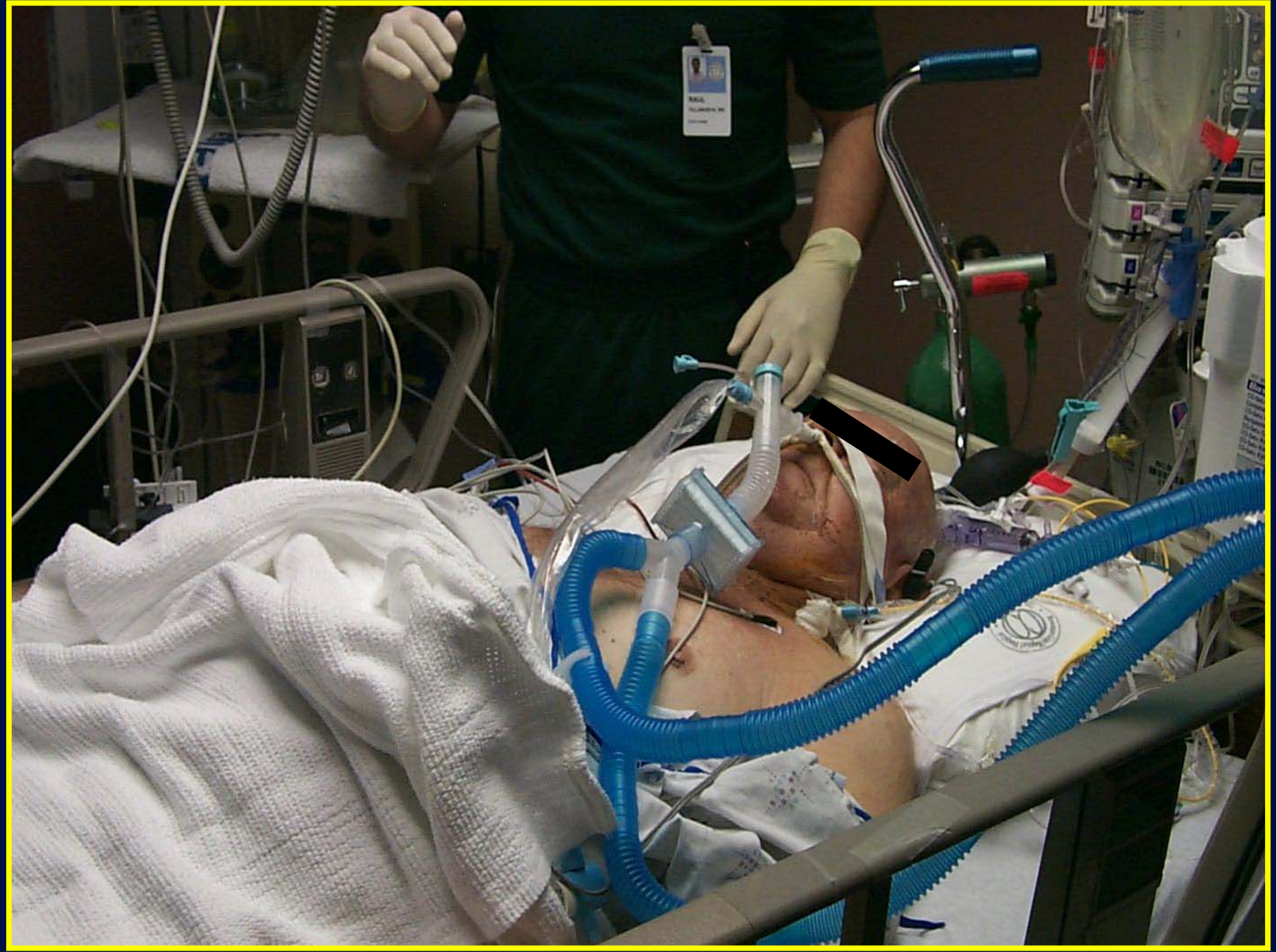
MANAGING HOSPITAL ACQUIRED INFECTIONS IN AN ERA OF GROWING ANTIBIOTIC RESISTANCE

David Jay Weber, M.D., M.P.H.
Professor of Medicine, Pediatrics & Epidemiology
Associate Chief of Staff
University of North Carolina at Chapel Hill, USA

HEALTHCARE-ASSOCIATED INFECTIONS IN THE US: IMPACT

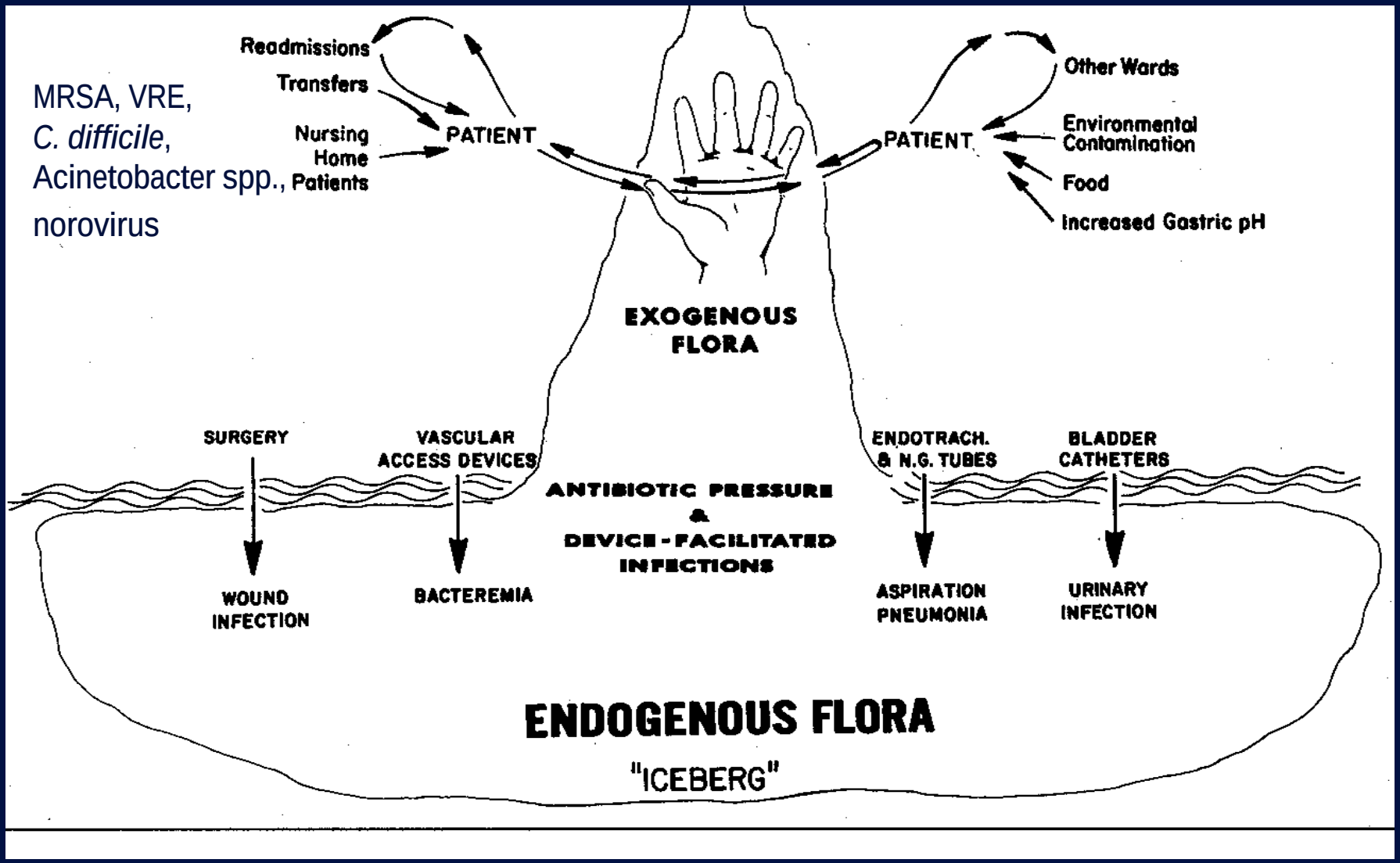
- 1.7 million infections per year
- 98,987 deaths due to HAI
  - Pneumonia 35,967
  - Bloodstream 30,665
  - Urinary tract 13,088
  - SSI 8,205
  - Other 11,062
- 6th leading cause of death (after heart disease, cancer, stroke, chronic lower respiratory diseases, and accidents)[1]

[1] National Center for Health Statistics, 2004



HAZARDS IN THE ICU

MRSA, VRE,
C. difficile,
Acinetobacter spp.,
norovirus



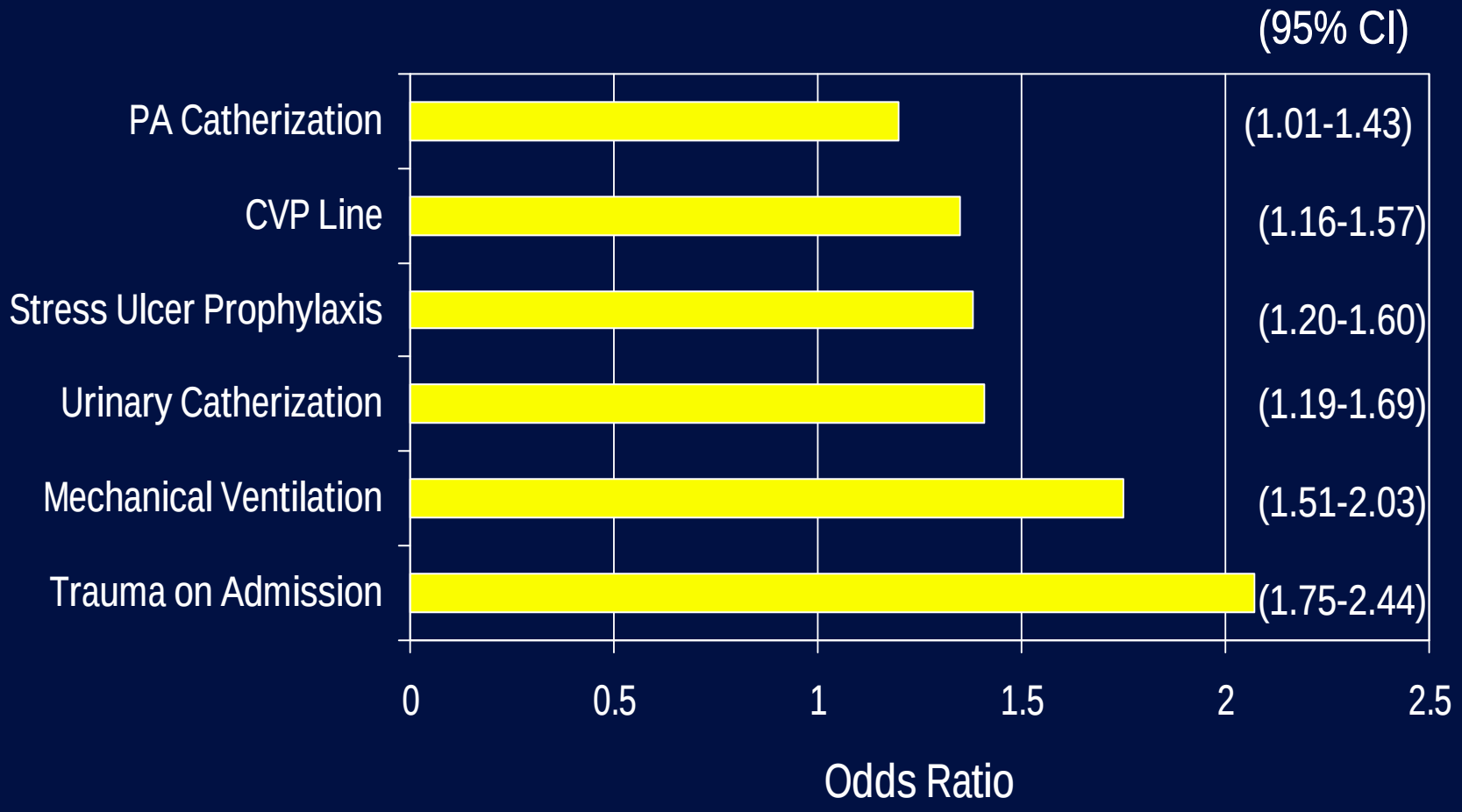
Weinstein RA. Am J Med 1991;91(suppl 3B):180S

PREVALENCE: ICU (EUROPE)

- Study design: Point prevalence study (29 April 1992)
  - 17 countries, 1447 ICUs, 10,038 patients
- Frequency of infections: 4,501 (44.8%)
  - Community-acquired: 1,876 (13.7%)
  - Hospital-acquired: 975 (9.7%)
  - ICU-acquired: 2,064 (20.6%)
    - Pneumonia: 967 (46.9%)
    - Other lower respiratory tract: 368 (17.8%)
    - Urinary tract: 363 (17.6%)
    - Bloodstream: 247 (12.0%)

Vincent J-L, et al. JAMA 1995;274:639

RISK FACTORS FOR ICU-ACQUIRED INFECTIONS

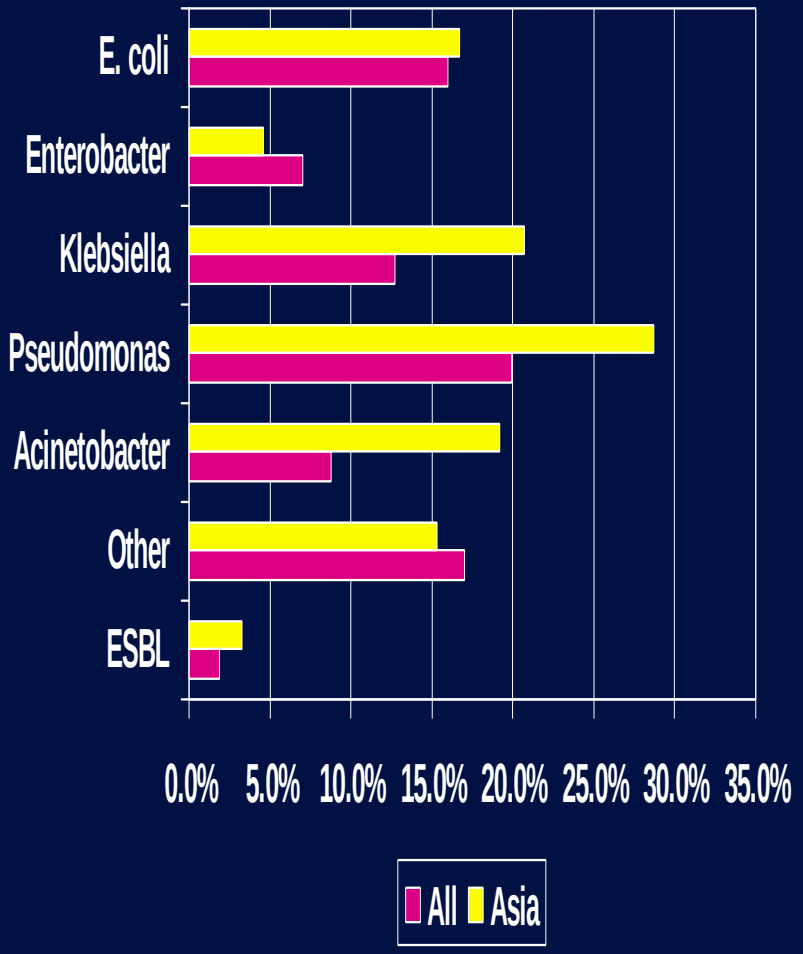


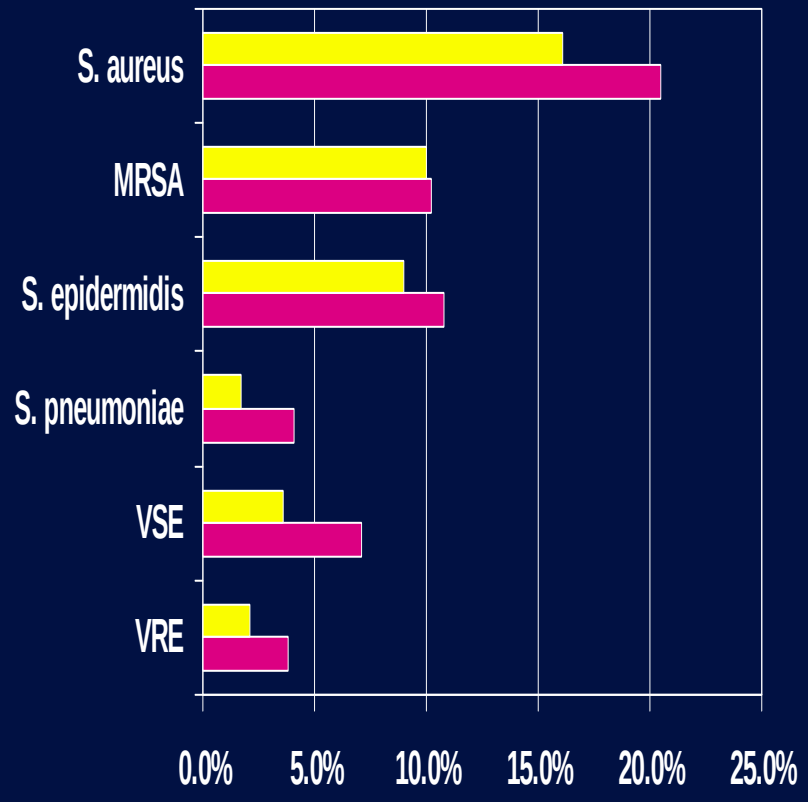
INTERNATIONAL STUDY OF PREVALENCE AND OUTCOMES OF INFECTION IN ICUs

- Study design: Point prevalence study (8 May 2007)
  - 75 countries, 1265 ICUs, 13,796 adult patients
- Frequency of infection: 7,087 (51%)
  - Site: Lungs 64%, abdomen 20%, bloodstream15%, renal/GU system 14%
  - Microbe isolated 70%: Gram (+) 47%, Gram (-) 62%, Fungi 19%
  - Longer ICU associate with higher rates of infection, especially due to resistant *S. aureus, Acinetobacter, Pseudomonas*, and *Candida* spp.
- Antibiotics (all patients): 71%
- Mortality
  - ICU: Infected (25%) vs non-infected (11%)
  - Hospital mortality: Infected (33%) vs non-infected (15%)

