Management of HAP MRSA infection

HK MARCH 2010

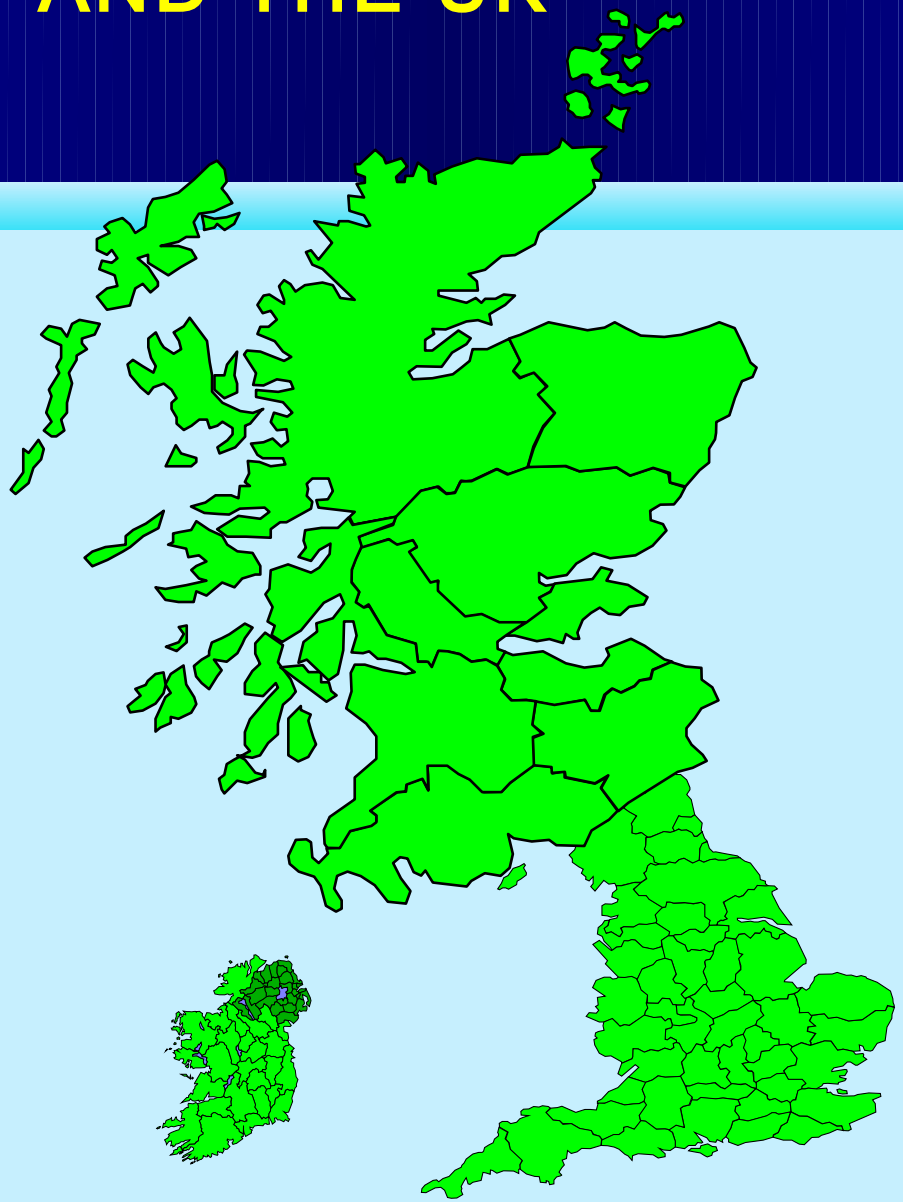
Dilip Nathwani

Consultant Physician & Professor

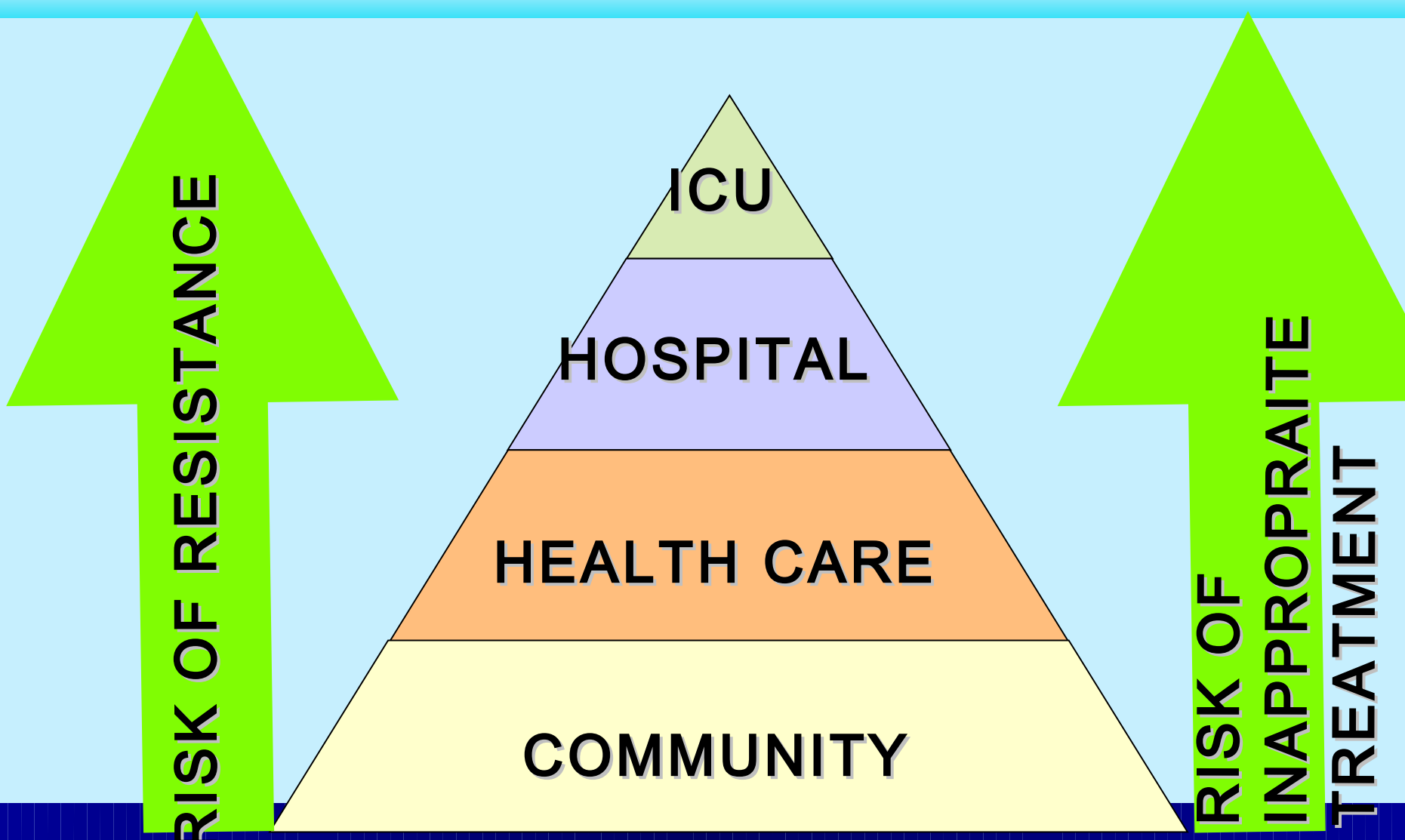
Ninewells Hospital & Medical School

Dundee, Scotland DD1 9SY

SCOTLAND AND THE UK

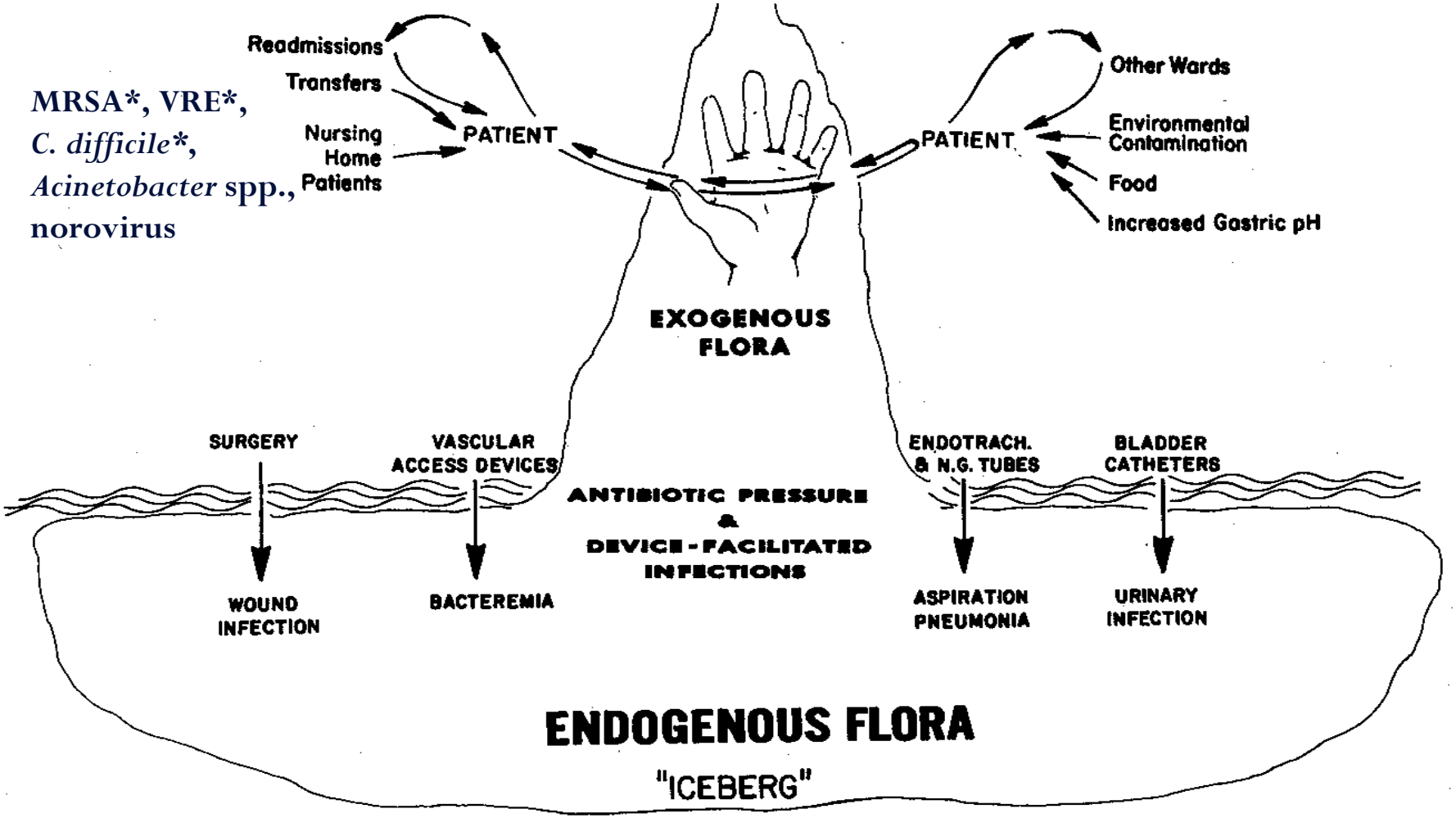


Infection Setting, Resistances, and Inadequacy of Treatment



HAZARDS IN THE ICU

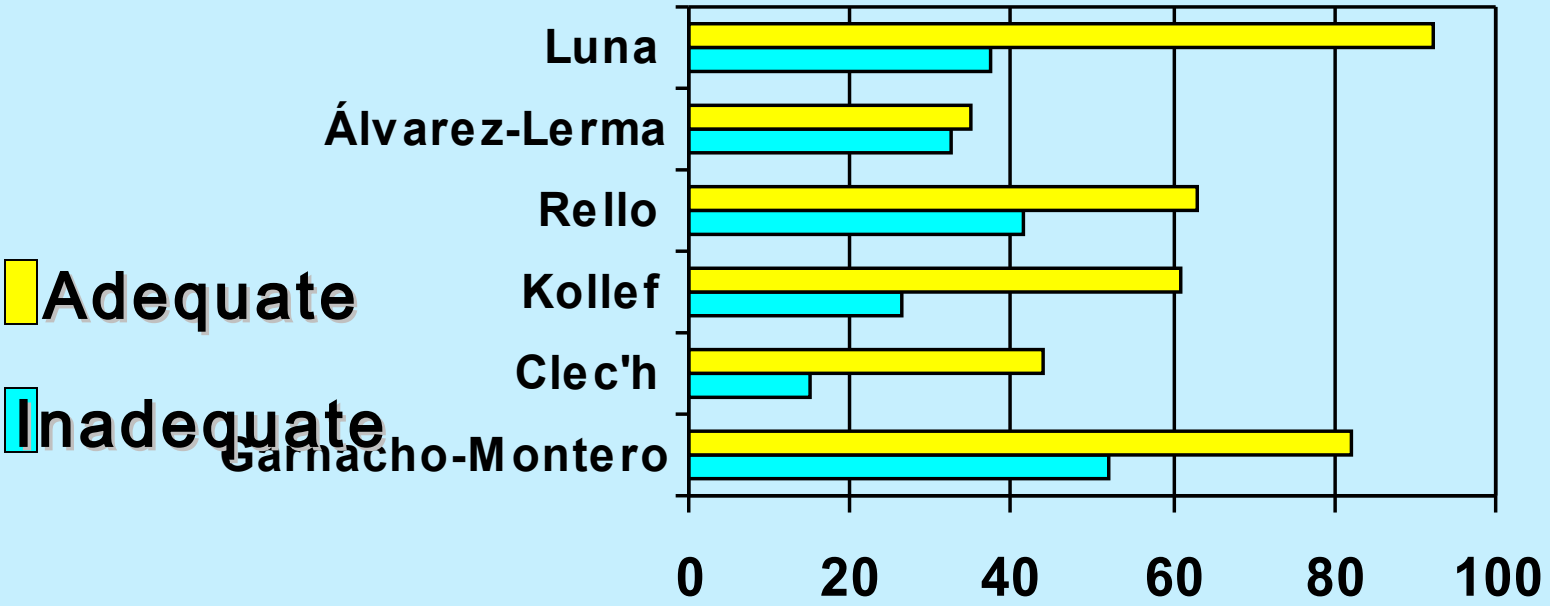
MRSA*, VRE*, *C. difficile, *Acinetobacter* spp., norovirus**



* *Acquisition linked to admission to a room previously occupied by a colonized patient* Weinstein RA. Am J Med 1991;91(suppl 3B):180S

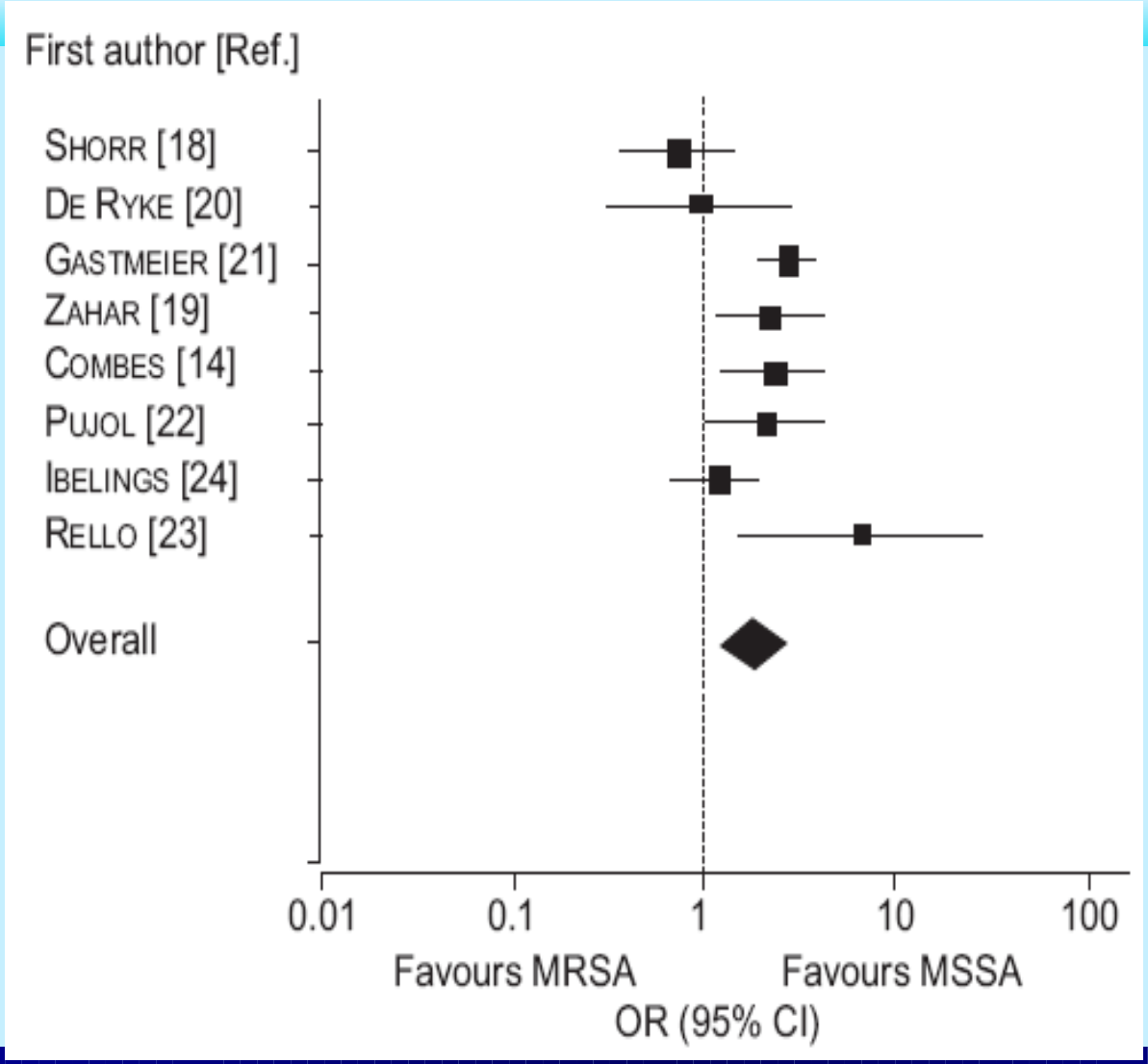
Mortality Impact of Inadequate Therapy

Ventilator Associated Pneumonia



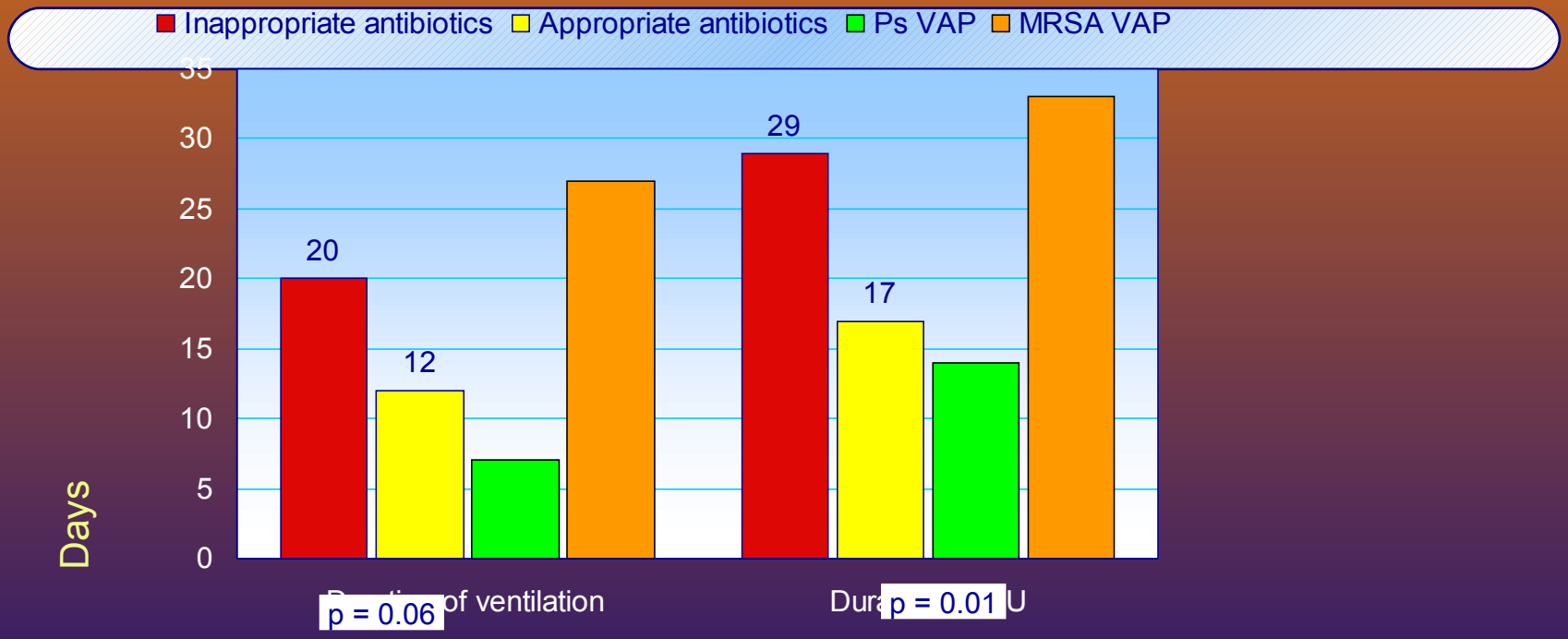
Luna C, et al. Chest 1997; 111: 676-685
Álvarez-Lerma F, et al. Intensive Care Med 1996; 22: 387-394
Rello J, et al AmJ Resp Crit Care Med 1997; 156; 196-200
