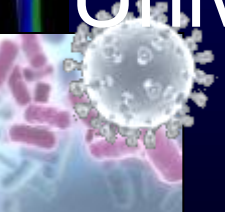
Antibiotics: How broad do you go?

Professor Jeffrey Lipman

Department of
Intensive Care Medicine
Royal Brisbane Hospital
University of Queensland

THE UNIVERSITY OF QUEENSLAND



THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

RBWH FOUNDATION

Burns Trauma & Critical Care Research Centre

MAJOR SPONSOR

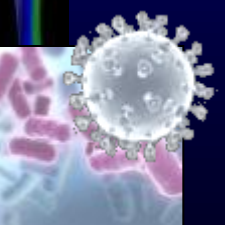
WORMALD
Protecting People & Property

SUPPORTING SPONSORS

smith&nephew

Edwards

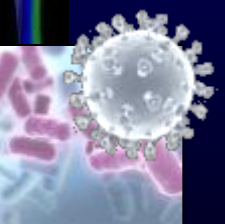
AstraZeneca



EXTRA DECLARATION

Trip out to SA sponsored by

ADCOCK INGRAM

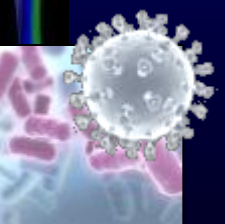


HOW BROAD?

SINGLE AGENT or DBL COVER?

1 CAP: DBL COVER BETTER

2 GM NEG INFECTIONS



Double gram negative cover

Double gram negative cover for infections largely comes from 2 studies, one in neutropaenic patients (cancer), the other in Pseudomonas infections and from *in vitro* synergy

The EORTC International Antimicrobial Therapy Cooperative Group Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. N Engl J Med 1987;317:1692-1698.

Hilf et al Am J Med 1989:87:5490-6.

This doesn't stand up to systematic analysis

Dbl Gm -ve

LEVEL 1 EVIDENCE

Three meta-analyses have recently compared β-lactam monotherapy versus β-lactam-aminoglycoside combination. **All have shown no benefit of combination therapy**.

In fact side effects were more with combination therapy (aminoglycoside divided doses, though)

Paul M, Soares-Weiser K, Leibovici L. β-lactam monotherapy versus β-lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. Br Med J 2003; 326:1111-5.

Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. β-lactam monotherapy versus β-lactam-aminoglycoside combination therapy in immunocompetent patients: systematic review and meta-analysis of randomised trials. Br Med J 2004; 328: 668-81.

Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis 2004; 4:519-27.

Dbl Gm -ve

LEVEL 1 EVIDENCE

MAJOR ARTICLE

Effect of Aminoglycoside and β-Lactam Combination Therapy versus β-Lactam Monotherapy on the Emergence of Antimicrobial Resistance: A Meta-analysis of Randomized, Controlled Trials

Ioannis A. Bliziotis,[1] George Samonis,[3] Konstantinos Z. Vardakas,[1] Stavroula Chrysanthopoulou,[1] and Matthew E. Falagas[1,2,4]

Clinical Infectious Diseases 2005;41:149-158

Conclusions. **Compared with ß-lactam monotherapy, the aminoglycoside/ß-lactam combination was not associated with a beneficial effect on the development of antimicrobial resistance among initially antimicrobial-susceptible isolates.**

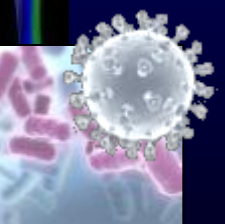
EVEN RESISTANCE

HOW BROAD?

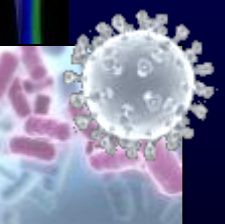
SINGLE AGENT or DBL COVER?

1 CAP: DBL COVER BETTER

2 GM NEG INFECTIONS
a) Meta-analyses



BUT



Getting therapy right first time

There is now significant evidence that correct antibiotic choices will save more lives than virtually all other ICU therapy

Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003; 31:2742-2751.

Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999; 115:462-474.

Rello J, Gallego M, Mariscal D, Sonora R, Valles J. The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 1997; 156:196-200.

Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 2002;122:262-268.

Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, Jolly EC. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest 1997; 111:676-685.

Leibovici L, Drucker M, Konigsberger H et al. Septic shock in bacteremic patients: risk factors, features and prognosis. Scand J Infect Dis 1997; 29:71-75.

Valles J, Rello J, Ochagavia A, Garnacho J, Alcala MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest 2003; 123:1615-1624.

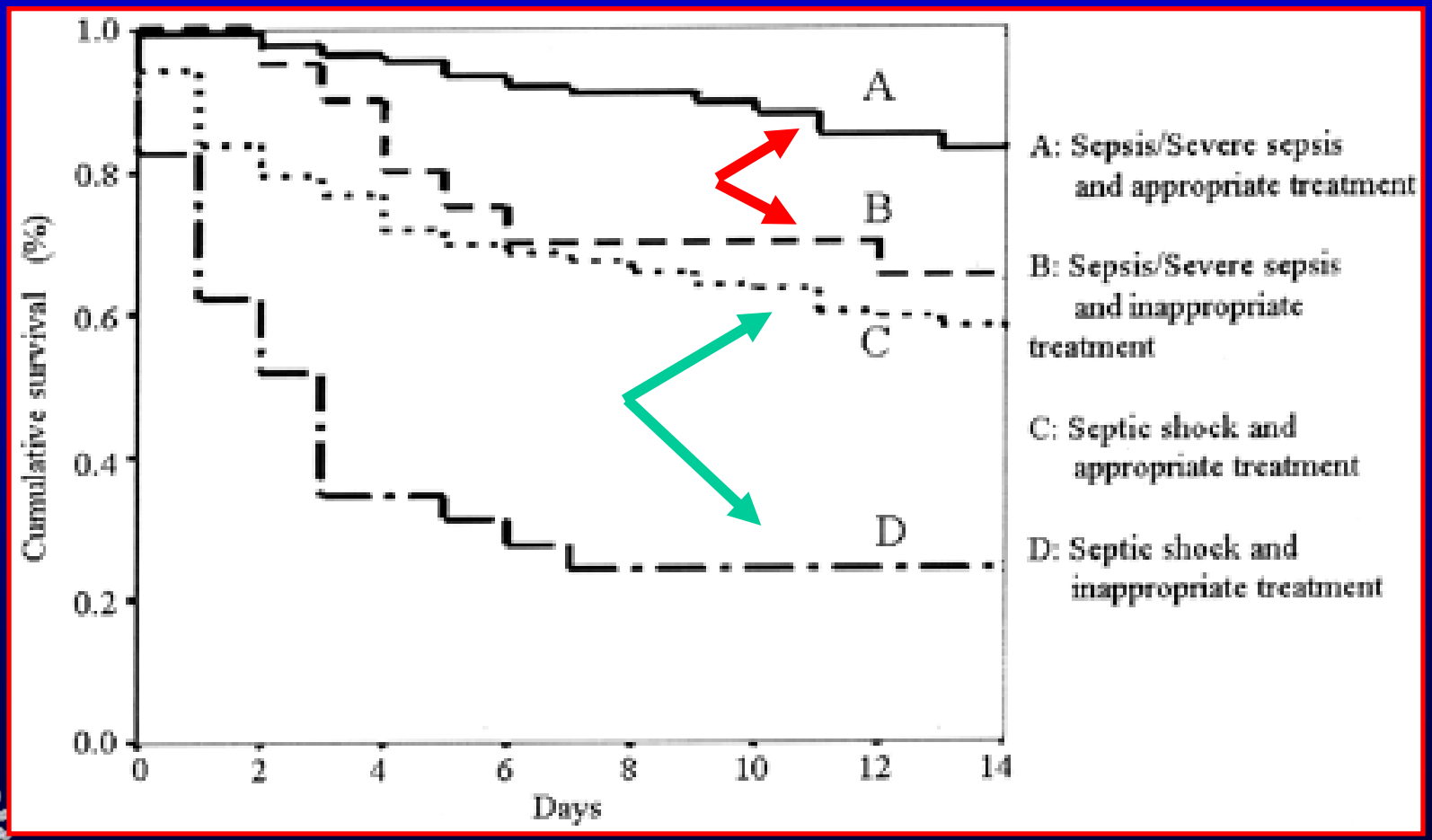
Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000; 118:146-155.

Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med 1996; 22:387-394. MacArthur RD, Miller M, Albertson T et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: Experience from the MONARCS Trial. Clin Infect Dis 2003; 38:284-288.

Harbarth S, Garbino J, Pugin J et al. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003; 115:529-535.

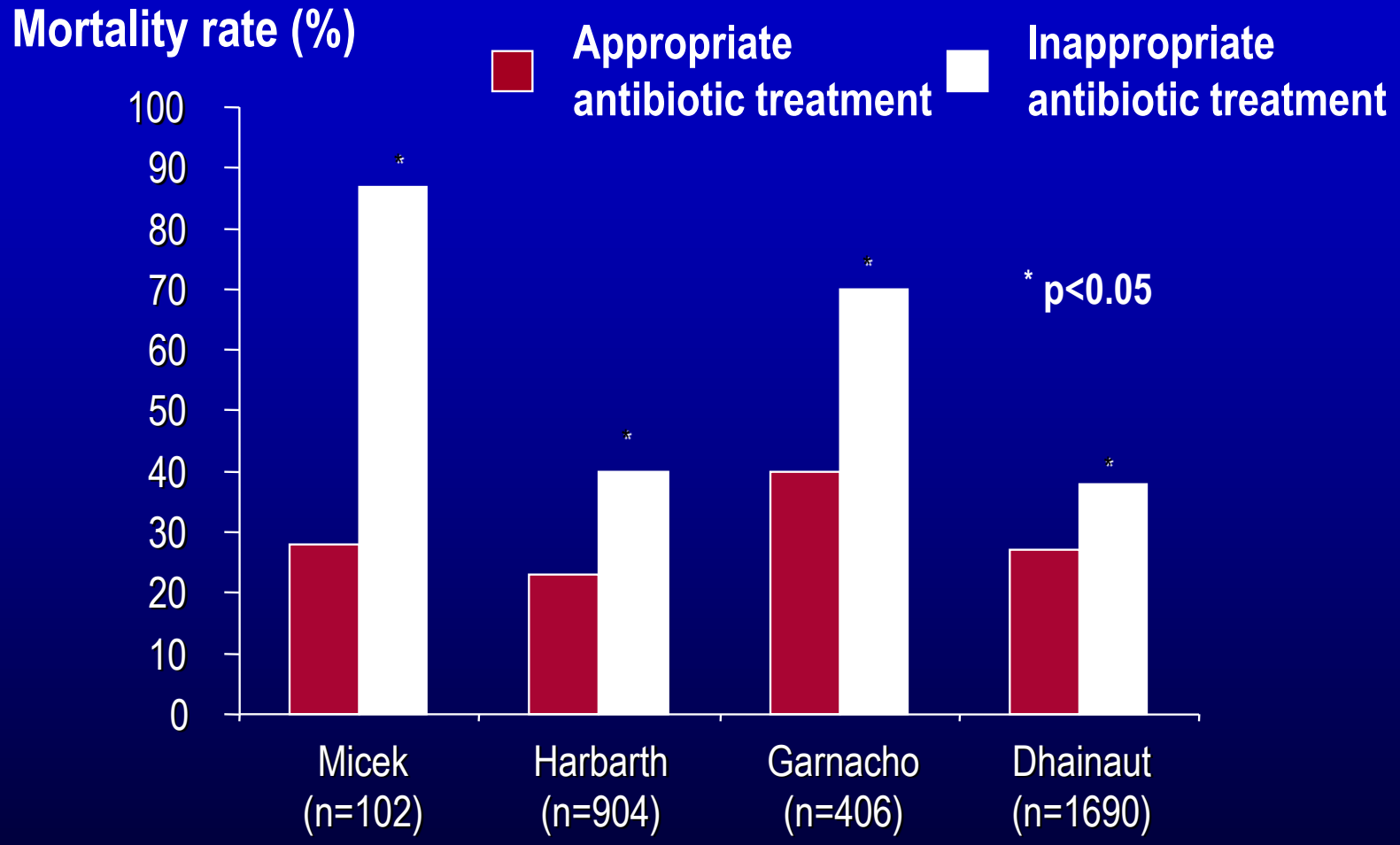
MacArthur RD, Miller M, Albertson T et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: Experience from the MONARCS Trial. Clin Infect Dis 2003; 38:284-288.