Vincent J-L, et al. JAMA 2009;302:2323-2329

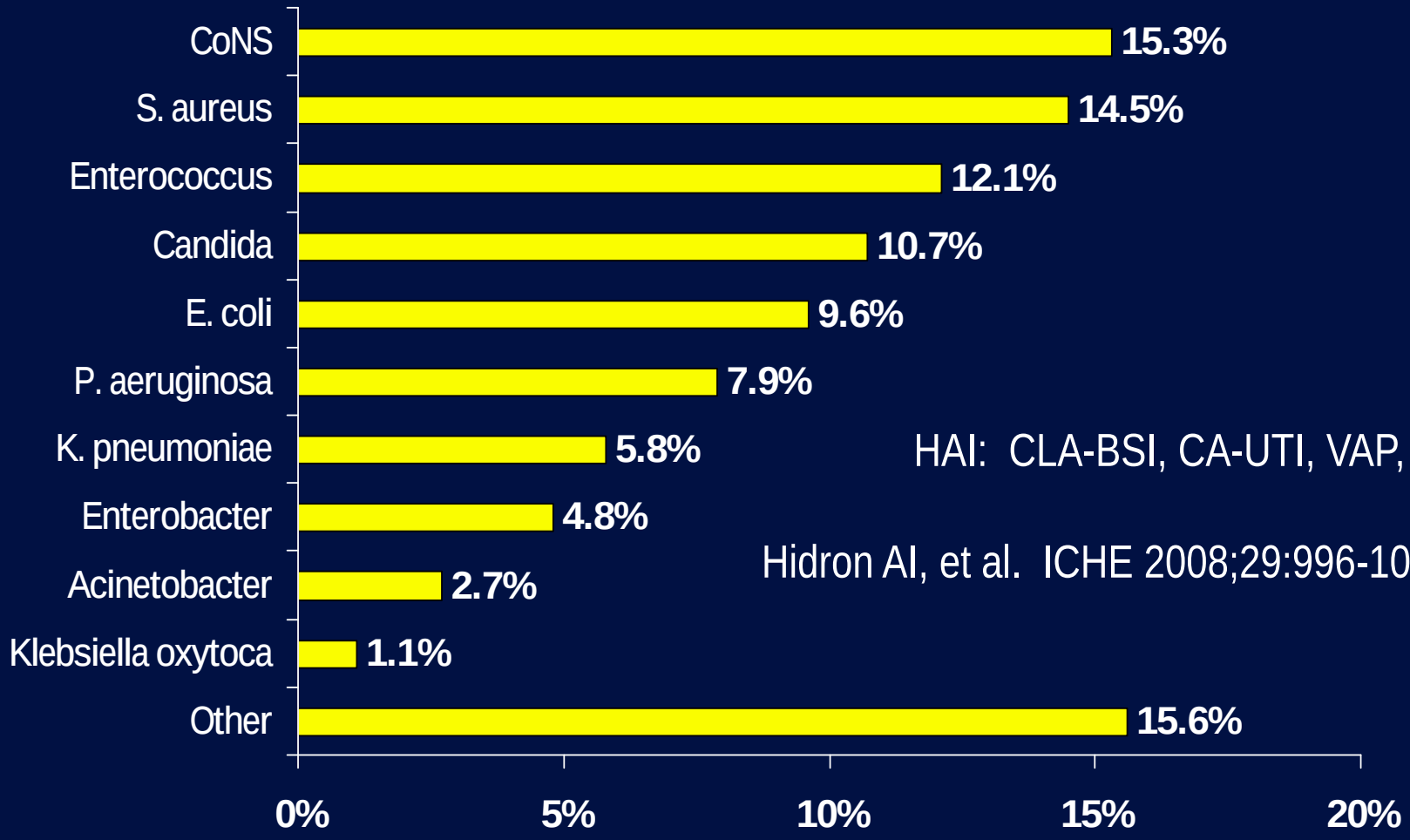
INTERNATIONAL STUDY OF PREVALENCE AND OUTCOMES OF INFECTION IN ICUs



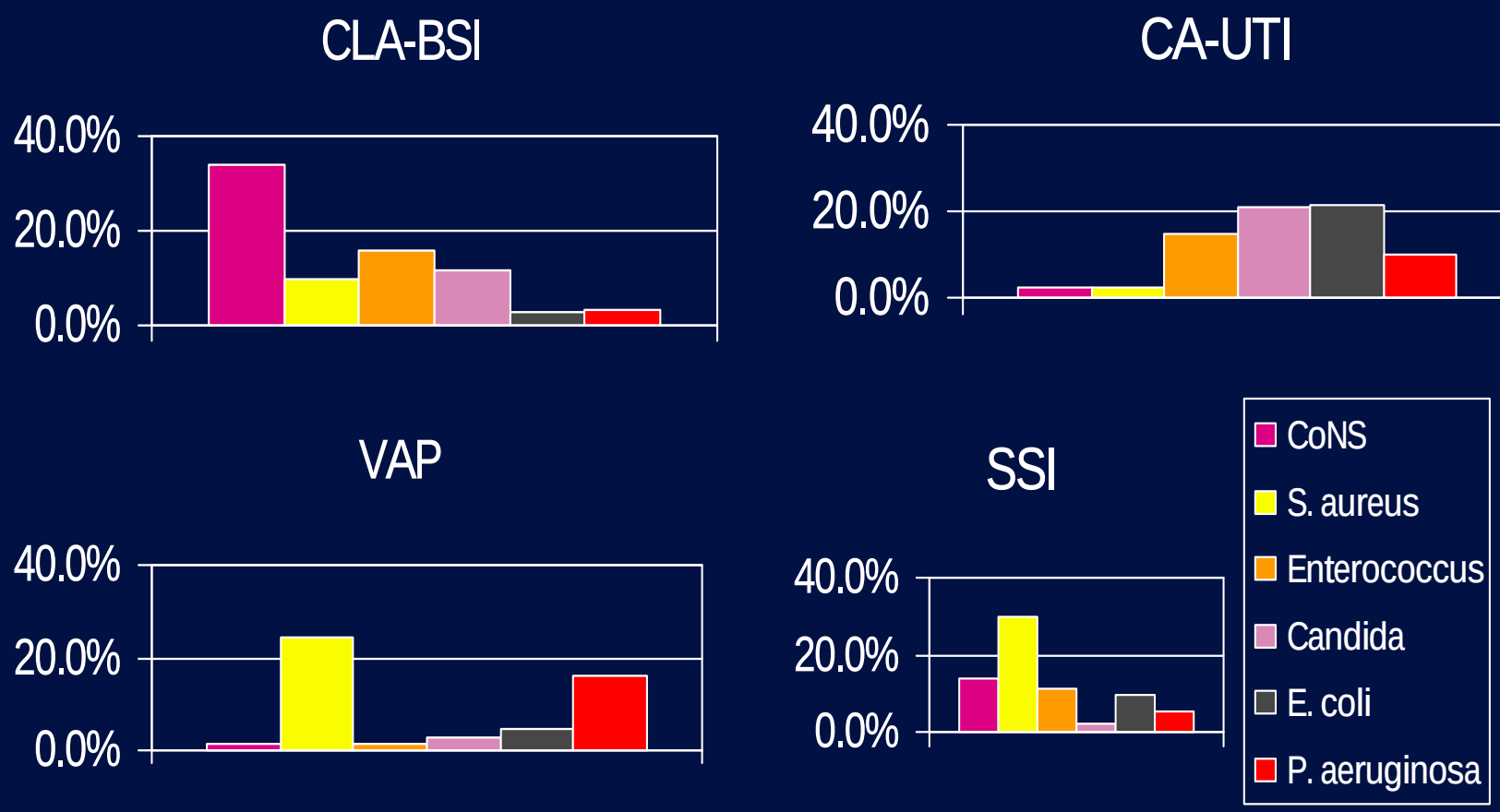


Vincent J-L, et al. JAMA 2009;302:2323-2329

PATHOGENS ASSOCIATED WITH HAIs*: NHSN, 2006-2007

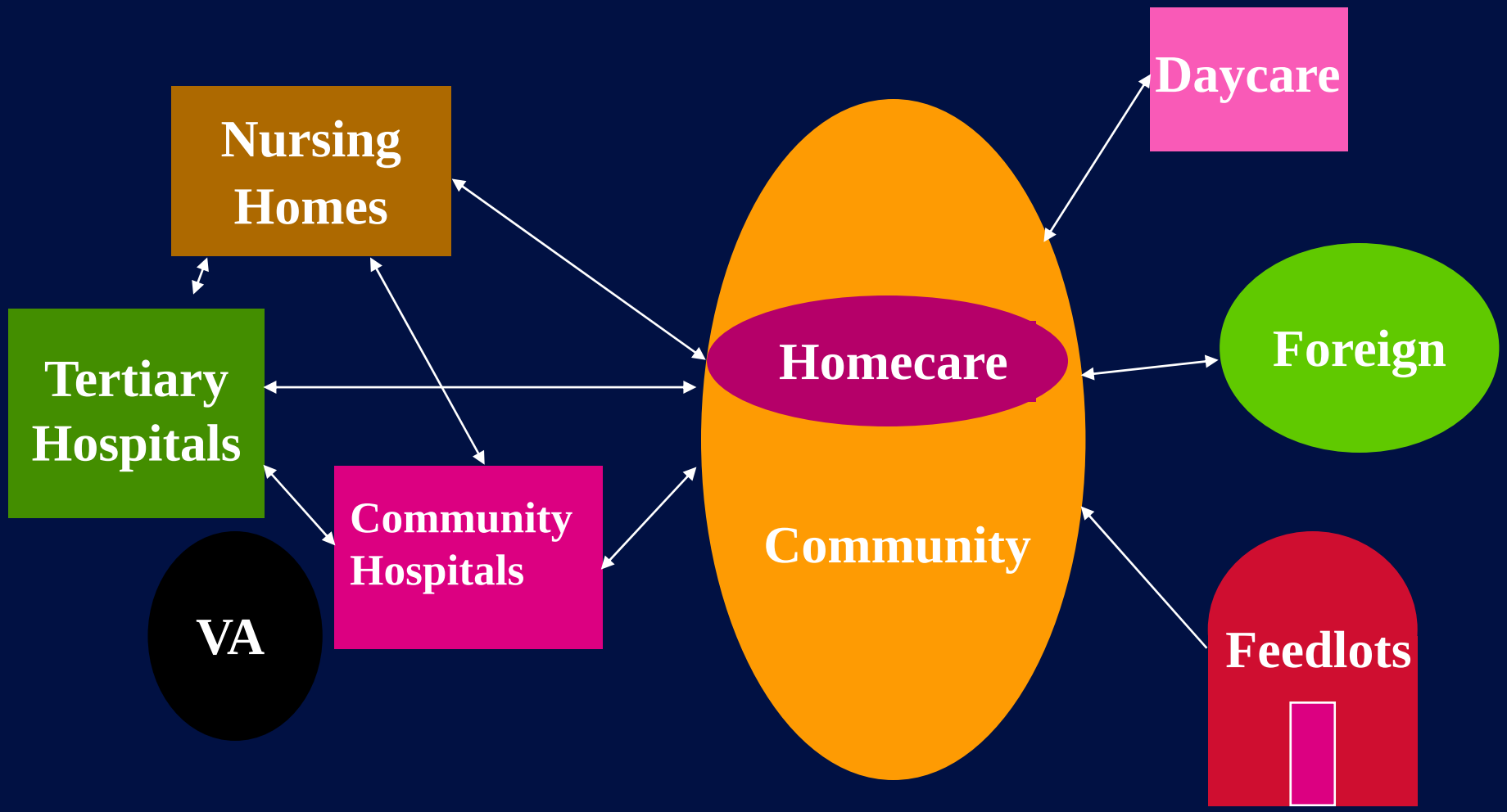


PATHOGENS CAUSING HAIs, NHSN, 2006-2007



Hidron AI, et al. ICHE 2008;29:996-1011

Environments Where Antibiotic Resistance Develops and Their Relationships



Adapted from B. Murray

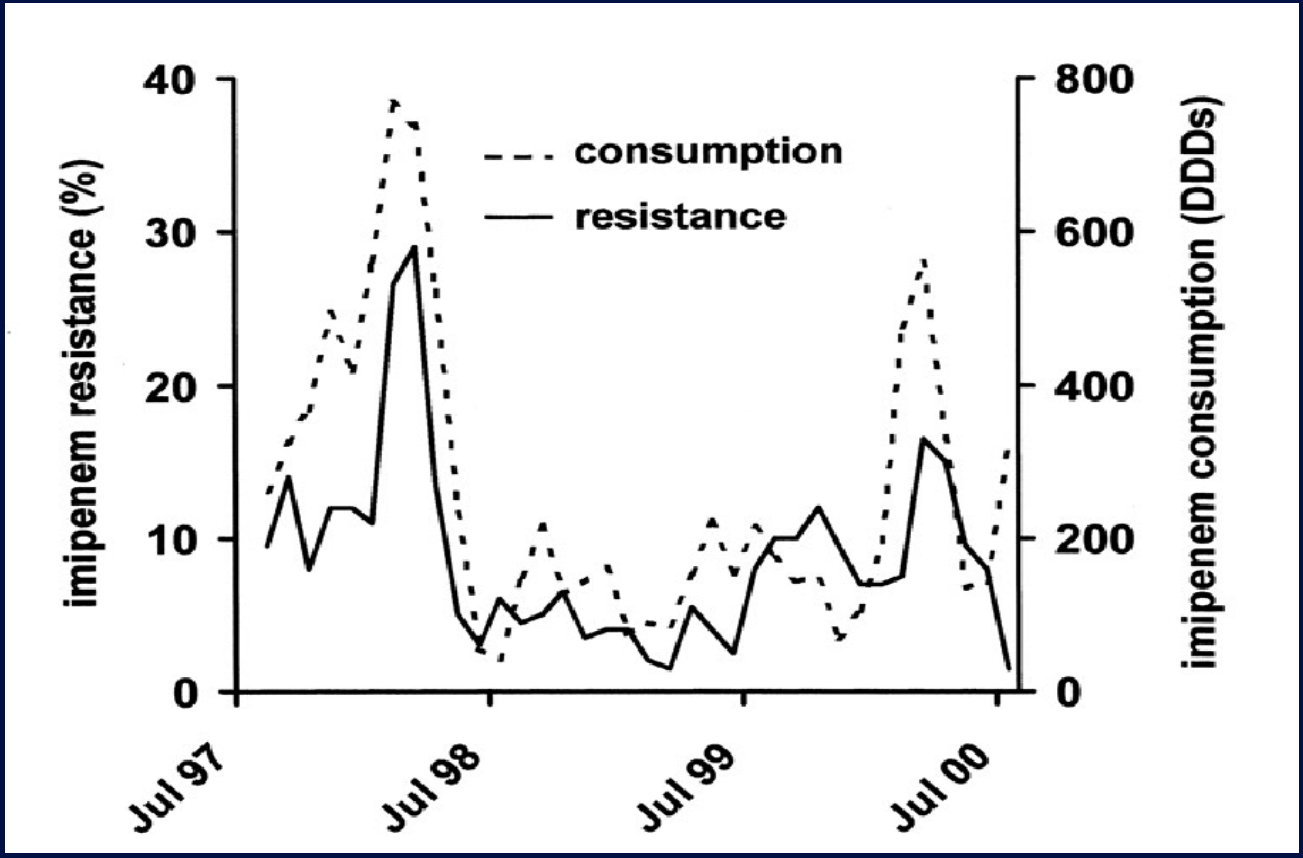
ANTIBIOTIC RESISTANCE IN HOSPITALS:

FACTORS CONTRIBUTING TO SPREAD IN HOSPITALS

- Greater severity of illness of hospitalized patients
- More severely immunocompromised patients
- Newer devices and procedures in use
- Increased introduction of resistant organisms from the community
- Ineffective infection control & isolation practices (esp. compliance)
- Increased use of antimicrobial prophylaxis
- Increased use of polymicrobial antimicrobial therapy
- High antimicrobial use in intensive care units

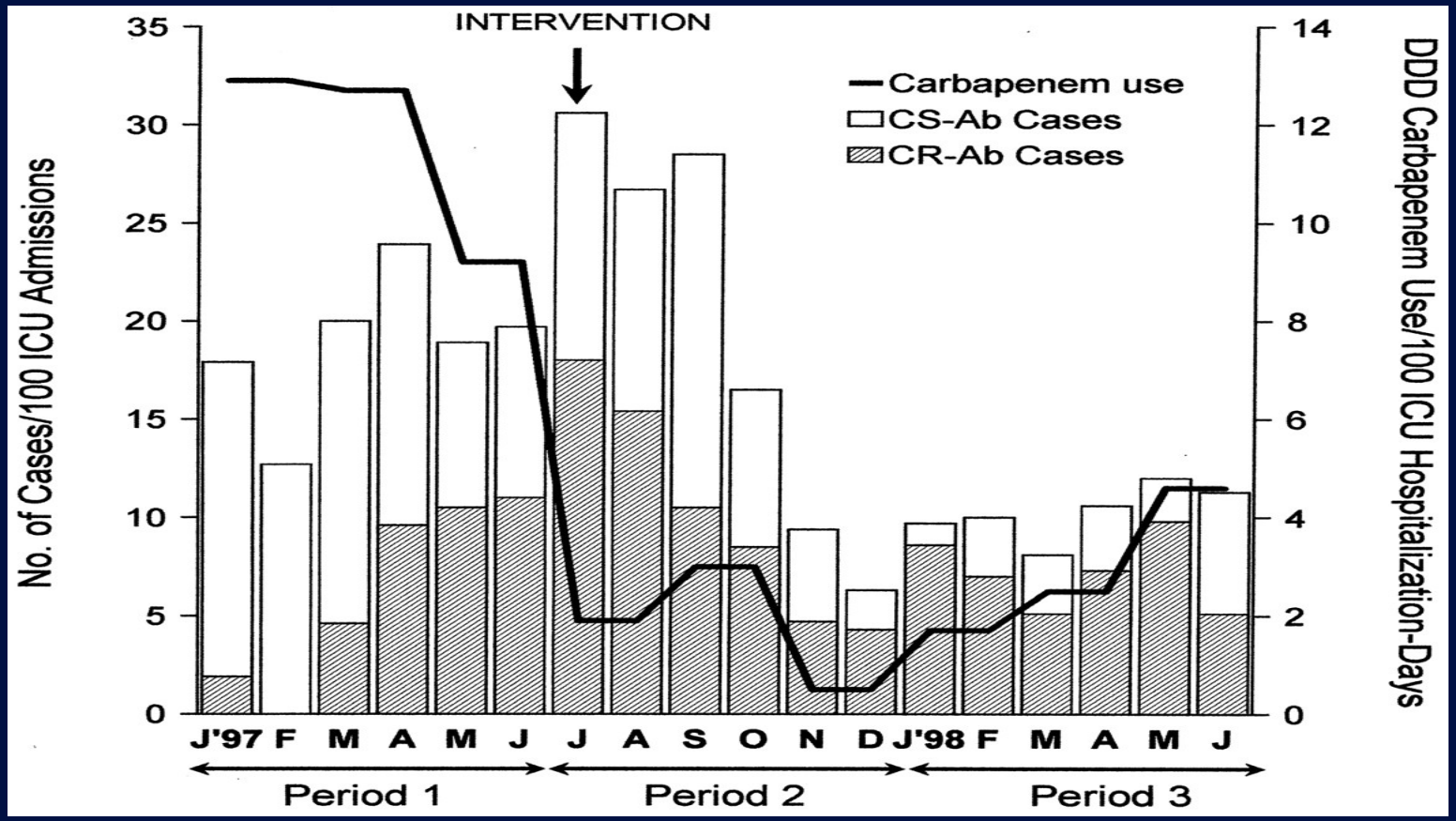
Source: Shales D, et al. Clin Infect Dis 1997;25:684-99.

Correlation Between Consumption of Imipenem and Resistance of *P. aeruginosa*



Lepper PM, et al. *Antimicrob Agents Chemother*. 2002;46:2920-2925.

RELATIONSHIP BETWEEN IMIPENEM CONSUMPTION AND COLONIZATION/INFECTION WITH *ACINETOBACTER*



Corbella X, et al. *J Clin Microbiol*. 2000;38:4086-4095

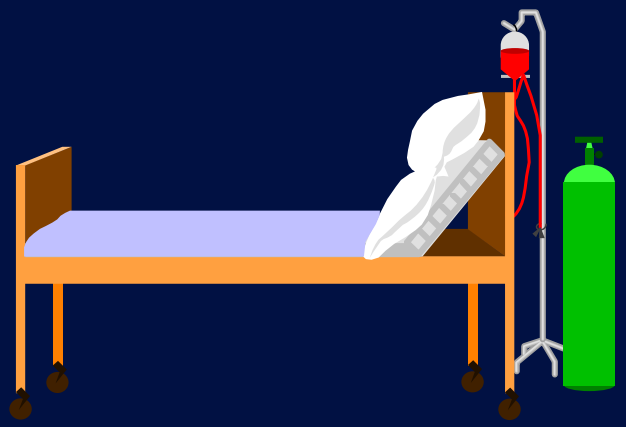
PRINCIPLES OF ANTIBIOTIC RESISTANCE

(Levy SB. NEJM, 1998)

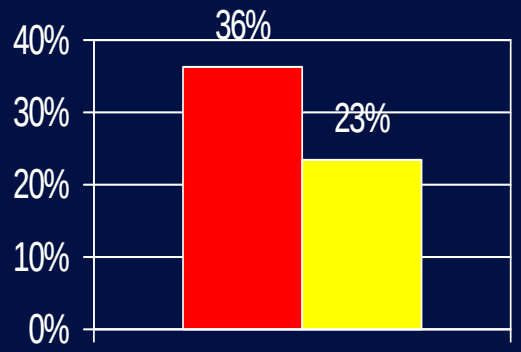
1. Given sufficient time and drug use, antibiotic resistance will emerge.
2. Resistance is progressive, evolving from low levels through intermediate to high levels.
3. Organisms resistant to one antibiotic are likely to become resistant to other antibiotics.
4. Once resistance appears, it is likely to decline slowly, if at all.
5. The use of antibiotics by any one person affects others in the extended as well as the immediate environment.

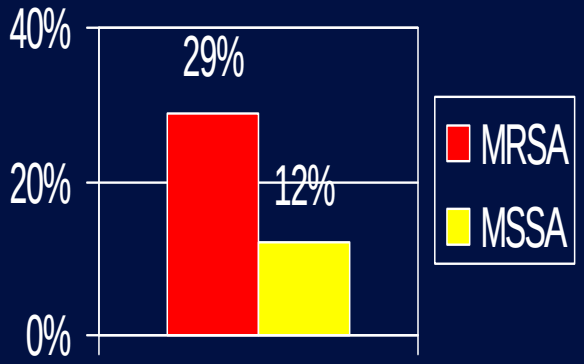
EMERGING RESISTANT PATHOGENS: HEALTH CARE FACILITIES

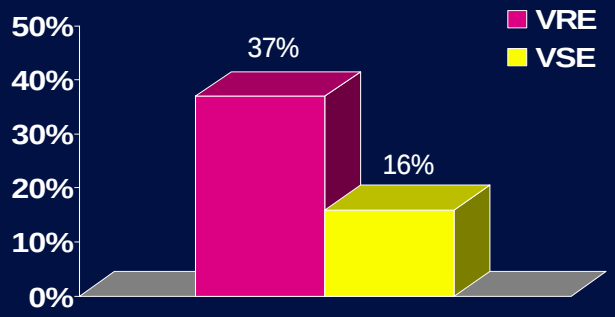
- *Staphylococcus aureus*: Oxacillin, vancomycin, linezolid
- *Enterococcus:* Penicillin, aminoglycosides, vancomycin, linezolid, dalfopristin-quinupristin
- *Enterobacteriaceae:* ESBL producers, carbapenems
- *P. aeruginosa*, *Acinetobacter* spp.: Multidrug-resistance
- *Candida spp*.: Fluconazole
- *Mycobacterium tuberculosis*: MDR (INH, rifampin), XDR (INH, rifampin, others)



MORTALITY ASSOCIATED WITH MRSA AND VRE







Impact of resistant pathogens

- Increased length of stay
- Delays in transferring patient to extended care facility
- Increased cost
- Increased mortality

Cosgrove SE et al. *CID*. 2003;36:53-59.
Whitby M et al. *MJA*. 2001;175:264-267.
CDC. MMWR 1993;42:597-599

ANTIBIOTIC RESISTANCE FOR PATHOGENS ASSOCIATED WITH DEVICE RELATED INFECTIONS, 2006-07, NHSN, US

Bug	Drug	CLA-BSI	CA-UTI	VAP	Pooled
S. aureus	Oxacillin	56.8%	65.2%	54.4%	56.2%
E. faecium	Ampicillin	90.5%	89.9%	NR	90.4%
	Vancomycin	78.9%	81.0%	NR	80.0%
E. faecalis	Ampicillin	4.2%	3.1%	2.9%	3.8%
	Vancomycin	7.5%	6.1%	2.9%	6.9%

NHSN Date

ANTIBIOTIC RESISTANCE FOR PATHOGENS ASSOCIATED WITH DEVICE RELATED INFECTIONS, 2006-07

Bug	Drug	CLA-BSI	CA-UTI	VAP	Pooled
Klebsiella pneumoniae	CTR, TAZ	27.1%	21.2%	23.7%	NR
	IMI, MERO, ETP	10.8%	10.1%	3.6%	NR
Klebsiella oxytoca	CTR, TAZ	15.9%	17.6%	17.1%	16.8%
	IMI, MERO, ETP	0.0%	2.6%	5.0%	2.8%
E. Coli	CTR, TAZ	8.1%	5.5%	11.0%	NR
	IMI, MERO, ETP	0.9%	4.0%	1.8%	NR
	FQ	30.8%	24.8%	22.7%	NR
A. baumannii	IMI or MERO	29.2%	25.6%	85.7%	NR
P. aeruginosa	FQs	30.5%	33.8%	27.8%	30.7%
	PTZ	20.2%	17.1%	17.0%	17.5%
	TAZ	18.7%	12.6%	13.1%	NR
	IMI or MERO	23.0%	25.1%	26.4%	25.3%
	AMK	4.3%	7.9%	4.9%	6.0%

AMK, amikacin; CTR, ceftriaxone; FQ, fluoroquinolones; IMI, imipenem; MERO, meropenem; PTZ, piperacillin-tazobactam; TAZ, ceftazidime;

“ESKAPE” Pathogens Today

Global Hospital-Wide Resistance Rates

United States

VRE (*E. faecium*)	66.96%
MRSA	55.46%
K. pneumoniae (CAZ-R)	12.37%
A. baumannii (IMP-R)	10.84%
P. aeruginosa (IMP-R)	7.74%
Enterobacter cloacae (CAZ-R)	21.50%

Europe

VRE (*E. faecium*)	15.36%
MRSA	25.13%
K. pneumoniae (CAZ-R)	14.98%
A. baumannii (IMP-R)	12.62%
P. aeruginosa (IMP-R)	9.73%
Enterobacter cloacae (CAZ-R)	29.07%

Latin America

VRE (*E. faecium*)	43.13%
MRSA	46.64%
K. pneumoniae (CAZ-R)	35.05%
A. baumannii (IMP-R)	33.36%
P. aeruginosa (IMP-R)	18.79%
Enterobacter cloacae (CAZ-R)	39.03%

Asia Pacific

VRE (*E. faecium*)	22.32%
MRSA	40.75%
K. pneumoniae (CAZ-R)	23.56%
A. baumannii (IMP-R)	28.40%
P. aeruginosa (IMP-R)	10.21%
Enterobacter cloacae (CAZ-R)	35.47%

Wyeth. Available at www.testsurveillance.com. Last accessed April 9, 2009.

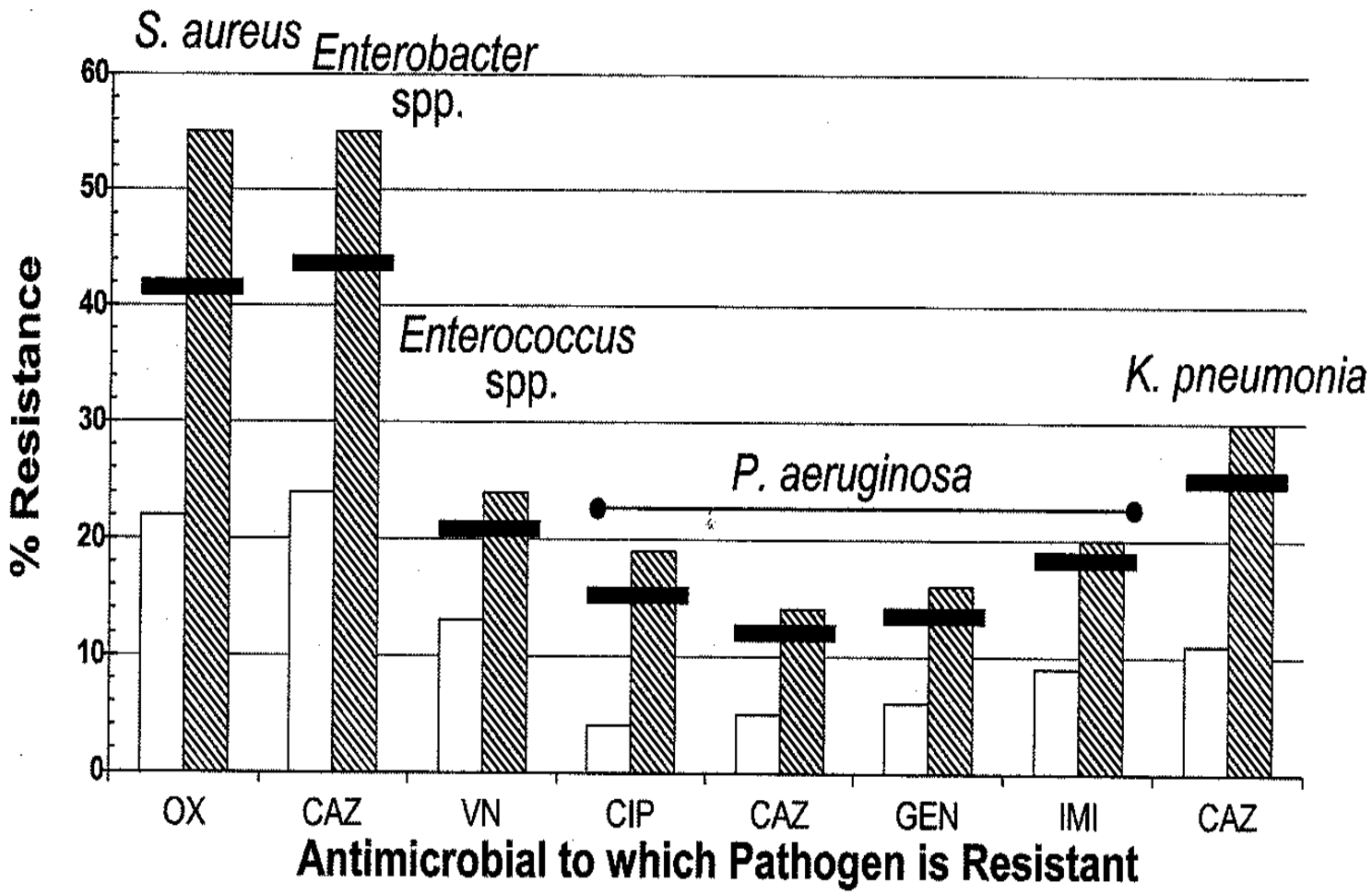
IMPACT OF DRUG RESISTANT PATHOGENS

- Prolonged hospitalization
  - Increased difficulty with placement in an extended care facility
- Need of isolation precautions (may negatively impact on quality of patient care)
- Increased cost
- Higher mortality

