Beta-lactamase and breakpoints: do we have the right ones?

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Disclosure

- Achoagen Inc
- Allecra
- AstraZeneca
- Basilea Pharmaceutica LTD
- Biomerieux
- DaVolterra
- Durata
- Merck & Co. Inc.
- Rempex/The medicines company
- Rib-X
- Synthezza
- Valneva

The short answer: No

I will argue that:

- The principal of breakpoint is problematic especially for MDR
- There are inconsistencies in determination of breakpoint
- Breakpoint provide easy to generate but are misleading
- Use examples from ESBL and CRE

ANTIBIOTIC SENSITIVITY TESTS: A RAPID METHOD SUITABLE FOR MULTIPLE CULTURES

BY

J. G. P. HUTCHISON

FIG. 3.—A view of the apparatus showing the general layout of the grid table and reflector together with accessories.

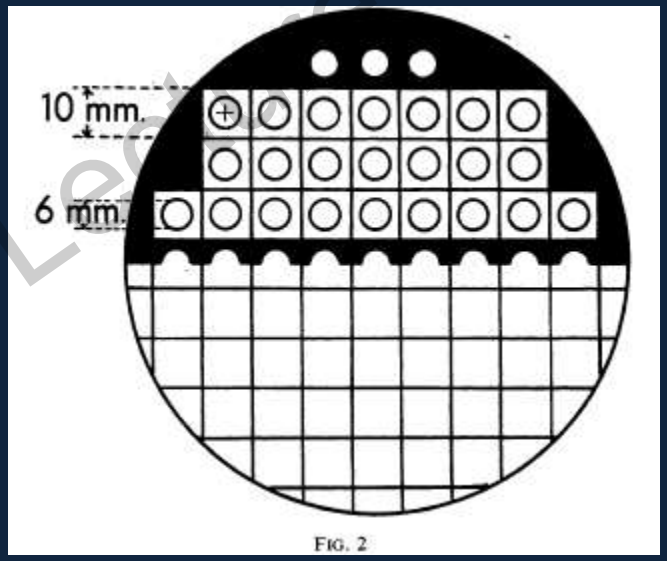


FIG. 2

"for routine purposes three level of penicillin, and two levels of streptomycin and chloramphenicol are tested"

J Clin Pathol 1954

Susceptibility testing

- Same principal is used today
- Specimen is received in the la
  - isolate identified
  - based on identification tested for susceptibilities
- Performed in standard media
- At standard inoculum
- Using various antibiotic concentrations
  - Often for practical reasons growth on few concentrations of interest are examined
  - MIC is not determined for most isolates

Reporting (Use of the breakpoint(

- Based on growth at the tested concentrations results are reported as S (I) R
- The interpretation of the clinician in the trenches is:
  - (S) OK to treat with an agent
  - (R) not OK to treat
- Even by expert this is often the interpretation:
  - Most outcomes studies dichotomize analysis by adequate or inadequate treatment
  - Adequacy is determined by the report S or R
- The result may have legal implications

The breakpoint

- The concentration of antibiotic that when tested according to standard methodology an organism shows:
  - No growth: signifies “report as (S)” i.e. give permission to treat with the agent
  - Growth: report as R (no permission to treat)

Breakpoint and the SIR report

- Very convenient for the microbiology laboratory
  - Simple scheme
  - Few drug concentration needs to be tested
  - Relatively easy to determine
  - Relatively little expertise is required (see the near extinction of clinical microbiologists in many countries)
- Very convenient for the clinician
  - An orthopedic surgeon who does not know if Morganella is gram negative or positive can interpret the result and choose treatment
- Excellent for epidemiology and research
  - groups are clearly defined

Do we have the right breakpoint?

- I would like to argue that the concept of breakpoint is misleading and there is no correct breakpoint
- When considering MDR organisms breakpoints should not be reported.
- The exact MIC is required
  - Only specialists should make antibiotic decisions regarding these patients and they should make decision using MICs among other considerations
- Mechanism of resistance should be reported

What is a breakpoint?

- Breakpoints are hopeless attempt by human beings to describe in one number a very complex interaction between
  - Host (single species) with great between-individuals biological variability
  - Pathogen (multiple species) with infinite between bacteria variability
  - Antibiotic reaching variable free drug concentrations at the site of infection
- This one number dichotomizing the decision treat/do not treat with an agent