Inadequate antibiotic therapy: a risk factor for mortality



Vallés et al. Chest 2003 123:1615–1624

Inappropriate antibiotic treatment



Micek et al . Pharmacotherapy 2005;25:26-34

The American Journal of Medicine (2006) 119, 970-976

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

CLINICAL RESEARCH STUDY

AJM Theme Issue: Infectious Disease

Benefit of Appropriate Empirical Antibiotic Treatment: Thirty-day Mortality and Duration of Hospital Stay

Abigail Fraser, MPH,[a] Mical Paul, MD,[a,b] Nadja Almanasreh, MD,[c] Evelina Tacconelli, MD,[d] Uwe Frank, MD,[c] Roberto Cauda, MD,[d] Sara Borok, MD,[a] Michal Cohen, MD,[e] Steen Andreassen, PhD,[f] Anders D. Nielsen, MSc,[f] Leonard Leibovici, MD,[a,b] on behalf of the TREAT Study Group

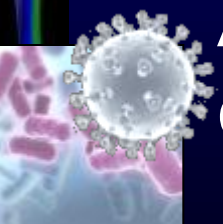
920 patients from 3 countries (Israel, Germany, Italy)

Inappropriate therapy in 319

All cause 30 day mortality 20% vs 11%

Adjusting for med centre + other variables

Odds ratio 1.58 95%CI 0.99-2.54 p=.058



Fraser et al. Am J Med 2006;119:970-6

Getting therapy right first time

CHEST

Original Research

CRITICAL CARE MEDICINE

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

CHEST 2009; 136:1237–1248

Anand Kumar, MD; Paul Ellis, MD; Yaseen Arabi, MD, FCCP;

CHEST 2009;136:1237- 48

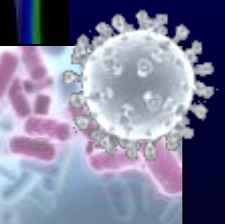
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2010, p. 4851–4863 Vol. 54, No. 11
0066-4804/10/$12.00 doi:10.1128/AAC.00627-10

Systematic Review and Meta-Analysis of the Efficacy of Appropriate Empiric Antibiotic Therapy for Sepsis▽†

Mical Paul,[1]* Vered Shani,[2] Eli Muchtar,[2] Galia Kariv,[2] Eyal Robenshtok,[2] and Leonard Leibovici[2]

Assuming 34% mortality with inappropriate empirical treatment number needed to treat to prevent one fatal outcome, 10 patients

Conclusion: Appropriate empirical antibiotic treatment is associated with a significant reduction in all-cause mortality

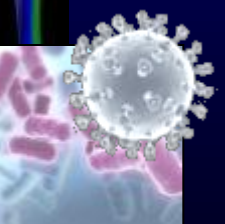


Paul et al *AAC* 2010;54:4851-63

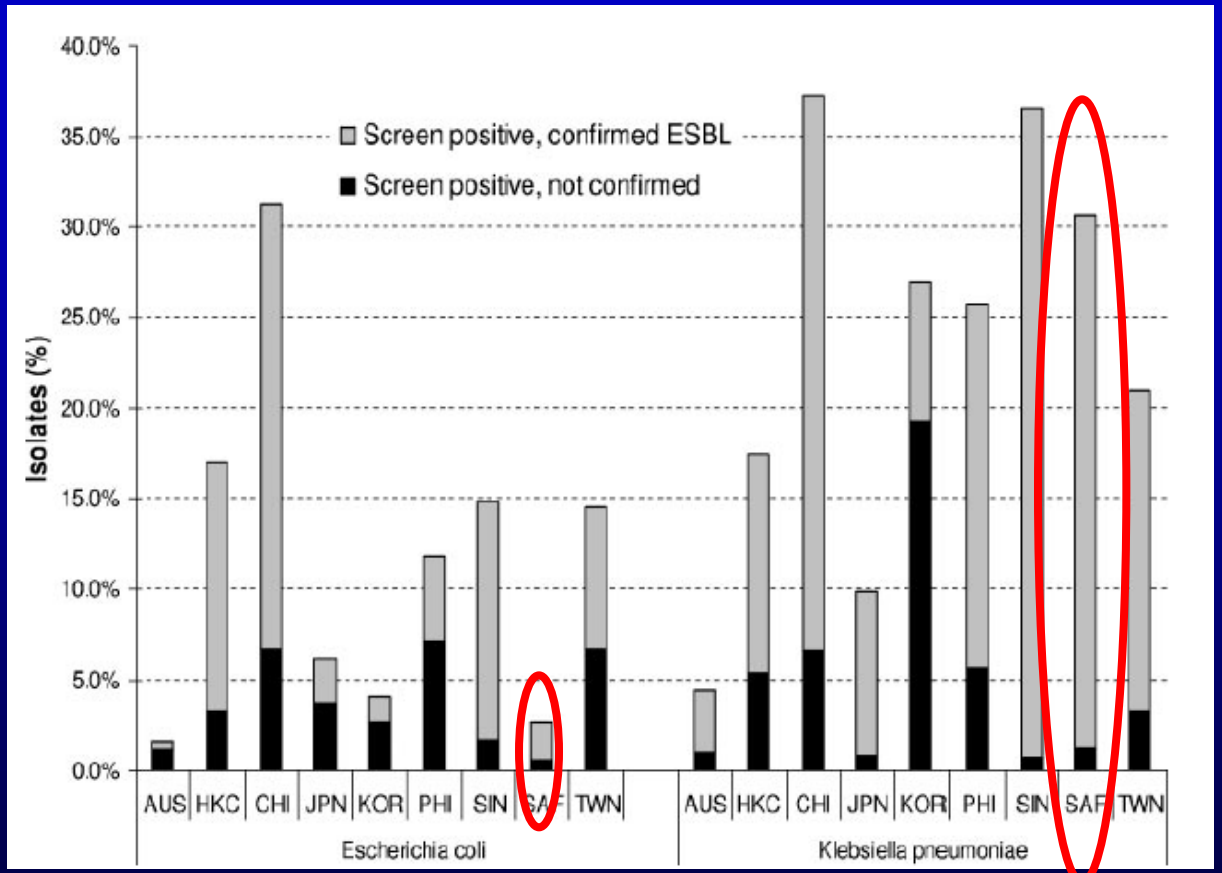
Regional Variations of resistances

KNOW YOUR LOCAL ORGANISMS AND SENSITIVITIES

BECAUSE THAT DETERMINES MUCH OF YOUR ANTIBIOTIC CHOICES

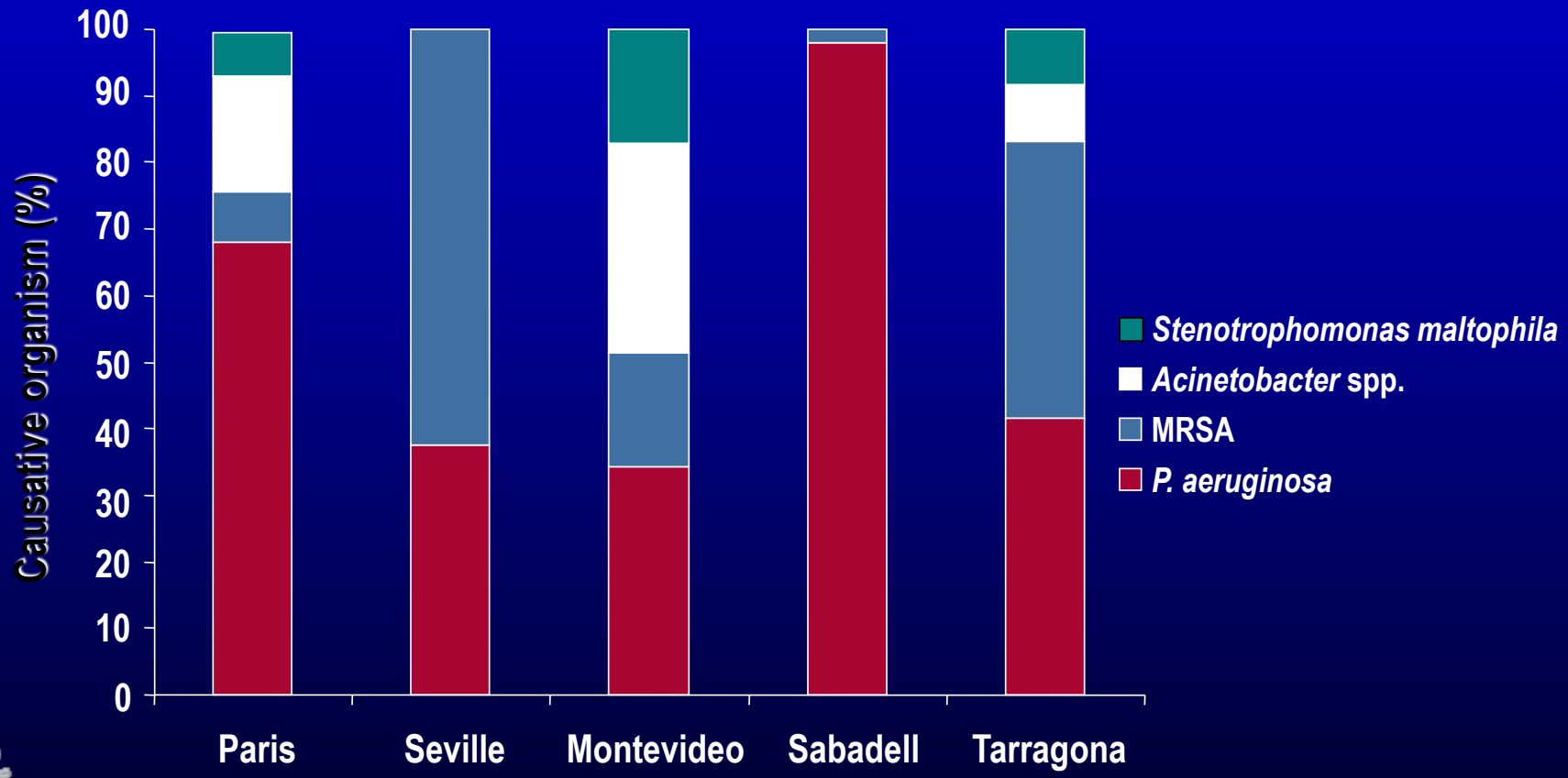


ESBL in South Africa



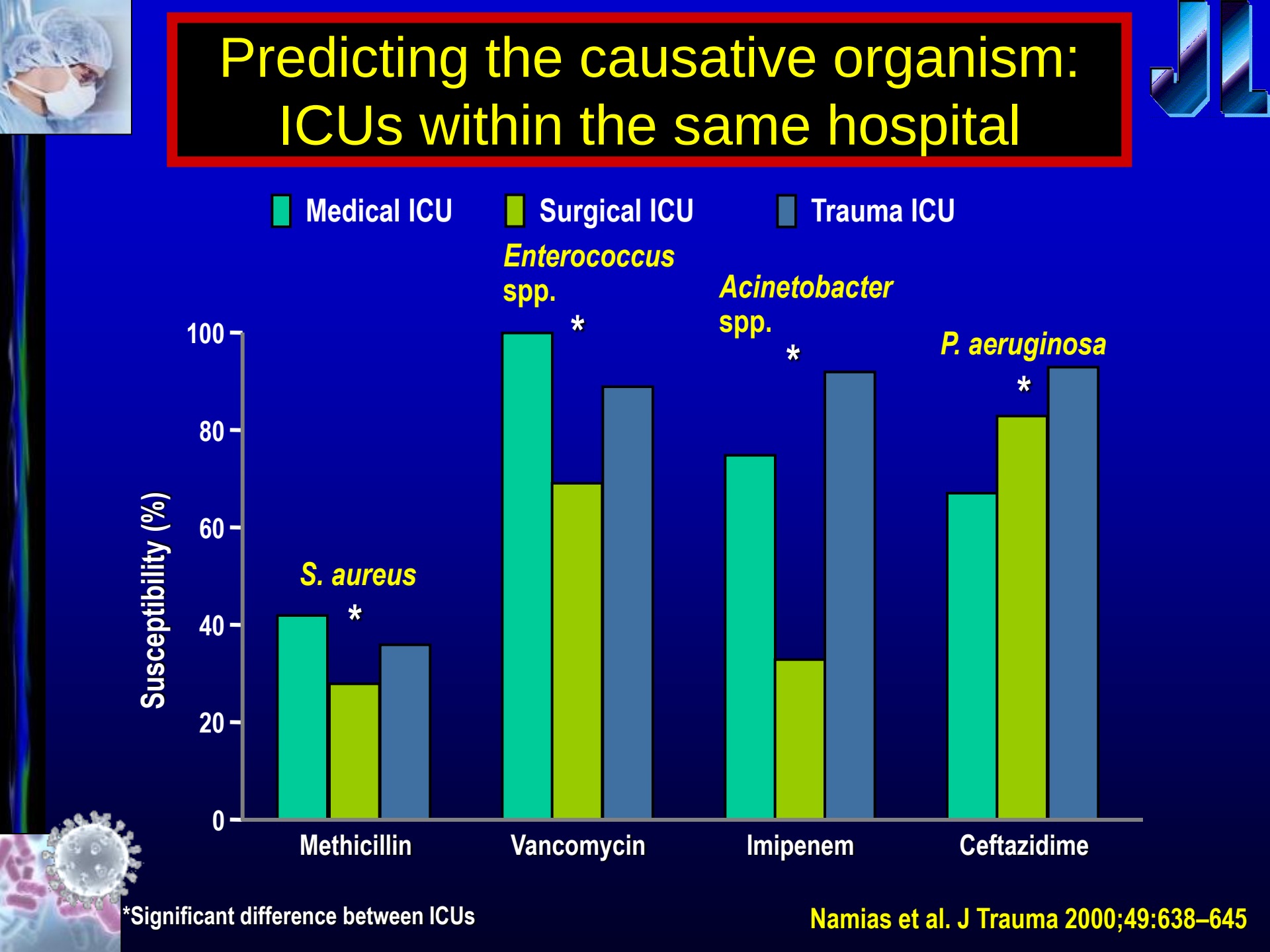
Bell et al J Clin Microbiol 2007;45:1478-82