FACTORS ASSOCIATED WITH RESISTANT PATHOGENS

- All resistance is local
- Hospital demographics
  - Size
  - Teaching versus non-teaching
  - Location
- Care in an intensive care unit
- Duration of hospitalization and use of an invasive medical device (central venous catheter, endotracheal tube for mechanical ventilation, urinary catheter)
- Prior antimicrobial use

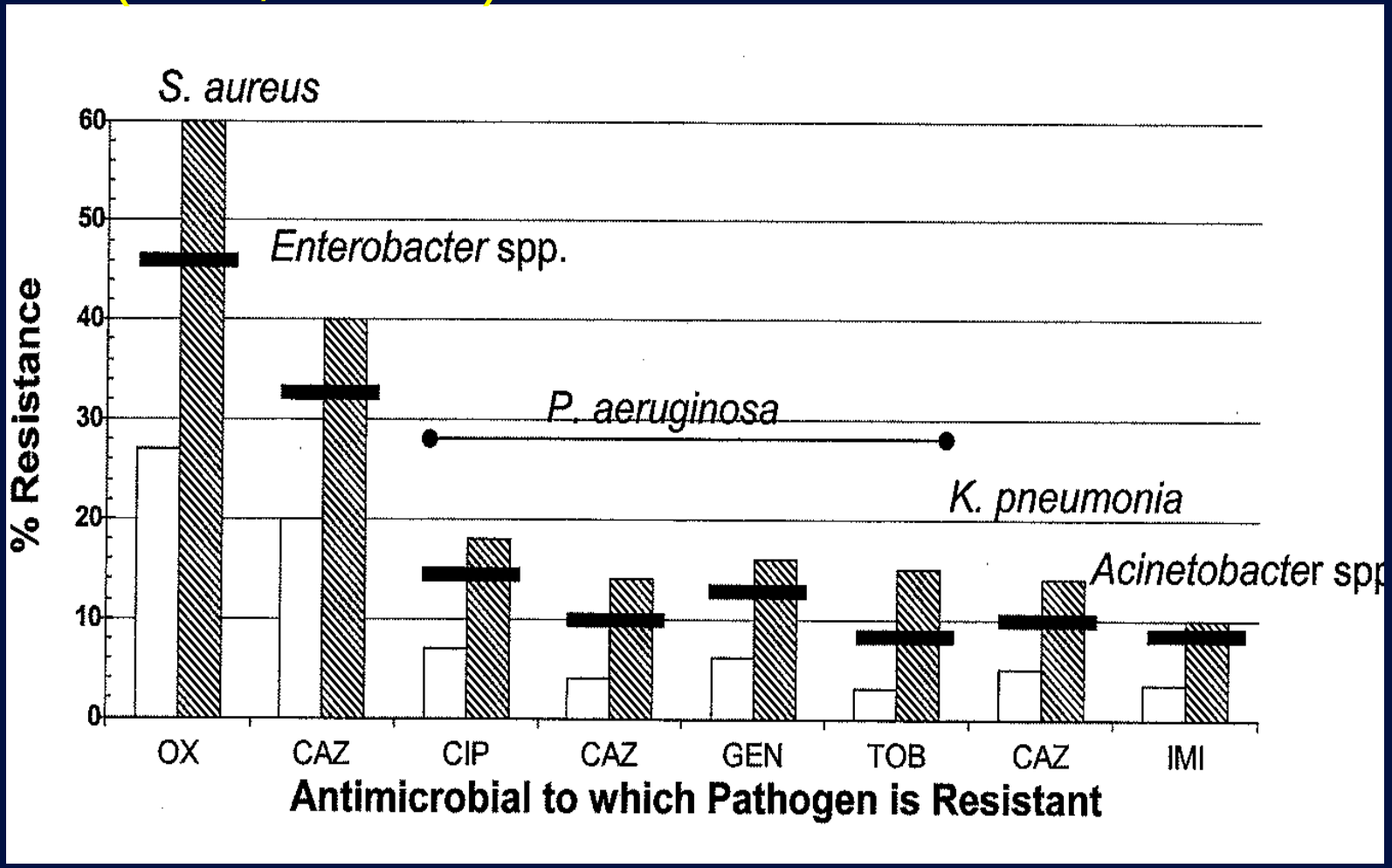
ICU (NNIS, 1989-99): Primary Bloodstream Infection



Black bar = pooled percentage resistance during hospitalization

Open bars ≤7 days hospitalization Closed bars >7 days hospitalization

ICU (NNIS, 1989-99): Ventilator-Associated Pneumonia



Black bar = pooled percentage resistance during hospitalization

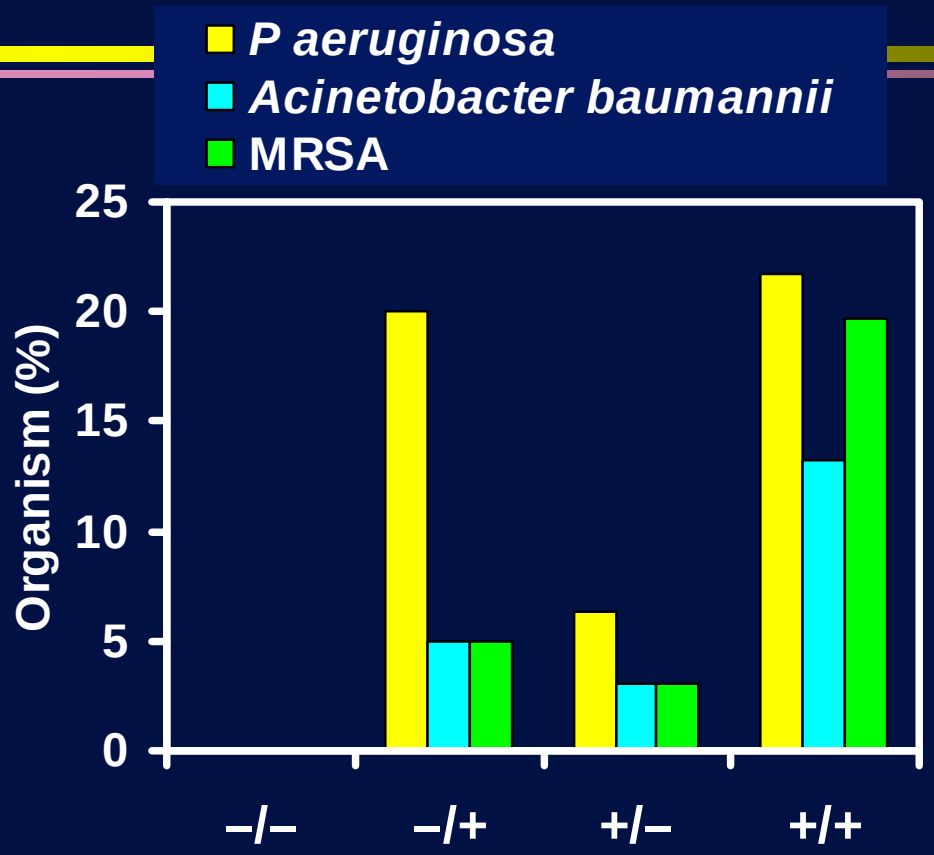
Open bars ≤7 days hospitalization Closed bars >7 days hospitalization

Fridkin SK. Crit Care Med 2001;29:N67

Antibiotic-Resistant VAP

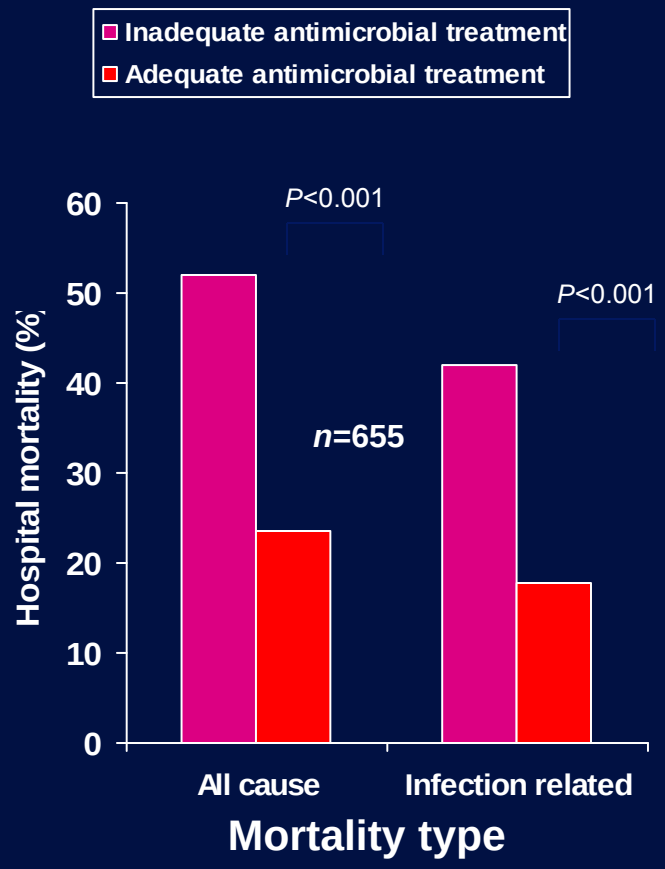
Variable	*Odds Ratio*	P *Value*
Prior MV		
>7 days	*6*	*0.009*
Prior ABs	*13*	*<0.001*
Broad ABs	*4*	*0.025*

MV = Mechanical ventilation.
MRSA = Methicillin-resistant *S aureus.*



Trouillet JL, et al. *Am J Respir Crit Care Med*. 1998;157:531-539.

The "Impact" of Inadequate Empiric Therapy



Independent risk factors for hospital mortality[a]		
Risk factor	AOR[b]	95% CI
Inadequate abx therapy	4.26	3.35-5.44
Acquired organ system derangements (one-organ increments)	3.25	2.98-3.54
Use of vasopressors	2.20	1.81-2.66
Underlying malignancy	1.81	1.44-2.27
APACHE II score (one-point increments)	1.05	1.04-1.07
Increasing age (1-yr increments)	1.02	1.01-1.03
Surgical inpatient	0.40	0.33-0.49

[a]Includes logistic regression model, where hospital mortality is the dependent outcome variable and the study population was the entire patient cohort (*n*=2,000)
[b]AOR=adjusted odds ratio
All *P* less than 0.01

Kollef MH, et al. *Chest*. 1999;115:462-474.

ESKAPE Pathogens: Clinical Outcomes

	VRE	VSE	
Bacteremia[1]	n=683	n=931	OR, 2.52*
	MRSA	MSSA	
Bacteremia[2]	11.8% (n=382)	5.1% (n=433)	*P*<.001
	KPN-ESBL+	KPN-ESBL-	
Bacteremia[3]	52% (n=48)	29% (n=99)	*P*=0.007
	AB (IMP-R)	AB (IMP-S)	
Bacteremia[4]	57.5% (n=40)	27.5% (n=40)	*P*<0.05
	MDR-Pae	No-MDR-Pae	
Bacteremia[5]	21% (n=40)	12% (n=40)	*P*=0.08
	EB (IMP-R)	EB (IMP-S)	
Serious infections[6]	11% (n=33)	3% (n=33)	*P*=0.038

***95% CI, 1.9–3.4**

[1]DiazGranados et al. *Clin Infect Dis*. 2005; 41:327–33.
[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.
[6]Marchaim D. et al. *Antimicrob Agents Chemother.* 2008; 52:1413-1418.

Abbreviations: 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*.

DEALING WITH RESISTANT PATHOGENS

Community

- Provide recommended vaccines
- Avoid unnecessary antibiotics
- Use appropriate drug to cover antibiotic resistant pathogens
- Provide appropriate dose and duration
- Use short course therapy if validated

Hospital

- Provide recommended vaccines
- Avoid unnecessary antibiotics
- Practice appropriate infection control
- Avoid prophylactic therapy unless supported by scientific evidence
- Use appropriate drug to cover antibiotic resistant pathogens
- Provide appropriate dose and duration
- Use short course therapy if validated
- Practice de-escalation
- Use early IV to PO switch

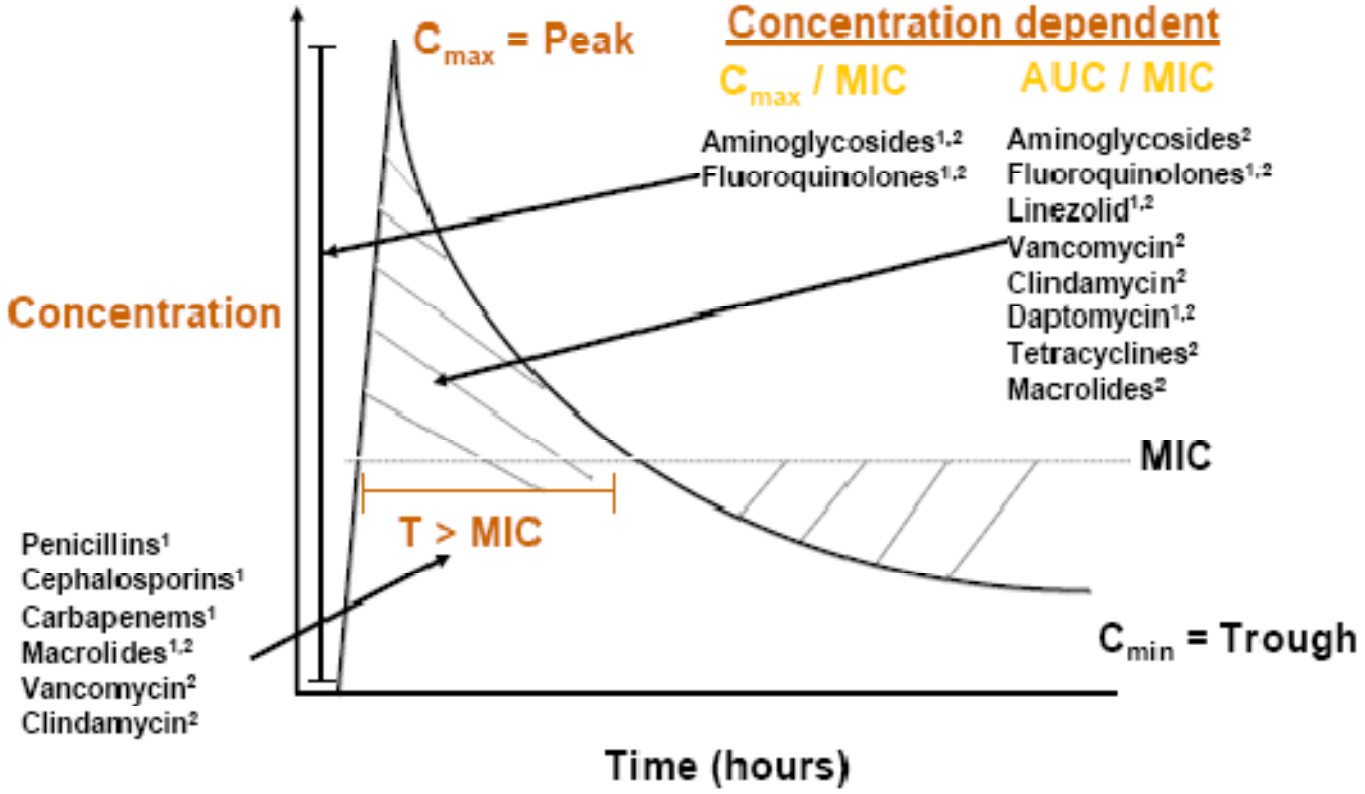
KEY INTERVENTIONS IN INFECTION CONTROL FOR RESISTANT PATHOGENS

- Hand hygiene
- Surveillance
  - Active surveillance cultures for MRSA
- Contact precautions
  - Gloves when entering the room
  - Gowns when entering the room
  - Environmental disinfection
- Antibiotic stewardship

PILLARS OF OPTIMAL ANTIBIOTIC THERAPY

- Timely
  - Delays increase mortality
- Appropriate: Effective against the pathogen(s)
- Administered at adequate dosage and intervals consistent with pK/pD parameters
- Timely streamlining based on clinical response and microbiologic data
- Prompt discontinuation when appropriate