Kollef MH, et al. Ann Inter Med 1995; 122: 743-748
Clec'h C, et al. Intensive Xare Med 2004; 30: 1327-1333
Garnacho-Montero J, et al. Intensive Care Med 2005; 31: 649--55

Methicilin Resistance Impact on Mortality in *S. aureus* VAP



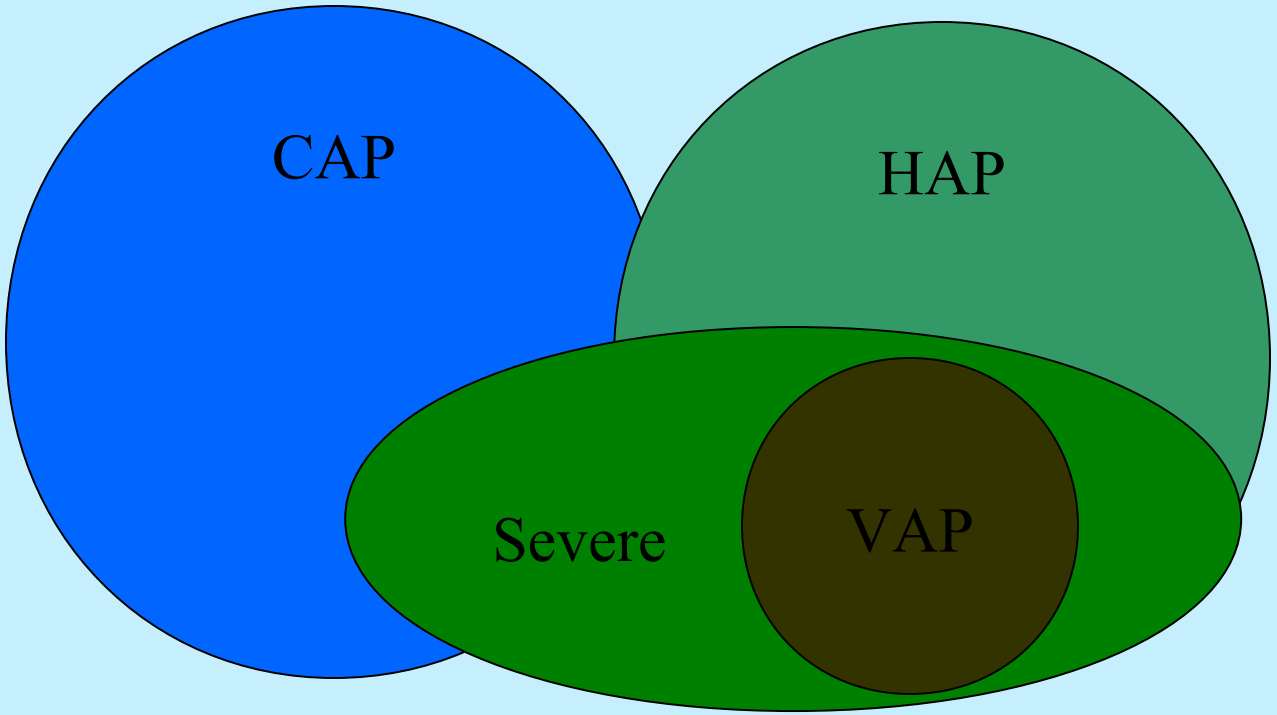
Athanassa et al. Eur Respir J 2008; 31:625-32

Morbidity in Ventilator-associated Pneumonia



Dupont H et al. Intensive care Med 2001;27;355-362.
Vidaur et al. CHEST 2008

Problems with definitions



Hospital-Acquired Pneumonia (HAP): Definitions

- HAP:
  - Arises 48 hours or more after hospital admission
  - Is not incubating at the time of admission
- Ventilator-associated pneumonia (VAP):
  - Arises 48-72 hours or more after endotracheal intubation
- Healthcare-associated pneumonia (HCAP):
  - Arises within 90 days of having been admitted to an acute care facility & pt. has resided in a nursing home or LTCF.