Predicting the causative organism: ICUs across continents



Rello et al. Am Journal Respir Crit Care Med 1999;160:608–613

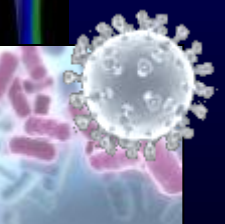
Predicting the causative organism: ICUs within the same hospital



*Significant difference between ICUs

Namias et al. J Trauma 2000;49:638–645

TO COVER ALL ORGANISMS MEANS BROAD COVER UP FRONT

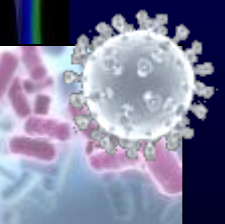


Dbl Gm -ve

LEVEL 1 EVIDENCE

All meta-analyses leave caveat for double gram-negative cover…
…something like….

Caveat **"MAYBE"**
for *Pseudomonas*
and
difficult-to-treat infections,
with worry of resistance developing.



Dbl Gm -ve

TRANSLATION OF EVIDENCE

Caveat **MAYBE** for *Psuedomonas* and difficult-to-treat infections, with worry of resistance developing.

With data of inadequate initial therapy causing morbidity – this translates into

BROAD THERAPY INITIALLY

even possibly dbl gm –ve cover

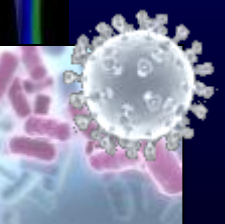
TAILOR AFTER 48 HOURS OR WHEN CULTURES BACK

HOW BROAD?

SINGLE AGENT OF DBL COVER?

1 CAP: DBL COVER BETTER

2 GM NEG INFECTIONS
- a) Meta-analyses
- b) Ps Infections
- c) Empiric cover

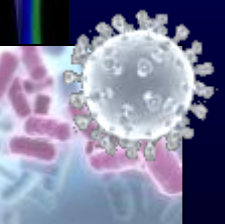


DOUBLE GM NEG COVER

August Critical Care Medicine

A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent on the risk of death: A meta-analytic/meta-regression study

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD



Crit Care Med **2010;38:1651-64**

Antimicrobial Agents and Chemotherapy, May 2010, p. 1742–1748 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.01365-09

Empiric Combination Antibiotic Therapy Is Associated with Improved Outcome against Sepsis Due to Gram-Negative Bacteria: a Retrospective Analysis[▽]

Scott T. Micek,[1] Emily C. Welch,[1] Junaid Khan,[2] Mubashir Pervez,[2] Joshua A. Doherty,[3] Richard M. Reichley,[3] and Marin H. Kollef[2]*

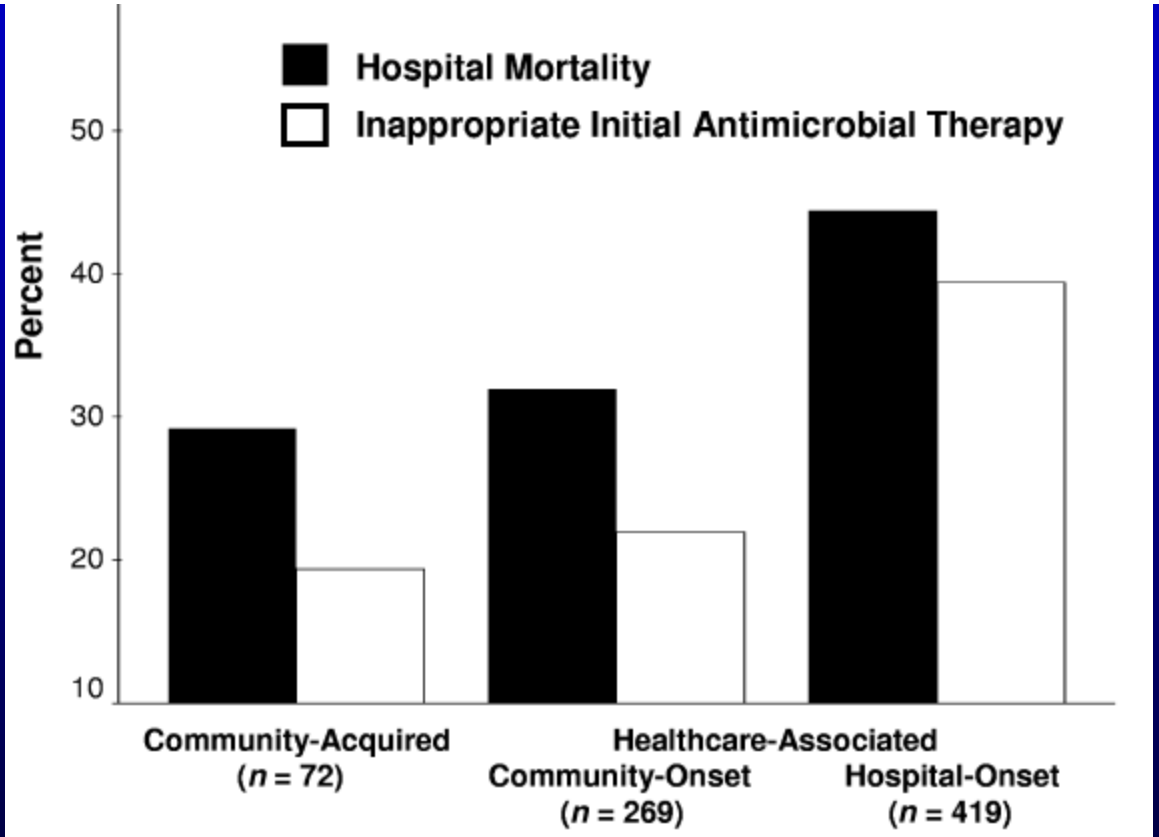


FIG. 2. Hospital mortality and inappropriate initial antimicrobial therapy (IIAT) according to classification of infection source. ($P <$ 0.001 for differences in hospital mortality and IIAT).

Micek et al

Antimicrob Agents Chemother

May 2010

DOUBLE GM NEG COVER

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2010, p. 3590–3596 Vol. 54, No. 9
0066-4804/10/$12.00 doi:10.1128/AAC.00115-10

Influence of Empiric Therapy with a β-Lactam Alone or Combined with an Aminoglycoside on Prognosis of Bacteremia Due to Gram-Negative Microorganisms▽

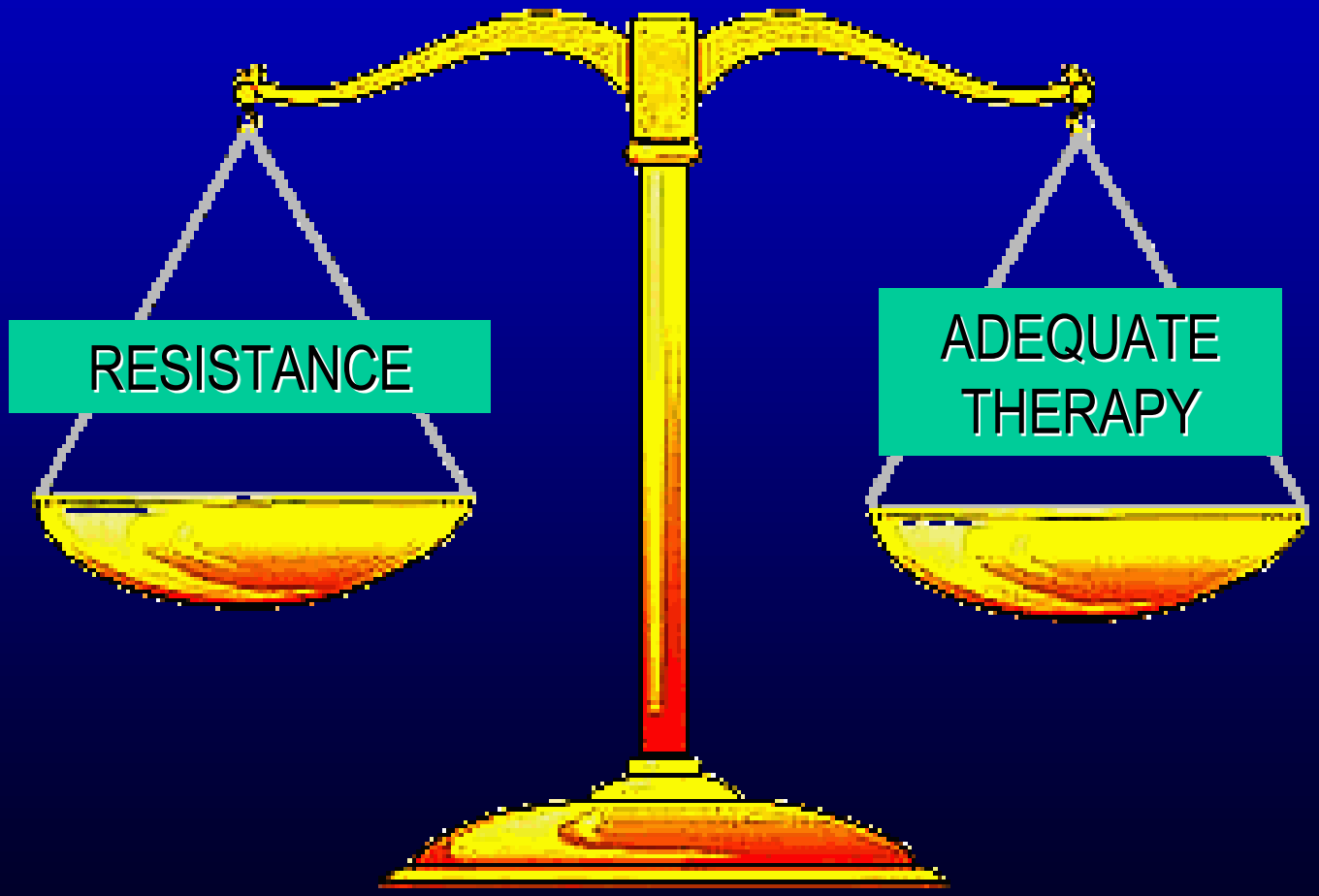
J. A. Martínez,[1]* N. Cobos-Trigueros,[1] A. Soriano,[1] M. Almela,[2] M. Ortega,[1] F. Marco,[2] C. Pitart,[2] H. Sterzik,[1] J. Lopez,[1] and J. Mensa[1]

"..A total of 4,863 episodes were assessed, of which 678 (14%) received combination therapy and 467 (10%) were fatal….." .. "..Combination therapy improved the appropriateness of empirical therapy in episodes due to ESBL- or AmpC-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*…."

Combination therapy also should be considered for patients at risk of being infected with resistant organisms, if only to increase the appropriateness of empirical therapy.