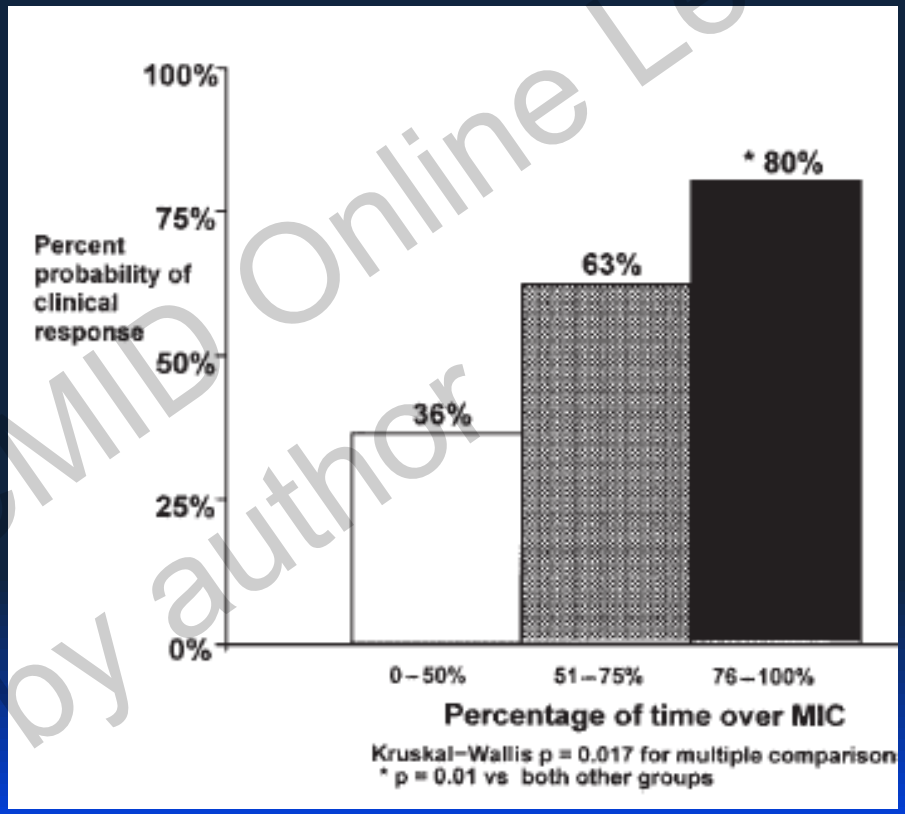
For MDR organisms

- "Major errors": i.e. reporting (R) when there is good chance that treatment will cure the infection, or reporting (S) when there is high likelihood that treatment will fail.
  - Traditionally laboratories opt to report on the "safe side" i.e. reporting (R)
- For MDR this may be the wrong strategy as very few treatment options are available many of which have questionable clinical efficacy
- Various individual considerations may change the likelihood of target attainment for 2-3 fold difference in MIC

The immune status of the patient

Pharmacokinetics and Pharmacodynamics of Meropenem in Febrile Neutropenic Patients with Bacteremia

Robert E Ariano, Anna Nyhlén, J Peter Donnelly, Daniel S Sitar, Godfrey KM Harding, and Sheryl A Zelenitsky



Ann pharmacotherapy 2005

Pharmacodynamics of meropenem in critically ill patients with febrile neutropenia and bacteraemia

Sutep Jaruratanasirikul[a,*], Thanya Limapichat[a], Monchana Jullangkoon[a], Nanchanit Aeinlang[a], Natnicha Ingviya[b], Wibul Wongpoowarak[c]