(American Thoracic Society/IDSA. Am J Respir Crit Care Med 2005;171:388-416)

FACTORS ASSOCIATED WITH RESISTANT PATHOGENS

- All resistance is local (patterns may be hospital/region specific)
- Hospital demographics
  - Size (Larger hospitals associated with higher rates)
  - Academic hospitals have higher rates than non-academic
- Care in an intensive care unit
- Duration of hospitalization
- Prior antimicrobial use

Risk Factors for MDR Microorganisms

1.- Prior antimicrobial therapy (90 d)

2.- Five or more days of hospital stay

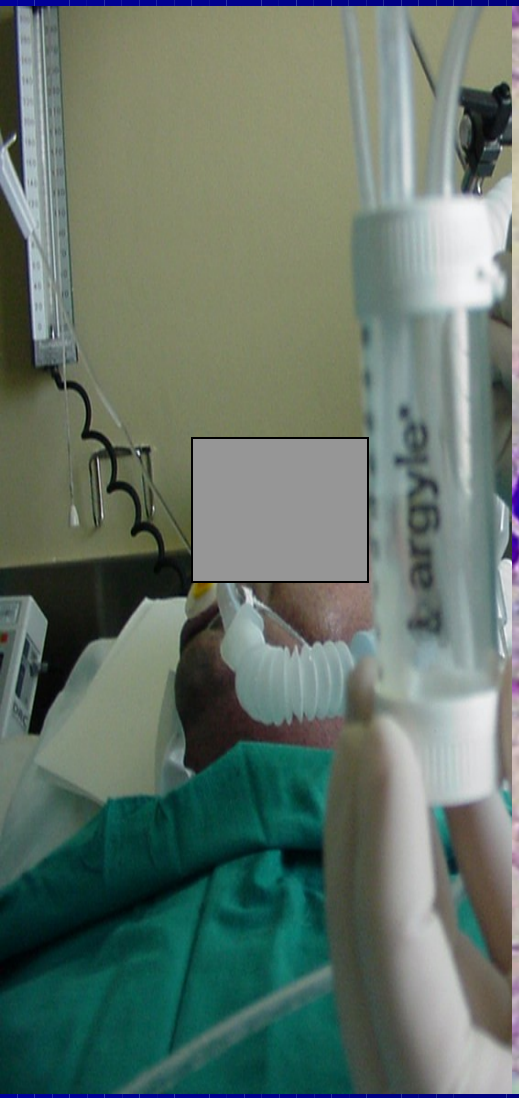
3.- MDR microorganisms in the Unit

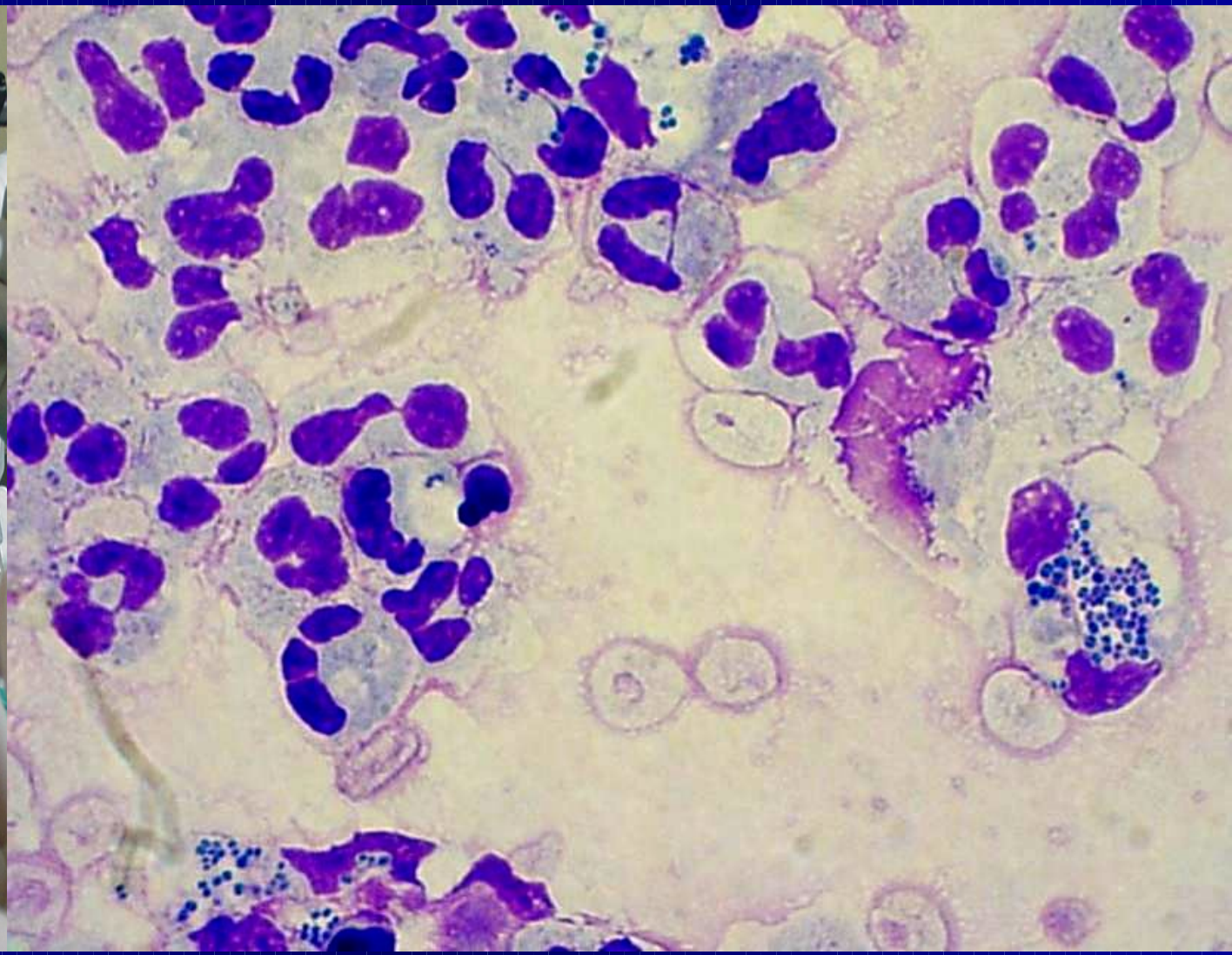
4.- Late onset

5.- Immuno-suppression

Bouza E. Inf Dis In Crit CareMed. 2008

Atieology





The Microbiology of HAP

Early-Onset Pneumonia (< 5 days)	**Late-Onset Pneumonia (> 5 days)**	**Others based on Specific Ricks**
S. pneumoniae	*P. aeruginosa*	Anaerobic bacteria
H. influenzae	*Enterobacter* sp	*Legionella pneumophila*
S. aureus	*Acinetobacter* sp	
Enterobacteriaceae	*K. pneumoniae*	
	S. marcescens	Influenza A and B
	E. coli	Respiratory syncitial virus
	Other GNB	
	S. aureus (MRSA)	Fungi

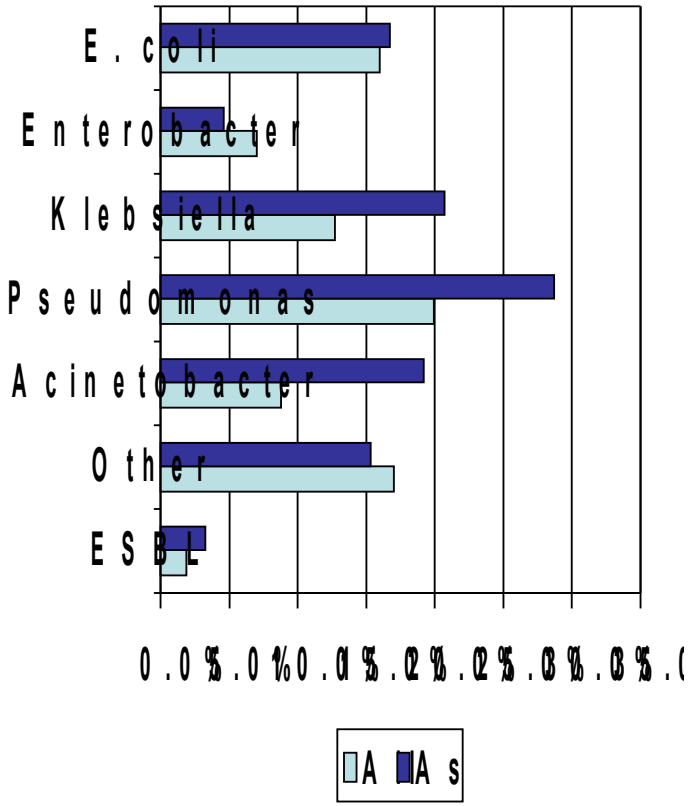
Adapted from Am J Respir Crit Care Med. 2005;171:388–416.

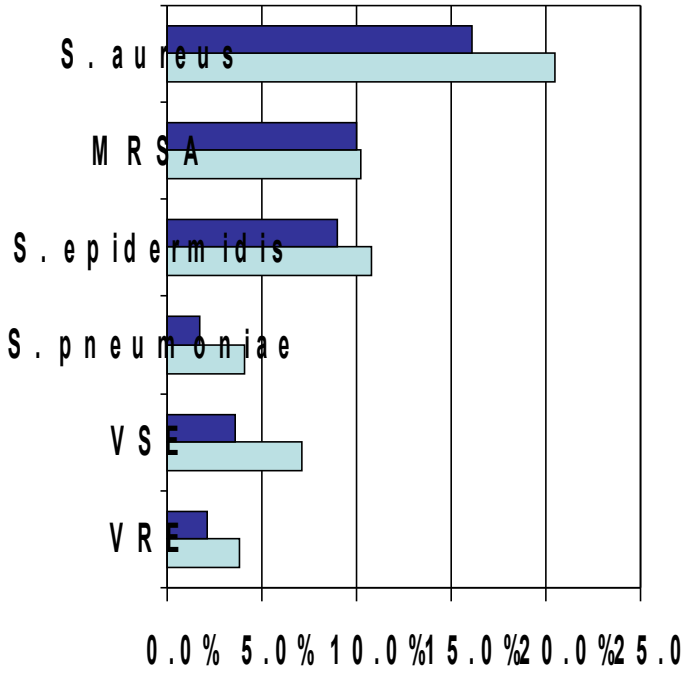
INTERNATIONAL STUDY OF PREVALENCE AND OUTCOMES OF INFECTION IN ICUs

- 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 mortality: Infected (25%) vs non-infected (11%)**
  - **Hospital mortality: Infected (33%) vs non-infected (15%)**

