Antimicrobial Stewardship: An Important Piece of the Puzzle To Improving Patient Outcomes and Reducing Healthcare-Associated Infections

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Objectives

At the end of this presentation attendees will be able to:

- Define antimicrobial stewardship and describe its importance in healthcare systems
- Describe specific examples of the two most commonly used methods of antimicrobial stewardship
- Describe how implementation of institutional guidelines may improve antimicrobial use and patient outcomes

Risking Threat of Infections Unfazed by Antibiotics

The New York Times

A minor-league pitcher in his younger days, Richard Armbruster kept playing baseball recreationally into his 70s, until his right hip started bothering him. Last February he went to a St. Louis hospital for what was to be a routine hip replacement.

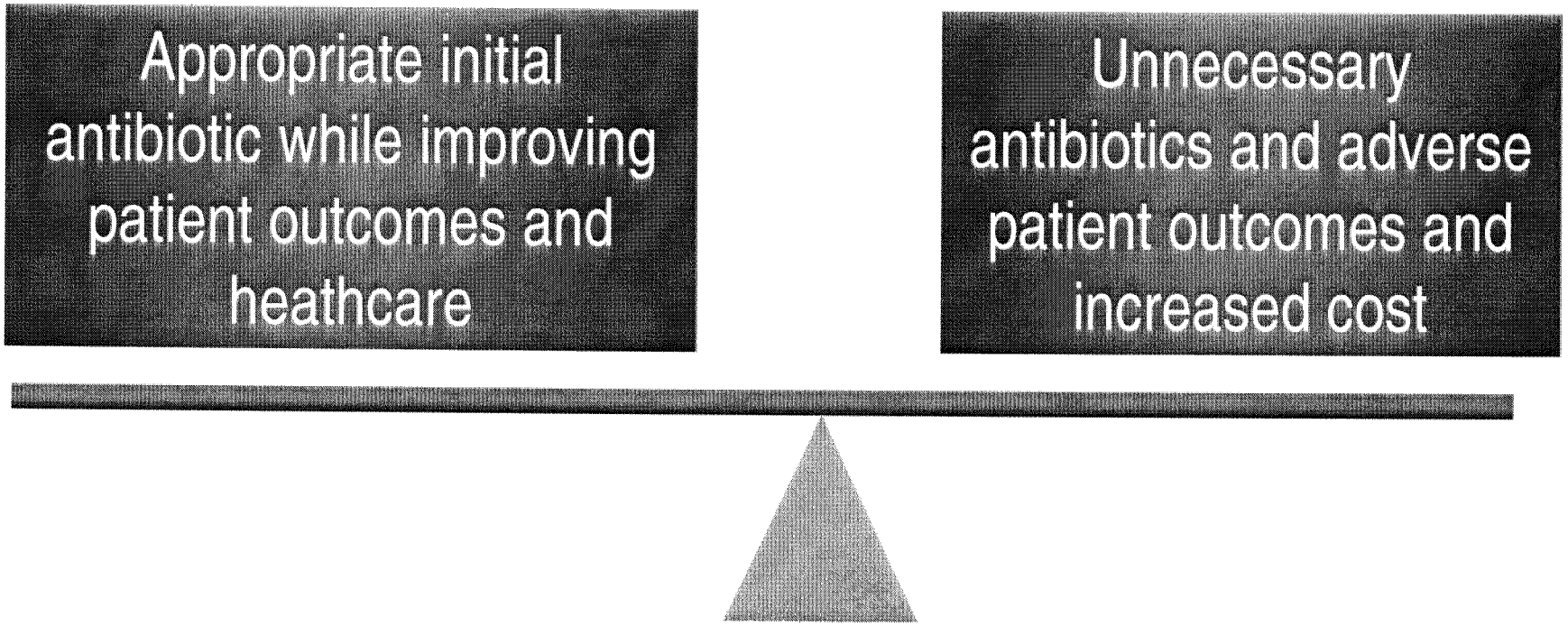
By late March, Mr. Armbruster, then 78, was dead. After a series of postsurgical complications, the final blow was a bloodstream infection that sent him into shock and resisted treatment with antibiotics.

"Never in my wildest dreams did I think my dad would walk in for a hip replacement and be dead two months later," said Amy Fix, one of his daughters.

Mr C.

- Mr C is a 35 year old healthy man who comes to GMA complaining of 7 days of a runny nose, frontal sinus congestion, sore throat, and myalgias.
- His vital signs are stable and he is afebrile. His exam is notable for mild tonsillar erythema and some generalized sinus tenderness
- He states that he is really busy working for a big financial services company and has 2 young kids at home (who both have colds). His symptoms have been going on for a week and he wants a prescription so he get better fast.

Antimicrobial Therapy



A Balancing Act

Antimicrobial Prescribing

Empiric

- Initial administration of a broad-spectrum antibiotic regimen that attempts to improve outcomes and minimize resistance.

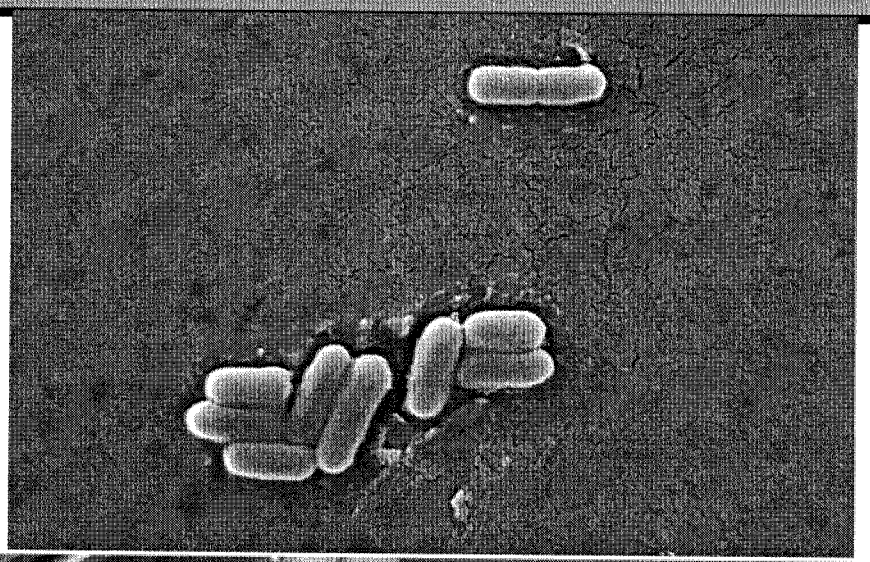
Defined or Targeted

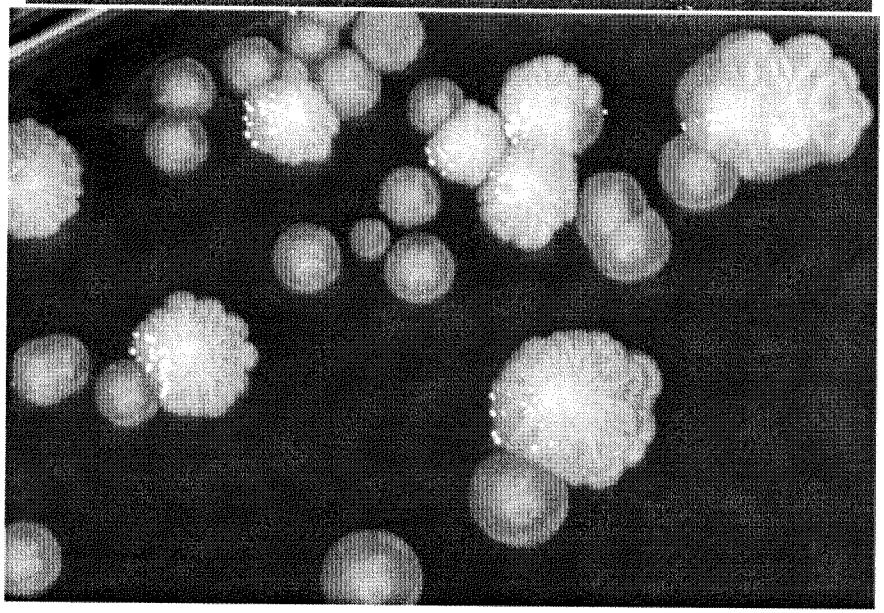
- Modification of antimicrobial therapy once the cause of infection is identified. Therapy may also be discontinued if the diagnosis of infection becomes unlikely.[1]
- Focus on de-escalation of antibiotic therapy with the goal of minimizing resistance and toxicity, and improving cost-effectiveness.[2,3]

1. Kollef MH. *Drugs*. 2003;63:2157–2168.
2. Kollef MH. *Crit Care Med*. 2001;29:1473–1475.
3. Evans RS et al. *N Engl J Med*. 1998;338:232–238.