Sept ***Antimicrob Agents Chemother.*** **2010;54:3590-6**

Broad spectrum
Dbl gm neg cover
= Problem



De-escalation

De-escalation involves the practice of:

- Starting with a broad-spectrum empiric therapy regimen designed to avoid inappropriate therapy, combined with a commitment to:
  - Change from broad- to narrow-spectrum therapy
  - Reduce the duration of therapy
  - Stop therapy in selected patients, as dictated by the patient's clinical response and by culture results

Culture data are used to narrow, focus or even stop therapy

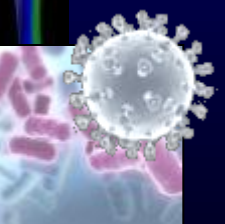
Does De-Escalation of Antibiotic Therapy for Ventilator-Associated Pneumonia Affect the Likelihood of Recurrent Pneumonia or Mortality in Critically Ill Surgical Patients?

Soumitra R. Eachempati, MD, FACS, Lynn J. Hydo, MBA, Jian Shou, MD, FACS, and Philip S. Barie, MD, MBA, FACS, FC

J Trauma Injury Infect Crit Care MAY 2009

Conclusion: De-escalation therapy did not lead to RP or increased mortality in critically ill surgical patients with VAP. De-escalation therapy was also shown to be safe in patients with septic shock. Because of its acknowledged benefits and lack of demonstrable risks, de-escalation therapy should be used whenever possible in critically ill patients with VAP.

DURATION OF ANTIBIOTIC THERAPY

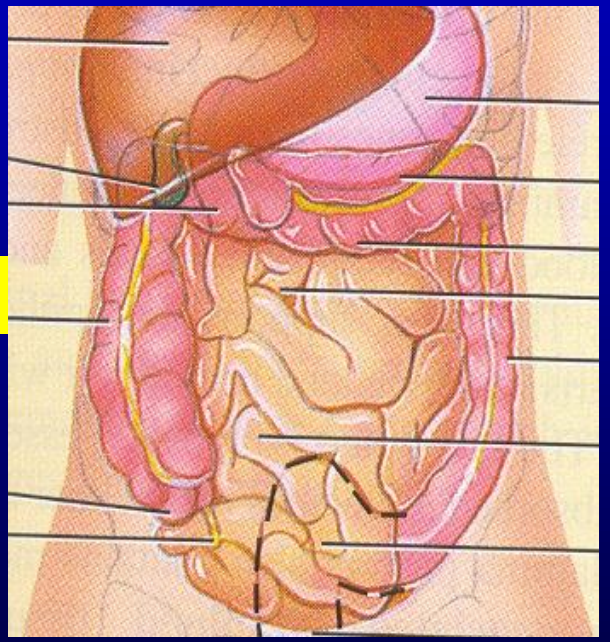


BOWEL BACTERIAL LOAD

MORE BACTERIA IN/ON OUR BODY THAN CELLS

10 quadrillion cells

100 quadrillion bacterial cells



ANTIBIOTICS KILL BACTERIA, BUT NOT ALL

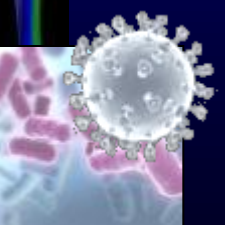
DURATION OF ANTIBIOTIC THERAPY

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

Jean Chastre, MD

- Prospective, randomised, multicentre trial
- Comparing the outcome of therapy with a ‘short’ (8-day) or ‘long’ (15-day) course of antibiotics
  - patients with microbiologically proven VAP (bronchoscopic bronchoalveolar lavage protected specimen brush or Combicath)
  - receiving appropriate initial empiric treatment
  - double-blind until Day 8
- Major endpoints (Day 28):
  - mortality
  - recurrence of pulmonary infection
  - antibiotic use



Chastre et al. JAMA 2003;290:2588–2598

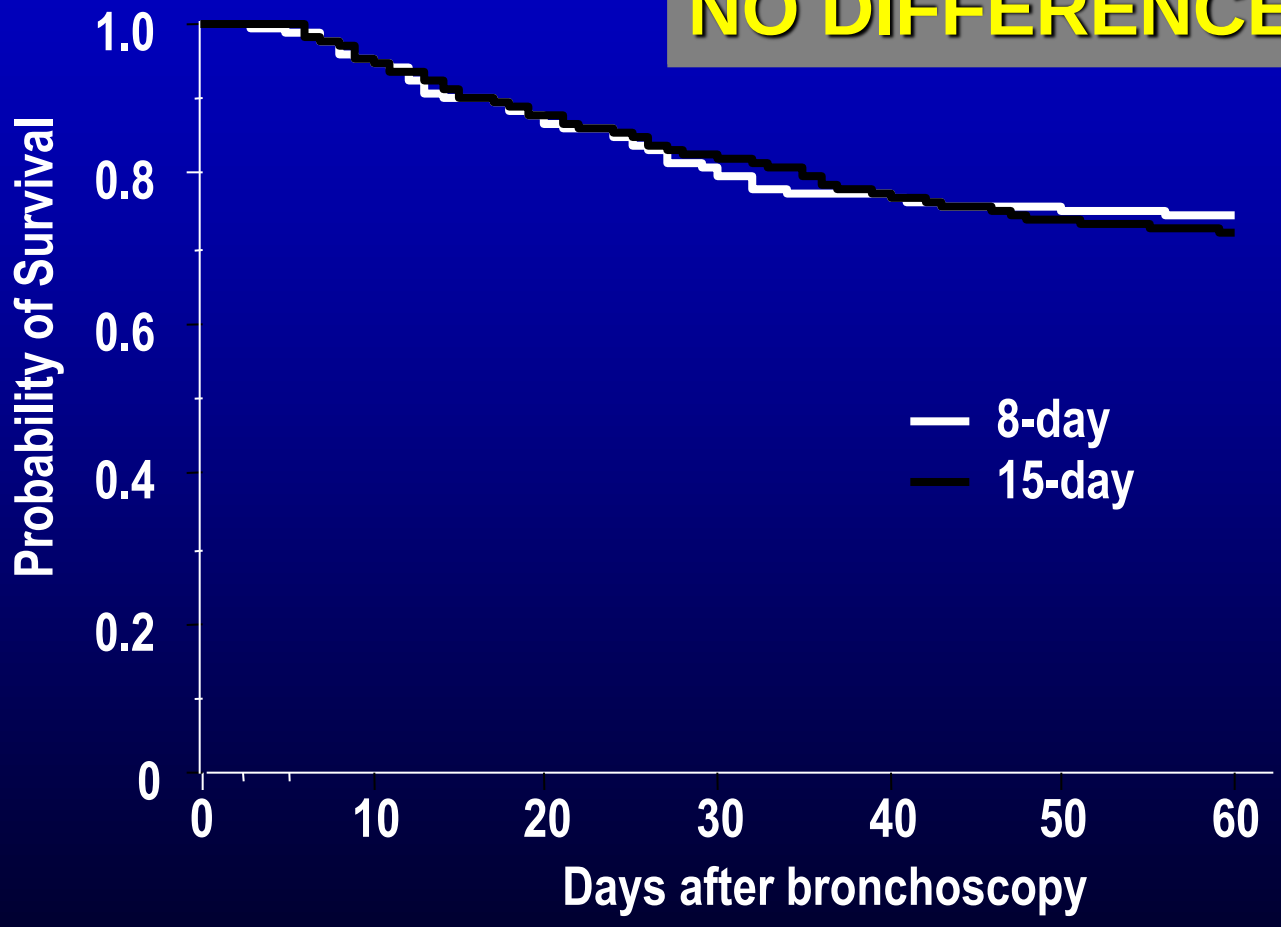
DURATION OF ANTIBIOTIC THERAPY

Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

Jean Chastre, MD

NO DIFFERENCE



Chastre et al. JAMA 2003;290:2588–2598

DURATION OF ANTIBIOTIC THERAPY

Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

NINA SINGH, PAUL ROGERS, CHARLES W. ATWOOD, MARILYN M. WAGENER, and VICTOR L. YU

AJRCCM 2000:162: 505-11

CPIS≤ 6 : "std" vs 3 days cipro

MAIN RESULTS: ICU Mortality – same,

BUT: ICU LOS LESS, 30 DAY MORTALITY LESS

Resistance 15% vs 35%,

COMMENTS: Small study, low risk pts, a start

Some other OPD trials

International Journal of Antimicrobial Agents 36S (2010) S50–S54

Contents lists available at ScienceDirect

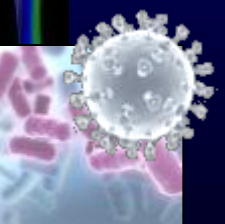
International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Multidrug-resistant Gram-negative bacteria: how to treat and for how long

Helen Giamarellou*

CONCLUSION : "..... the strict application of infection control measures is the cornerstone of nosocomial infection prevention, and antibiotic stewardship, exemplified by appropriate duration of therapy and de-escalation policies, should not be overlooked."



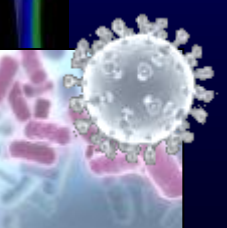
Giamarellou H. *IJAA* 2010;36:s50-s54

SUMMARY
DURATION

THERE IS AN INTERNATIONAL TREND TO USE SHORTER COURSES OF ANTIBIOTICS

***Ps* VAP probably needs 7-10 days**

In my Unit we seldom use greater than a 7 day course – more often a 5 day course
PROVIDED THERE IS SOURCE CONTROL



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3430–3436 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.01361-08

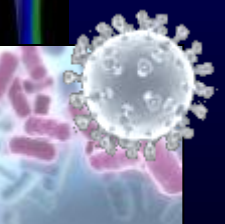
Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria▽†

D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]

PK analysis of 18 pts given colistin methanesulfonate (CMS) 240mg Q8H (3million units CMS)