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

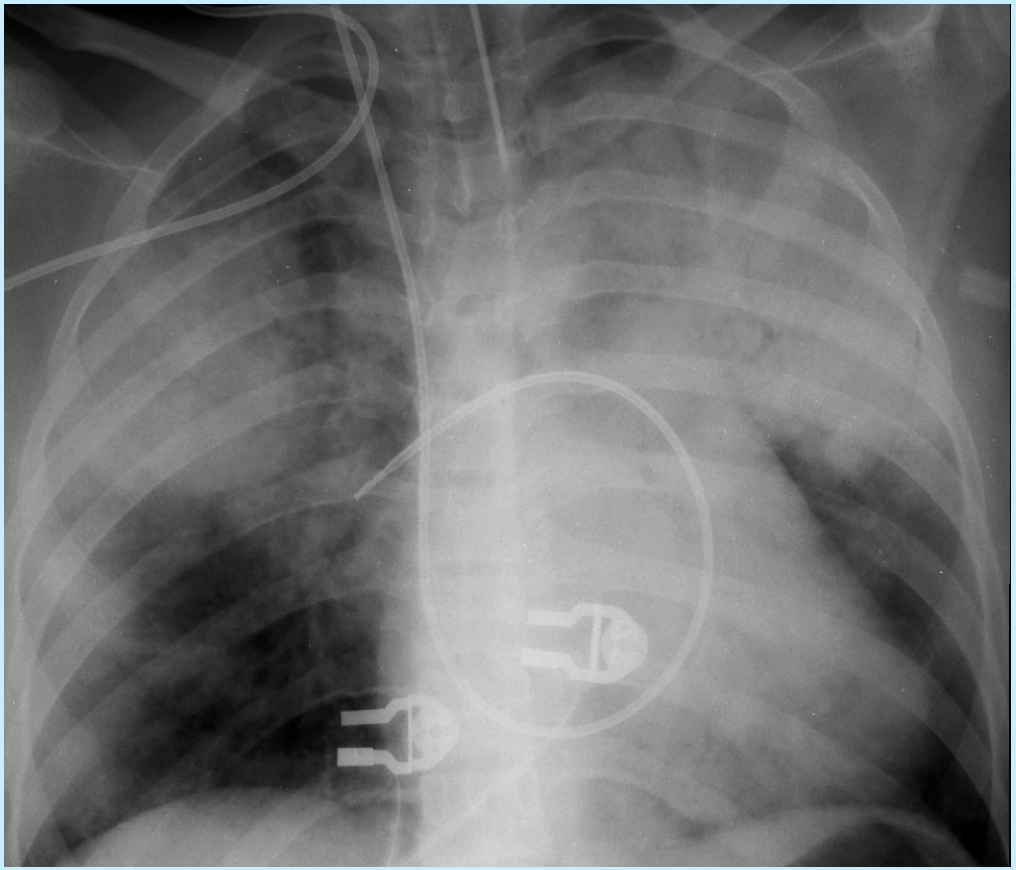
INTERNATIONAL STUDY OF PREVALENCE AND OUTCOMES OF INFECTION IN ICUs





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

Case Presentation



- 67 y old male
-Diabetes mellitus
- High blood pressure
- CABG x 2
- 7 post-op day
- Fever (39° C)
- Purulent secretions
- WBC 16,700/μL
- PAO2 / FIO2 < 240

CPIS score: 9

Author Opinion

Diagnosis

VAP: Clinical Judgment

Determinants of outcome in patients with a clinical suspicion of ventilator-associated pneumonia☆

John G. Muscedere MD[a,b], Chris McColl MD[a], Andrew Shorr MD, MPH[c], Xuran Jiang MSc[b], John Marshall MD[d], Daren K. Heyland MD, MSc[a,b,*,1] for the Canadian Critical Care Trials Group

Clinical judgment does not correlate with the processes of care and outcomes.....

Muscedere JG. J. Crit. Care. 2008

VAP: Diagnosis

Utility of Gram stain in the clinical management of suspected ventilator-associated pneumonia
Secondary analysis of a multicenter randomized trial

M. Albert MD[a], J.O. Friedrich MD, DPhil[b], N.K.J. Adhikari MDCM, MSc[b], A.G. Day MSc[d], C. Verdant MD[a], Daren K. Heyland MD, MSc[c,*], for the Canadian Critical Care Trials Group

Poor overall correlation of Gram stain with the cultures results.
High NPV for Gram positive microorganisms in culture.

Albert M. J. Crit. Care. 2008

VAP: Diagnosis and Treatment

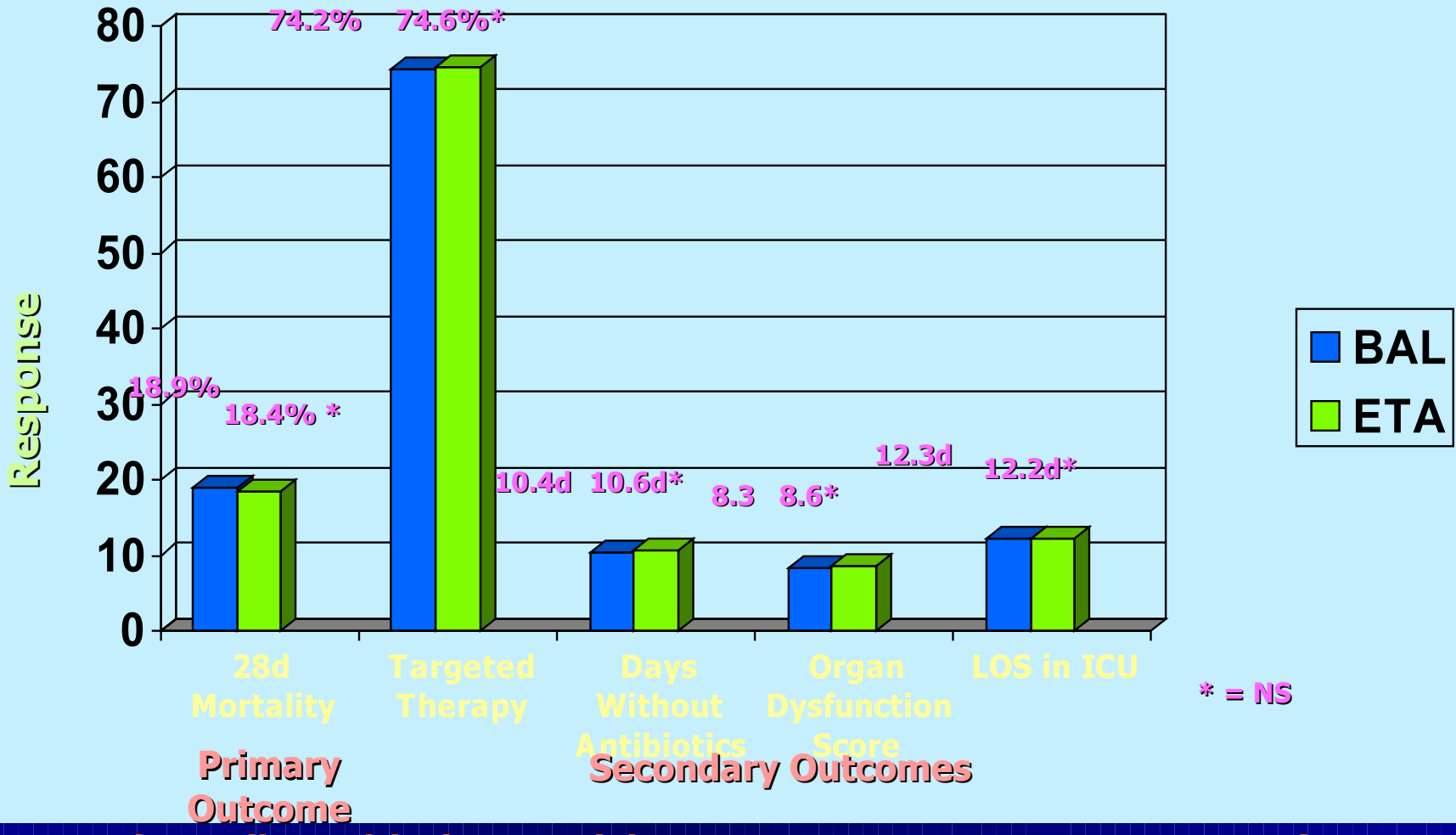
Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: Diagnosis and treatment

John Muscedere MD[a], Peter Dodek MD, MHSc[b], Sean Keenan MD, MSc[b], Rob Fowler MDCM, MS[c], Deborah Cook MD, MSc[d], Daren Heyland MD, MSc[a,*], for the VAP Guidelines Committee and the Canadian Critical Care Trials Group[1]

We recommend that if empiric antibiotic therapy is being initiated at the time VAP is suspected, endotracheal aspirates with non quantitative cultures be used as the initial diagnostic strategy

Muscedere J. J.Crit.Care. 2008

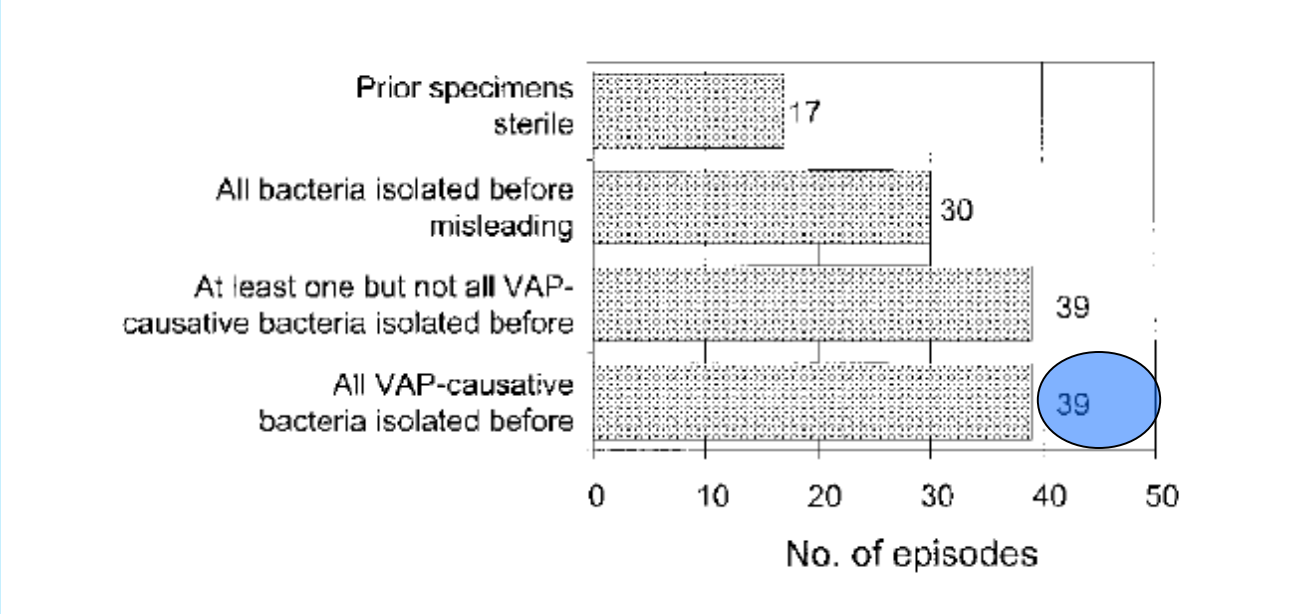
Diagnosis of VAP in the ICU: Quantitative BAL vs. Non-quantitative Endotracheal Aspirate (ETA)



(Canadian Critical Care Trials Group. NEJM 2006;355:2619-2630)

Prior microbiologic specimens and causative microorganisms

125 episodes of VAP: PSB or BAL



39 of 125 episodes = 31.2%

Am J Respir Crit Care Med. 2002;165:41-46

Direct E-test on Lower Respiratory Tract Samples: A way to improve antimicrobial use in VAP

- Prospective Study In VAP
  - Group A: E-test (135 patients)
  - Group B: Conventional Microbiology (65 patients)
- Baseline Characteristics were similar in both groups
- Days of fever, duration of antimicrobial therapy, adverse events caused by antibiotics, and costs were significantly lower in Group A
- Mortality did not differ between the two groups

Clin Infect Dis. 2007; 44:382-387.

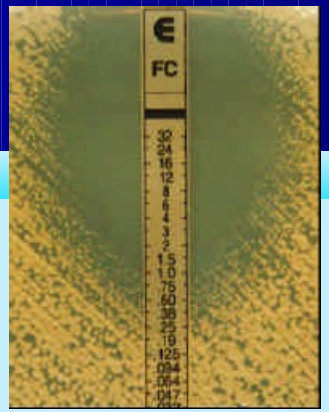


Figure a. MIC 1 mg/ml.