Bad Bugs: No ESKAPE

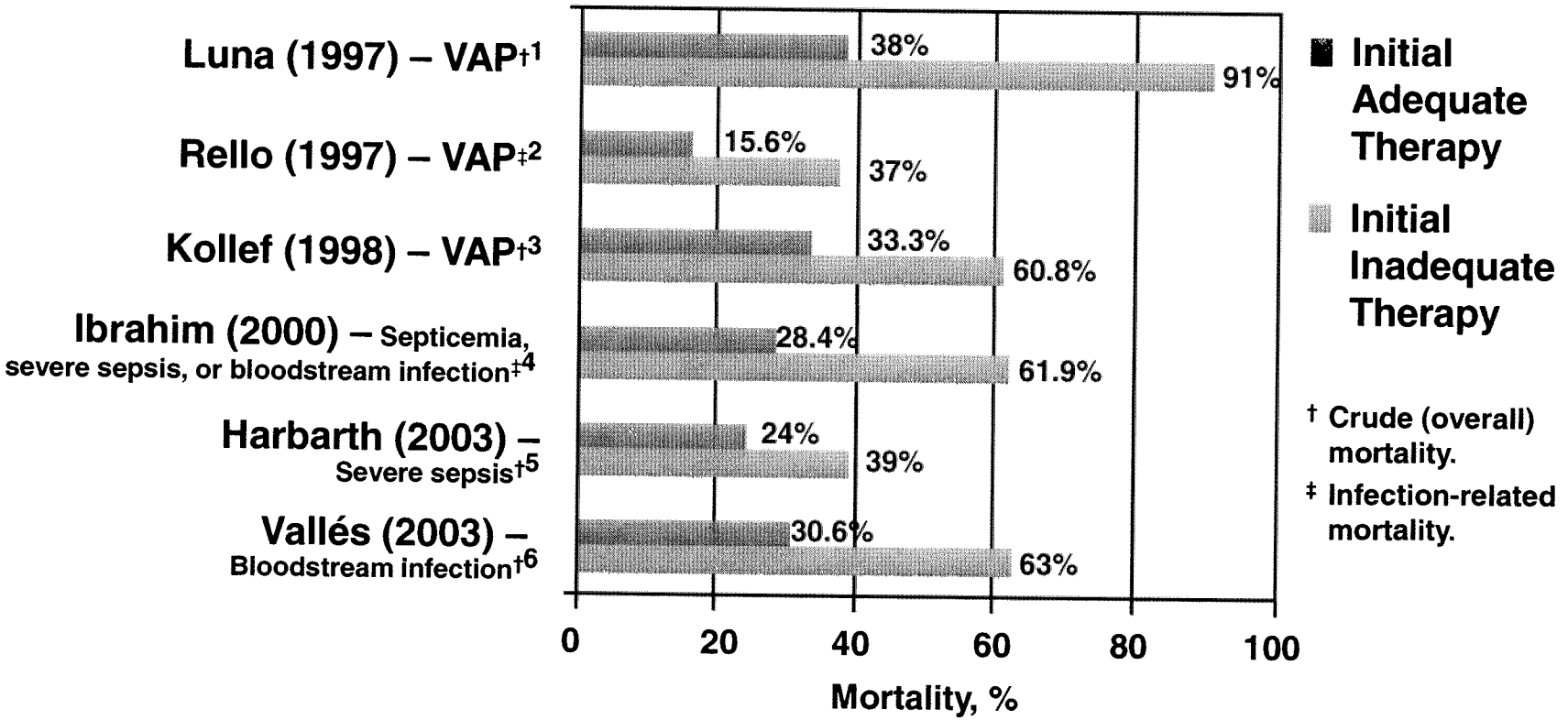
- *Enterococcus*
- *S. aureus*
- *Klebsiella spp.*
- *Acinetobacter*
- *P. aeruginosa*
- *Enterobacter spp.*





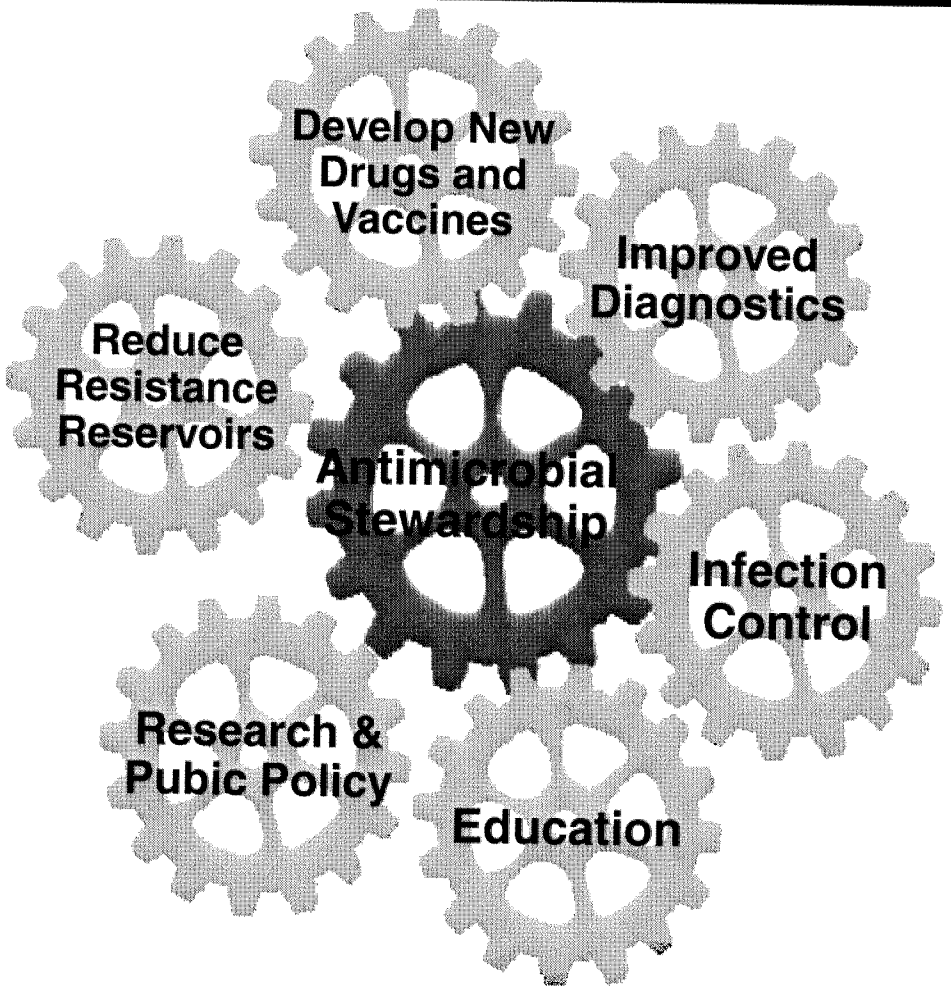
Boucher H, et al, Clin Infect Dis 2009;48:1-12

Mortality Associated With Initial Inadequate* Therapy in Critically Ill Patients With VAP or Septicemia, Severe Sepsis, or Community-Acquired Bloodstream Infection in Critically Ill Patients