Antimicrobial Pharmacodynamic Parameters Predictive of Success



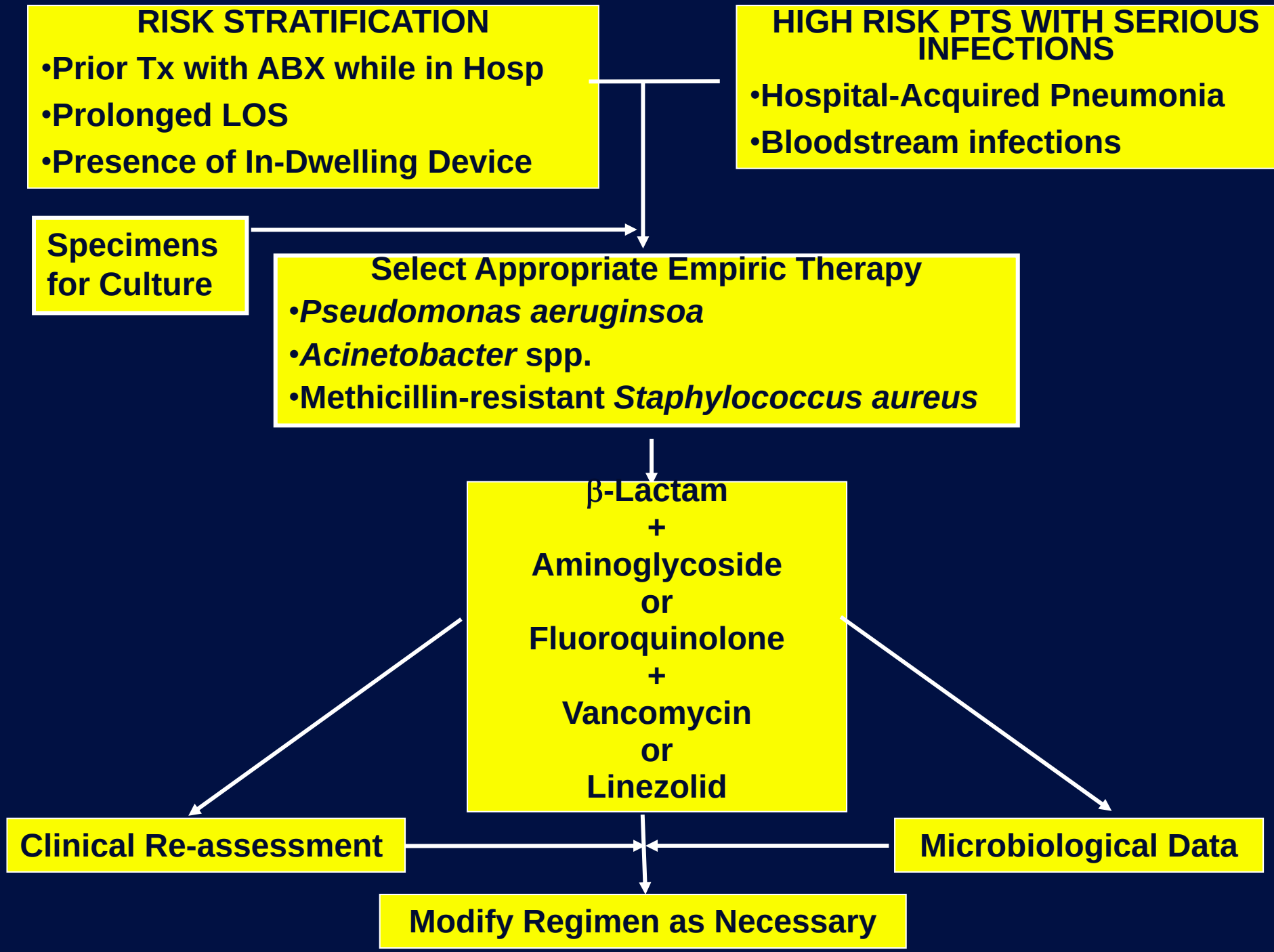
ANTIBIOTIC STEWARDSHIP

- Optimize clinical outcomes while minimizing unintended consequences of antibiotic use
  - Toxicity
  - Selection of pathogen organisms (e.g., *C. difficile*)
  - Emergence of resistance
- Combine with comprehensive infection control to limit emergence and transmission of resistance
  - Reduce healthcare costs without adversely impacting quality of care

ANTIMICROBIAL STEWARDSHIP: INTERVENTIONS (IDSA)

Tactic	Comment	Level of Evidence
Prospective audit with direct intervention & feedback	Core strategy	A-I
Formulary restriction and pre-authorization	Core strategy	A-II
Guidelines & clinical pathways	Supplemental	A-I
Streamlining or de-escalation	Supplemental	A-II
Dose optimization	Supplemental	A-II
Education	Supplemental	A-III
IV to PO switch	Supplemental	A-III
Antimicrobial order forms	Supplemental	B-II
Antibiotic cycling	Insufficient data	C-II
Combination therapy	Insufficient data	C-II

Dellit TH, et al. IDSA/SHEA Guideline. Clin Infect Dis 2007;44:159-77


RISK STRATIFICATION
•Prior Tx with ABX while in Hosp
•Prolonged LOS
•Presence of In-Dwelling Device
HIGH RISK PTS WITH SERIOUS INFECTIONS
•Hospital-Acquired Pneumonia
•Bloodstream infections
Specimens for Culture
Select Appropriate Empiric Therapy
•Pseudomonas aeruginsoa
•Acinetobacter spp.
•Methicillin-resistant Staphylococcus aureus
β-Lactam
+
Aminoglycoside
or
Fluoroquinolone
+
Vancomycin
or
Linezolid
Clinical Re-assessment
Microbiological Data
Modify Regimen as Necessary

DURATION OF THERAPY: STUDY DESIGN

- Study compared 8 vs 15 days of therapy for VAP (Chastre J, et al)
- Design: Prospective, randomized, double-blind (until day 8), clinical trial in 51 French ICUs (N=401 patients)
- Outcomes: Assessed 28 days after VAP onset (ITT analysis)
  - Primary measures = death from any cause
  - Also: Microbiologically documented pulmonary infection recurrence
- Primary outcomes (8 vs 15 days)
  - Mortality (18.8% vs 17.2%); Recurrent infection (28.9% vs 26.0%)
- Secondary outcomes (8 vs 15 days)
  - Similar frequency death at day 60, 25.4% vs 27.9%
  - *Multi-resistant pathogen (recurrent infection)*, 42% v 62% (p=0.04)

Antimicrobial Stewardship
Computer-assisted Order Entry

- Order entry-program recommended antibiotic, dose and length of therapy
- Clinicians were not required to follow program recommendations
- Data on indices of quality of care were compared between computer regimen and non-regimen patients pre and post implementation.

IMHS: Evans et. al.; NEJM 1998

TABLE 4. ADJUSTED OUTCOMES OF PATIENTS WHO RECEIVED ANTIINFECTIVE AGENTS DURING THE PREINTERVENTION AND INTERVENTION PERIODS.*

VARIABLE	PREINTERVENTION PERIOD (N=766)	INTERVENTION PERIOD		OVERALL P VALUE	P VALUE FOR COMPUTER REGIMEN FOLLOWED VS. PREINTERVENTION
		COMPUTER REGIMEN FOLLOWED (N=203)†	COMPUTER REGIMEN OVERRIDDEN (N=195)‡		
No. of different antiinfective agents ordered	2.0 (1.9–2.1)	1.5 (1.3–1.7)	2.7 (2.5–3.0)	<0.001	<0.001
Duration of antiinfective therapy — hr	214 (177–251)	103 (45–160)	330 (270–392)	<0.001	<0.001
No. of antiinfective-agent doses	23.6 (20.2–26.9)	11.4 (6.2–16.7)	27.6 (22.0–33.1)	<0.001	<0.001
Days of excess antiinfective dosage	5.4 (4.5–6.4)	1.4 (0–2.7)	3.6 (2.0–5.1)	<0.001	<0.001
Cost of antiinfective agents — $	340 (273–407)	102 (0–206)	427 (316–538)	<0.001	<0.001
No. of microbiology cultures	6.8 (5.7–7.9)	3.2 (1.5–4.9)	10.6 (8.7–12.6)	<0.001	<0.001
Length of stay in ICU — days	4.9 (4.1–5.8)	2.7 (1.5–4.0)	8.3 (7.0–9.5)	<0.001	<0.001
Days from ICU admission to hospital discharge	10.5 (9.3–11.8)	7.8 (5.9–9.7)	14.3 (12.2–16.3)	<0.001	<0.001
Total length of stay — days	12.9 (11.5–14.4)	10.0 (7.7–12.3)	16.7 (14.2–19.1)	<0.001	<0.003
Total cost of hospitalization — $	35,283 (31,448–39,118)	26,315 (20,393–32,237)	44,865 (38,564–51,166)	<0.001	<0.005

*Values shown are means per patient and 95 percent confidence intervals. Outcome variables have been adjusted for age, sex, Computer Severity Index score on admission to the Shock–Trauma–Respiratory Intensive Care Unit (ICU), medical service, and mortality.

†These patients always received the computer-suggested antiinfective regimen.

‡These patients did not always receive the computer-suggested antiinfective regimen.

CHOOSING AN ANTIBIOTIC RATIONALLY

- Efficacy
- Safety
- Compliance
- Cost

ANTIBIOTICS FOR RESISTANT GRAM POSITIVE COCCI

- "Old" therapy
  - Vancomycin (covers MRSA but not VRE)
- New therapy
  - Streptogramins: Quinupristin/dalfopristin
  - Oxazolidones: Linezolid
  - Cyclic lipids: Daptomycin
  - Glycylcyclines: Tigecycline
  - Cephalosporins: Ceftibiprole

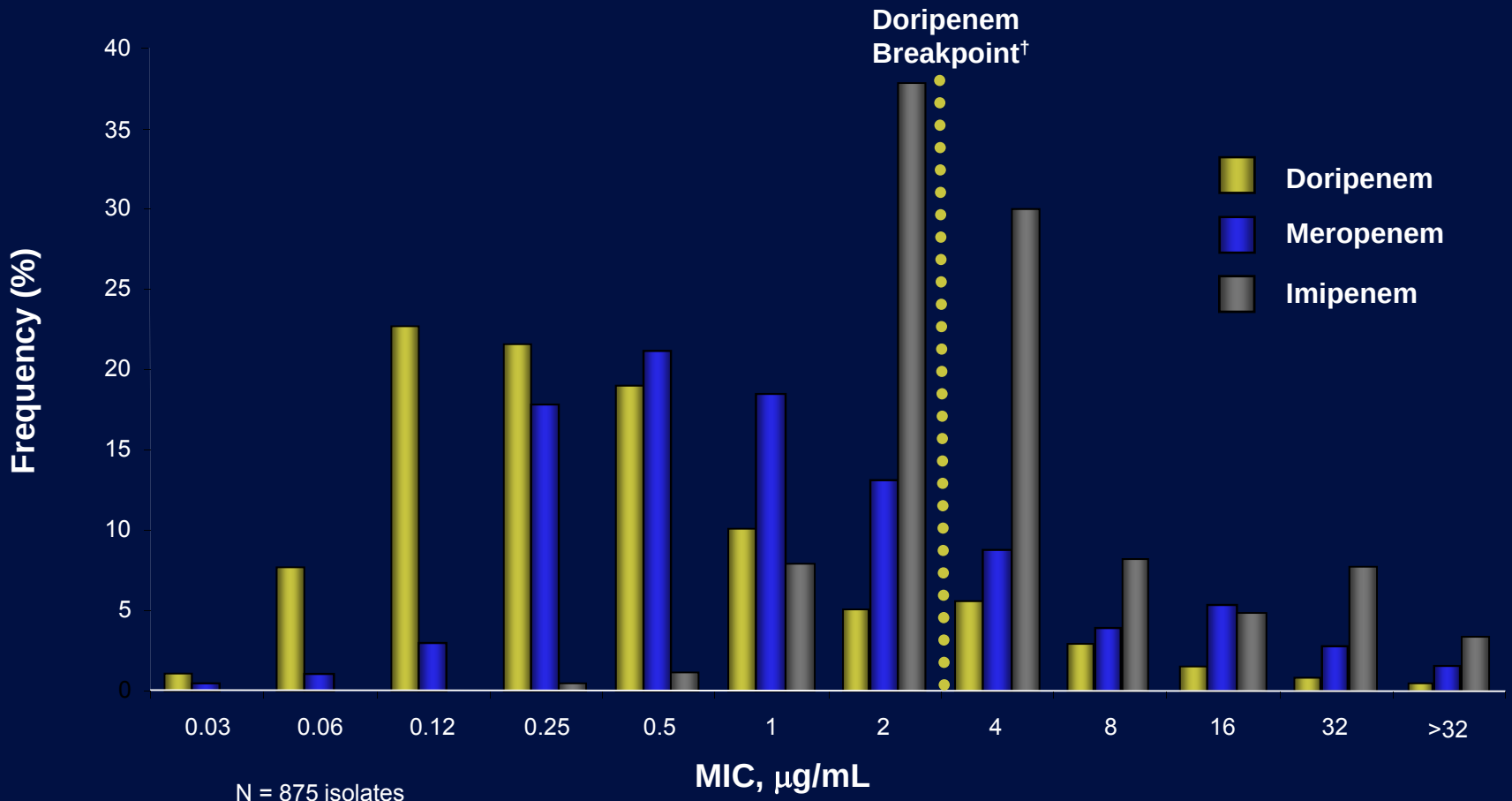
TREATMENT OF MRSA

Indication	Primary Rx	Alternatives	Comments
CAP HAP	Vancomycin, Linezolid, Ceftobiprole	Q-d, Tigecycline	Avoid daptomycin
Skin-soft tissue	Vancomycin, Daptomycin, Linezolid, Tigecycline Ceftobiprole	Q-d	Δ to PO when afebrile x 2 d Consider ceftobiprole when MRSA and *P. aeruginosa* suspected (e.g., diabetic or decubitus ulcer)
Intra-abdominal infection/wound	Vancomycin, Tigecycline	Linezolid, Daptomycin, Ceftobiprole	
Septic arthritis	Vancomycin	Linezolid, Daptomycin, Tigecycline, Ceftobiprole	Total 3-4 wk (IV → PO therapy may be acceptable in some cases)
Osteomyelitis	Vancomycin	Daptomycin, Tigecycline, Ceftobiprole	Total 4-6 wk (IV → PO therapy may be acceptable in some cases)

TREATMENT OF EMERGING GRAM NEGATIVE BACILLI

- Doripenem
  - Class: Carbapenem
  - Advantages: Most active carbapenem against enteric Gram negative bacilli and *P. aeruginosa*
  - Disadvantages: No coverage of MRSA or VRE
- Tigecycline
  - Class: Minocycline derivative
  - Advantages: Covers MRSA, VRE, most ESBLs, many *Acinetobacter*
  - Disadvantages: Static, no coverage of *P. aeruginosa*
- Ceftobiprole (not available in the US)
  - Class: Cephalosporin
  - Advantages: Covers MRSA, enteric Gram negative bacilli, *P. aeruginosa*
  - Disadvantages: Limited coverage of vancomycin-resistnt *Enterococcus faecium*

MIC Distribution of Doripenem, Meropenem, and Imipenem in *P aeruginosa* Isolates*



N = 875 isolates

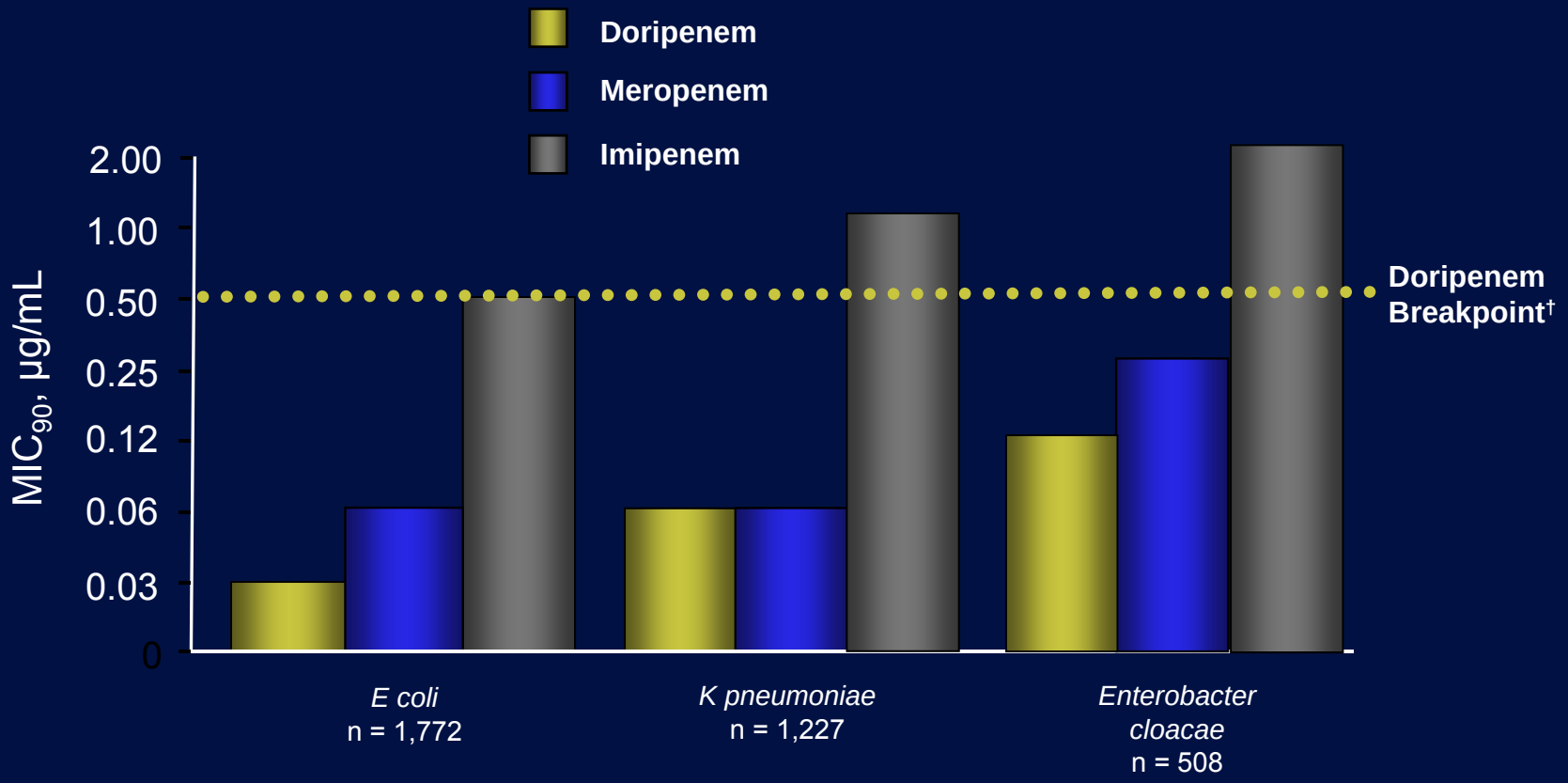
*During 2005-2006, 875 *P aeruginosa* isolates were collected from 9 Census Bureau regions across the US and centrally tested against DORIBAX and several other antibacterials.