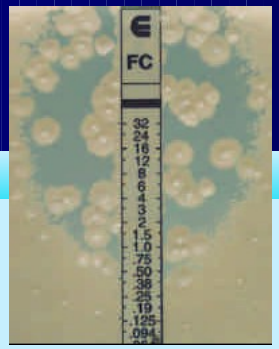


Figure b. MIC >32 mg/ml (macrocolonies in ellipse).

Figure c. MIC >32 mg/ml (homogeneously resistant).

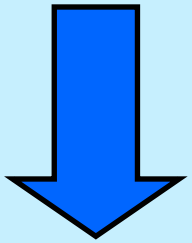
E-test.

- This commercially-prepared strip creates a gradient of antibiotic concentration when placed on an agar plate
- The MIC corresponds to the point where the bacterial growth crosses the numbered strip.
- MIC and PK/PD for targeting therapy of critical infections in critical care
- Results in < 24 hours

Empirical Therapy

New treatment paradigm

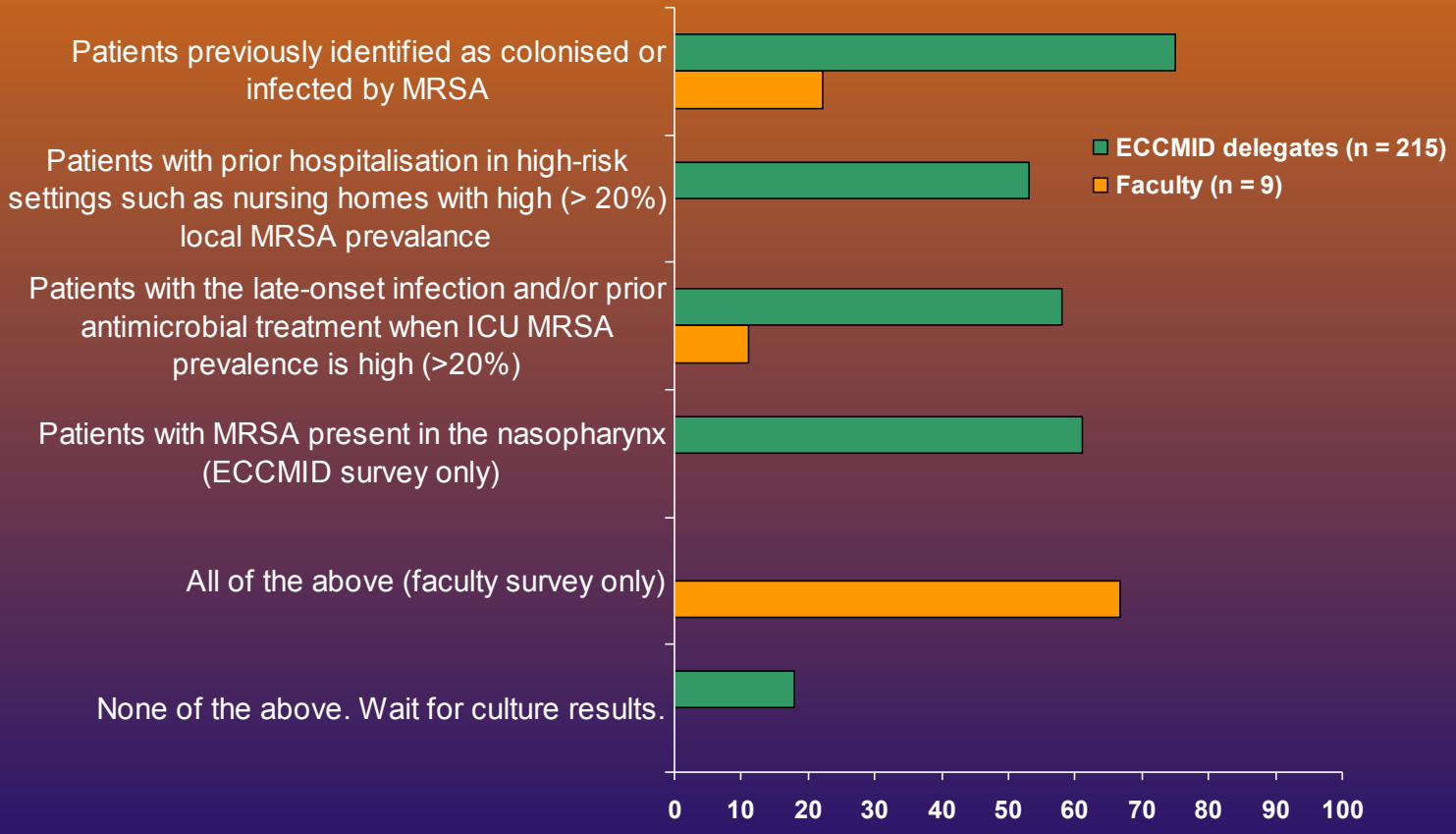
Hit hard and early with adequate antibiotic(s)



Reassess antimicrobial therapy

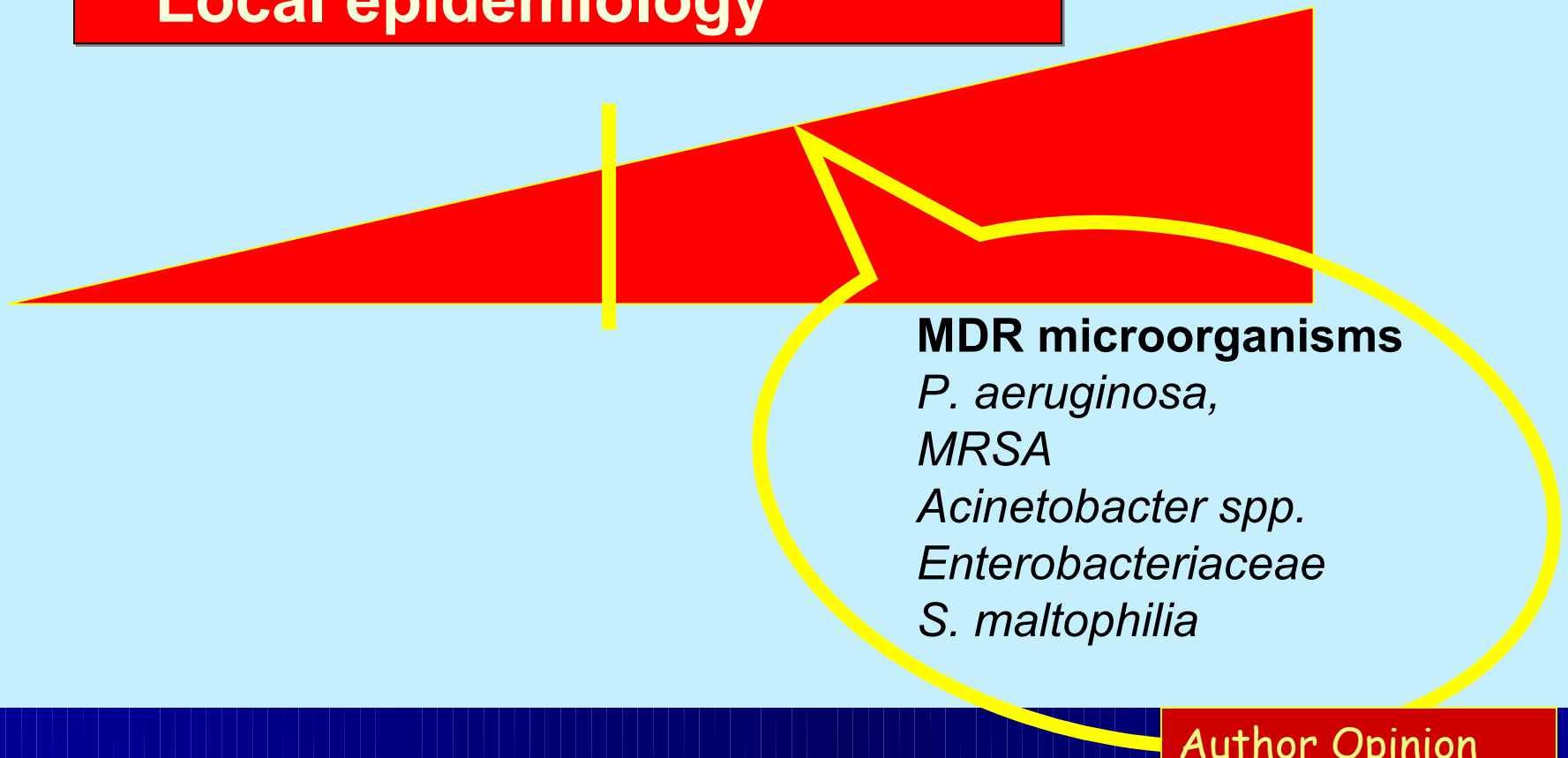
Which categories of patients with a clinical suspicion of HCAP/HAP/VAP should be treated with an antimicrobial agent active against MRSA?

Dryden M et al CMI 2010; 16[Suppl.1], 3-30



Empiric Therapy: Late, High Risk, HAP

More than 5 days
prior antibiotics
Local epidemiology



Empiric Therapy: Late, High Risk, HAP/VAP

One of each group	Drug	Normal dose
1	Pip-Tazo Mero/ Imi /Doripenem	4,5g /IV/6h 1g/IV/ 8h
2 +	Ciprofloxacin Levofloxacin Amikacin or gentamicin	400mg/IV/8h 500mg/IV/12h
3 +	Linezolid Vancomycin	600 mg/IV/12h 2g/IV cont/24h

Author Opinion

Treatment Guidelines

HAP/VAP/HCAP Guidelines (ATS and IDSA, USA, 2005)

Potential Pathogens	Antibiotic Therapy
Late HAP and MDR Pathogens	
Pseudomonas aeruginosa	Anti-pseudomonal cephalosporin **or** carbapenem **or** BLBLI *+* quinolone or aminoglycoside
Klebsiella pneumoniae	
Acinetobacter sp	
	plus
MRSA	**Linezolid or vancomycin**

BLBLI, β-lactam/β-lactamase inhibitor.