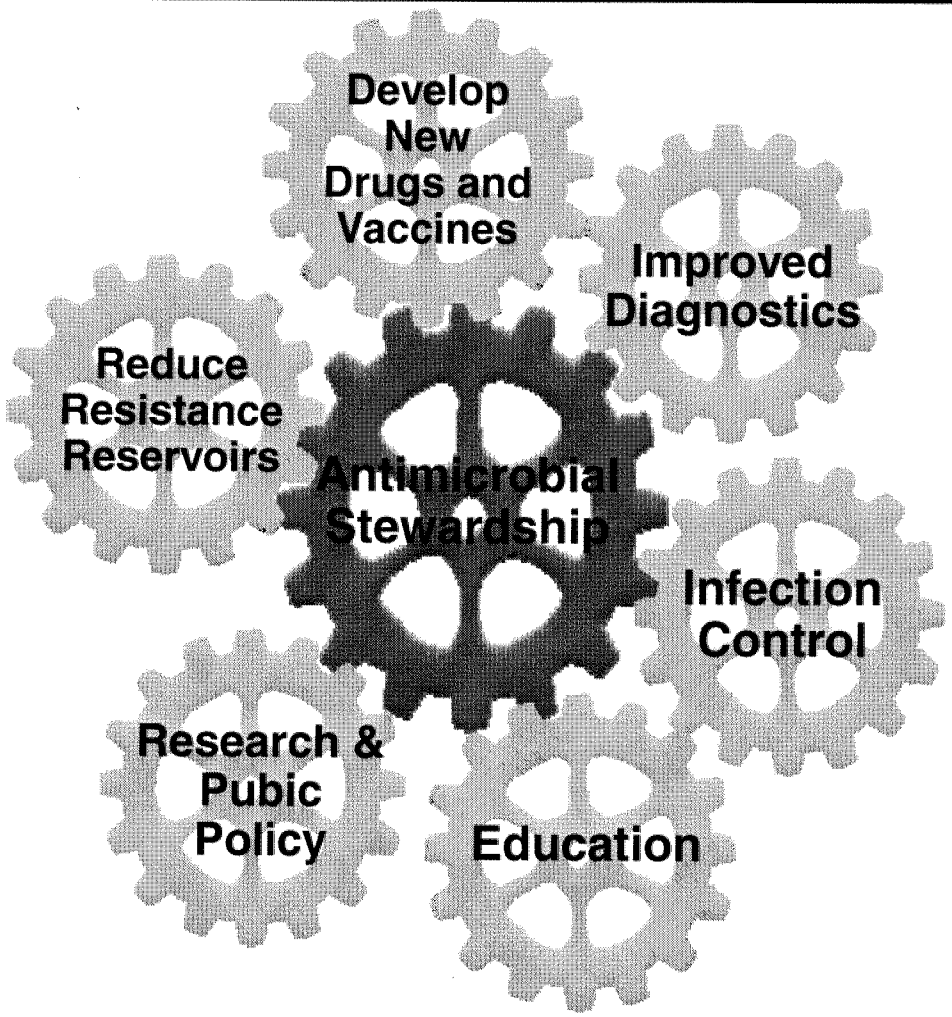


1. Luna CM et al. *Chest.* 1997;111:676–685. **2.** Rello J et al. *Am J Respir Crit Care Med.* 1997;156:196–200.
3. Kollef MH et al. *Chest.* 1998;113:412–420. **4.** Ibrahim EH at al. *Chest.* 2000;118:146–155.
5. Harbarth S et al. *Am J Med.* 2003;115:529–535. **6.** Vallés J et al. *Chest.* 2003;123:1615–1624.

Efforts to Improve Antimicrobial Prescribing and Control Resistance



Efforts to Control Resistance



What is Antimicrobial Stewardship

- Antimicrobial stewardship involves the *optimal selection, dose and duration* of an antibiotic resulting in the cure or prevention of infection with minimal unintended consequences to the patient including emergence of resistance, adverse drug events, and cost.

Ultimate goal is improved patient care and healthcare outcomes

Dellit TH, et al. CID 2007;44:159-77,
Hand K, et al. Hospital Pharmacist 2004;11:459-64
Paskovaty A, et al IJAA 2005;25:1-10
Simonsen GS, et al Bull WHO 2004;82:928-34

ASHP Statement on ASP 2009

ASHP Statement on the Pharmacist's Role in Antimicrobial Stewardship and Infection Prevention and Control

Promoting optimal antimicrobial use
Reducing the transmission of infections

What Every Health Care Executive Should Know: The Cost of Antimicrobial Resistance

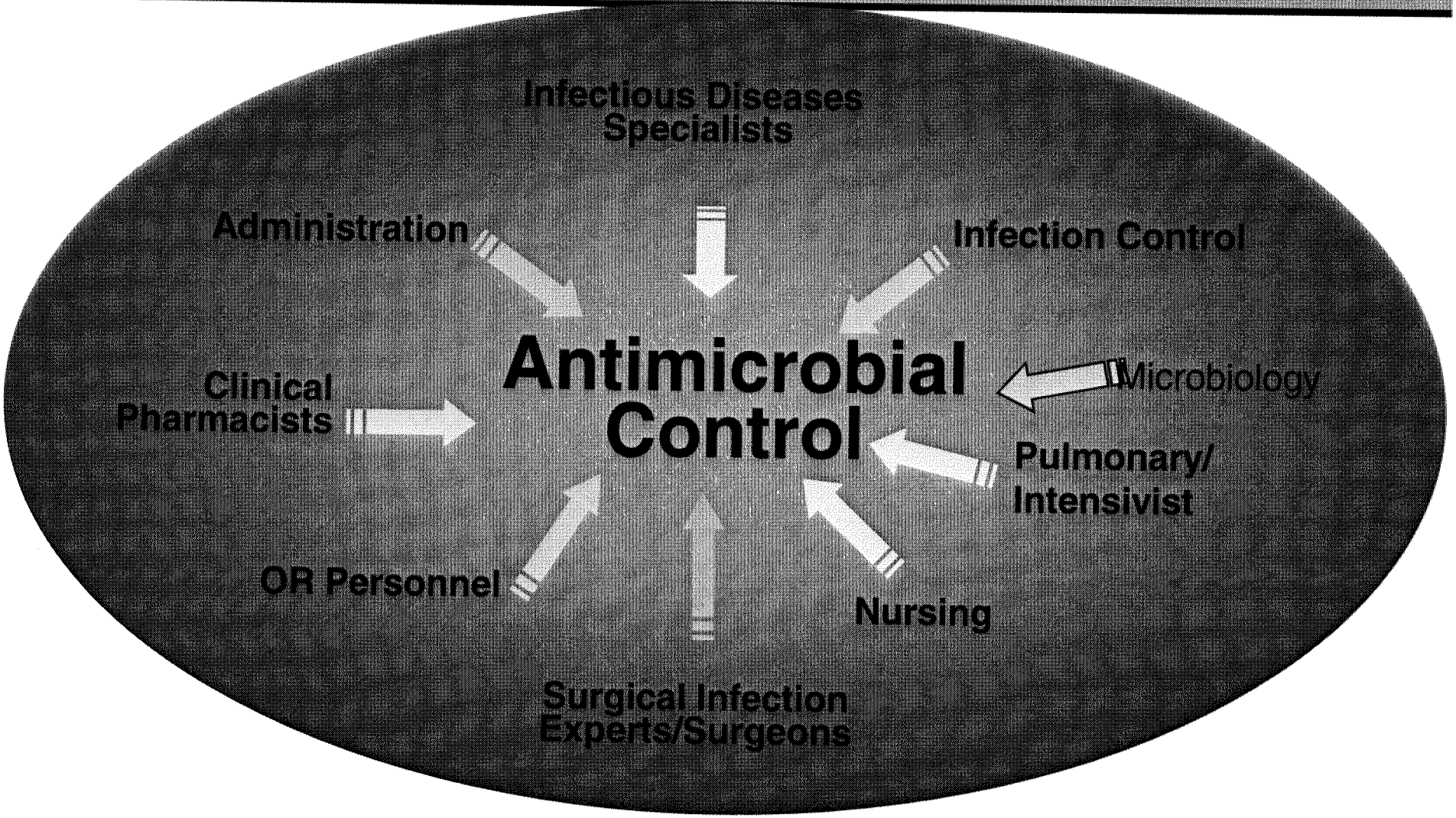
- Antimicrobial Resistance: Patients and hospitals in Peril
- The Clinical Consequences of Antimicrobial Resistance
- Transmission Control to Prevent the Spread of MDROs in Health Care Facilities
- Antimicrobial Stewardship

Critical Aspects of Antimicrobial Stewardship Programs

- Must gain support and collaboration
- Hospital administration
  - Medical/surgical staff
  - Local providers
- Must coordinate activities
  - Infection control
  - Pharmacy and Therapeutics
- ID and PharmD should be compensated, have authority, and clear expectations from hospital administration
- Should be under the umbrella of quality and patient safety

Dellit TH, et al. CID 2007;44:159-77,
Hand K, et al. Hospital Pharmacist 2004;11:459-64
Paskovaty A, et al. IJAA 2005;25:1-10

Building The Team



Antimicrobial Stewardship Strategies

- Prospective audit with intervention and feedback
- Formulary restriction and preauthorization

Supplemental Strategies

- Education, guidelines, clinical pathways
- Dose optimization via PK-PD
- De-escalation/Streamlining
- Antimicrobial order forms/order sets if CPOE
- IV-PO switch
- Computerized decision support
- Others

Dellit TH, et al. CID 2007;44:159-77
Hand K, et al Hospital Pharmacist 2004;11:459-64
Paskovaty A, et al IJAA 2005;25:1-10

Antimicrobial Stewardship at Tufts Medical Center: ?? years and Going Strong

- Improve patient outcomes
- Slow antimicrobial resistance
- Ensure appropriate empirical antimicrobial therapy
  - Antimicrobial choice, dosage, route, and duration
- Educate providers on the importance of prudent antimicrobial prescribing
- Reduce medication errors related to antimicrobials
- Reduce cost
  - Duration of treatment
  - IV to PO
  - Antimicrobial de-escalation and stopping unneeded treatment
- 2 part time ID physicians, 1 full time ID PharmD