†Breakpoint for doripenem vs *P aeruginosa* is MIC ≤ 2.0 μg/mL.

In vitro activity does not necessarily correlate with clinical results.

Data on file. Ortho-McNeil, Inc.

Doripenem In Vitro Activity Against Enterobacteriaceae*



*During 2005-2006, isolates were collected from 9 US Census Bureau regions and tested against DORIBAX and several other antimicrobials.

†Breakpoint for doripenem vs Enterobacteriaceae is MIC ≤ 0.5 µg/mL.

In vitro activity does not necessarily correlate with clinical results.

Data on file. Ortho-McNeil, Inc.

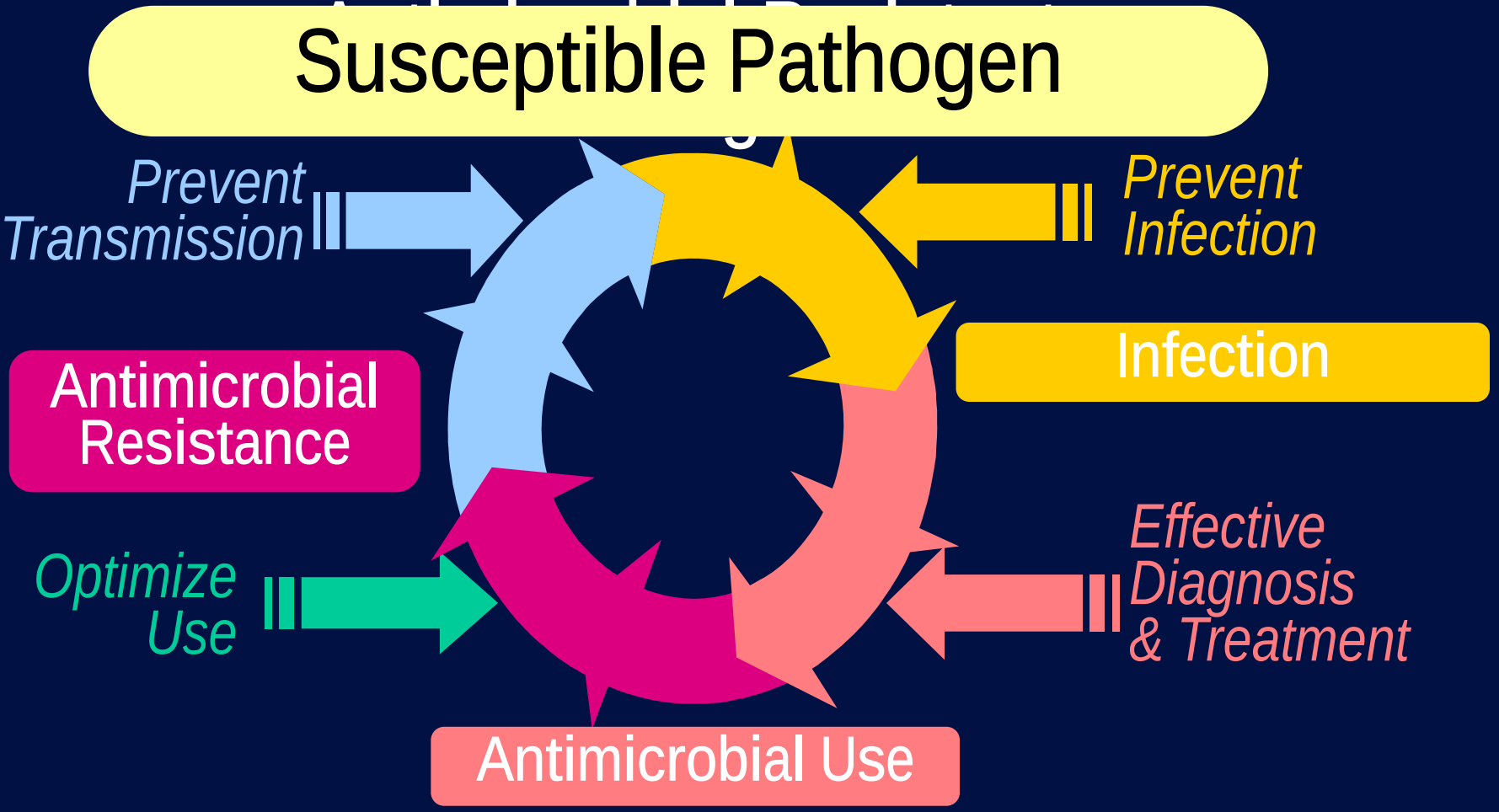
Putative Mechanisms of Carbapenem Resistance in *P aeruginosa*

	Doripenem[1-3]	Meropenem[1-3]	Imipenem[1-3]
Major mechanism(s) required for development of resistance*	Efflux + Loss of OprD	Efflux + Loss of OprD	Loss of OprD

- Doripenem and meropenem are affected by efflux, whereas imipenem may escape this mechanism
- Multiple mechanisms (efflux plus permeability) are usually needed for resistance to doripenem and meropenem
- Loss of OprD alone generally confers resistance to imipenem

1. Mushtaq S, et al. *Antimicrob Agents Chemother*. 2004;48:3086-3092. 2. Sakyo S, et al. *J Antibiotics (Tokyo)*. 2006;59:220-228. 3. Livermore DM. *J Antimicrob Chemother*. 2001.47;247-250. 4. Livermore DM. *J Antimicrob Chemother*. 1997.39;673-676.

Antimicrobial Resistance: Key Prevention Strategies



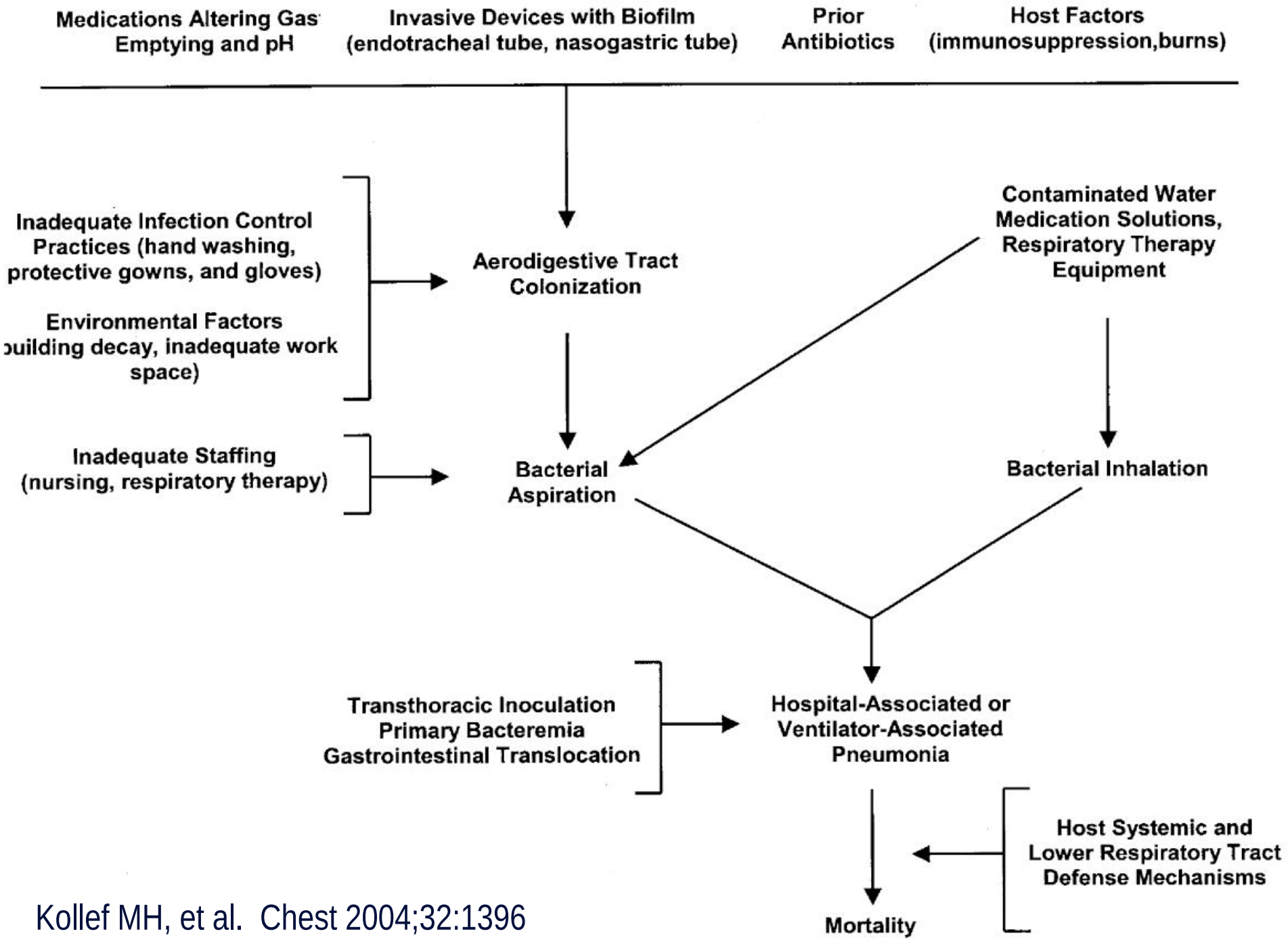
VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Prevalence, Incidence and Impact

- Prevalence 9 to 27% of intubated patients
- Cases per year: ~275,000
- Incidence in ICUs (infections/1,000 ventilator days): 0.5 to 10.7 (NHSN)
- Incidence in non-ICU patients: 0.4 to 3.0 (NHSN)
- VAP independently increases hospital cost and length of stay
- RR for mortality in patients with VAP compared to non-infected = 27%

Risk Factors For VAP

- Age >60 years
- Supine patient positioning
- Decrease of gastric pH
- Surgery (especially, abdominal)
- Presence of nasograstric tube
- Enteral feeding
- Sinusitis
- Transport out of the ICU
- Emergent intubation
- ARDS
- Head trauma or coma

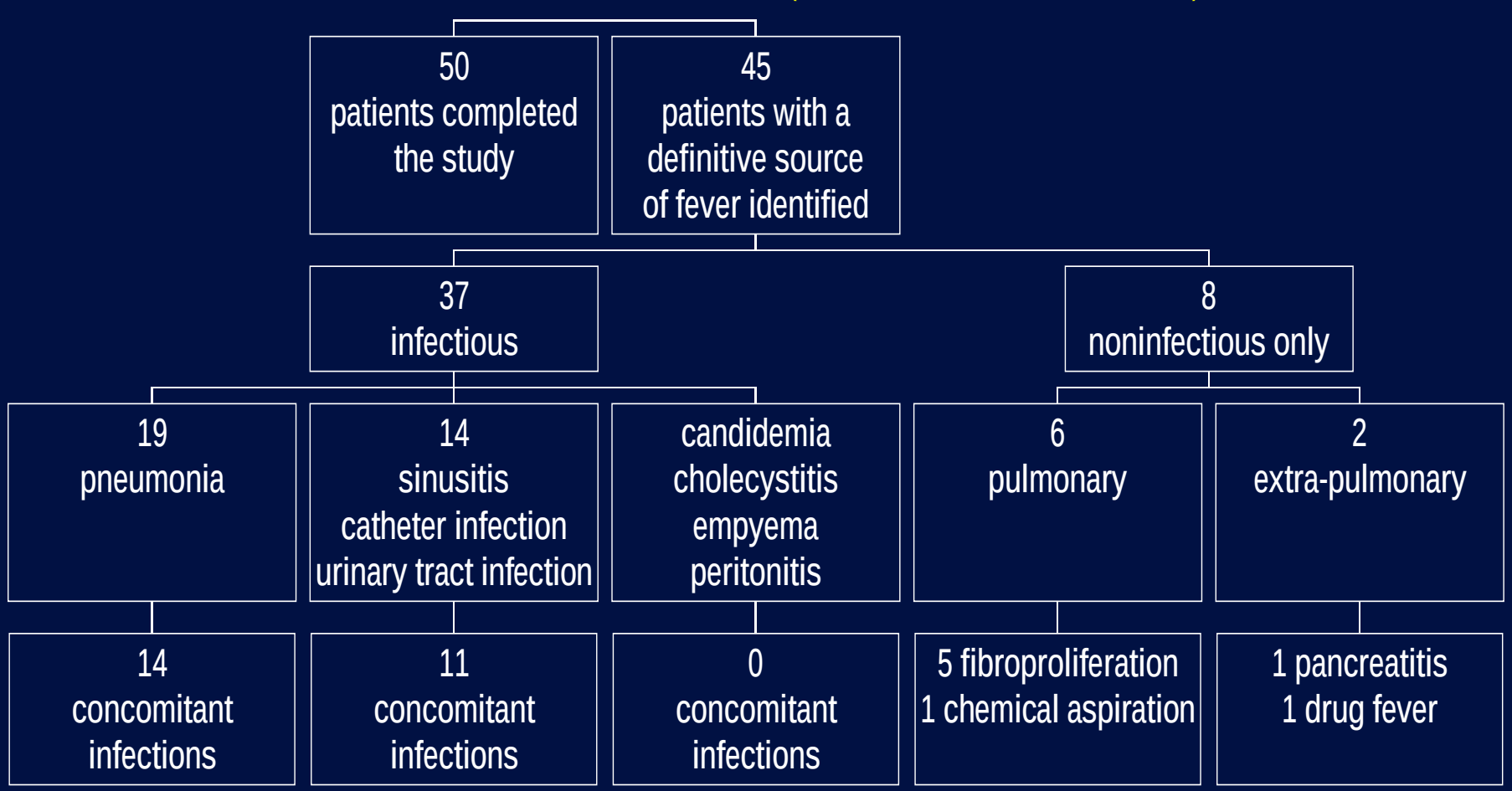


Kollef MH, et al. Chest 2004;32:1396

METHODS OF DIAGNOSIS

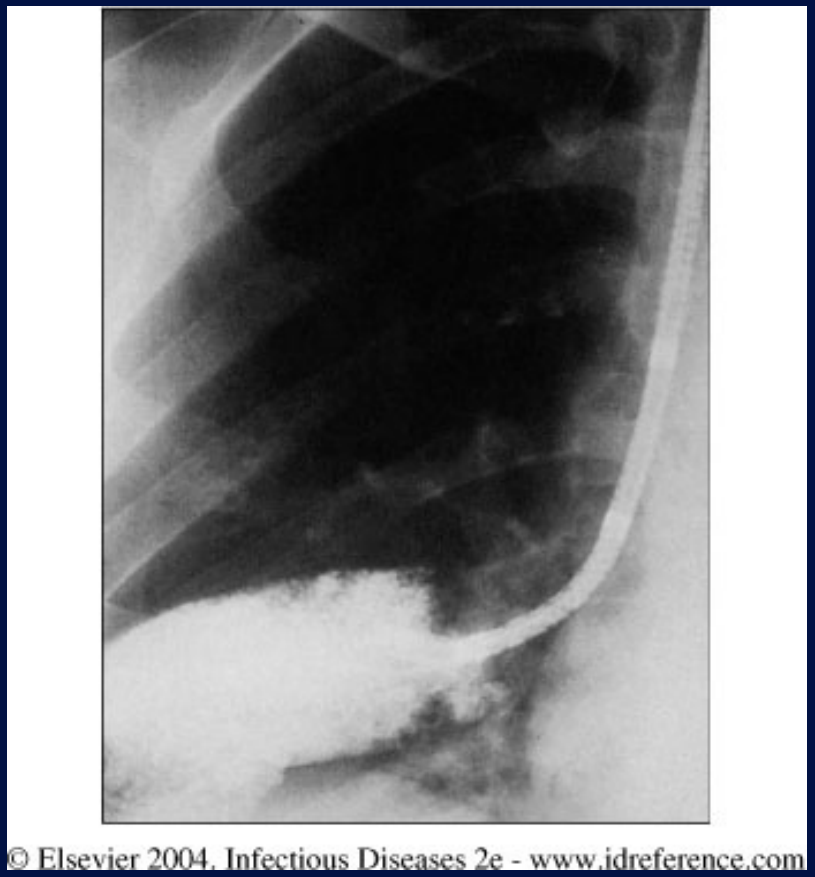
- Clinical findings (symptoms, signs)
- Blood, pleural fluid analysis & cultures, tissue diagnosis
- Non-bronchoscopic
  - Endotracheal aspiration
  - Percutaneous needle aspiration
  - Blind bronchial sampling (“Blind” BAL)
- Bronchoscopic techniques
  - Protected specimen brush (PSB)
  - Bronchoalveolar lavage (BAL)