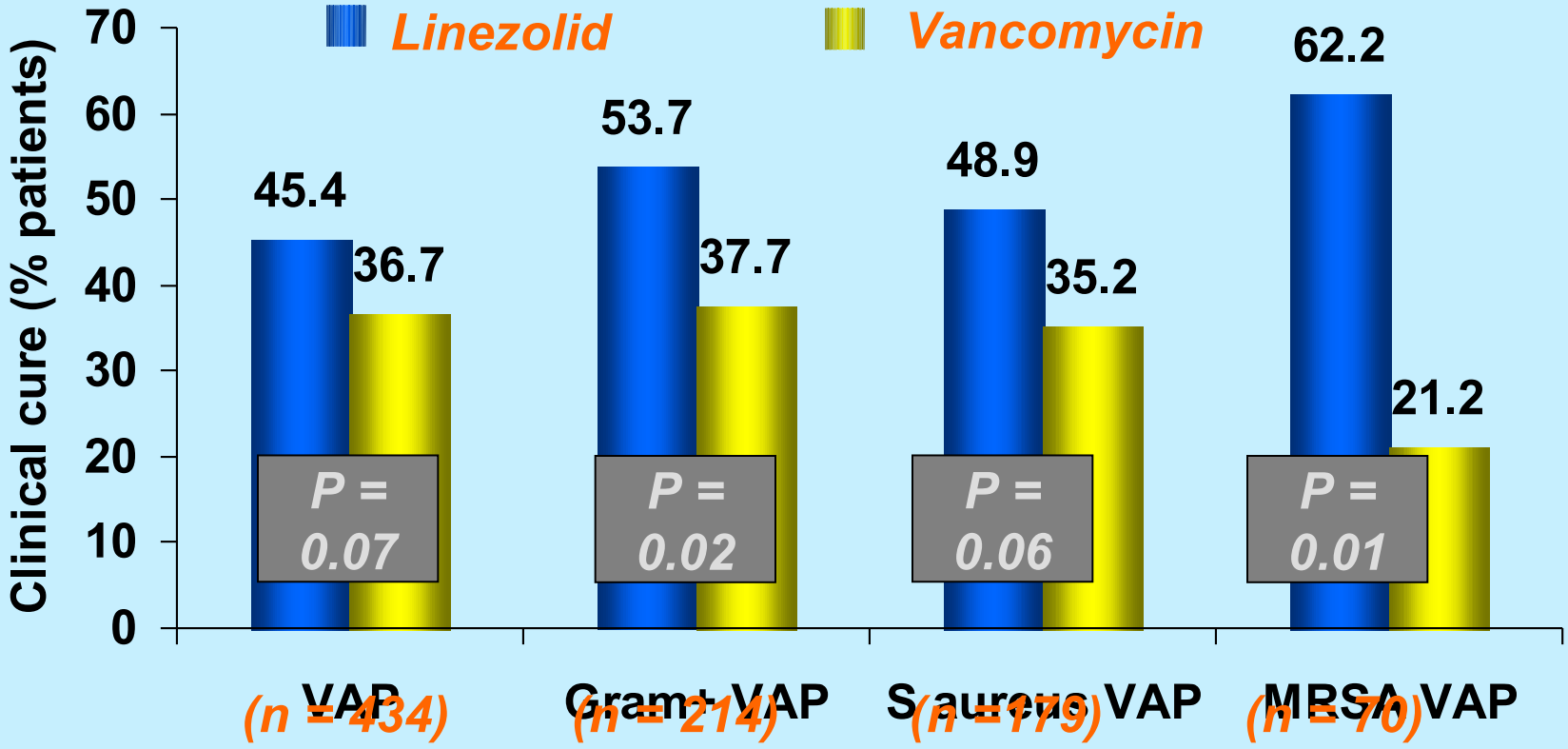
Pneumonia and Other RTI

Society	Location	Vancomycin MIC		Comments
		<1.5 µg/ml	≥1.5 µg/ml	
SEQ 2008	Pneumonia	Linezolid or vancomycin	Linezolid	Necrotizing pneumonia (PVL+) add IgG 2 g/kg/day
UK 2006-2009	Pneumonia	Glycopeptides or linezolid (A-I)		
UK 2008	CA-MRSA pneumonia	Unresolved issue Linezolid preferred with clindamycin high dose		Category C

Mensa J *et al. Rev Esp Quimioter* 2008;21:234-258
Gemmell CG *et al. J Antimicrob Chemother* 2006;57:589-608
Gould FK *et al. J Antimicrob Chemother* 2009;63:849-861

Clinical Cure Rate in VAP Patients: Linezolid Versus Vancomycin

Retrospective analysis of 2 randomized, double-blind studies



VAP, ventilator-associated pneumonia.

Adapted from Kollef MH, Rello J, et al. Intensive Care Med. 2004;30:388-394.

Early microbiological response to linezolid versus vancomycin in VAP due to MRSA
Wunderink R et al Chest on line August 21, 2008

- Prospective, open labelled, multi-center trial compared the early microbiological efficacy of linezolid with that of vancomycin in patients with BAL proven MRSA VAP
- Primary outcome was microbiological response based on second BAL performed 72-96h post treatment
- Secondary outcome was healthcare resource utilisation
- Low patient numbers- target enrollement of 300 patients not achieved due to requirement of 2 BAL's

Linezolid bacteriological response and resource use in MRSA VAP

	Linezolid	Vancomycin	P value	95%CI
mITT	20	20		
Patients analysed	23	19		
Cured %	**13(56.5%)**	**9 (47.4%)**	**0.757**	**-21.1,39.4**
Failed%	10(43.5%	10(52.6%)		
Mean ICU stay	12.2	16.2	ns	**-4d**
Ventilation (mean,days)	**10.4**	**14.3**	ns	**-3.9d**
Hospitalisation (mean,days)	18.8	20.1	ns	**-1.3d**

Trends towards better outcomes; other factors other then bacterial clearance may impact on possibly better outcomes

Animal models of lung MRSA pneumonia Martinez-Olondris et al ERJ 2010

Small animals [mice,rats]

- Routes of infection
- Role of virulence and strains
- Effectiveness of antibiotics
- Vaccines

- **Do not replicate human physiology**

Large animals [ovine or porcine]

- Injury risk factors [smoke]
- Time course of biological markers and pathology
- Potential for comparative antibiotic trials, effect of co-morbid lung and different strains

Pneumonia and Other RTI

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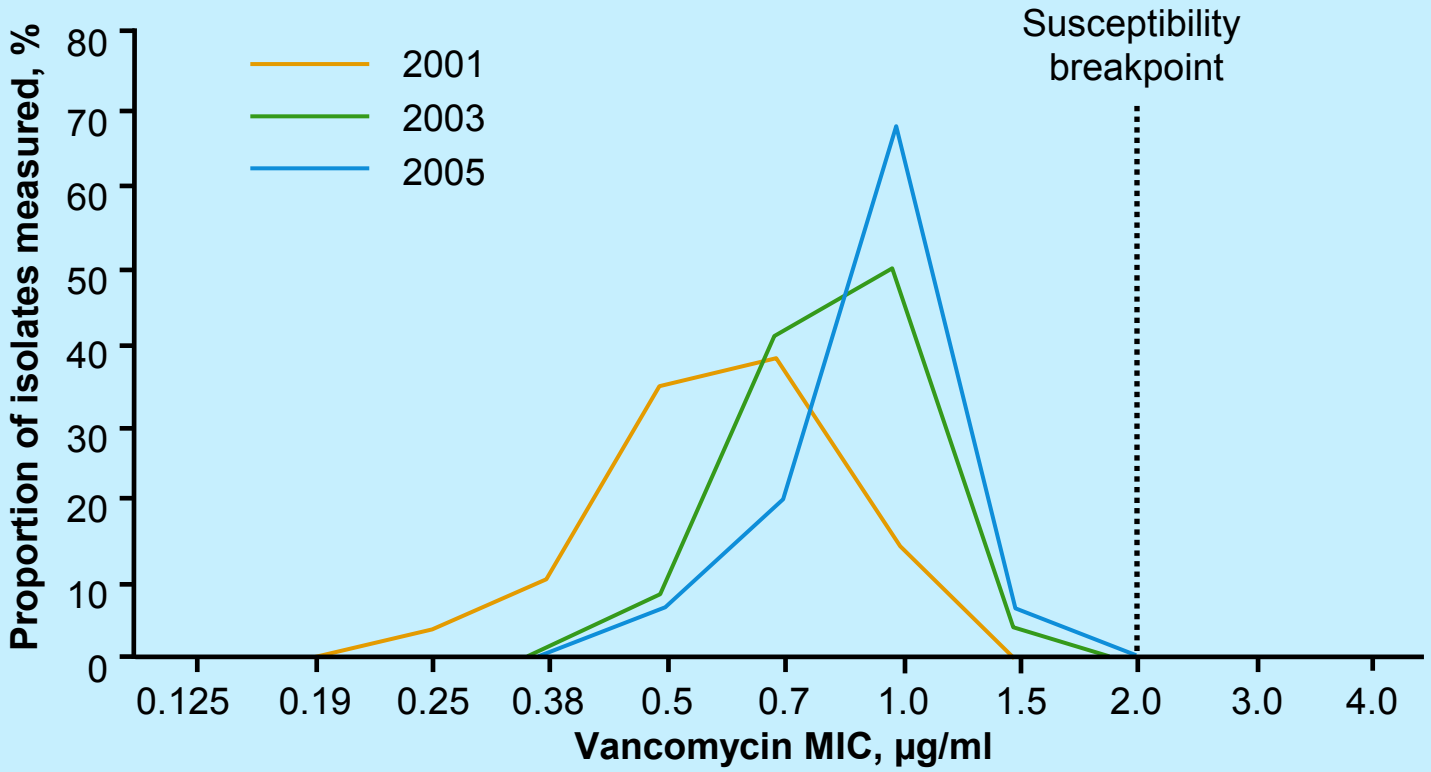
Vancomycin MIC creep detected in single-centre studies

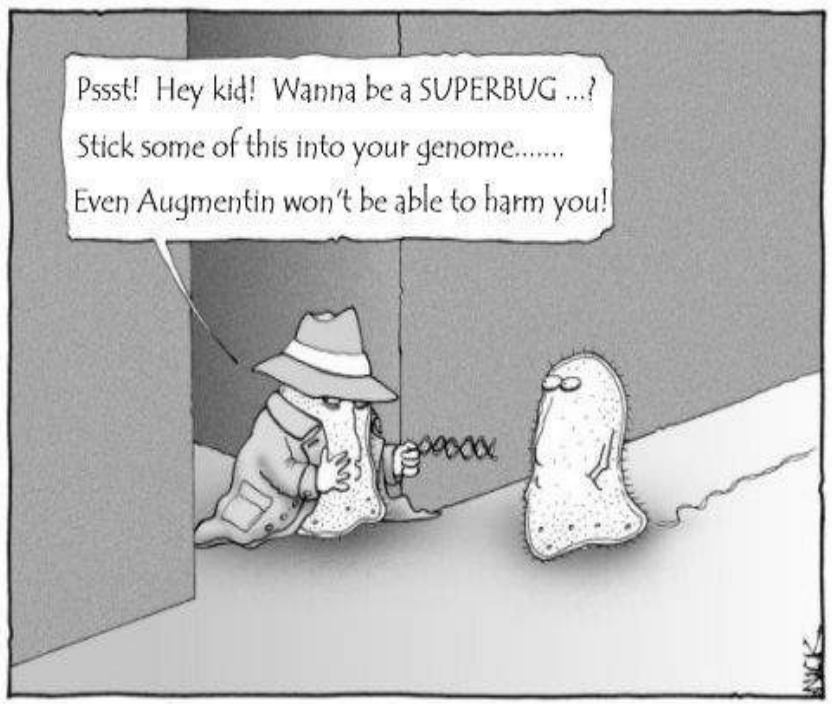
MRSA isolates (n=662) measured in a single US tertiary care institution



MICs measured by Etest

Steinkraus G *et al. J Antimicrobial Chemother* 2007;60:788–794

Reduced Glycopeptide Susceptibility (VISA/GISA) Is Not About Acquiring Mobile Elements of Resistance



Cell wall thickening

Increased muropeptides
Reduced peptidoglycan cross-link
Increased D-ala-D-ala residues

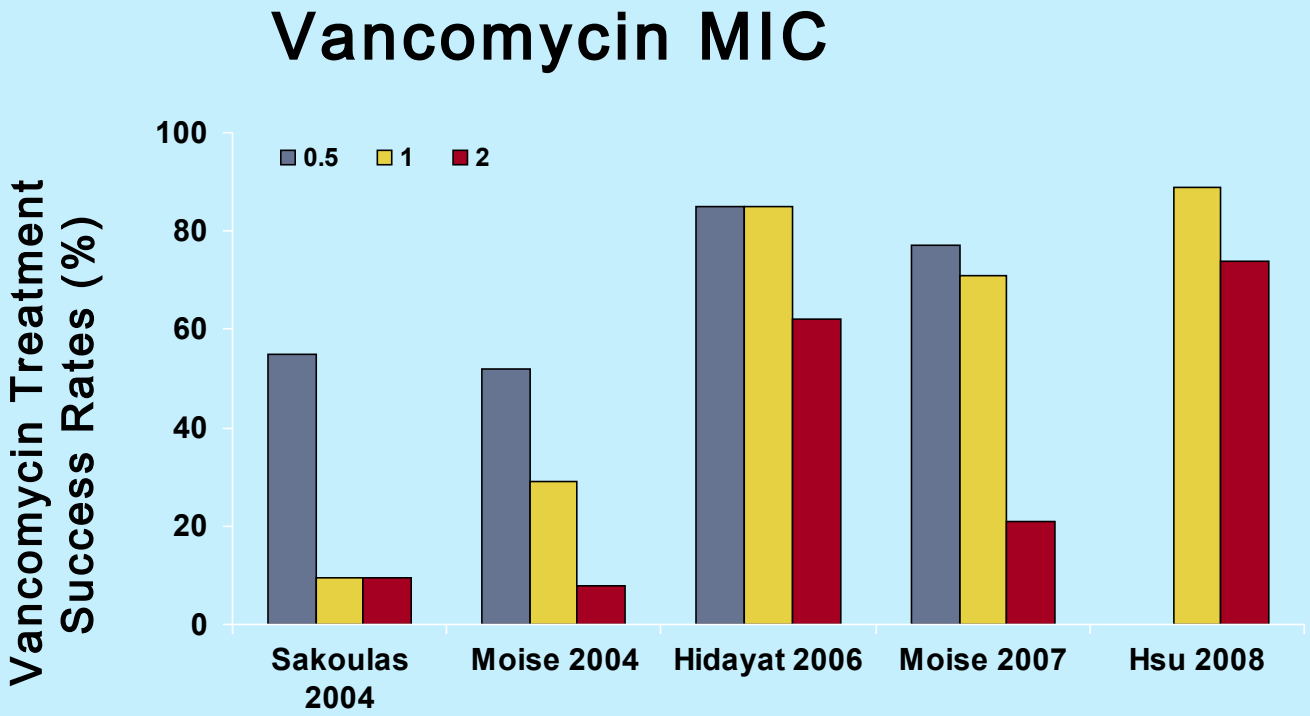
Reduced growth rate
Reduced autolysis

It's about **GLOBAL METABOLIC CHANGES**, that confer other phenotypes as collateral damage

MIC "CREEP" : Key Points

- Recent years have shown increases in vancomycin MICs among *S. aureus* in many medical centers, although resistance remains rare
- Reduced Glycopeptide Susceptibility Conveys more than a microbiologic phenotype
  - Antibiotic Resistance
  - Bacterial Virulence
- What alternative drugs offer to clinicians
- Can increases in vancomycin MIC be overcome pharmacologically?
  - Higher doses?
  - Alternative drugs?
  - Combination therapy?