Survey of Antimicrobial Stewardship Practices in the Northeast

Table 1. Characteristics of Survey Participants

	Number	Percent
Response Rate	35	76.1%
Practice Area		
Pharmacy Director	21	60.0%
Clinical Pharmacist/Coordinator/Other	11	31.4%
ID Pharmacist	3	8.6%
Antimicrobial % of Total Pharmacy Drug Budget		
< 10%	7	20.0%
10-15%	13	37.1%
16-25%	9	25.7%
> 26%	1	2.9%
Unknown	5	14.3%
Healthcare System Type		
Not a teaching hospital	17	48.6%
University (affiliated) hospital	7	20.0%
Rural/critical access	6	17.1%
Non-university teaching hospital	5	14.3%
Acute/rehab	2	5.7%
Antimicrobial Management Pharmacist		
Yes	6	17.1%
No	29	82.9%

	Number	Percent
Existence of ASP		
Yes	15	42.9%
No	20	57.1%
Antibiogram		
Yes	33	94.3%
No	2	5.7%
Number of Licensed Beds		
< 100	7	20.0%
101-300	20	57.1%
301-500	7	20.0%
>500	1	2.9%
Number of Annual Admissions		
< 2,500	5	14.3%
2,501-5,000	6	17.1%
5,001-10,000	11	31.4%
> 10,000	6	17.1%
Unknown	7	20.0%
ID Consult Service		
Yes	28	80.0%
No	7	20.0%

Nadkarni L, et al. International Conference on Healthcare-associated Infections 2010, Poster 98

Stewardship Strategies: Prospective Audit & Feedback

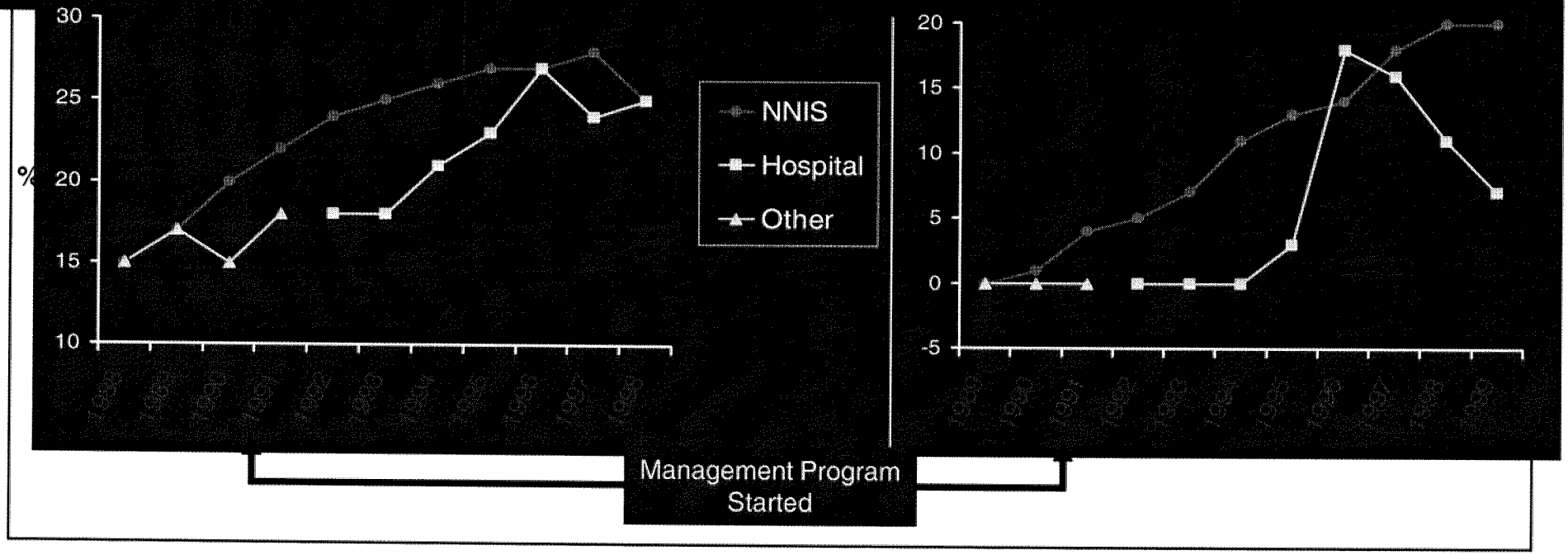
- Design:
  - Prospective evaluation of antimicrobial management program implemented
  - Originally started in 1991 to minimize inappropriate use of 3rd-generation cephalosporins, broadened to audit use of other antimicrobials
  - Time period: 7 years
  - ¼-time ID physician, full-time ID PharmD
- Assessed incidence of *C. difficile*, resistant Enterobacteriaceae, VRE, and MRSA in NNIS system hospitals of comparable size

NNIS = National Nosocomial Infections Surveillance system

Carling P, et al. *Infect Control Hosp Epidemiol.* 2003;24:699-706.

Stewardship Strategies: Review & Feedback Example

MRSA & VRE rates before and after implementation of Antimicrobial Management Program vs. rates in NNIS system hospitals



Also: Reduction in CDAD (p=0.002)

Carling P, et al. *Infect Control Hosp Epidemiol.* 2003;24:699-706.

Antimicrobial Stewardship Care Bundle

- Prospective audit system
  - Stewardship program
  - Outcomes
    - Reason for treatment, cultures, empirical, and de-escalation
    - LOS, mortality, and % interventions accepted

Indicator	Fraction (%) Courses Compliant With Indicator		p
	Control Phase	Intervention Phase	
Documented indication for antibiotic therapy	76/80 (95)	80/80 (100)	0.12
Appropriate cultures collected	70/80 (87)	76/80 (95)	0.09
Appropriate empirical therapy	55/80 (69)	65/80 (81)	0.06
Appropriate deescalation[a]	41/57 (72)	52/58 (90)	0.01
All indicators concurrently	13/80 (16)	43/80 (54)	<0.001

IV to Oral interchange

Toth NR, et al Am J Health-Syst Pharm 2010;67:747-9

Antimicrobial Stewardship in LTACs

- Eight public LTACs in Montreal
- Two prescriber groups (N=36)
- Educational intervention (twice, Q4 months)
  - Antimicrobial guide
  - Prescribing profiles (appropriate or inappropriate)
  - Targeted infections: UTI, LRTI, SSSI, and sepsis
- Inappropriate prescribing decreased 20% vs. 5%
- Prescribers less likely to prescribe inappropriate therapy

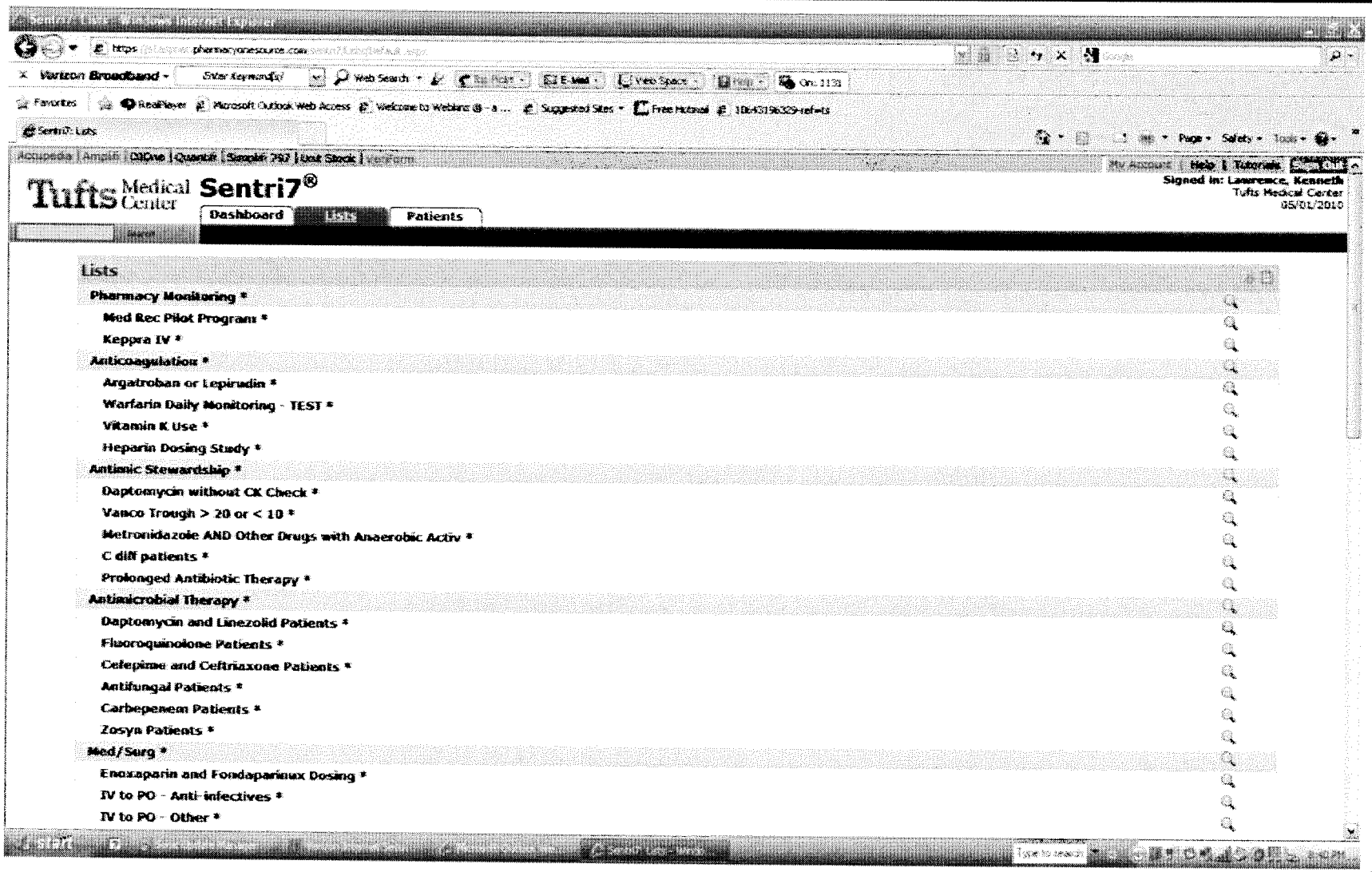
Monette J, et al. J Am Geriatr Soc. 2007 Aug;55(8):1231-5