Measured both CMS as well as active colistin

Showed plasma colistin concentrations insufficient

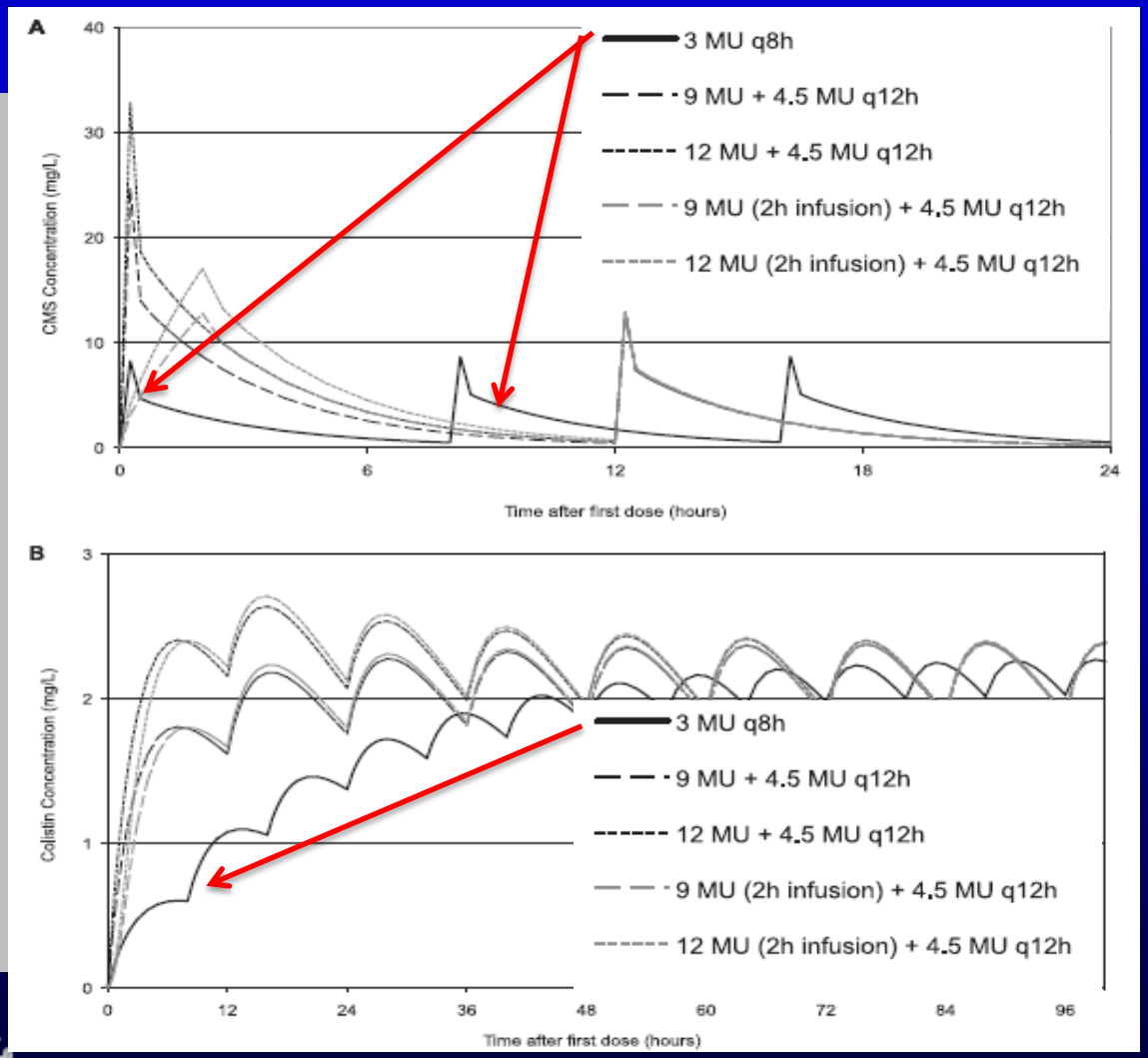


Plachouras et al *Antimicrob Agents Chemother* 2009;53:3420-6

STANDARD DOSE INSUFFICIENT

CMS

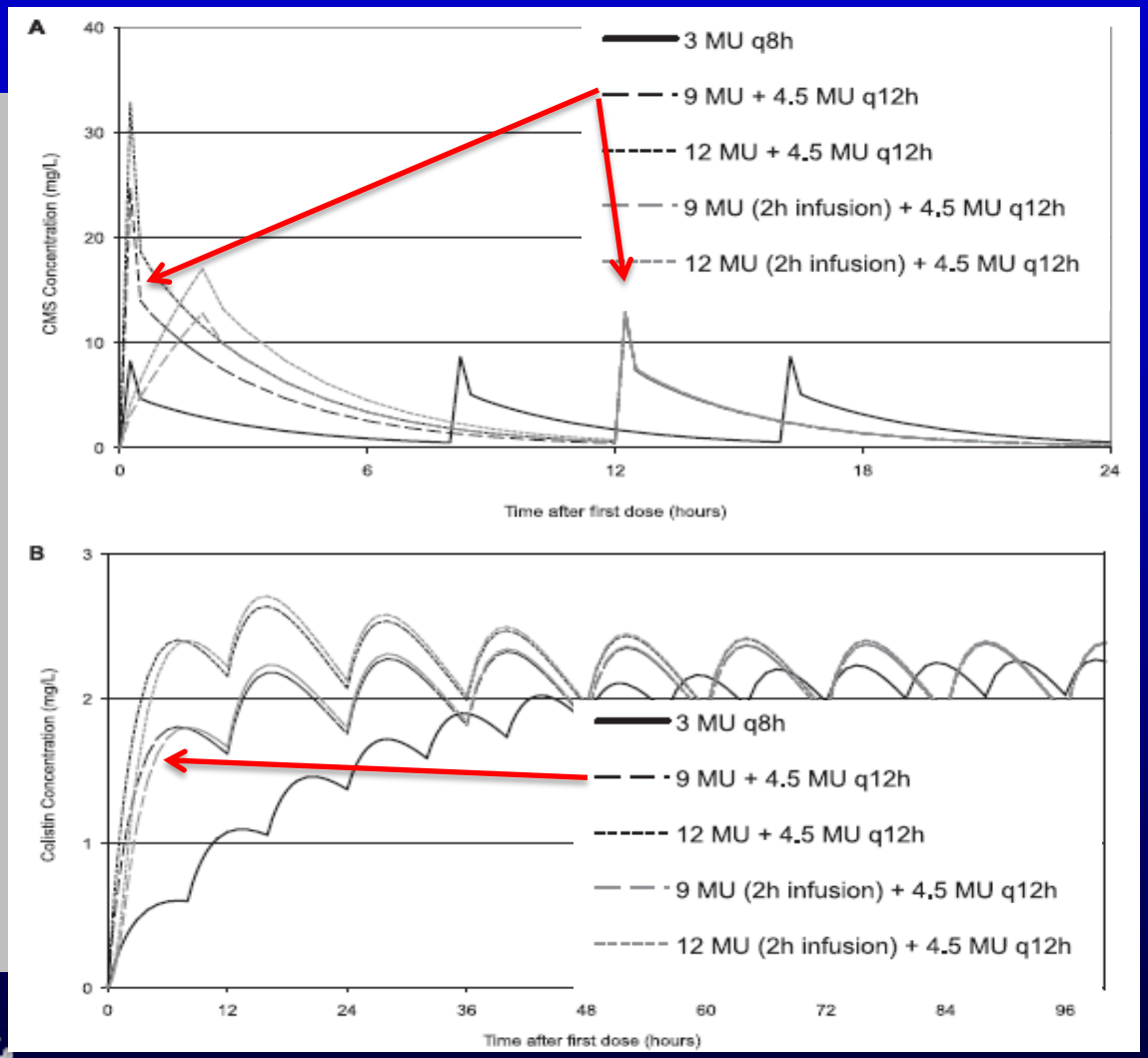
Colistin



Plachouras et al *Antimicrob Agents Chemother* 2009;53:3420-6

STANDARD DOSE INSUFFICIENT

Colistin CMS



Suggest

Loading dose
9MU (720mg !)

FOLLOWED BY

4.5MU (360mg) every12 hours

Plachouras et al *Antimicrob Agents Chemother* 2009;53:3420-6

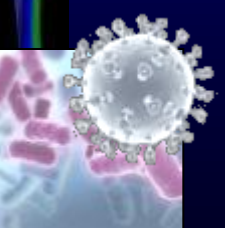
Nephrotoxicity associated with the use of intravenous colistin

CECILIA SANTAMARÍA, ANALIA MYKIETIUK, ELENA TEMPORITI, MARTIN E. STRYJEWSKI, FABIAN HERRERA & PABLO BONVEHI

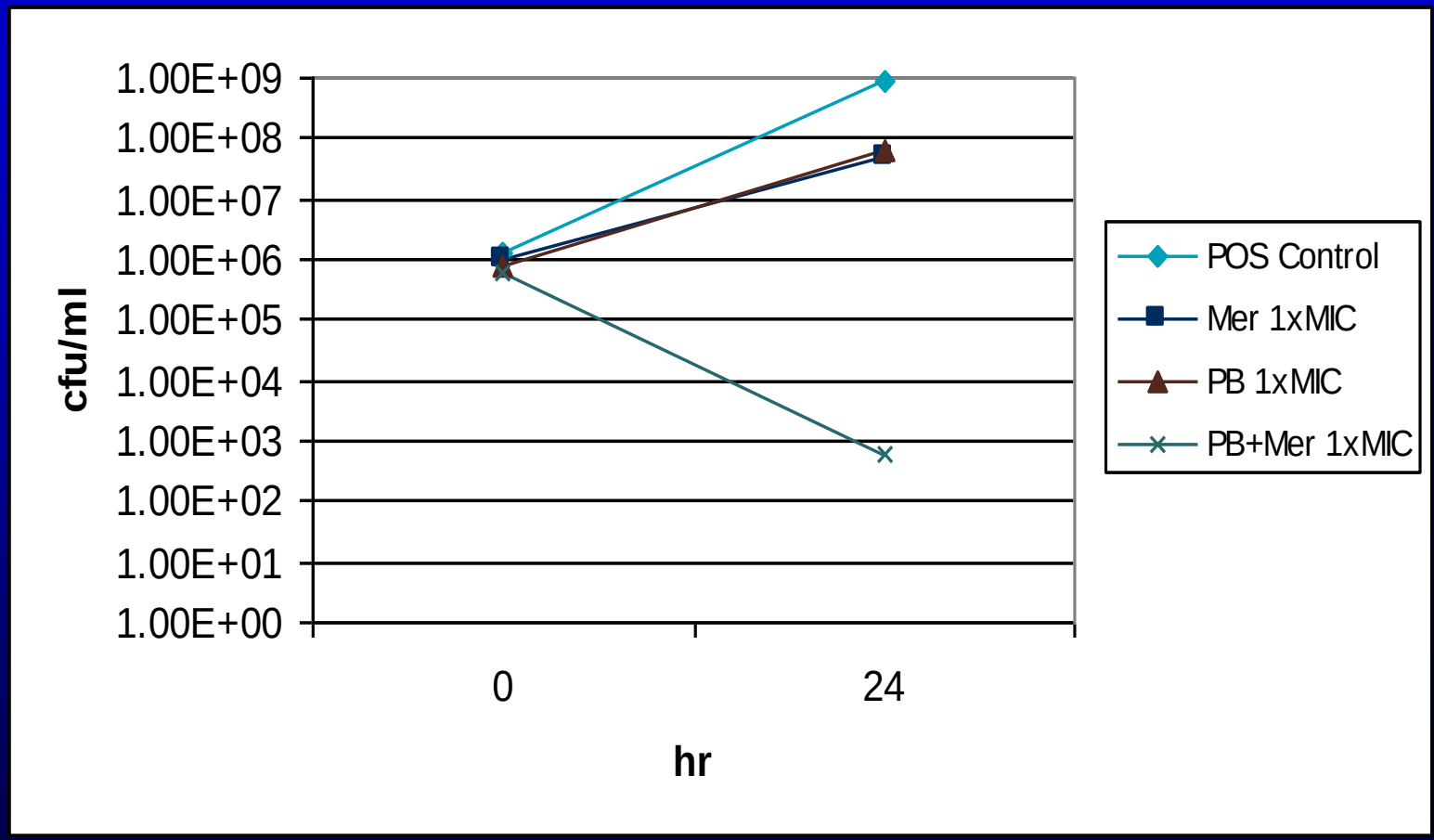
Scand J Infect Dis 2009 Aug 14:1-3

- Fifty-four patients with multidrug-resistant Acinetobacter infections were included
- 6/54 patients (11%) suffered renal impairment
- Renal impairment associated with the use of colistin is less frequent than initially reported

Santamaria C et al *Scand J Infect Dis* 2009 Aug 14:1-3



Time-kill assay: synergy with PB + MEROPENEM



Time-kill assay (mean colony counts of all isolates)

Pankey GA and Ashcraft DS ***Diagn Microb Inf Dis*** **2009;63:228-32.**

In Vitro Antimicrobial Activity and Mutant Prevention Concentration of Colistin against *Acinetobacter baumannii*[▽]

Yun Cai, Ran Li, Beibei Liang, Nan Bai, Youning Liu, and Rui Wang*

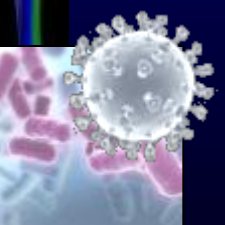
Antimicrob Agents Chemother. 2010;54:3998-9

"….combination therapy for colistin treatment of *A. baumannii* would be prudent to slow the emergence of resistance…."

Sept *Antimicrob Agents Chemother.* 2010;54:3998-9

THE BURNING QUESTIONS

4. HOW AND HOW MUCH?



LOW EXPOSURE TO ANTIBIOTICS ENABLES DEVELOPMENT OF RESISTANCE

Antibiotic resistance—What's dosing got to do with it?

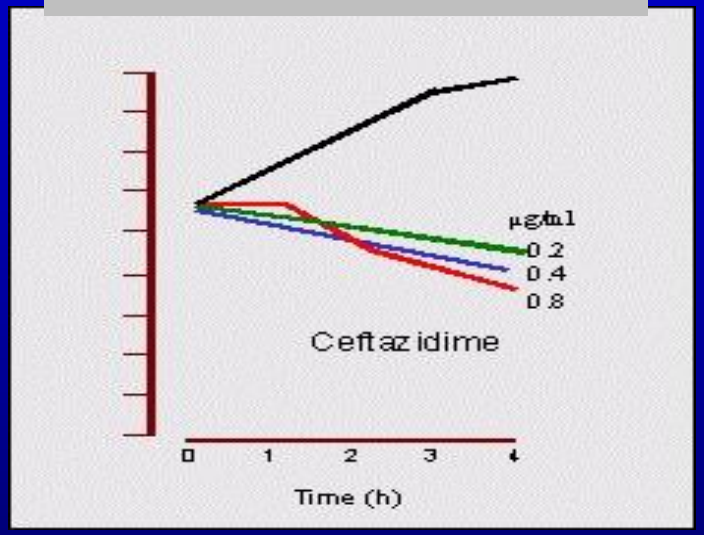
Jason A. Roberts, B Pharm (Hons); Peter Kruger, MBBS, FJFICM; David L. Paterson, MBBS, FRACP, PhD; Jeffrey Lipman, MBBCh, FJFICM, MD

Critical Care Medicine August 2008;36:2433-40

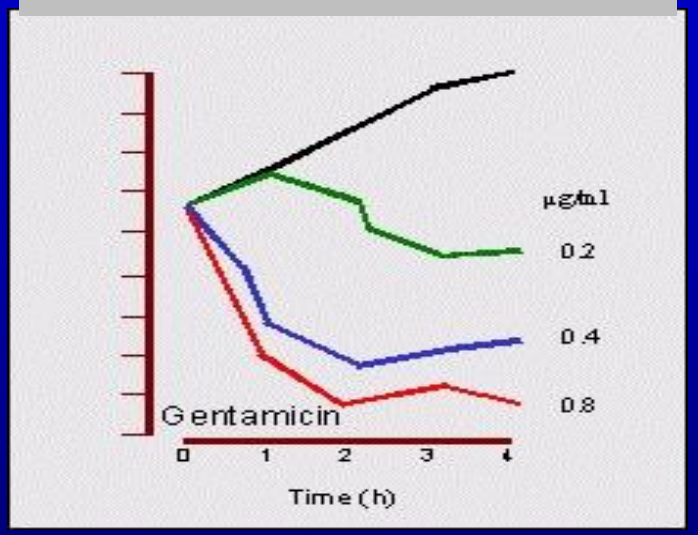
IF YOU DON'T LOOK PROPERLY YOU WON'T SEE IT.

