acquired ($)
Vancomycin Resistant Enterococci	$66,416	$73,481
Methicillin Resistant *Staphylococcus aureus*	$46,236	$60,984
Acinetobacter resistant to amikacin or imipenem	$97,444	$111,062
Klebsiella* or *E. coli resistant to quinolones or third-generation cephalosporins	$26,549	$39,403
Multiple ARIs	**$157,835**	

Roberts RR, et al. *Clin Infect Dis.* 2009;49:1175-1184.

Strategies to Optimizing Efficacy and Minimize Collateral Damage In Our Patients

- **Prevent it –**
  - **Vaccination programs in the community**
  - **Utilization of non-antibacterial interventions** (i.e., probiotics, medicines able to stimulate the body's defense against infections)
  - **Strong infection control practices in the hospital**
- **Respect it –**
  - **Despite our efforts infection will develop in patients in both the community & the hospital setting**
- **Do Not Yield to it –**
  - **Understand the likely causative pathogens and local resistance**
  - **Utilization of real-time, point of care molecular diagnostics**
  - **Make good decisions regarding the choice, dosage and duration [use of biomarkers] of antibiotic(s)**
  - **Understand that the MOST EXPENSIVE antibiotic is the one that does not work**