Computer Surveillance and Decision Support in Antimicrobial Stewardship

- Sentri7
- SafetySurveillor
- TheraDoc
- Computerized physician order entry
- Benchmarking and local antimicrobials point prevalence surveys (state may consider doing this)

Claridge JA, et al. Surg Infect 2010;11:125-31

Decision Support for Antimicrobial Stewardship



Education

Antimicrobial Management Team Question of the Week
Doron, Shira
To: Tufts MC Antimicrobial Management Team
Cc:

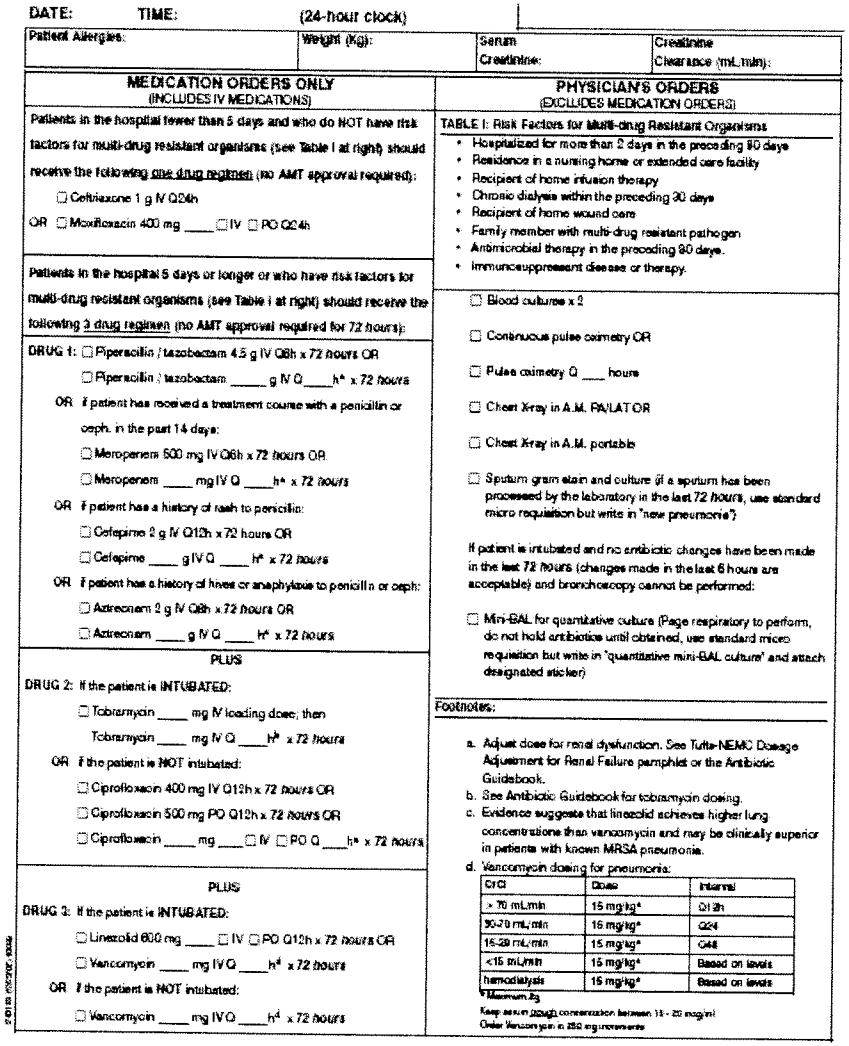
Q: Three days ago, I admitted a 72 year old patent from a long-term acute care facility to the MICU with ventilator associated pneumonia (VAP). The patient had recently been treated with a cephalosporin for a complicated UTI and I was concerned about infection due to an Extended Spectrum Beta-lactamase (ESBL) producing organism, so I prescribed meropenem, as well as cipro and vancomycin. The sputum culture on admission to the MICU did indeed grow an ESBL *Klebsiella pneumoniae*. The isolate was susceptible to ertapenem (MIC<0.5) , meropenem (MIC<1), and amikacin (MIC<2). Since the antibiotics prescribed using the VAP order form are about to expire I want to renew the patient's antibiotics to finish an 8 day course. Should I continue meropenem? Is there a difference in the clinical efficacy between ertapenem and meropenem for the treatment of pneumonia?

A: Ertapenem has excellent penetration into the lung tissue and the epithelial lining fluid and is a good choice for treatment of pneumonia caused by Gram positive or Gram negative pathogens. In this case, there would be no reason to continue treatment with meropenem. At Tufts, one of the most common causes of late-onset VAP is *Pseudomonas aeruginosa,* against which ertapenem does not provide sufficient *in vitro* activity, making it a poor choice for empiric therapy (before you know the culture results) . However, in this case, since you know the organism is Klebsiella, ertapenem would be the most appropriate. We always recommend de-escalating antibiotics; since the spectrum of ertapenem is narrower than meropenem, we would recommend switching to ertapenem for the remainder of the treatment course. In addition, once the organism is identified there is no need for double coverage with cipro, and the vancomycin can be safely discontinued as well.

The recommendations in this e-mail are based on published guidelines and the clinical expertise of our staff and may not apply to every patient. Please use clinical judgment when applying these concepts. The Antimicrobial Management Team serves adult patients at Tufts Medical Center. Some of the concepts presented here may not be appropriate for pediatric patients. Please do not hit "reply all" when responding to this message. To view previous AMT questions of the week, please see http://intranet.nemc.org/nmPharm2/Guidelines__Forms-ID.htm.

The Antimicrobial Management Team
Shira Doron, MD Kenneth Lawrence, PharmD Lisa Davidson, MD

Antimicrobial Order Forms



DATE: TIME: (24-hour clock)

Patient Allergies:	Weight (Kg):	Serum Creatinine:	Creatinine Clearance (mL/min):

MEDICATION ORDERS ONLY
(INCLUDES IV MEDICATIONS)

Patients in the hospital fewer than 5 days and who do NOT have risk factors for multi-drug resistant organisms (see Table I at right) should receive the following one drug regimen (no AMT approval required):

☐ Ceftriaxone 1 g IV Q24h

OR ☐ Moxifloxacin 400 mg ____ ☐ IV ☐ PO Q24h

Patients in the hospital 5 days or longer or who have risk factors for multi-drug resistant organisms (see Table I at right) should receive the following 3 drug regimen (no AMT approval required for 72 hours):

DRUG 1: ☐ Piperacillin / tazobactam 4.5 g IV Q8h x 72 hours OR

☐ Piperacillin / tazobactam _____ g IV Q ____h[a] x 72 hours

OR if patient has received a treatment course with a penicillin or ceph. in the past 14 days:

☐ Meropenem 500 mg IV Q8h x 72 hours OR

☐ Meropenem ____ mg IV Q ____h[a] x 72 hours

OR if patient has a history of rash to penicillin:

☐ Cefepime 2 g IV Q12h x 72 hours OR

☐ Cefepime ____ g IV Q ____ h[a] x 72 hours

OR if patient has a history of hives or anaphylaxis to penicillin or ceph:

☐ Aztreonam 2 g IV Q8h x 72 hours OR

☐ Aztreonam ____ g IV Q ____ h[a] x 72 hours

PLUS

DRUG 2: If the patient is INTUBATED:

☐ Tobramycin ____ mg IV loading dose; then

Tobramycin ____ mg IV Q ____h[a] x 72 hours

OR If the patient is NOT intubated:

☐ Ciprofloxacin 400 mg IV Q12h x 72 hours OR

☐ Ciprofloxacin 500 mg PO Q12h x 72 hours OR

☐ Ciprofloxacin ____ mg ____ ☐ IV ☐ PO Q ____h[a] x 72 hours

PLUS

DRUG 3: If the patient is INTUBATED:

☐ Linezolid 600 mg ____ ☐ IV ☐ PO Q12h x 72 hours OR

☐ Vancomycin ____ mg IV Q ____h[d] x 72 hours

OR If the patient is NOT intubated:

☐ Vancomycin ____ mg IV Q ____h[d] x 72 hours

PHYSICIAN'S ORDERS
(EXCLUDES MEDICATION ORDERS)

TABLE I: Risk Factors for Multi-drug Resistant Organisms

- Hospitalized for more than 2 days in the preceding 90 days
- Residence in a nursing home or extended care facility
- Recipient of home infusion therapy
- Chronic dialysis within the preceding 30 days
- Recipient of home wound care
- Family member with multi-drug resistant pathogen
- Antimicrobial therapy in the preceding 90 days.
- Immunosuppressant disease or therapy.