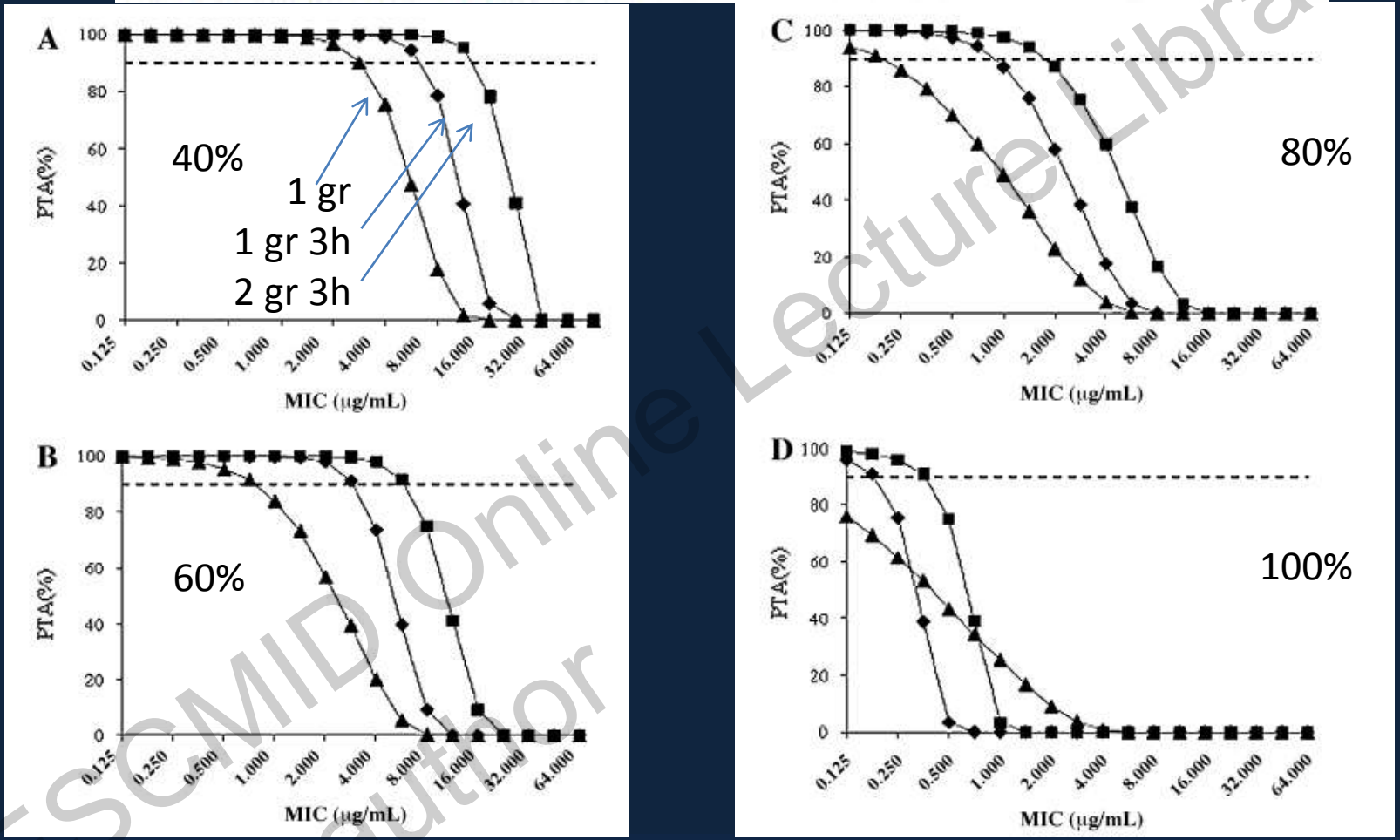


Fig. 2. Probability of target attainment (PTA) for meropenem regimens achieving (A) 40% *T*> MIC, (B) 60% *T*> MIC, (C) 80% *T*> MIC and (D) 100% *T*> MIC (D) at specific minimum inhibitory concentrations (MICs) in eight febrile neutropenic patients after administration of a 1 g bolus injection (▲), a 3-h infusion of 1 g (♦) and a 3-h infusion of 2 g (■). The broken line represents 90% PTA. *T*> MIC, time that concentrations in tissue and serum are above the MIC.

Int J Anti Agent 2011

CPE with carbapenem MIC <8 have similar mortality to non-CPE treated with carbapenem

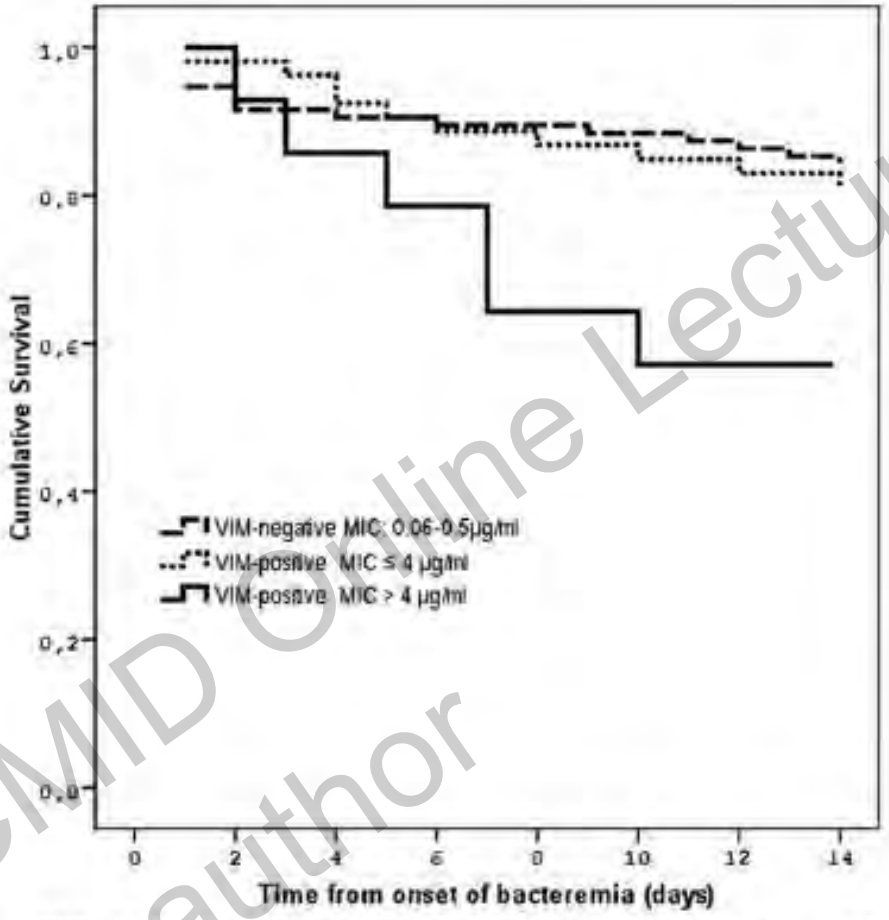


FIG. 1. Kaplan-Meier curves of survival probability of patients with *K. pneumoniae* bloodstream infections according to susceptibility of the infecting organism to carbapenems. Patients infected with a VIM-positive organism for which the MICs of both imipenem and meropenem were >4 µg/ml were more likely to die than those infected with a VIM-positive carbapenem-susceptible or VIM-negative organism (log rank = 6.27, $P = 0.044$).