KILL CHARACTERISTICS

TIME DEPENDENT



CONC. DEPENDENT



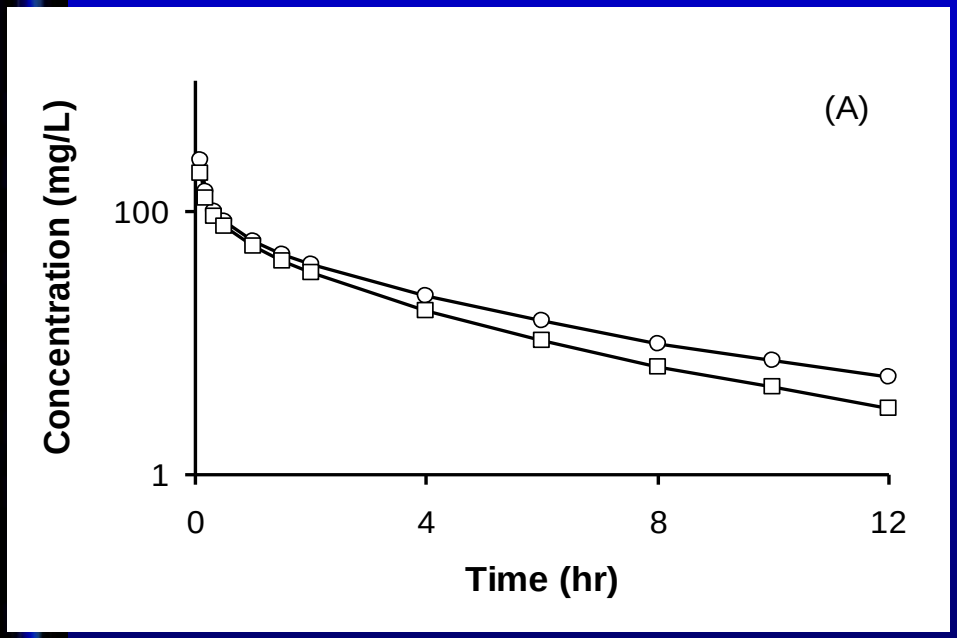
ß-lactams:
Time>MIC

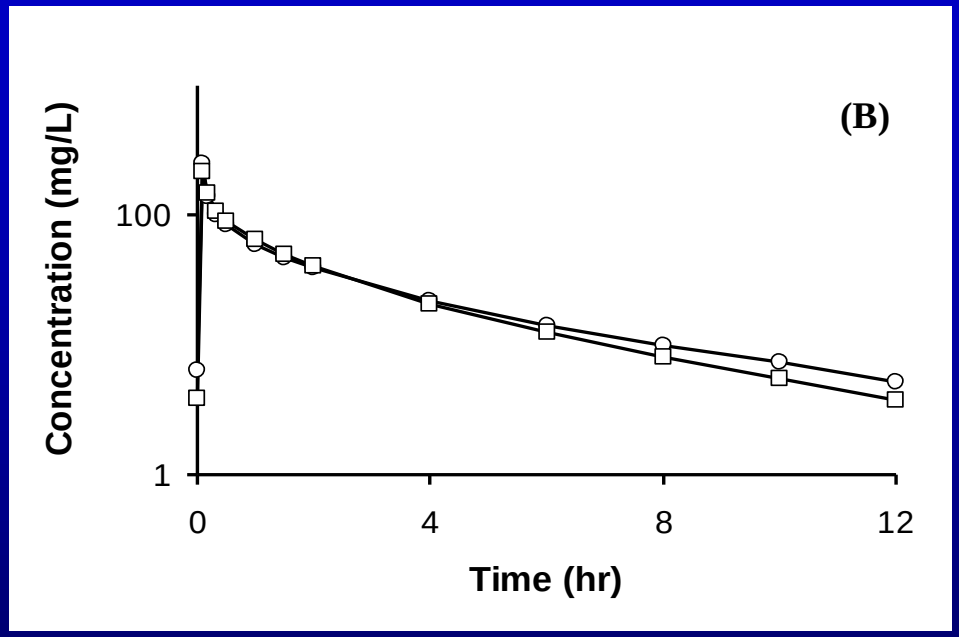
Aminoglycosides:
Dose dependent

Vancomycin
?Time>MIC

Fluoroquinolones:
Peak/MIC AUC/MIC

CEFEPIME (O) vs CEFPIROME (•)



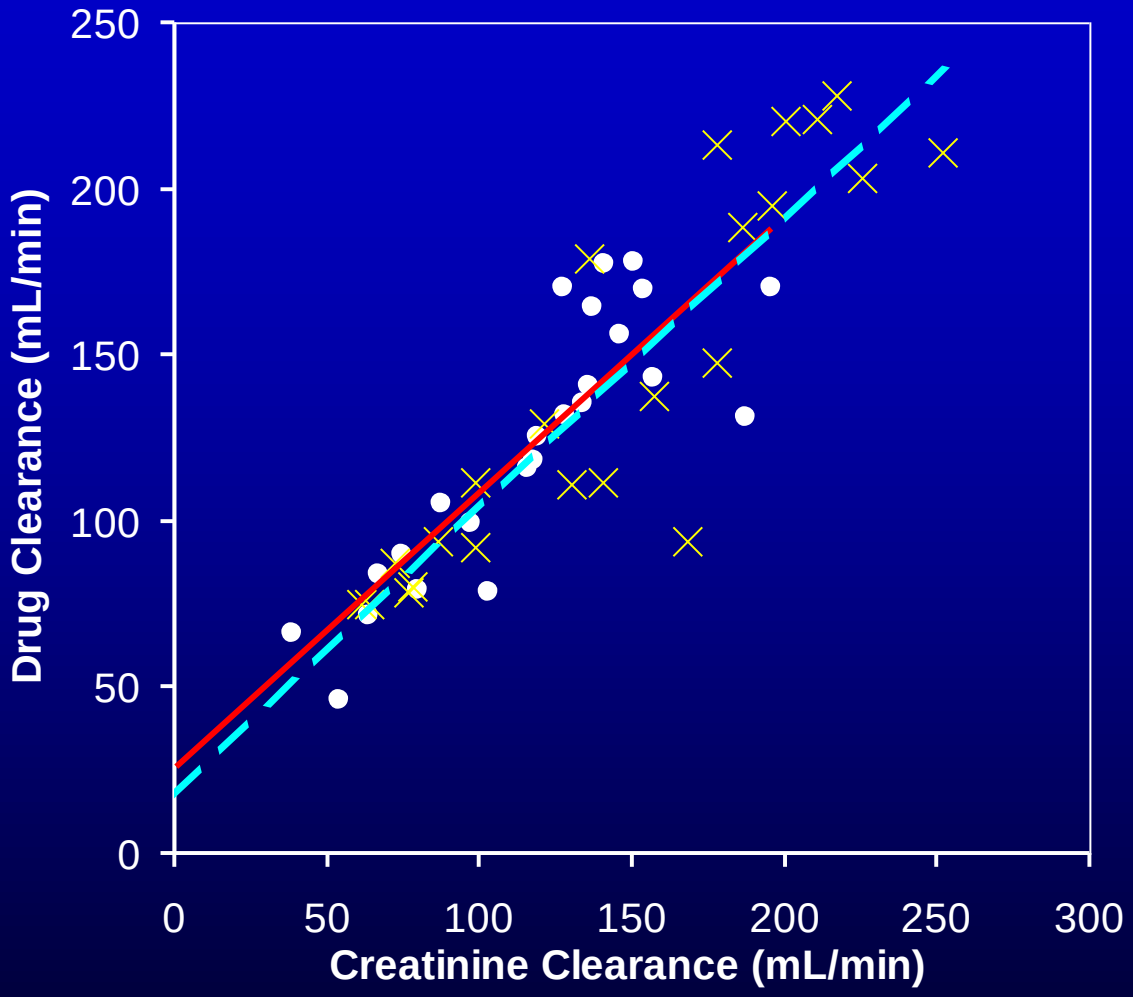


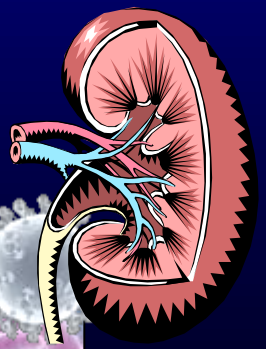
1st dose

Day 3-6

1. Cefpirome levels lower
2. No difference between D1 vs later dose

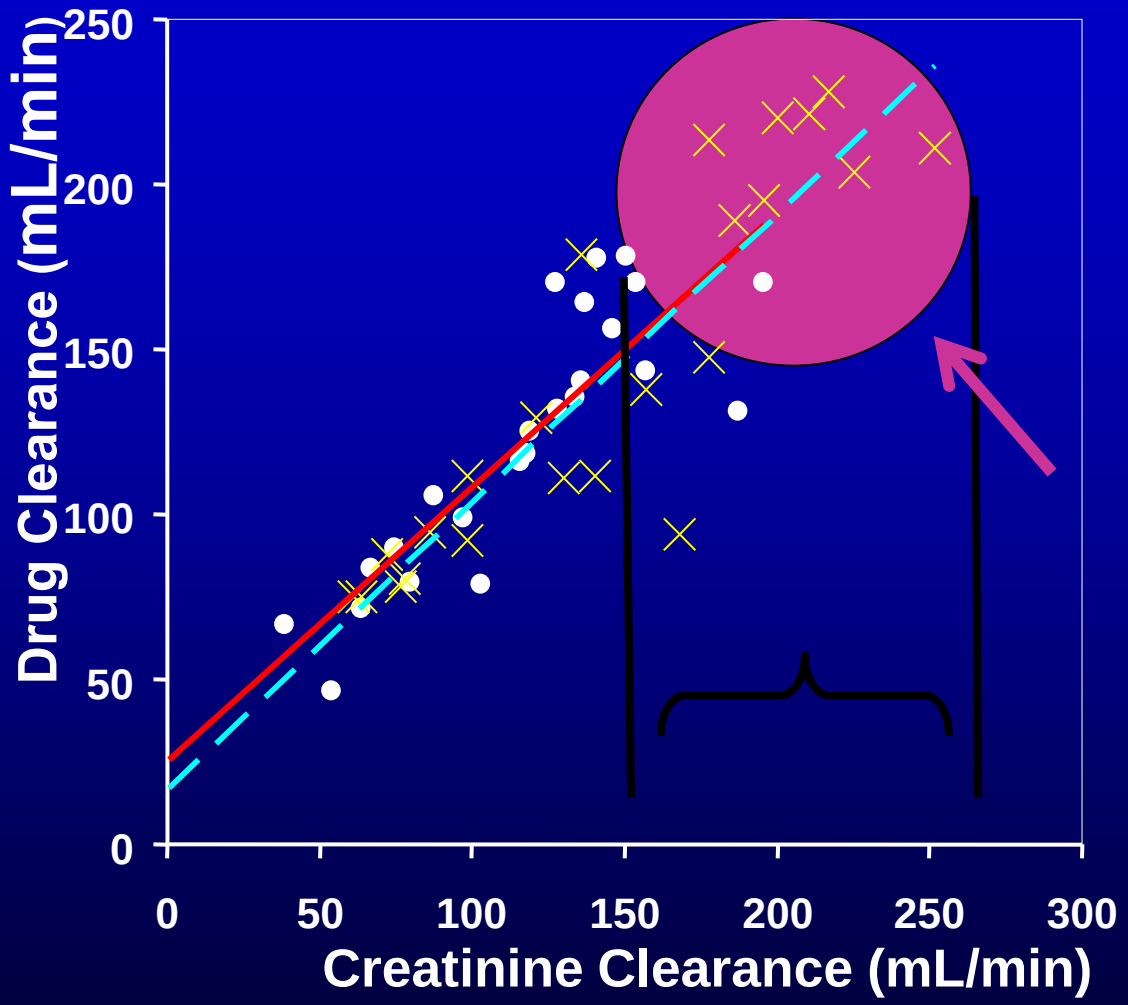
Creatinine clearance

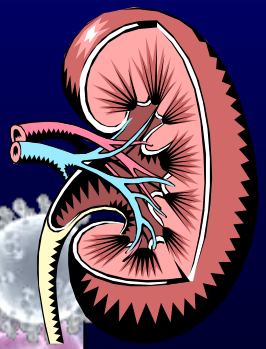




Lipman et al *Anesth Analg* 2003

Creatinine clearance





Lipman et al *Anesth Analg* 2003

Glomerular hyperfiltration and albuminuria in critically ill patients

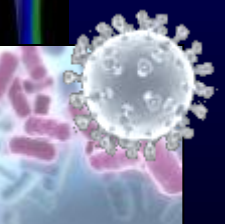
Anaesth Intensive Care 2008; **36:** 674-680