☐ Blood cultures x 2

☐ Continuous pulse oximetry OR

☐ Pulse oximetry Q ____ hours

☐ Chest X-ray in A.M. PA/LAT OR

☐ Chest X-ray in A.M. portable

☐ Sputum gram stain and culture (if a sputum has been processed by the laboratory in the last 72 hours, use standard micro requisition but write in "new pneumonia")

If patient is intubated and no antibiotic changes have been made in the last 72 hours (changes made in the last 6 hours are acceptable) and bronchoscopy cannot be performed:

☐ Mini-BAL for quantitative culture (Page respiratory to perform, do not hold antibiotics until obtained, use standard micro requisition but write in "quantitative mini-BAL culture" and attach designated sticker)

Footnotes:

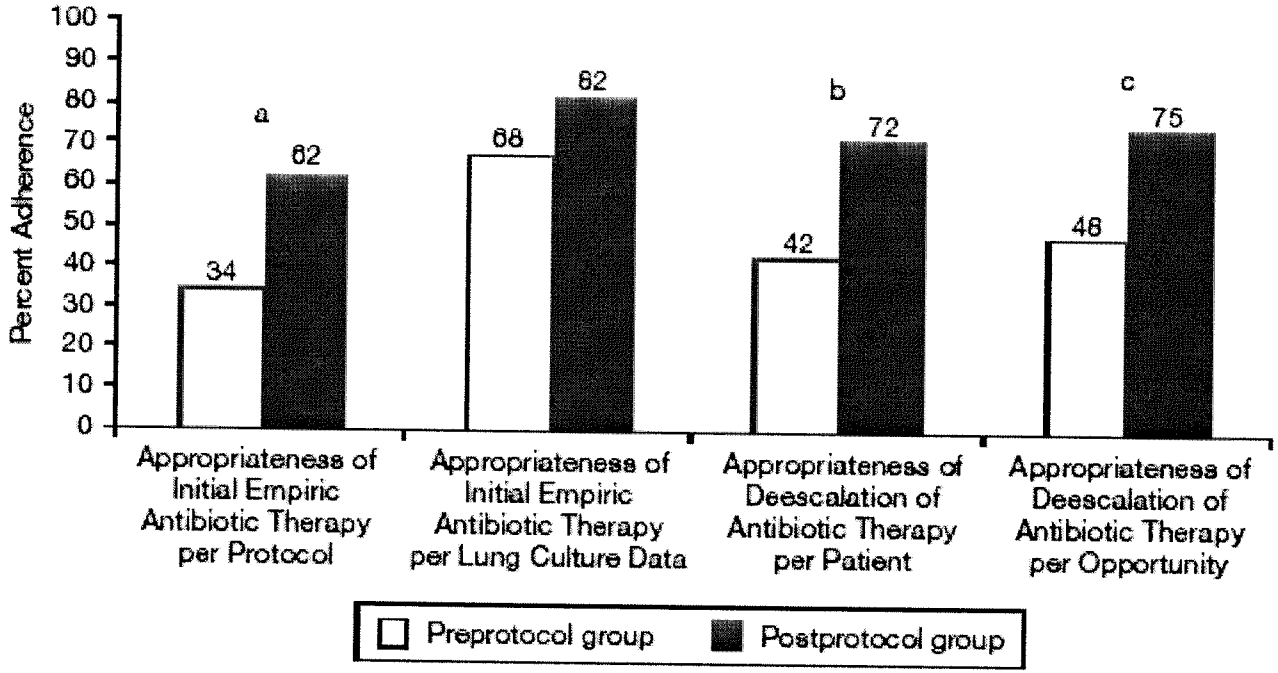
a. Adjust dose for renal dysfunction. See Tufts-NEMC Dosage Adjustment for Renal Failure pamphlet or the Antibiotic Guidebook.
b. See Antibiotic Guidebook for tobramycin dosing.
c. Evidence suggests that linezolid achieves higher lung concentrations than vancomycin and may be clinically superior in patients with known MRSA pneumonia.
d. Vancomycin dosing for pneumonia:

CrCl	Dose	Interval
> 70 mL/min	15 mg/kg*	Q12h
50-70 mL/min	15 mg/kg*	Q24
15-29 mL/min	15 mg/kg*	Q48
<15 mL/min	15 mg/kg*	Based on levels
hemodialysis	15 mg/kg*	Based on levels

* Maximum 2g

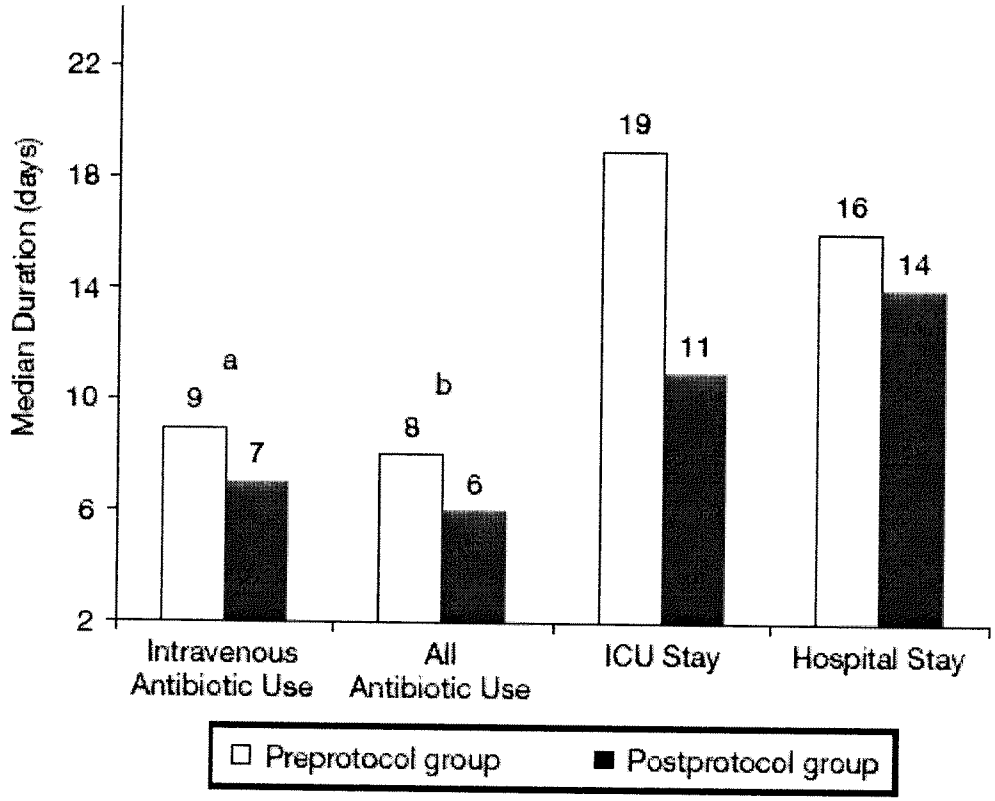
Keep serum (trough) concentration between 15 - 20 mcg/ml
Order Vancomycin in 250 mg increments

Benefits of a HAP Protocol at Tufts Medical Center



Lancaster JW, et al. Pharmacotherapy 2008;28(7):852-62

Impact of a HAP Protocol at Tufts Medical Center



Lancaster JW, et al. Pharmacotherapy 2008;28(7):852-62

Get SMART – Ms. T

- Ms. T is a 70-year-old admitted for community acquired pneumonia and started on moxifloxacin
- Cultures were not obtained on admission
- She is afebrile by hospital day 3 with normal vital signs and is tolerating room air and a regular diet, so you decide to discharge her

What Is the Appropriate Duration of Therapy for cIAI?

- Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control
- Bowel injuries due to penetrating, blunt, or iatrogenic trauma repaired within 12 h and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for ≤24 hours

Lack of evidence of infections includes, being afebrile, have normal WBC, and tolerating an oral diet.

Prescribers Opinions On Antimicrobial Stewardship: Tufts Experience

- 92% thought ASP was very or somewhat important
- 58% were sometimes confused about ASP procedures
- 96% reported a good or very good experience
- 84% reported a positive educational experience
- 66% reported a change in the drug prescribed due to AMT less than 40% of the time
- 23% said AMT prevented a medication error
- 43% stated that AMT reminded them to adjust for kidney function and 17% reminded them of patent's allergies

Diagnostic and Pathogen Identification Techniques

- Biomarkers
  - Procalcitonin
  - CRP
- PNA FISH
- PCR
- E-test of patient samples

Lawrence KL, et al. Am J Respir Crit Care Med 2009;198:434-8
Cals JWL, et al. Ann Fam Med 2010;8:124-33
Schuetz R, et al. JAMA 2009;302:1059-66
Bouza E, et al CID 2007;44:382-7

Measuring the Effectiveness of an Antimicrobial Stewardship Program

- Antimicrobial usage
  - Days of therapy
  - Appropriateness of treatment
- Antimicrobial cost
- Bacterial susceptibilities
- Patient outcomes
- Antimicrobial adverse events
- Acceptance of recommendations
- Prescribers surveys

Microbiology of Abscess Material, Deep Tissue or Blood*

Isolate	Abscess (n=77)	SSTI with Complications (n=73)
S aureus	52 (68)	45 (62)
MRSA	34(44)	30 (41)
Streptococci	29 (38)	31 (42)
S aureus or Streptococcus	75 (97)	70 (96)
S aureus or Streptococcus only	59 (77)	52 (71)
Aerobic Gram negative bacteria	10 (13)	10 (14)
Anaerobes	13 (17)	16 (22)

* Data are No (%) of patients

Antimicrobial Therapy

Therapy	Cellulitis (n=66)	Abscess (n=103)	SSTI with Complications (n=153)
Inpatient Antibiotics (at least 1 dose administered)			
Vancomycin	52 (79)	75 (73)	112 (73)
B-lactam/β-lactamase inhibitors	35 (53)	67 (65)	101 (66)
Cefazolin	13 (20)	21 (20)	26 (17)
Broad spectrum Gram negative Rx	40 (61)	69 (67)	123 (80)
3 or more antibiotics	34 (52)	41 (40)	74 (48)
Discharge Antibiotics			
Bactrim	32 (48)	49 (48)	38 (25)
Amox/Clav	12 (18)	23 (22)	40 (26)
Median Duration Inpatient	4 (3-5)	4 (3-5)	5 (3-7)
Median Duration Outpatient	7 (7-10)	10 (7-10)	9 (7-10)

* Data are No (%) of patients

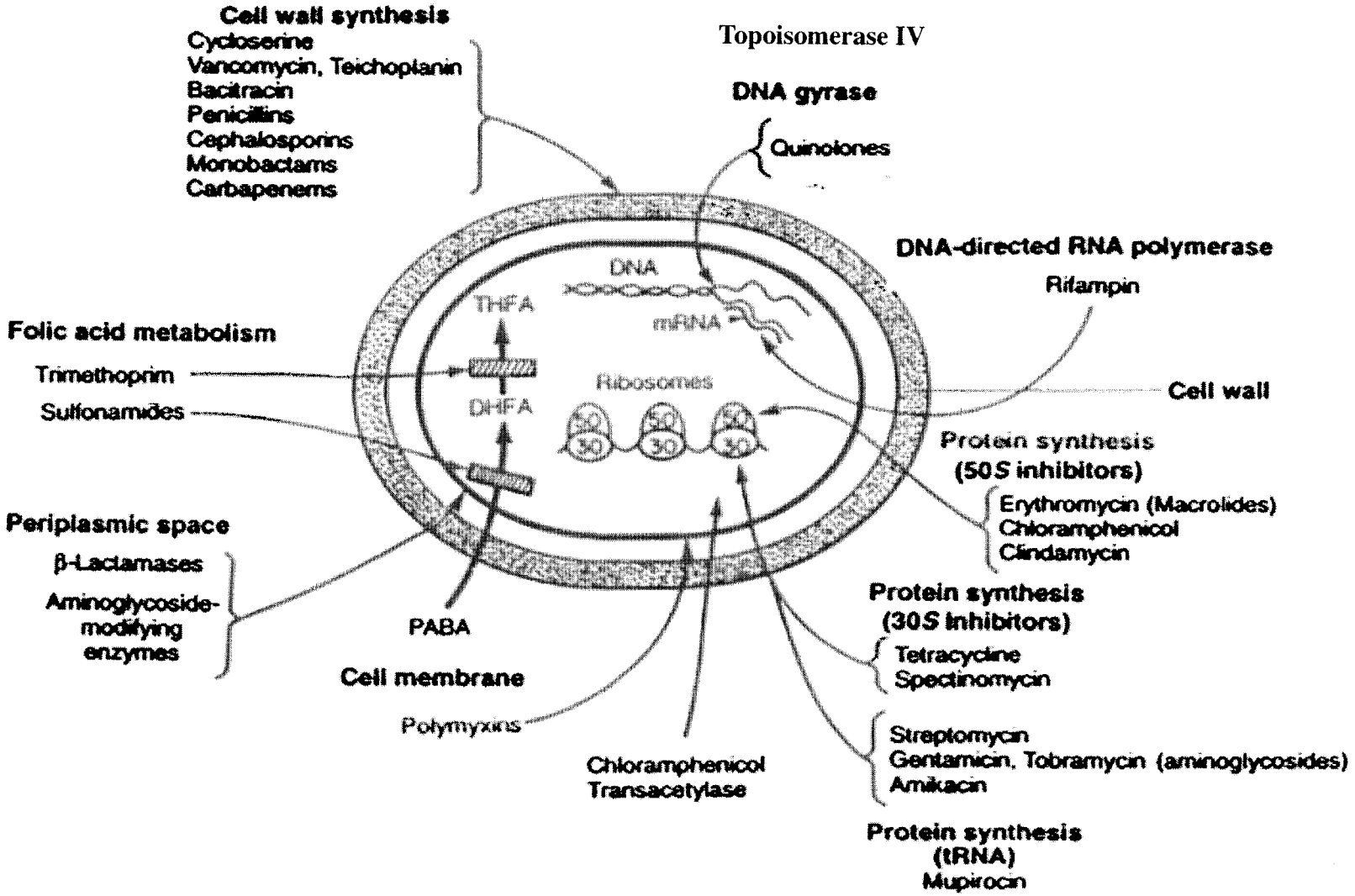
Modification of Risk Factors for CDI

- Antimicrobial use
  - Fluoroquinolones
  - Clindamycin
  - 3rd generation cephalosporins
- Prolonged antimicrobial therapy
- Proton pump inhibitors

Environmental Issues and CDI

- *C difficile* spores contaminate patients and equipment
  - These are reservoirs for disease
  - Little contamination outside of rooms
- Develop protocols for daily and terminal cleaning for patient rooms
  - 1:10 dilute sodium hypochlorite
  - Adequate training and education of personel

Sites of Action of Antimicrobial Agents in Clinical Use



Neu HC. Science 1992; 257:1064-73

Bowel Colonization Sub-Study Methods: OASIS-2

- OASIS-2 was a prospective, open-label, multicenter, multinational trial of ertapenem (1 g once a day) versus ceftriaxone (2 g once a day or 1 g every 12 hours) plus metronidazole (30 mg/kg/day, in 2–4 divided doses) in patients with intra-abdominal infection
- The objective of the bowel colonization sub-study of OASIS-2 was to compare the frequency with which ertapenem and ceftriaxone plus metronidazole selected for resistant Enterobacteriaceae, ESBL-producing Enterobacteriaceae, and imipenem-resistant *P. aeruginosa* (n=450)
- Rectal swabs were collected at baseline, discontinuation of therapy, and follow-up (2–4 weeks post-therapy)
- Samples were shipped to Merck Research Laboratories for testing

Navarro N et al. Presented at 3rd ACCP, October 2003.
Friedland I et al. 3rd ACCP, Santa Margherita, Portofino, Italy, October 2003.

OASIS-1 Sub-analysis in Patients with IAI (n=341): Low Risk for Resistance Selection among *P. aeruginosa* in the Bowel

P. aeruginosa resistant to imipenem	Baseline	DCOT	DCOT and/or TOC
Ertapenem	0/169 (0%)	0/152* (0%)	0/153* (0%)
Piperacillin/tazobactam	2/172 (1.2%)	1/153 (0.7%)	1/153 (0.7%)

Ertapenem did not select for imipenem-resistant *P. aeruginosa* in the bowel.