Daikos G. AAC 2009

Renal clearance, volume of distribution, protein binding

Augmented Renal Clearance

Implications for Antibacterial Dosing in the Critically Ill

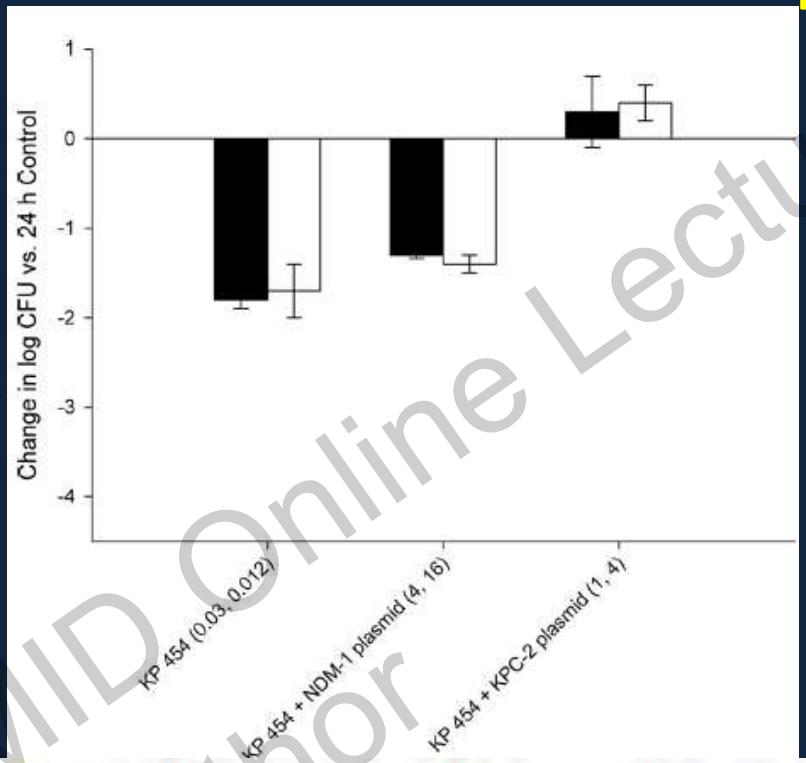
Andrew A. Udy,[1,2] *Jason A. Roberts,*[1,2,3] *Robert J. Boots,*[1,2] *David L. Paterson*[4,5] and *Jeffrey Lipman*[1,2]

The Effects of Hypoalbuminaemia on Optimizing Antibacterial Dosing in Critically Ill Patients

Marta Ulldemolins,[1,2,3] *Jason A. Roberts,*[1,4,5] *Jordi Rello,*[2,3,6] *David L. Paterson*[7,8] and *Jeffrey Lipman*[1,4]

Clin pharmacother 2010, 2011

Diffrences in response to treatment with ertapenem or doripenem between isogenic strains with NDM or KPC not explained by MIC



Wiskirchen DE. AAC 2013

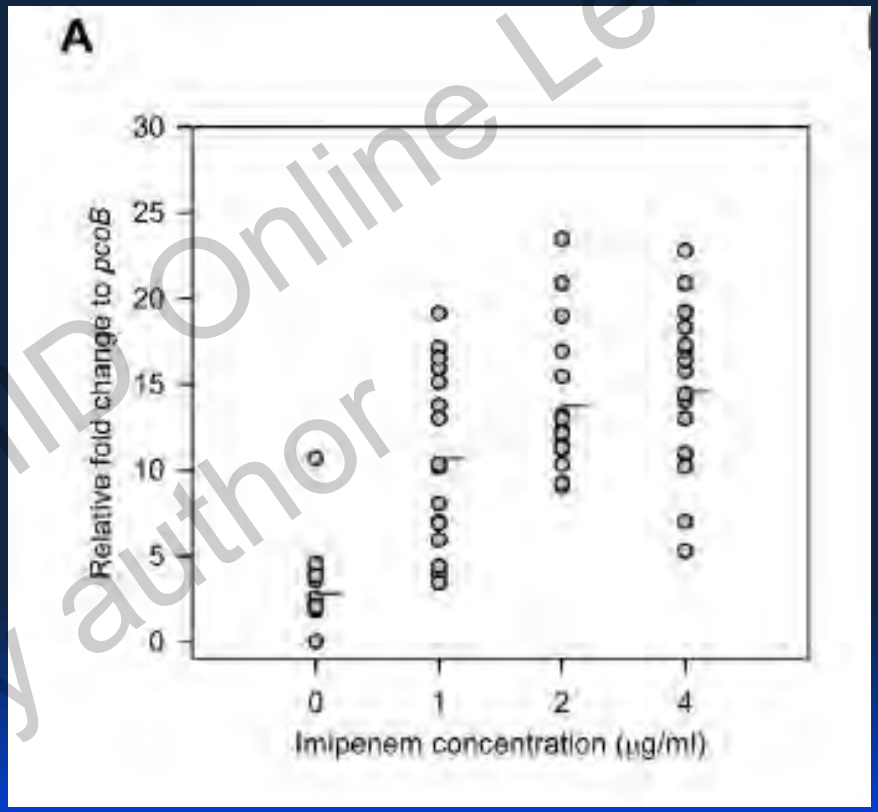
FIG 1 Change in $\log_{10}$ CFU/ml after 24 h observed in a wild-type *K. pneumoniae* strain and its derived isogenic strains harboring either an NDM-1 or a KPC-2 plasmid after treatment with human-simulated doripenem at 2 g every 8 h as a 4-h infusion (black bars) or ertapenem at 1 g every 24 h (white bars) in an immunocompetent mouse thigh infection model. Each value is the mean ± standard deviation for infected thighs for each isolate.