O. FUSTER-LLUCH*, M. GERÓNIMO-PARDO†, R. PEYRÓ-GARCÍA‡, M. LIZÁN-GARCÍA§

Departments of Clinical Analysis, Anesthesiology and Reanimation and Preventive Medicine, Complejo Universitario of Albacete, Albacete, Spain

On admission 17% of patients had high Creatinine Clearances rising up to 30% during 1st week of ICU.

UP TO 30% of ICU pts had high creatinine clearances!!

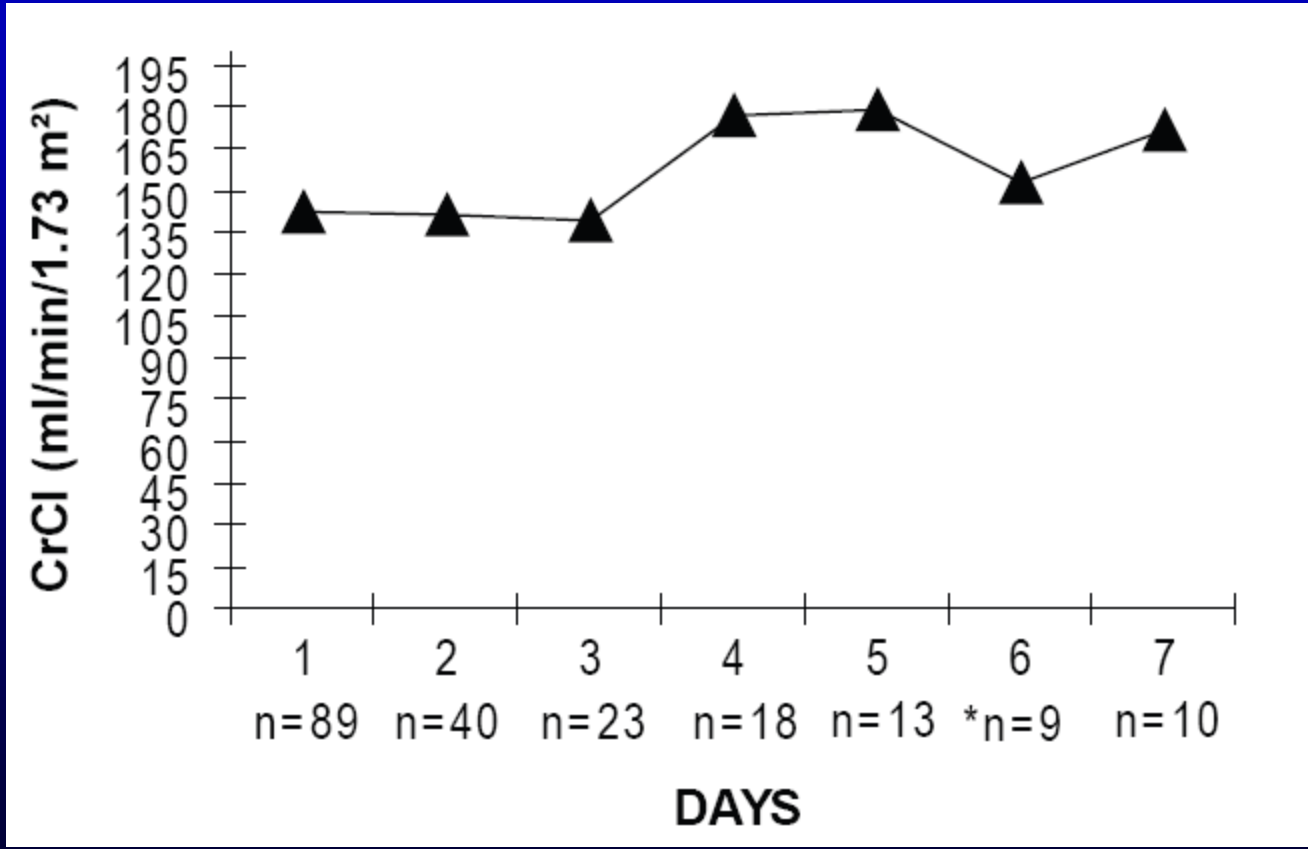


Glomerular hyperfiltration and albuminuria in critically ill patients

Anaesth Intensive Care 2008; **36:** 674-680

O. FUSTER-LLUCH*, M. GERÓNIMO-PARDO†, R. PEYRÓ-GARCÍA‡, M. LIZÁN-GARCÍA§

Departments of Clinical Analysis, Anesthesiology and Reanimation and Preventive Medicine, Complejo Universitario of Albacete, Albacete, Spain



AUGMENTED RENAL CLEARANCE

Editorial

Anaesth Intensive Care 2009; **37:** 11-13

You only find what you look for: the importance of high creatinine clearance in the critically ill

Udy A, et a

REVIEW ARTICLE

Clin Pharmacokinet 2010; 49:1-16

Augmented Renal Clearance

Implications for Antibacterial Dosing in the Critically Ill

Andrew A. Udy,[1,2] *Jason A. Roberts,*[1,2,3] *Robert J. Boots,*[1,2] *David L. Paterson*[4,5] and *Jeffrey Lipman*[1,2]

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

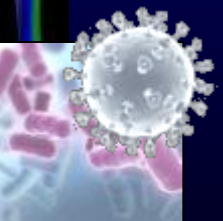
journal homepage: http://www.elsevier.com/locate/ijantimicag

Short communication

Augmented renal clearance in the Intensive Care Unit: an illustrative case series

Andrew A. Udy[a,b], Michael T. Putt[a,b], Sulochana Shanmugathasan[a], Jason A. Roberts[a,b,c], Jeffrey Lipman[a,b,*]

June 2010

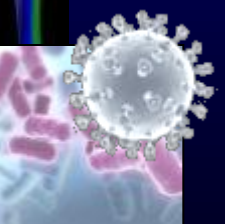


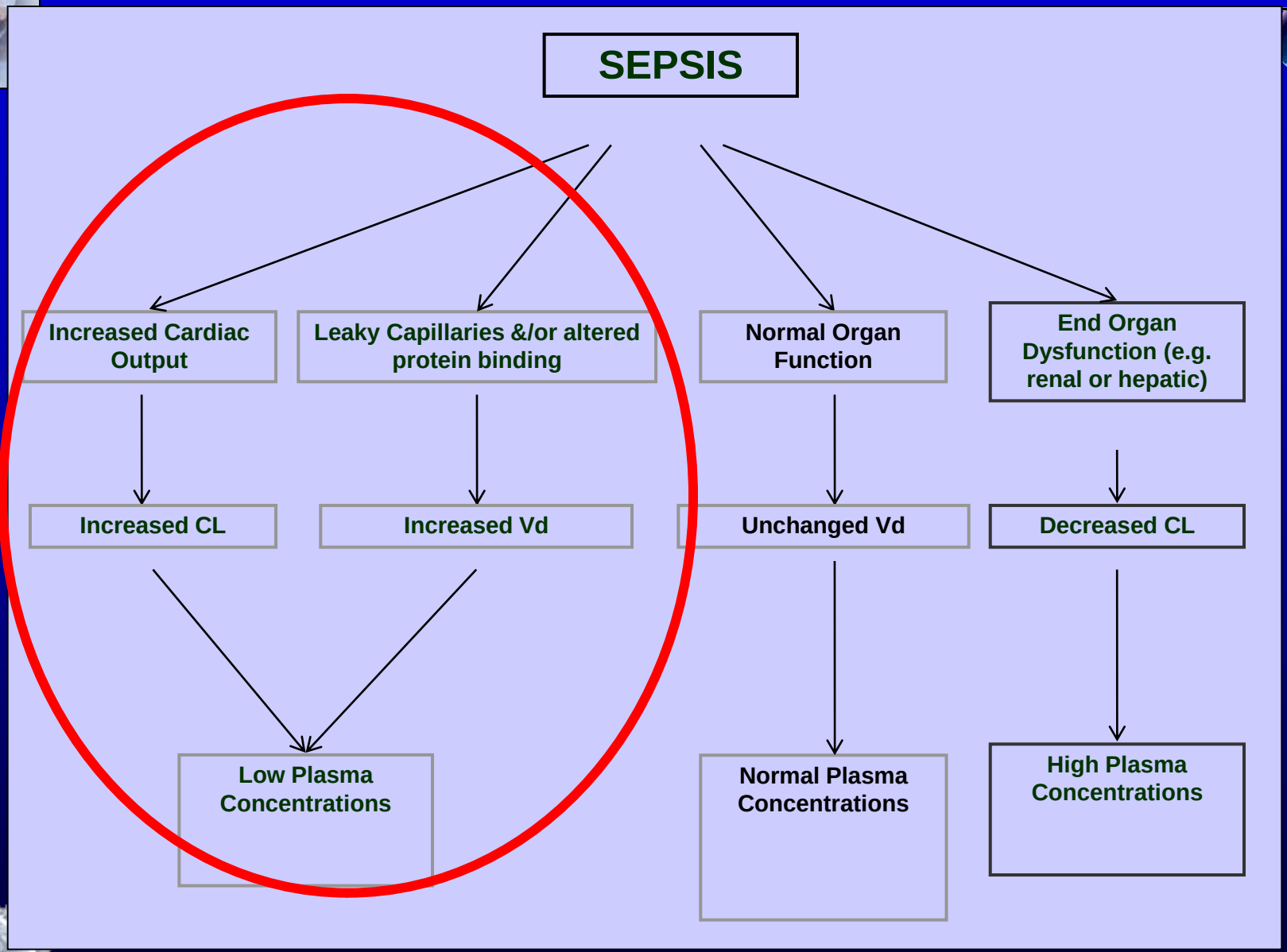
WATCH THIS SPACE!

HAEMODYNAMICS

INFLAMMATORY RESPONSE WITH CAPILLARY LEAK

1. **HUGE FLUID SHIFTS**
2. **DEFEND BLOOD PRESSURE OFTEN WITH INOTROPES**





Roberts and Lipman Critical Care Medicine 2009 ;37:840-851

CASE ONE

Mr SJ 33 M SEVERE CLOSED HEAD INJURY

3rd week into ICU - CoNS from Bld + EVD

Off inotropes, MAP 80, P 110, T 38, Na 140

Cr 41 U/O 1-1.5ml/kg/hr.

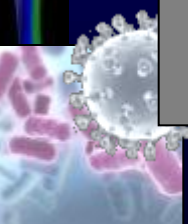
Vancomycin

1gm BD -> trough 6 1.5gm BD -> trough 11

3gm infusion->15 4gm infusion->steady state 21

8 hr Creat Clearance 200ml/min

USCOM Cardiac output 8 l/m



Udy et al *Int J Antimicrob Agents* 2010;35:606-8

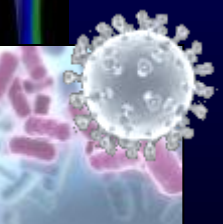
CASE TWO

Mr IF 29 M 40% BURNS + INHALATIONAL INJURY

3rd week into ICU - Cipro sensitive CRAB
On norad 5µ/min, MAP 70, P 80, T 38^{5}, Na 139
Cr 60 U/O <1.5ml/kg/hr.