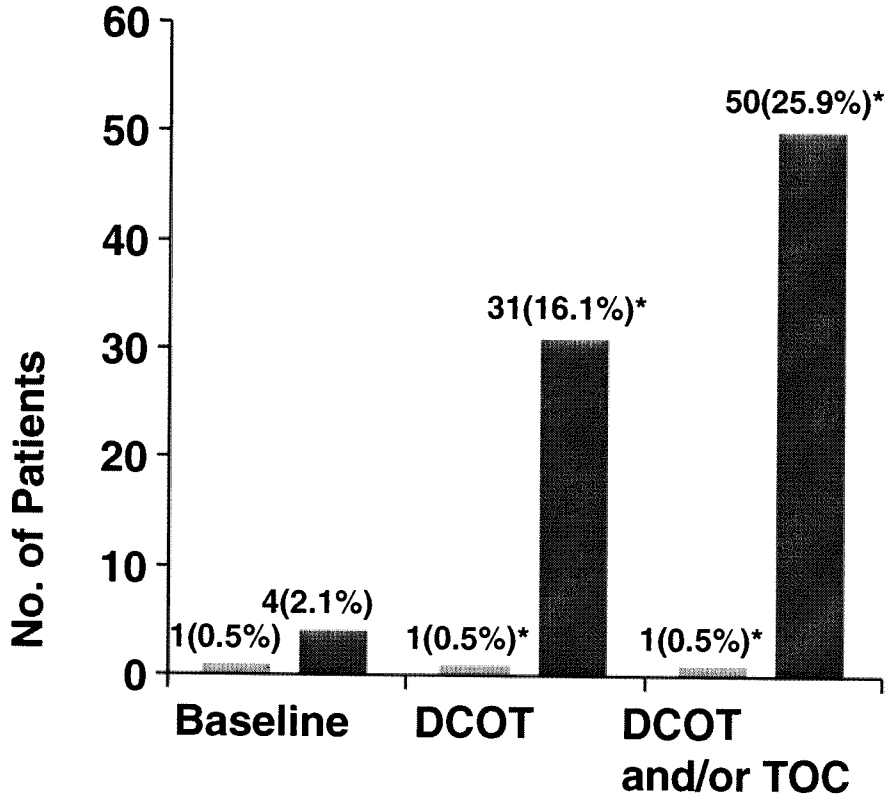
DCOT=Discontinuation of therapy; TOC=Test of cure, 2 weeks post therapy.

*One patient had an imipenem-intermediate *P. aeruginosa* at discontinuation of therapy.

Friedland I et al. Presented at 13th ECCMID, Glasgow, UK, May 10-13, 2003.

OASIS-2 Sub-analysis in Patients with IAI (n=389): Low Risk for Resistance Selection among Gram-Negative Bacilli in the Bowel

Enterobacteriaceae resistant to study drug



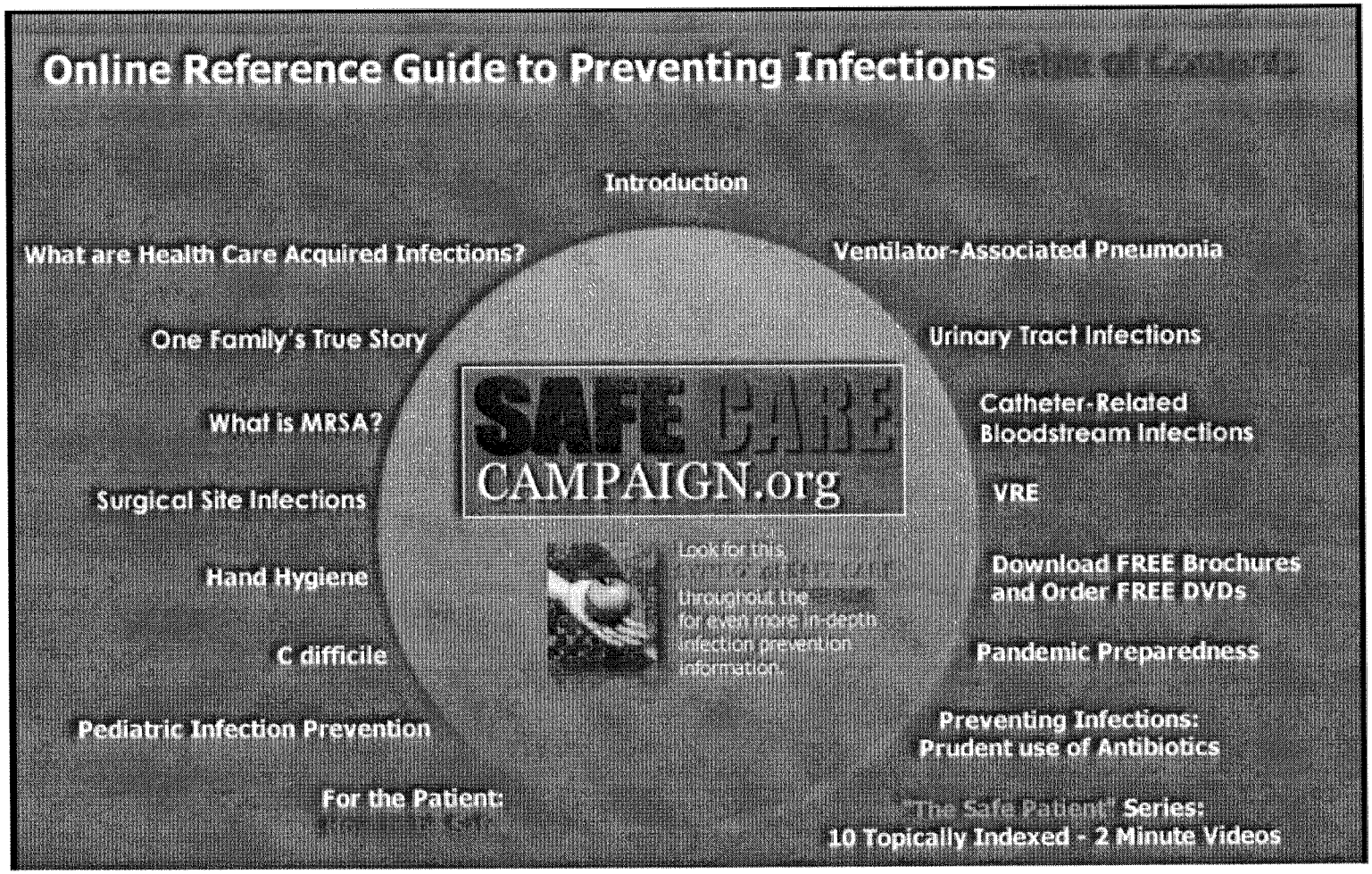
ertapenem (1 g once daily); n=196

ceftriaxone (2 g, once a day or 1 g twice daily) plus metronidazole (30 mg/kg/day in 2–4 divided doses after loading dose of 15 mg/kg); n=193

*p<0.001

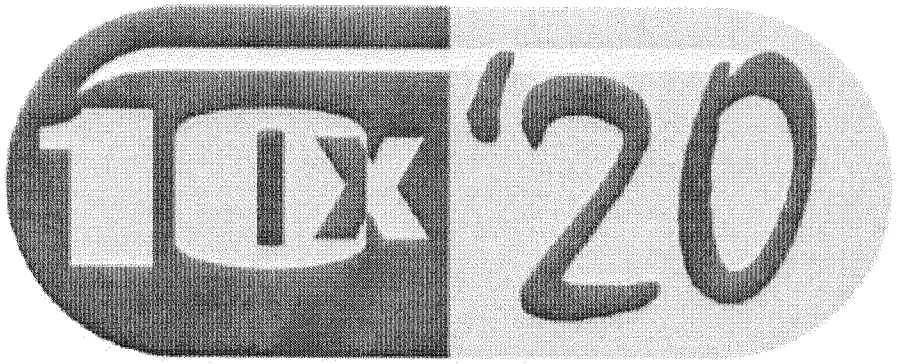
Friedland I et al. 3rd ACCP, Santa Margherita, Portofino, Italy, October, 2003.

The Public is Aware of Antimicrobial Resistance



Infectious Disease Society of America's

Bad Bugs Need Drugs



Ten new **ANTIBIOTICS** by 2020

Summary

- Antibiotic resistance in GNRs is a serious and complex issue.
- Antimicrobial stewardship and infection prevention are critical keys to mitigating the dissemination of MDROs.
- Effective antimicrobial therapy for treatment of some MDROs is lacking.
- Governments and private industry must work together to develop compounds for treatment of MDROs.