OPEN ACCESS Freely available online

PLOS ONE

Copy Number Change of the NDM-1 Sequence in a Multidrug-Resistant *Klebsiella pneumoniae* Clinical Isolate

Tzu-Wen Huang[1], Te-Li Chen[3,4,7], Ying-Tsong Chen[1,5,6], Tsai-Ling Lauderdale[2], Tsai-Lien Liao[1], Yi-Tzu Lee[7,10], Chien-Pei Chen[3], Yen-Ming Liu[1], Ann-Chi Lin[1], Ya-Hui Chang[1], Keh-Ming Wu[8], Ralph Kirby[9], Jui-Fen Lai[2], Mei-Chen Tan[2], Leung-Kei Siu[2], Chung-Ming Chang[1], Chang-Phone Fung[4,7], Shih-Feng Tsai[1,8,9]*



KPC producing *E. Cloacae*

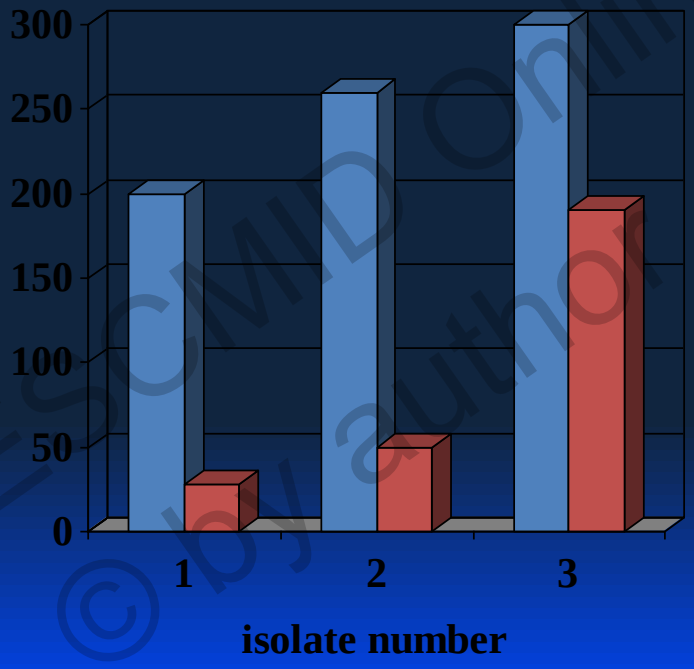
- Isolated from respiratory specimen of ventilated patients with pneumonia
- Reported as:
  - Meropenem R (MIC 4)
  - Colistin S (MIC 0.25)
  - Tigecycline S (MIC 1)
  - Amikacin S (MIC <=2)
- Is this report provide good guidance?
  - How accurate is a machine reported MIC?
  - The reports implies that colistin, tigecycline and amikacin are better options than meropenem
  - Why should tigecycline be reported on a respiratory specimen
  - What is the meaning of S for the 3 agents in VAP

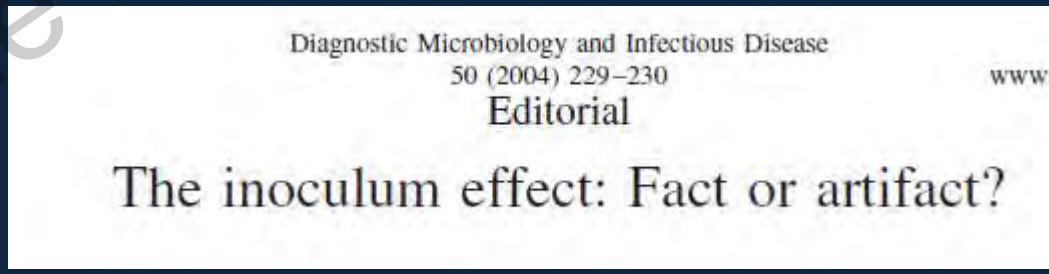
Breakpoints are determined and validated (?) in easy to treat compartments

- Should we have site specific breakpoint?
- Committees have been inconsistent with decisions
  - Strep pneumonia meningitis vs other sites
  - Should we expect different effects with other organisms, especially MDR?