DIAGNOSING VAP PNEUMONIA



INVASIVE METHODS OF DIAGNOSIS

Protected specimen brush

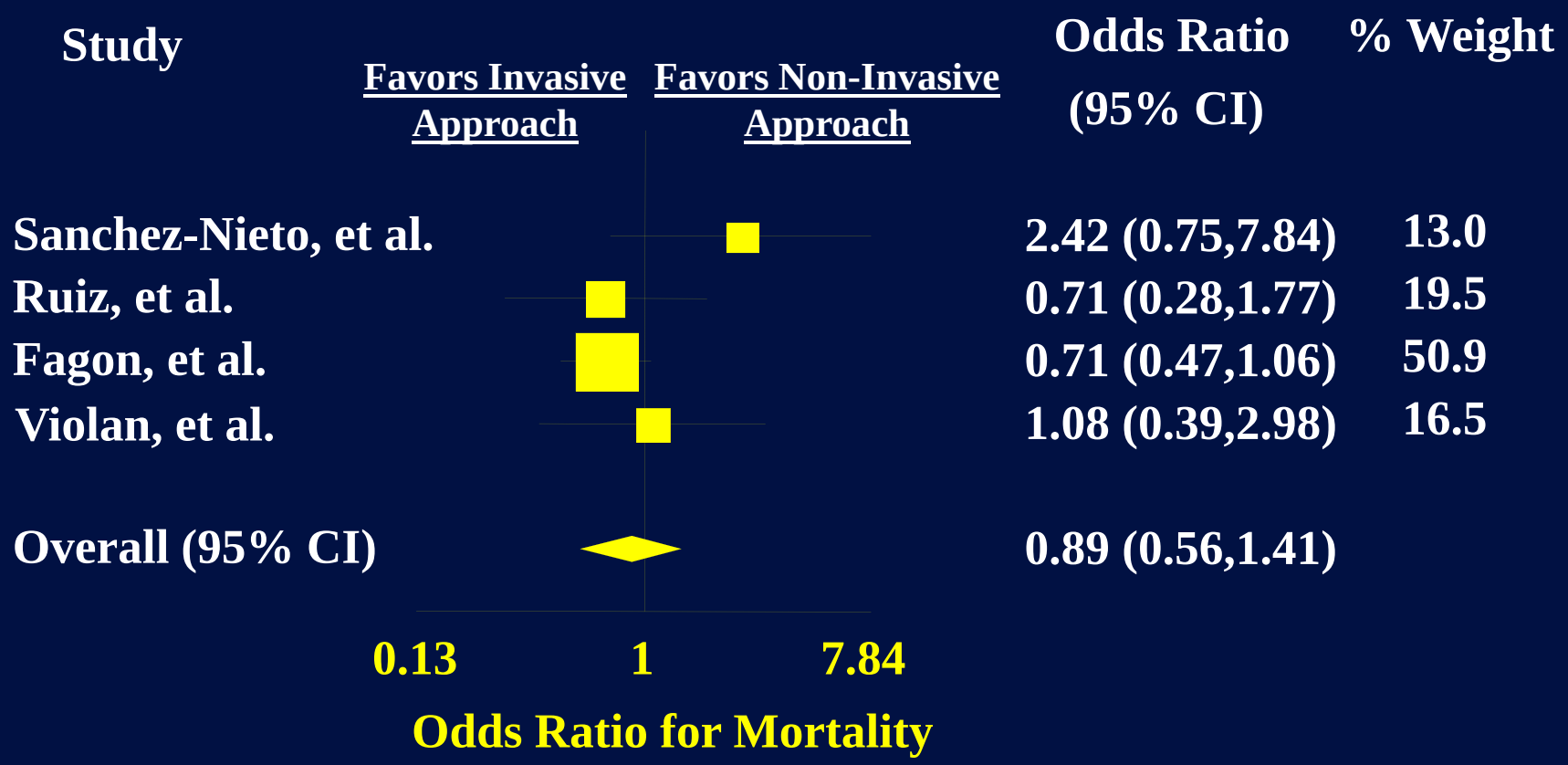


Bronchoalveolar lavage

INDICATIONS FOR INVASIVE DIAGNOSIS

- Routine for all patients with possible nosocomial pneumonia?
- Targeted use of invasive diagnosis
  - Critically ill
  - Immunocompromised patient (esp. T-cell defect)
  - Deterioration on empiric therapy
  - Failure to respond to empiric therapy
  - Other therapeutic consideration (e.g., foreign-body)

Meta-analysis of Invasive Strategies for the Diagnosis of Ventilator-Associated Pneumonia & their Impact on Mortality*



*Random effects model; Test of heterogeneity p=0.247, for Odds ratio p=0.620

Shorr A, Kollef. MH Crit Care Med 2005;33:46.

INITIAL EMPIRIC THERAPY FOR HAP/VAP:
EARLY ONSET & NO KNOWN RISK FACTORS FOR MDR PATHOGENS

Common Pathogen	Initial Empiric Therapy
Streptococcus pneumoniae *Haemophilus influenzae* OSSA Antibiotic-sensitive GNR *E. coli, K. pneumoniae,* *Enterbacter spp., Proteus spp.,* *S. marcescens*	Ceftriaxone (3^0 cephalosporin) OR Levofloxacin, Moxifloxacin, Ciprofloxacin (FQ) OR Ampicillin/sulbactam (β-lactam- β-lactamase inhibitor) OR Ertapenem (carbapenem)

ATS/IDSA. Am J Respir Crit Care Med 2005;171:388-416

INITIAL EMPIRIC THERAPY FOR HAP/VAP/HCAP:
LATE ONSET OR RISK FACTORS FOR MDR PATHOGENS

Common Pathogen	Initial Empiric Therapy
MDR-GNR *P. aeruginosa* *K. pneumoniae* (ESBL) *Acinetobacter spp*. Non-MDR GNR *L. pneumophila* MDR-Gram-Positive Cocci ORSA	Antipseudomonal cephalosporin (Cefepime, Ceftazidime) OR Antipseudomonal carbapenem (Imipenem, Meropenem) OR β-lactam/inhibitor (Piperacillin-tazobactam) PLUS Antipseudomonal FQ (Cipro or Levo) OR Aminoglycoside (Gent, Tobra, Amikacin) PLUS Linezolid or vancomycin (ORSA suspected)

ATS/IDSA. Am J Respir Crit Care Med 2005;171:388-416

COMMENTS ON THERAPY FOR VAP

- In large teaching hospitals use the same therapy for early and late infections
- For Gram positive coverage vancomycin drug of choice
  - Alternative = linezolid or ceftibiprole
  - Ciprofloxacin should NOT be used as it does NOT cover *S. pneumoniae*
- For Gram negative coverage doripenem should be used in place of imipenem or meropenem (improved coverage against enteric *P. aeruginosa* and Gram negative bacilli)
  - Levofloxacin 750 mg 1x/d equivalent to ciprofloxacin 400 mg 3x/day
  - Ertapenem should NOT be used as it does not cover *Acinetobacter* or *Pseudomonas*
  - For treatment of highly resistant *Acinetobacter* consider tigecycline, colistin, or ampicillin-sulbactam (choice dictated by susceptibily panel) – add amikacin if susceptible

RATIONALE FOR BROAD SPECTRUM THERAPY IN EARLY ONSET VAP/HAP

Pathogen, by class	No. (%) of isolates: Patients with early-onset VAP	Patients with late-onset VAP	*P*
Gram-positive cocci			
Staphylococcus aureus			
Oxacillin-susceptible	12 (18.75)	24 (7.19)	.006
Oxacillin-resistant	8 (12.50)	63 (18.86)	.149
Streptococcus pneumoniae	4 (6.25)	4 (1.20)	.026
Gram-negative bacilli			
Enterobacter species	1 (1.56)	8 (2.40)	.561
Escherichia coli	2 (3.13)	13 (3.89)	.556
Klebsiella pneumoniae	1 (1.56)	7 (2.10)	.623
Serratia marcescens	2 (3.13)	8 (2.40)	.497
Acinetobacter species	0 (0.00)	31 (9.28)	.003
Stenotrophomonas maltophilia	1 (1.56)	26 (7.78)	.049
Pseudomonas aeruginosa	8 (12.50)	61 (18.26)	.176
Moraxella catarrhalis	2 (3.13)	4 (1.20)	.176
Hemophilus species	12 (18.75)	10 (2.99)	<.001
Total, all pathogens	64	334	

Pathogen	No. (%) of isolates: Patients with early-onset HAP	Patients with late-onset HAP	*P*
Gram-positive cocci			
Staphylococcus aureus			
Oxacillin-susceptible	13 (19.40)	22 (11.00)	.063
Oxacillin-resistant	8 (11.94)	47 (23.50)	.028
Streptococcus pneumoniae	8 (11.94)	7 (3.50)	.015
Gram-negative bacilli			
Enterobacter species	2 (2.99)	6 (3.00)	.639
Escherichia coli	1 (1.49)	7 (3.50)	.361
Klebsiella species	3 (4.48)	12 (6.00)	.454
Serratia marcescens	2 (2.99)	3 (1.50)	.369
Acinetobacter species	2 (2.99)	7 (3.50)	.598
Stenotrophomonas maltophilia	1 (1.49)	2 (1.00)	.581
Pseudomonas aeruginosa	2 (2.99)	23 (11.50)	.026
Moraxella catarrhalis	3 (4.48)	4 (2.00)	.244
Hemophilus species	4 (5.97)	4 (2.00)	.122
Total, all pathogens	67	200	

Weber DJ, et al. Infect Control Hosp Epidemiol 2007;28:825-831

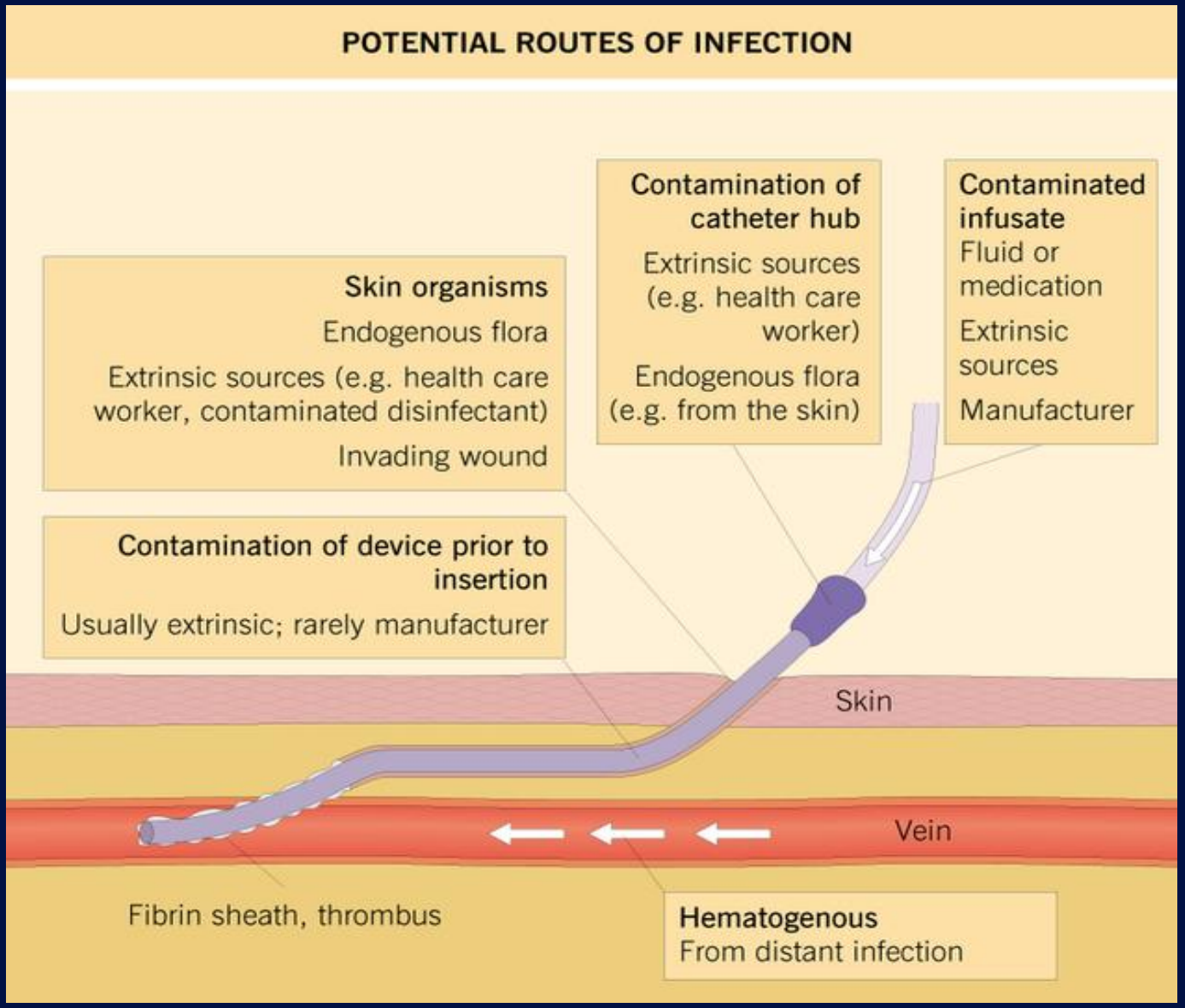
CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTIONS (CLA-BSI)