Lower Vancomycin-Treatment Response with Vancomycin for MRSA with MIC 2



Adapted from Sakoulas, et. al., JCM, June 2004; Moise-Broder, PA et al. Clin Infect Dis 2004; 38: 1700-5.; Hidayat L, Arch Intern Med. 2006;166:2138-2144; Moise PA et al. Antimicrob Agents Chemother 2007; 51:2582-6;
Hsu et al. Int J Antimicrob Agents; 2008 32 378-85

Vancomycin MIC & Risk of Mortality in MRSA Bacteraemia (n=414)

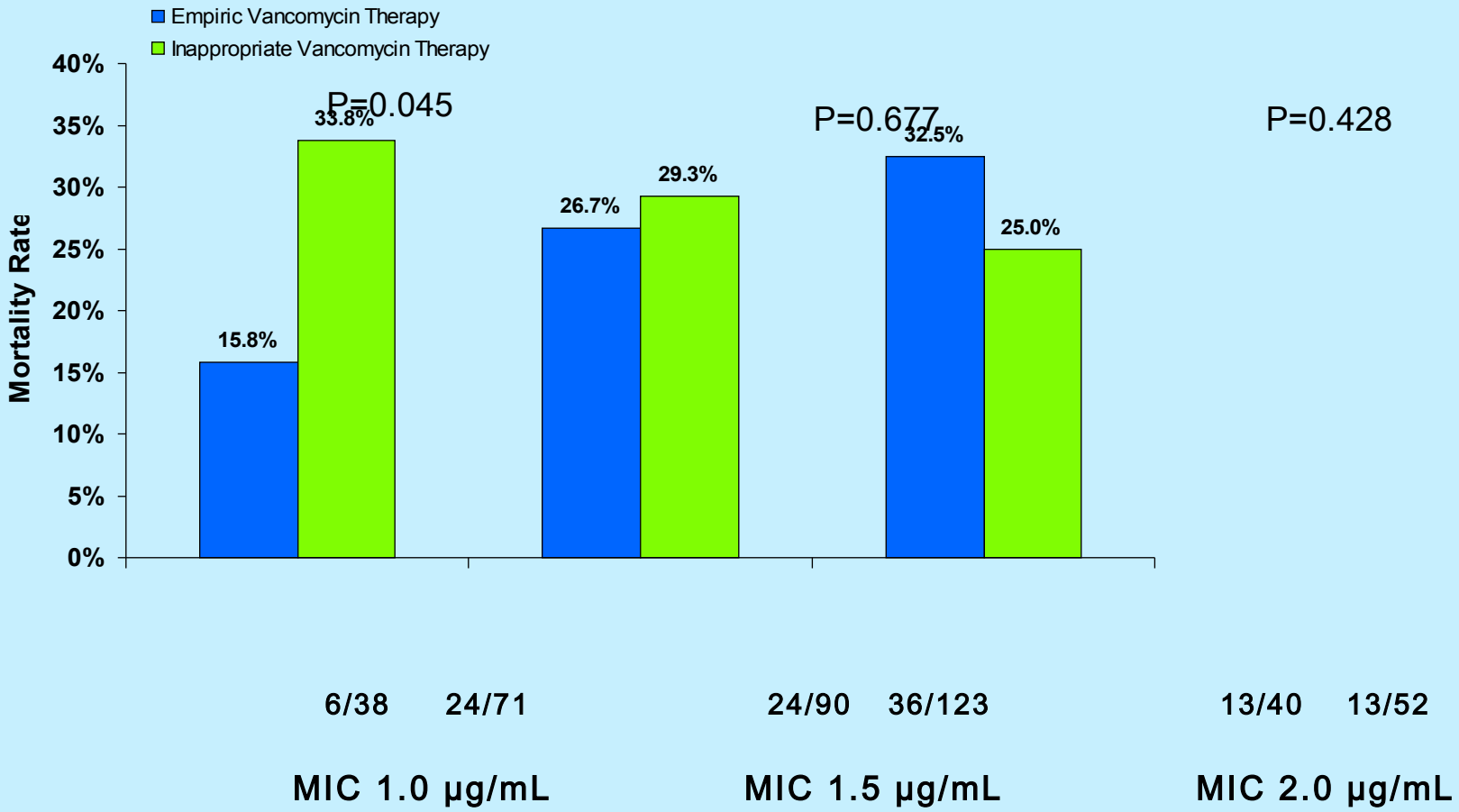
Treatment group	ROM (OR; 95% CI)	P value
Van MIC = 1	1	
Van MIC = 1.5	2.86 (0.87, 9.35)	0.08
Van MIC = 2	6.39 (1.68, 24.3)	< 0.001
Inappropriate treatment	3.62 (1.20,10.9)	<0.001

Soriano et al. Clin Infect Dis 2008;46:193-20

Why Would Mortality be Higher in Bacteremia Caused by MRSA with Vancomycin MIC > 1 mg/L?

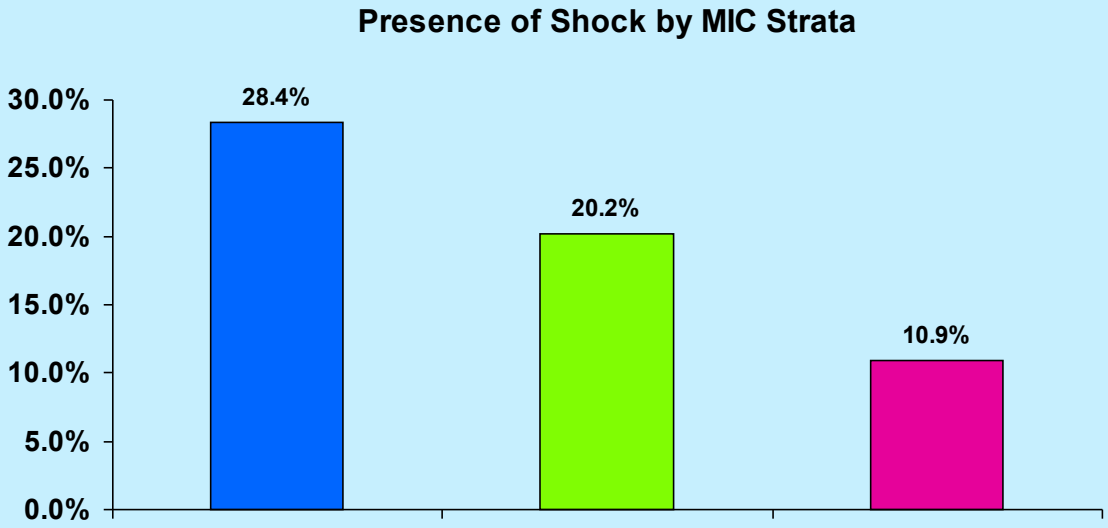
- Fundamental to What the Solution Is?
- Inappropriate treatment
- Hosts are sicker
- Pathogen is more virulent
  - We must be specific to site of infection
  - E.g. Virulent in blood = Virulent in Skin
- Drug is less effective
  - Can this be overcome with alternative drugs?
  - Higher dose of vancomycin?

Mortality rates among patients with methicillin-resistant *Staphylococcus aureus* bacteremia, stratified by empiric therapy (vancomycin versus inappropriate) and by the vancomycin MIC



Soriano et al. CID 46:193, 2008

Inverse Relationship of Shock and Vancomycin MIC (P=0.008)



Soriano et al. Clin Infect Dis 46:193, 2008

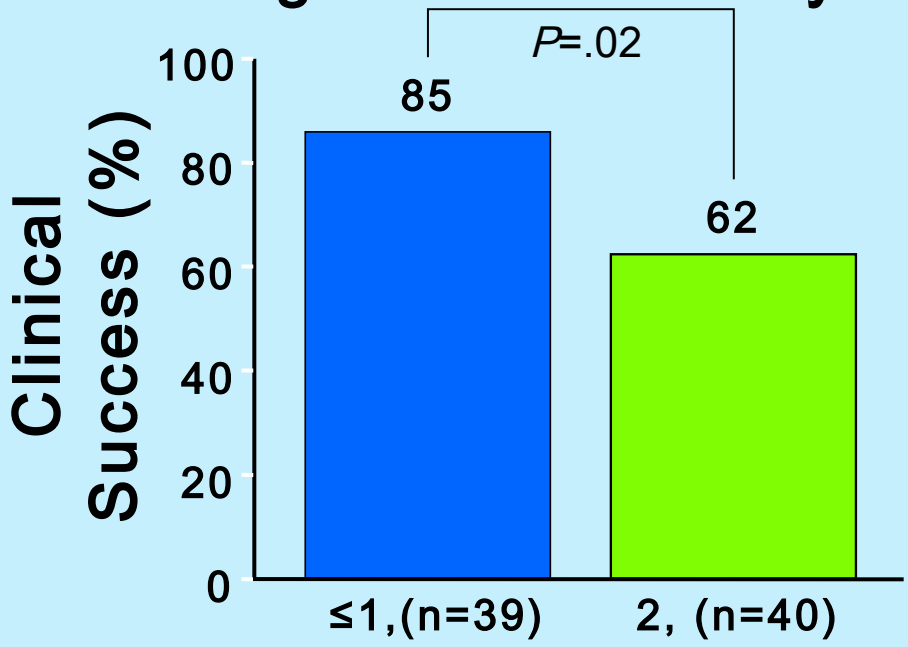
Vancomycin Consensus Summary

- PK/PD target is AUC/MIC
  - Target AUC/MIC ≥ 400
    - **Pneumonia**
    - Meningitis
    - Endocarditis
    - Osteomyelitis
- **Trough of 15-20 mg/L**
  - **~AUC/MIC of >400**
    - **Concentrations <10 mg/L encourages resistance**
- Dose on ABW
- LD of 25-30 mg/kg may be needed
  - Consider for serious infections

Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm.* 2009;66:82-98

Increasing the Dose of Vancomycin To Reach Higher Trough Levels May Not Improve Clinical Outcomes

Prospective Cohort Single-Center Study



Is Nephrotoxicity Limiting the Ability to Optimize Vancomycin AUC/MIC?

Trough <15 µg/mL	Trough 15-20 µg/mL
0%	12%

Trough <15 µg/mL	Trough >15 µg/mL
0%	15%

Trough <15 µg/mL	Trough ≥15 µg/mL
30.2%	58.8%

Target vancomycin trough levels, 15 to 20 µg/mL

Hidayat et al. Arch Int Med 116:2138, 2006; Lee-Such et al. ICAAC. Abstract L-1298, 2006; Jeffries et al. ICAAC. Abstract K789, 2006.

Reduced Glycopeptide Susceptibility May Be Accompanied By Properties of Host Evasion

What role does this play in inferior outcomes with vancomycin MIC≥2 mg/L?