Endocarditis with CTX-M-2 producing K. pneumonia failed pip/taz

- Initial isolate MIC 8
  - Inoculum effect (10^7) MIC >256
- 3rd isolate MIC >256

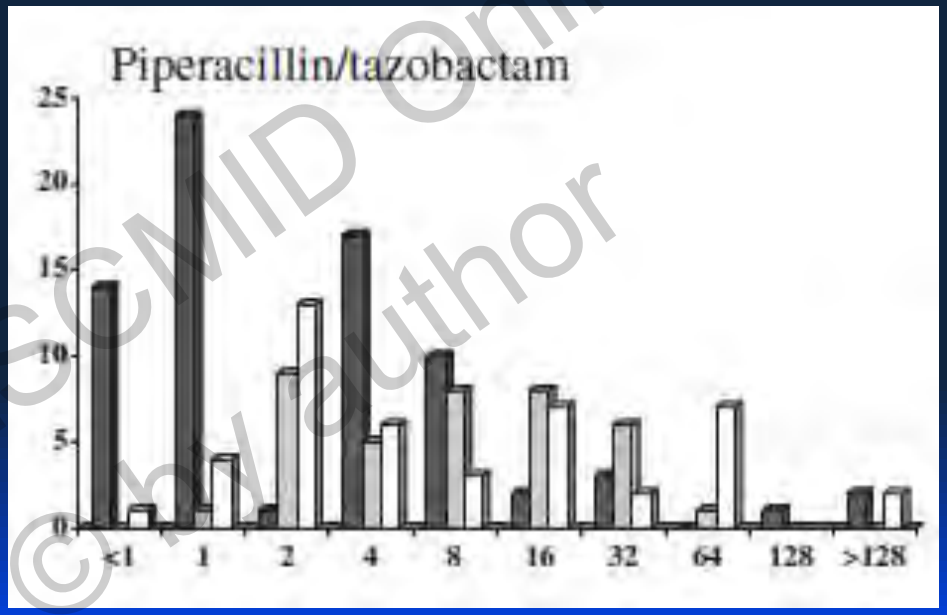



Diagnostic Microbiology and Infectious Disease
50 (2004) 229–230
Editorial
The inoculum effect: Fact or artifact?

Zimhony O. AAC 2005
Craig WA. 2004

Breakpoint for ESBL producing piperacillin/tazobactam

- Varies between 64 and 8 for by various authorities and time
- Many ESBL producing E. coli fall into the susceptible range