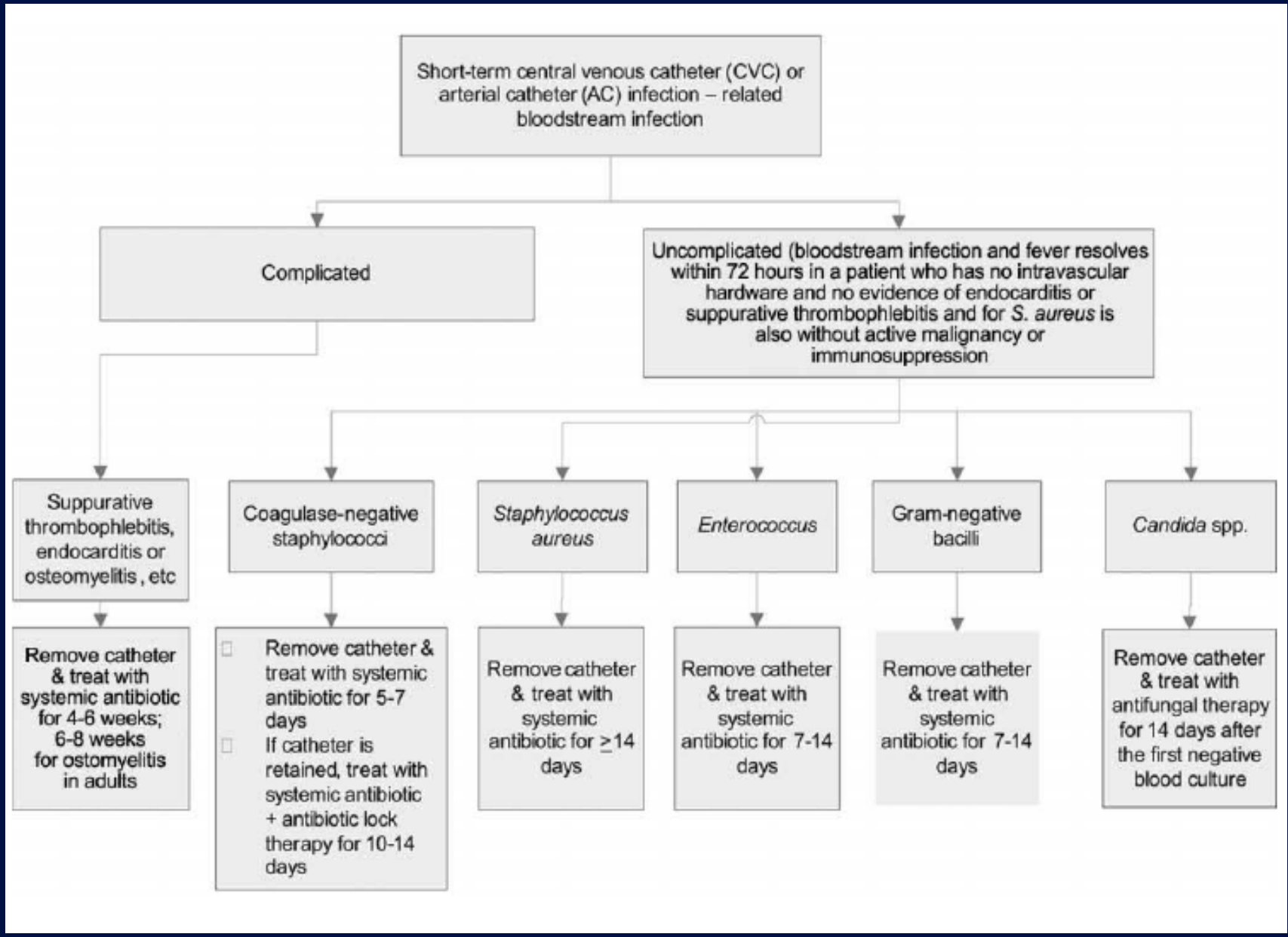
Prevalence, Incidence and Impact

- >150 million intravascular devices used each year
- ~80,000 CLA-BSI each year in ICUs
- Incidence in ICUs (infections/1,000 central line days): 1.4 to 5.5
- Incidence in non-ICU patients: 0 to 3.1
- CLA-BSI independently increases hospital cost and length of stay

Independent Risk Factors For CLA-BSI

- Prolonged hospitalization before catheterization
- Prolonged duration of catheterization
- Heavy microbial colonization at insertion site
- Heavy microbial colonization of the catheter hub
- Use of central vein other than subclavian (i.e., jugular, femoral)
- Neutropenia
- Prematurity
- Total parenteral nutrition
- Substandard care of the catheter


POTENTIAL ROUTES OF INFECTION
Skin organisms
Endogenous flora
Extrinsic sources (e.g. health care worker, contaminated disinfectant)
Invading wound
Contamination of device prior to insertion
Usually extrinsic; rarely manufacturer
Contamination of catheter hub
Extrinsic sources (e.g. health care worker)
Endogenous flora (e.g. from the skin)
Contaminated infusate
Fluid or medication
Extrinsic sources
Manufacturer
Skin
Vein
Fibrin sheath, thrombus
Hematogenous
From distant infection



IDSA Guideline. Mermel LA, et al. Clin Infect Dis 2009;49:1-45

IDSA: CLA-BIS
SPECIFIC TREATMENT RECOMMENDATIONS

- Coverage for Gram positive cocci
  - Vancomycin is recommended for empiric therapy
  - Consider daptomycin if institution has preponderance of MRSA with vancomycin MIC >2μg/mL
  - Avoid linezolid
- Coverage for Gram negative bacilli
  - Empiric coverage should be based on local susceptibility data
  - Consider 4th-generation cephalosporin (e.g., cefepime, ceftobiprole), β-lactam/ β-lactamase combination, or carbapenem with or without an aminoglycoside

100,000 LIVES CAMPAIGN: VAP AND CLA-BSI BUNDLES

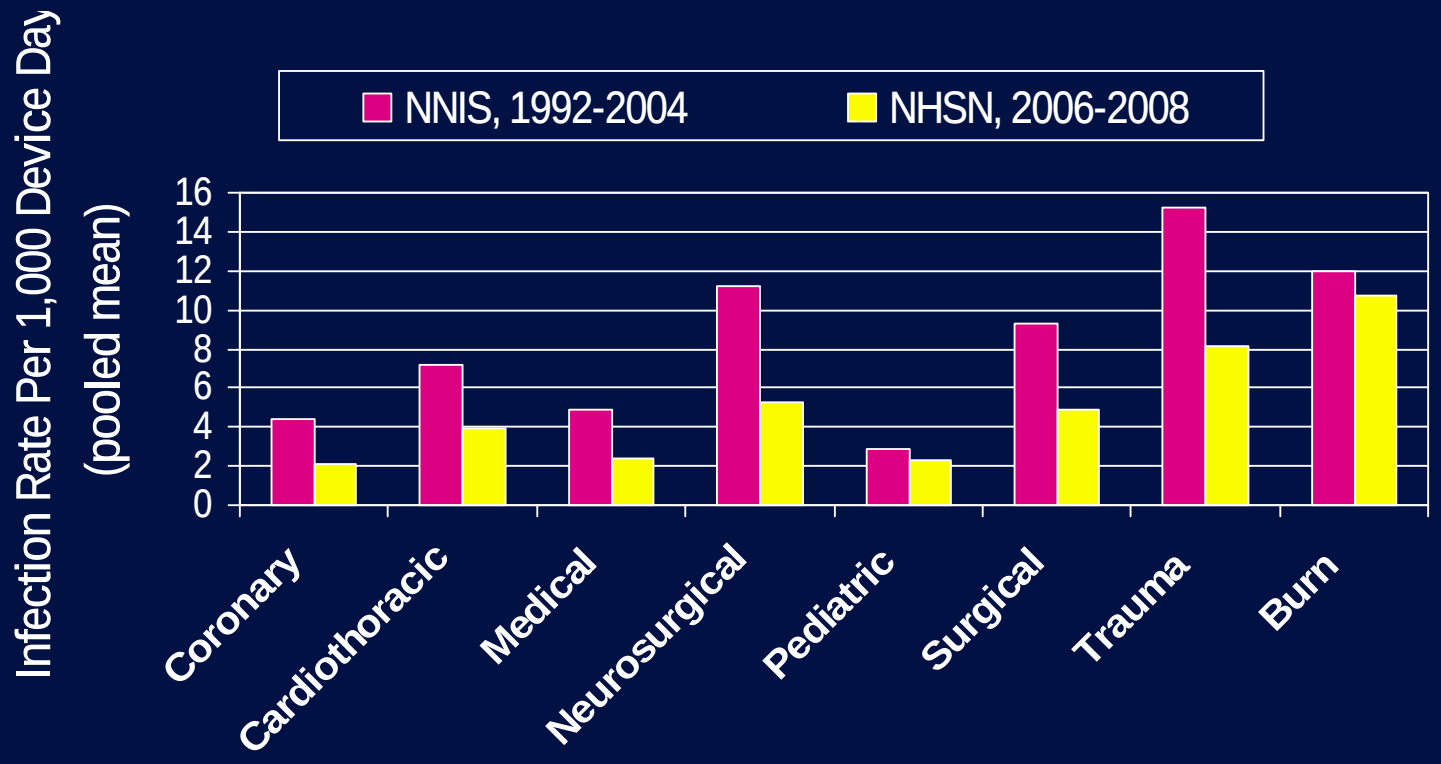
VAP Bundle

- Elevation of the head of the bed to between 30 and 45 degrees
- Daily “sedation vacation” and daily assessment of readiness to extubate
- Peptic ulcer disease (PUD) prophylaxis
- Deep venous thrombosis (DVT) prophylaxis (unless contraindicated)

CLA-BSI

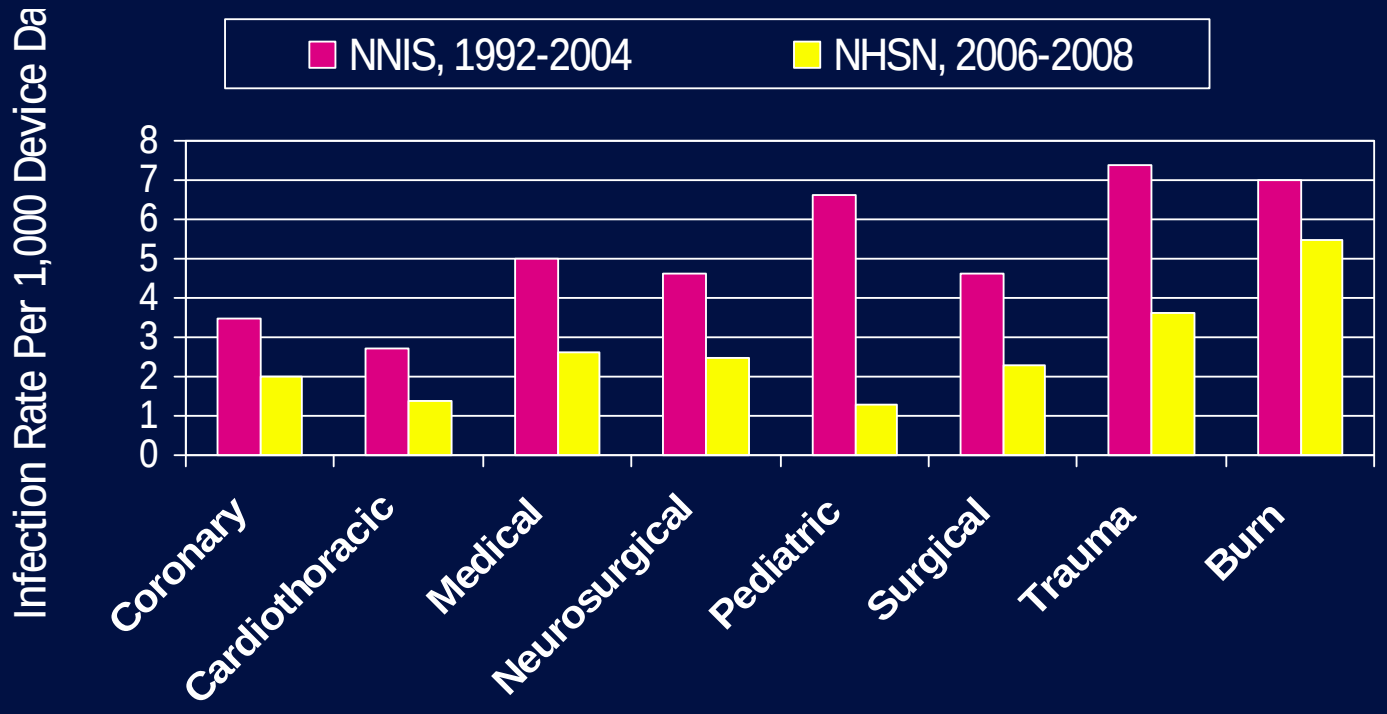
- Hand hygiene
- Maximal barrier precautions
- Chlorhexidine skin antisepsis
- Optimal catheter site selection, with subclavian vein as the preferred site for non-tunneled catheters
- Daily review of line necessity, with prompt removal of unnecessary lines

VAP RATES OVER TIME, US



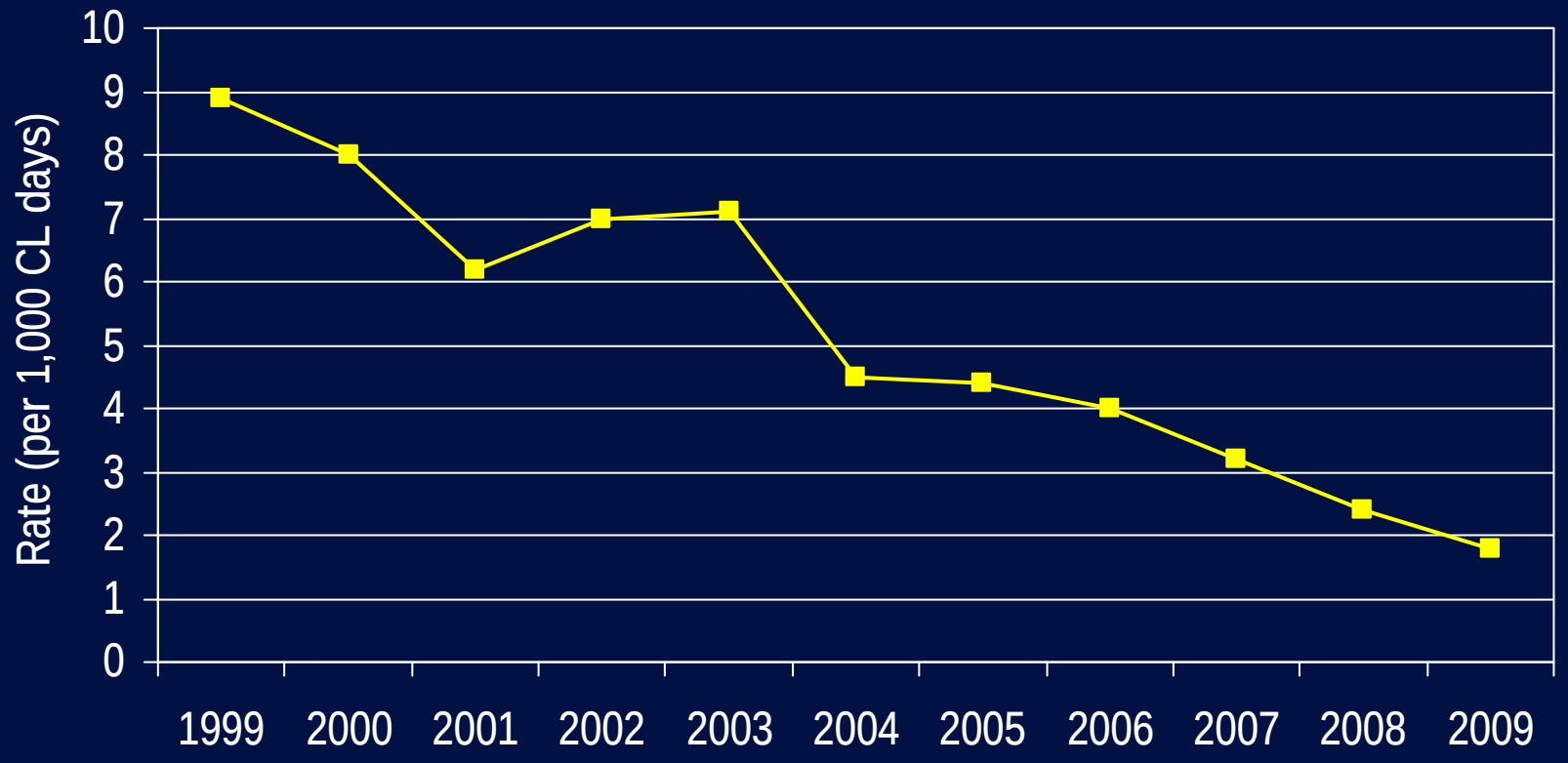
VAP = Ventilator-Associated Pneumonia

CLA-BSI RATES OVER TIME, US



CLA-BSI = Central line-associated bloodstream infections

RATE CLA-BSI, UNC HOSPITALS, 1999-2009



CONCLUSIONS

- Inappropriate antimicrobial use and failure to fully implement infection control recommendations are leading to the emergence of antimicrobial-resistant pathogens.
- Increased collaboration between clinicians, infectious disease, infection control and microbiology personnel, Federal and State public health authorities, and private industry will be needed to reduce antimicrobial use, improve infection control, and prevent the further emergence of antimicrobial-resistant pathogens.
- Few new antibiotics recently released
  - New antibiotics for Gram positive cocci: Daptomycin, linezolid, tigecycline, ceftobiprole
  - New antibiotics for Gram negative bacillin: Doripenem, tigecycline, ceftobiprole