Cationic Antimicrobial Peptides (CAMPs)

- CAMPs are increasingly recognized as key mechanisms in host innate immunity
- Resistance to CAMPs confer virulence phenotypes
  - Prolonged bacteremia
  - Endovascular focus
  - Metastatic infection
- Mechanisms of CAMP resistance
  - Increasing + surface charge
  - Efflux
  - Proteases/Trapping Proteins
- CAMP site of action: bacterial membrane

Treatment of MRSA VAP

1.ALGORITHM

2. PERSISTENCE

3. DURATION

THERAPEUTIC MANAGEMENT of VAP- When *S. aureus* is a consideration (J Infect 2009;59: S25-31) +AUTHOR

2 Main Risk Factors for MRSA (≥ 5 day in hospital + Prior Antibiotics) ? or Documented MRSA Colonization

YES

EMPIRIC THERAPY for MRSA

Renal impairment or Nephrotoxics use
Severe Sepsis or Age > 65 years

NO

VANCO / TEICO

? CONTINOUS INFUSION

YES

LINEZOLID

CULTURES

MSSA

OXACILLIN (if not betalactam allergy)

MRSA

Use LINEZOLID

Culture negative: Stop RX

CLINICAL RESPONSE

NO

If VANCO -> switch to LINEZOLID

If LINEZOLID -> add RIFAMPIN/AMG/? Or carbapenem?

OK

Continue

VANCOMYCIN COMBINATION FOR MRSA Deresinski S CID 2009; 49:1072-9

- **Mainly bacteraemia/endocarditis**

- V+R Good theoretical basis,lab.synergy contradictory, no clinical trials
- V+G No clinical, increased toxicity
- V+G+R Unconvincing, increased risk of adverse events
- V+BL Lack of clinical trials, strong theoretical basis, ? Use in early empiric therapy
- V+others (linezolid, synercid) Lack of data

MRSA PERSISTENT BACTERAEMIA SALVAGE TREATMENT CID 2009;49:395-401

TREATMENT	MIC.SUCCESS	CLINICAL SALVAGE	30D MORTALITY
VANCOMYCIN	0%	0%	53%
VANCOMYCIN AND AMINOGLY. OR RIFAMPICIN	17%	0%	80%
LINEZOLID	71%	100%	29%
LINEZOLID AND CARBAPENEM	78%	78%	22%

N=35 (28 SALVAGE ATTEMPTS
LINEZOLID SALVAGE THERAPY ERADICATED MRSA
WITH PERSISTENT BACTERAEMIA

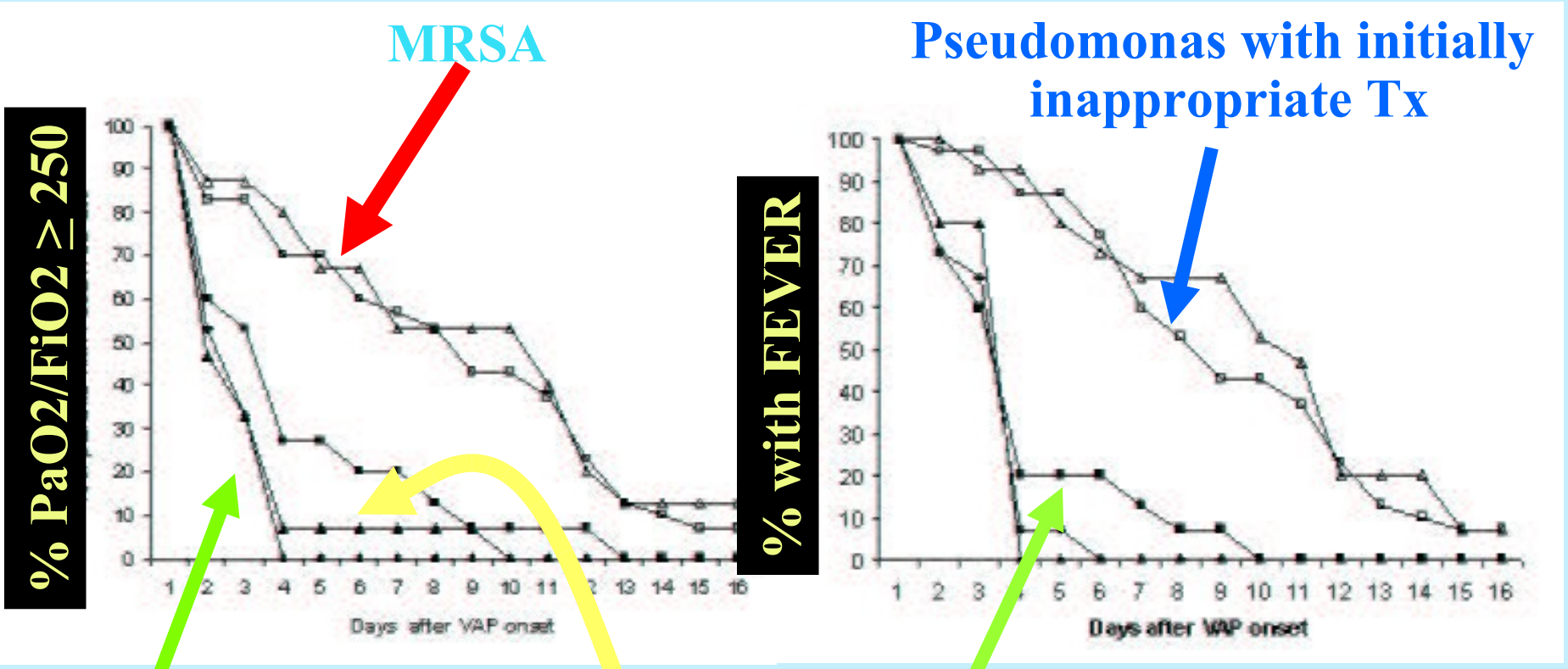
Length of Treatment

8 days better than 15, with some exceptions

MDR MRSA, *P. aeruginosa* and other GNR
Poor choice of empirical therapy
Severely immunocompromised

Chastre J. JAMA. 2003

Effect of Microorganism and Initially Appropriate Antibiotics on VAP Resolution

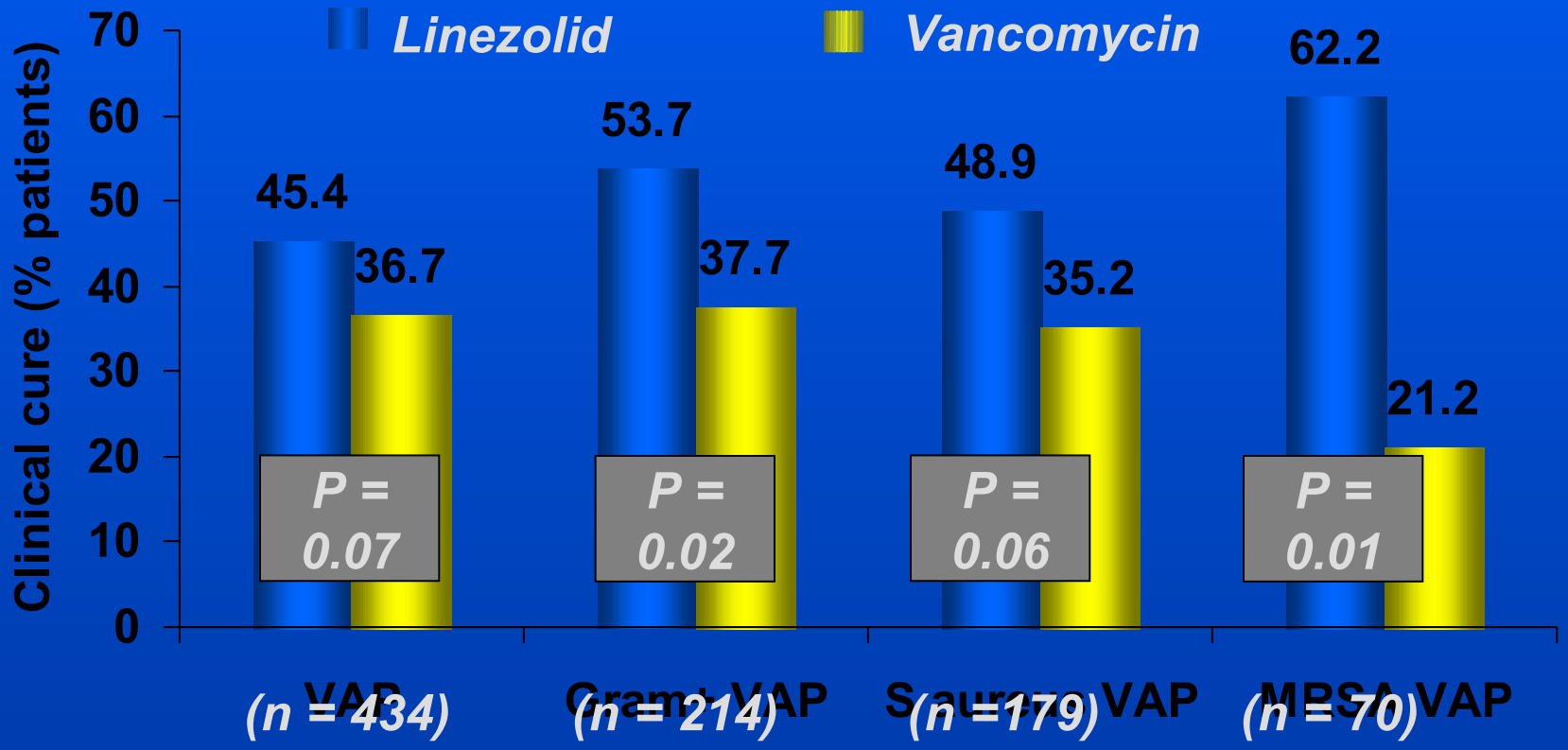


Vidaur, Chest 2008

Role of New Drugs for VAP

Clinical Cure Rate in VAP Patients: Linezolid Versus Vancomycin

Retrospective analysis of 2 randomized, double-blind studies



VAP, ventilator-associated pneumonia.

Adapted from Kollef MH, Rello J, et al. Intensive Care Med. 2004;30:388-394.

New Drugs for VAP

- **Doripenem:** Non-inferior to Pip-Tazo in nosocomial pneumonia, including non-ventilated patients and early VAP pneumonia.
  Non-inferior to imipenem in early and late VAP

- **Telavancin:** Vancomycin vs telavancin in Gram-positive HAP and VAP, 1532 patients randomized. Telavancin non-inferior to vancomycin

- **Tigecycline:** In vitro activity versus MRSA (> vancomycin, > linezolid). Bacteriostatic, well distributed in tissues. Approved for complicated intra-abdominal infections and SSSIs. Published trials in CAP only; non-inferior to levofloxacin. Failed non-inferiority trials in VAP

- **Ceftobiprole:** Phase III studies in HAP due to MRSA. Broad-spectrum activity against Gram-positive and Gram-negative including MRSA and *P. aeruginosa.* Non-inferior to vancomycin in SSSI. Inactive against ESBL-producing *Enterobacteriaceae, and Acinetobacter baumanii*

- **Daptomycin: NOT INDICATED FOR PNEUMONIA**
  In CAP RCTs, daptomycin cure rates inferior to Ceftriaxone.
  Antibacterial activity inhibited by pulmonary surfactant

Rubinstein E. ICAAC and ECCMID 2008; Rea Neto A. CMRO 2008; Chastre J. Crit Care Med 2008; Pertel PE, et al CID 2008; Man JA. J Inf Dis. 2005

New Antibiotic Drugs vs Vancomycin /SSP

Antibiotic	n	Clinical Cure RR (95% CI; p)
Ceftobiprole	1026	1.00 (0.96,1.06; p=0.86)
Dalbavancin	102	1.26 (0.98,1.61; p=0.07)
Daptomycin	1237	1.00 (0.93,1.08; p=1.00)
Linezolid	2074	1.03 (0.99,1.08; p=0.14)
Q/D	781	0.99 (0.94,1.05; p=0.84)
Telavancin	1057	0.98 (0.92,1.03; p=0.4)

Kalil AC et al (unpublished 2009)

KEY MESSAGES

SUMMARY

- MRSA HAP AND VAP HIGH BURDEN MORBIDITY AND MORTALITY
- EARLY APPROPRIATE THERAPY ESSENTIAL
- RISK FACTORS FOR RESISTANCE AND TOXICITY SHOULD GUIDE THERAPY
- MIC CREEP IS AN EVOLVING PROBLEM
- MIC MEASUREMENT IMPORTANT
- COMBINATION THERAPY ? VALUE
- NOVEL COMBINATIONS WORTH EXPLORING
- NEW DRUGS NON-INFERIOR