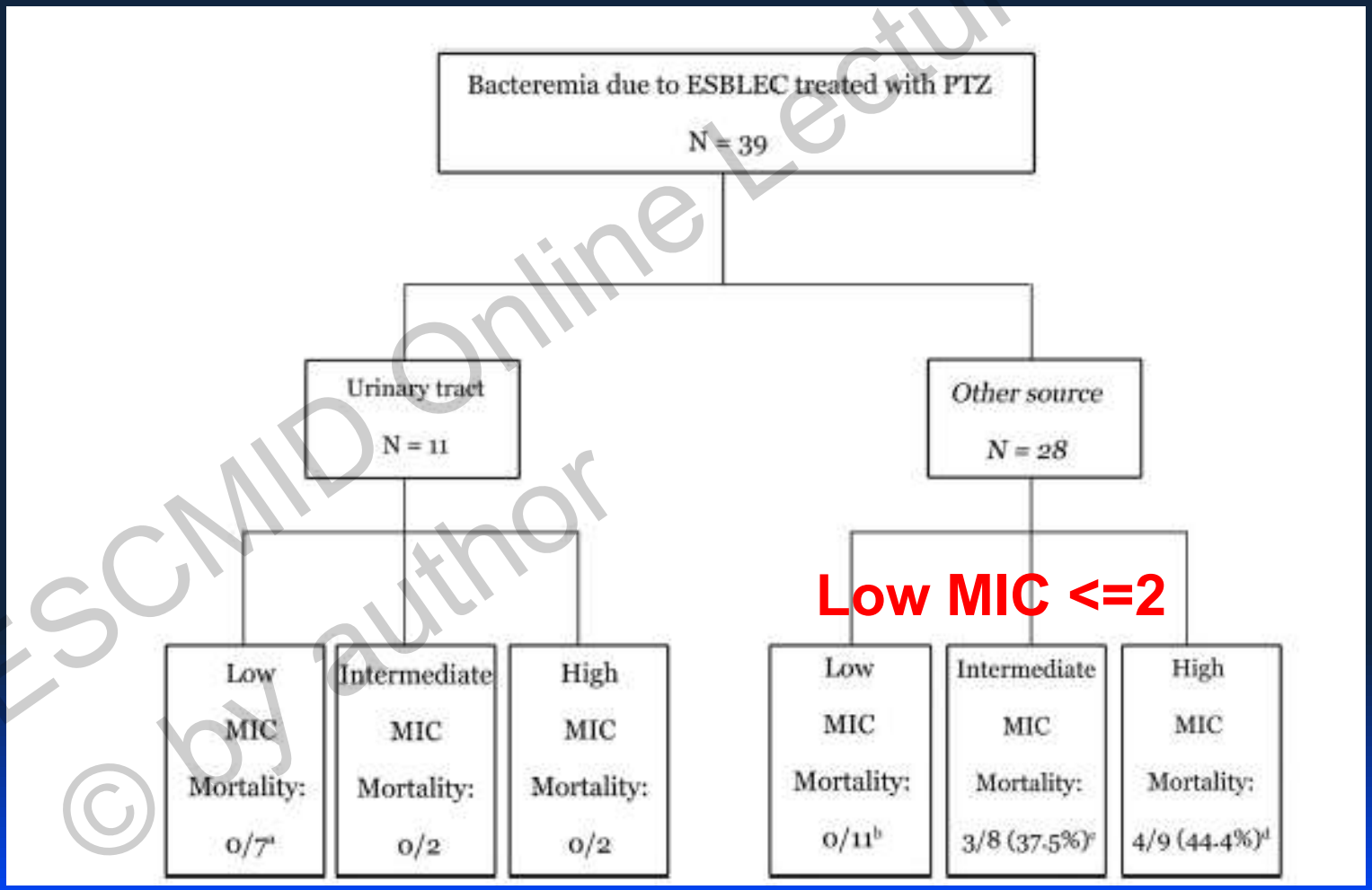


Each color represent different ESBL group

Rodrigez-bano CMI 2011

Impact of the MIC of Piperacillin-Tazobactam on the Outcome of Patients with Bacteremia Due to Extended-Spectrum-β-Lactamase-Producing *Escherichia coli*

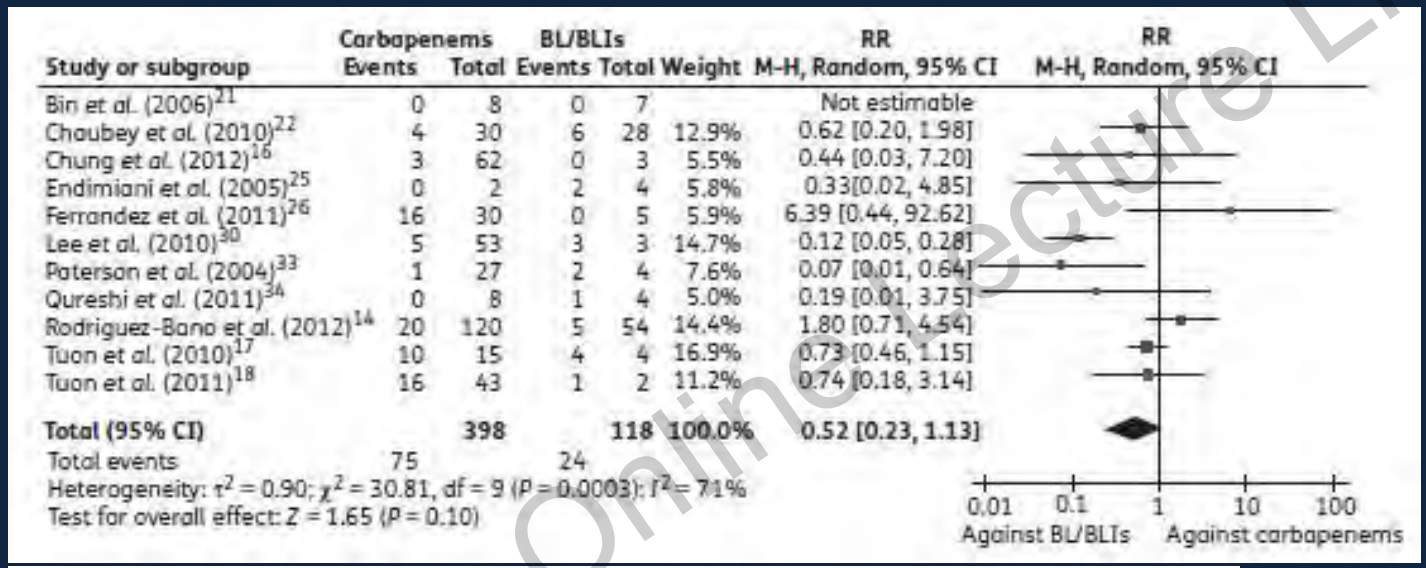
Pilar Retamar,[a] Lorena López-Cerero,[a] Miguel Angel Muniain,[a,b] Álvaro Pascual,[a,c] Jesús Rodríguez-Baño,[a,b] the ESBL-REIPI/GEIH Group