CIPROFLOXACIN

400mg tds level at 4hrs level 1.2mg/l
Lipman et al – should be about 2mg/l
USCOM Cardiac Output 10l/m



Udy et al *Int J Antimicrob Agents* 2010;35:606-8

CASE THREE

Mr RJ 29 M 28% BURNS + INHALATIONAL INJURY

2nd week into ICU - Amikacin sensitive CRAB

Off inotropes, MAP 80, P 100, T 38, Na 140

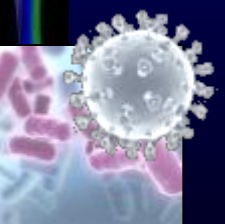
Cr 55, U/O <1.5ml/kg/hr.

AMIKACIN

20mg/kg/day 14hrs 1.2

30mg/kg/day 14hrs 2.4

30mg/kg/18hourly trough <1



Udy et al *Int J Antimicrob Agents* 2010;35:606-8

CASE FOUR

Mr CS 19 M MULTI-TRUAMA - SEVERE CLOSED HEAD INJURY->DECOMPRESSIVE CRANIECTOMY

3rd week into ICU - 5th day VAP

Off inotropes, MAP 100, P 116, T 38^{6}, Na 148

Cr 56, U/O 1-1.5ml/kg/hr.

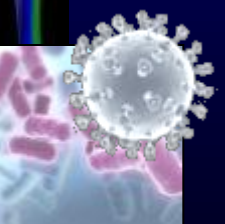
MEROPENEM

2gm 8 hourly

Trough - undetectable

Creatinine Clearance 224ml/min

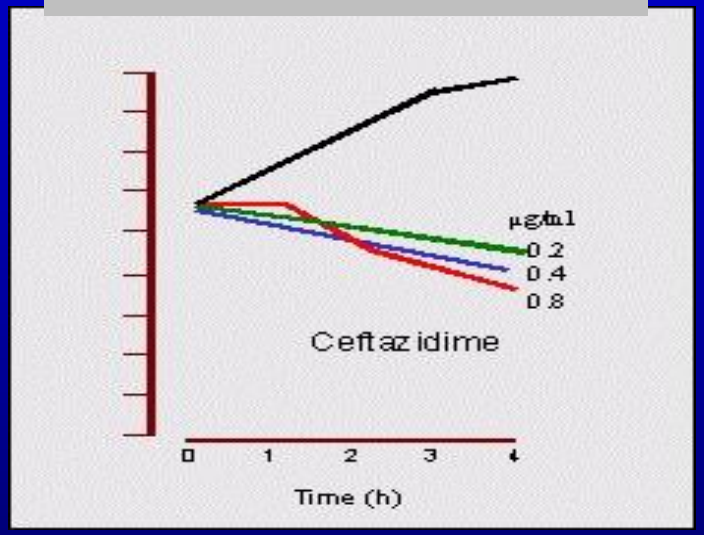
USCOM Cardiac Output 10l/min



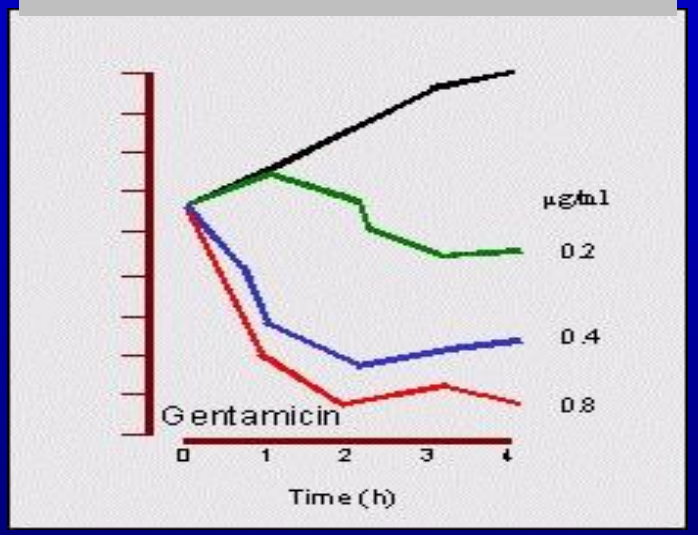
Udy et al *Int J Antimicrob Agents* 2010;35:606-8

KILL CHARACTERISTICS

TIME DEPENDENT



CONC. DEPENDENT



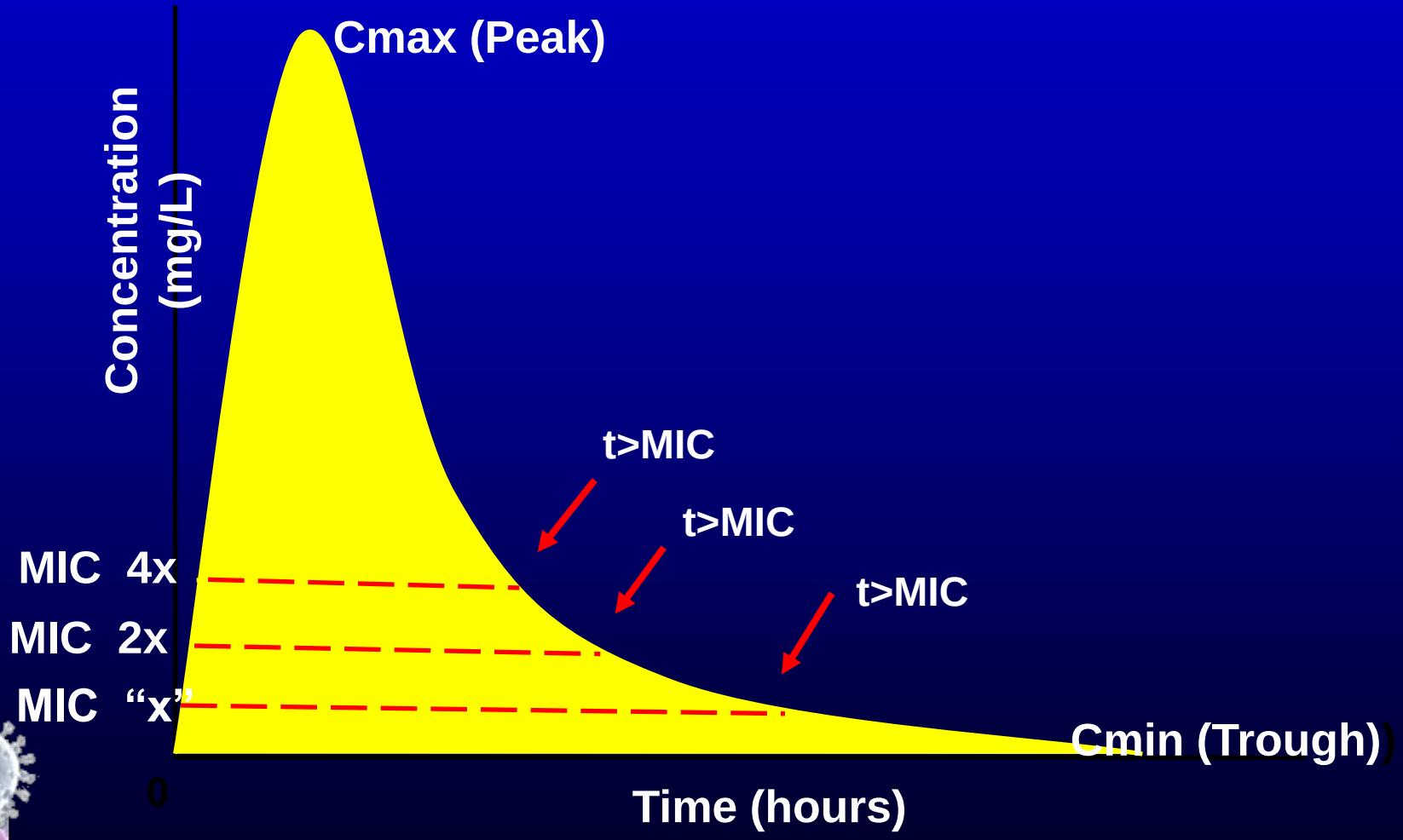
ß-lactams:
Time>MIC

Aminoglycosides:
Dose dependent

Vancomycin
?Time>MIC

Fluoroquinolones:
Peak/MIC AUC/MIC

Serum antibiotic levels over a dosing interval



EXTENDED INFUSIONS

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkn543

MARCH 2009;63: 560-563

JAC

Comparison of the pharmacodynamics of imipenem in patients with ventilator-associated pneumonia following administration by 2 or 0.5 h infusion

Sutep Jaruratanasirikul* and Teeratad Sudsai

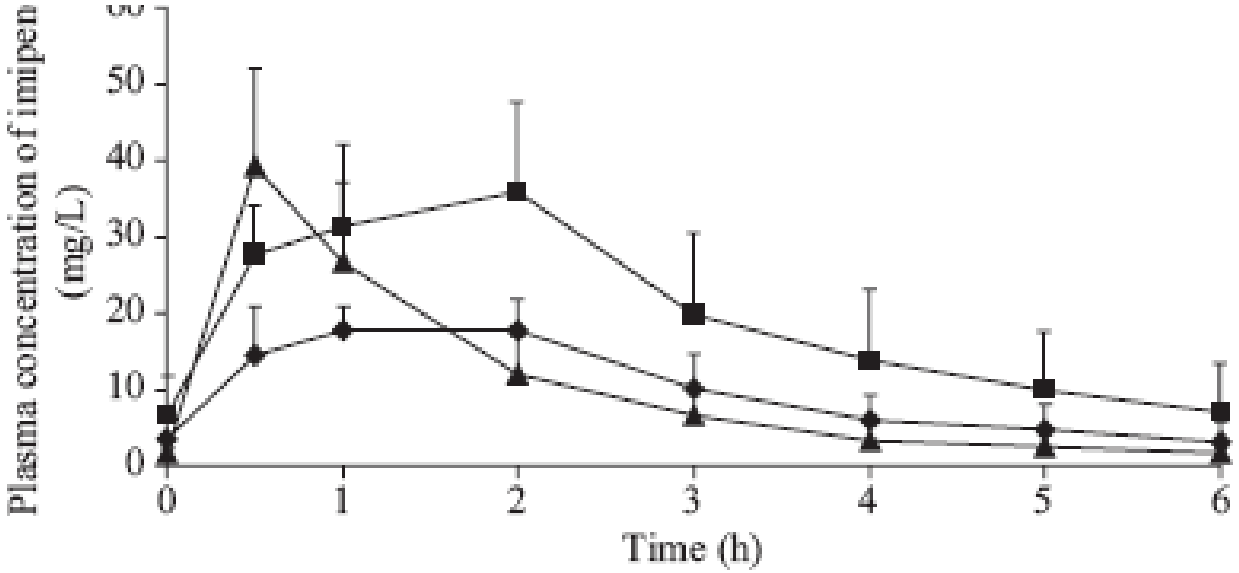
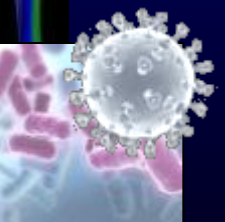


Figure 1. Mean plasma imipenem concentration–time data for nine patients with VAP following administration of: 0.5 g, 0.5 h infusion (filled triangles); 0.5 g, 2 h infusion (filled diamonds); and 1 g, 2 h infusion (filled squares).

NEW TREATMENT PARADIGM

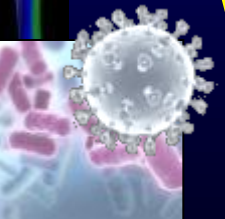
OLD	NEW
Start with penicillin	Get it right 1st time
Cost efficient low dose	Hit hard up front
Low doses=less side eff	Low dose → resistance
Long courses≥2 weeks	Seldom longer than 7d



Lipman and Boots *Crit Care Resusc* December 2009

RATIONAL USE OF ANTIBIOTICS

- Use only when necessary
- Start as quickly as possible (once decided)
- Start broad spectrum – to cover all likely organisms, send cultures and de-escalate
- Seldom need longer than a 1 week course
- **HIGHEST DOSE (USING PK/PD PRINCIPLES) WITHOUT SIDE-EFFECTS**



BROAD COVER
DOES NOT INCLUDE

- Antibiotics for SIRS/viral infections
- Cover all options doctor
  ("just in case")
- Inappropriate prophylaxis
  of long duration
  with broad spectrum A/Bs

"just in case" Doctor

We need staph cover !

Is it Pseudomonas ?