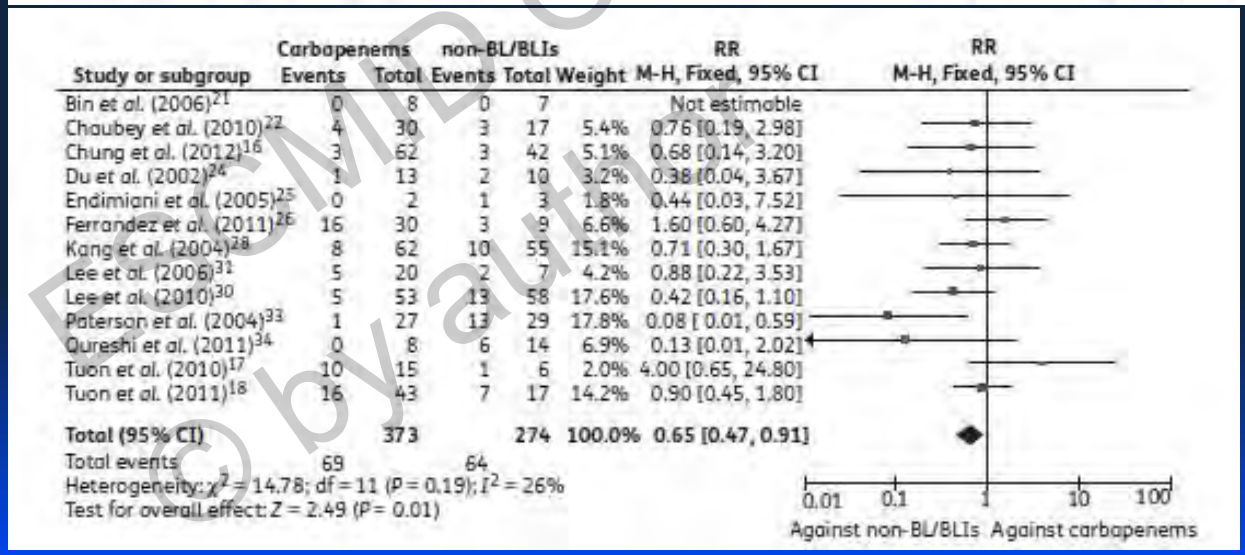


AAC 2013

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas[1,2], Giannoula S. Tansarli[1], Petros I. Rafailidis[1,2] and Matthew E. Falagas[1–3]*

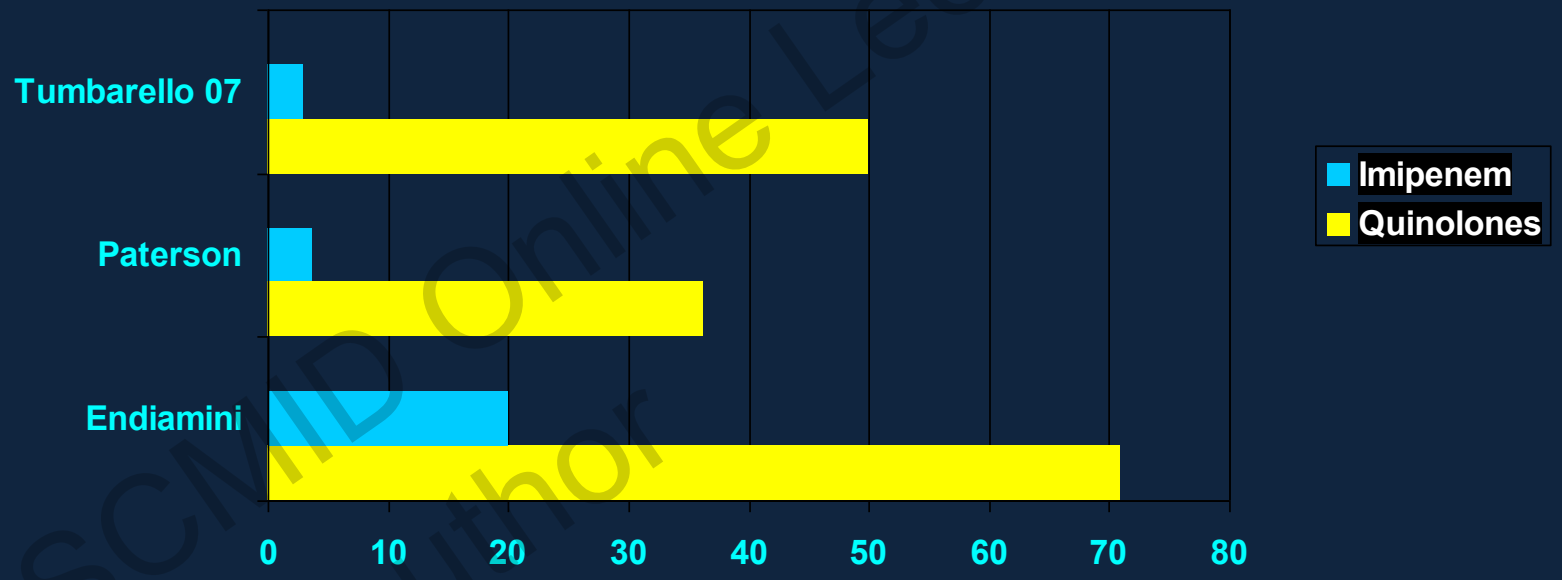




JAC 2012

Reporting mechanism of resistance adds information for treatment decision.

Mortality with ESBL bacteremia: quinolone susceptible isolates



Endiamini A. CID 2004
Paterson DL. CID 2004
Tumbarello M. AAC 2007

Breakpoints vary in time and place therefore can not be correct

- Various breakpoints
  - CLSI
  - EUCAST
  - FDA
  - PK/PD
- An organism will be considered resistant or susceptible based on the criteria that were used in the lab.
  - The patient will be treated differently based on where the culture was processed and which criteria were used.
  - Even from the same lab, if result was given on Dec 31st or January 1st, if laboratory adopted new changes

Breakpoints determination involves science but also fashions

Summary

- Correct breakpoint do not exist
  - In MDR breakpoints are misleading
- For MDR organism the laboratory should provide
  - exact accurate MIC determination without interpretation
  - Data on mechanism of resistance
  - These data should be used by experts together with clinical data to make treatment decisions
- In an era of MDR and XDR when we deal with diseases that carry high mortality rates
  - We need more sophisticated microbiology laboratories
  - Treatment by experts
  - This will be costly, however equivalent to other medical fields