How should susceptibility results (for carbapenems) be reported for carbapenemase-producers

Christian G. Giske, MD/PhD
Consultant physician / Associate professor
Karolinska University Hospital
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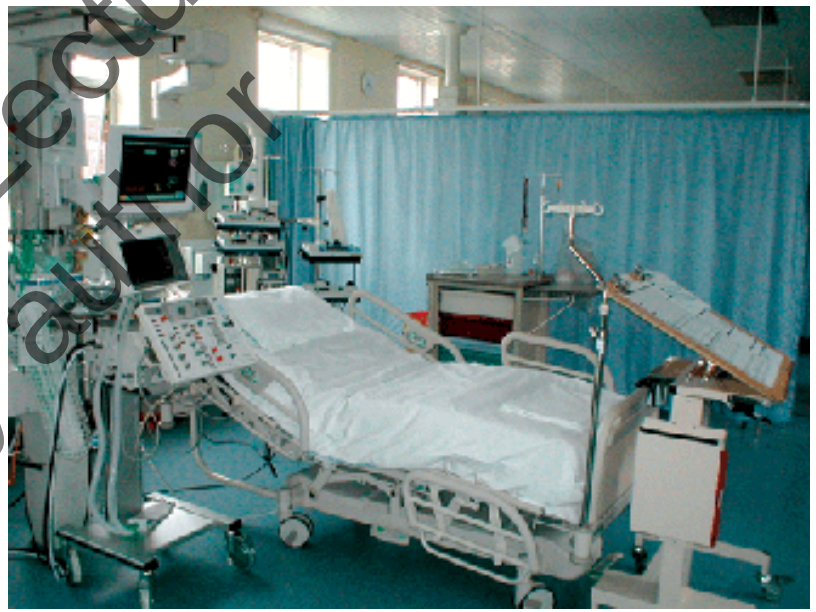
Key topics

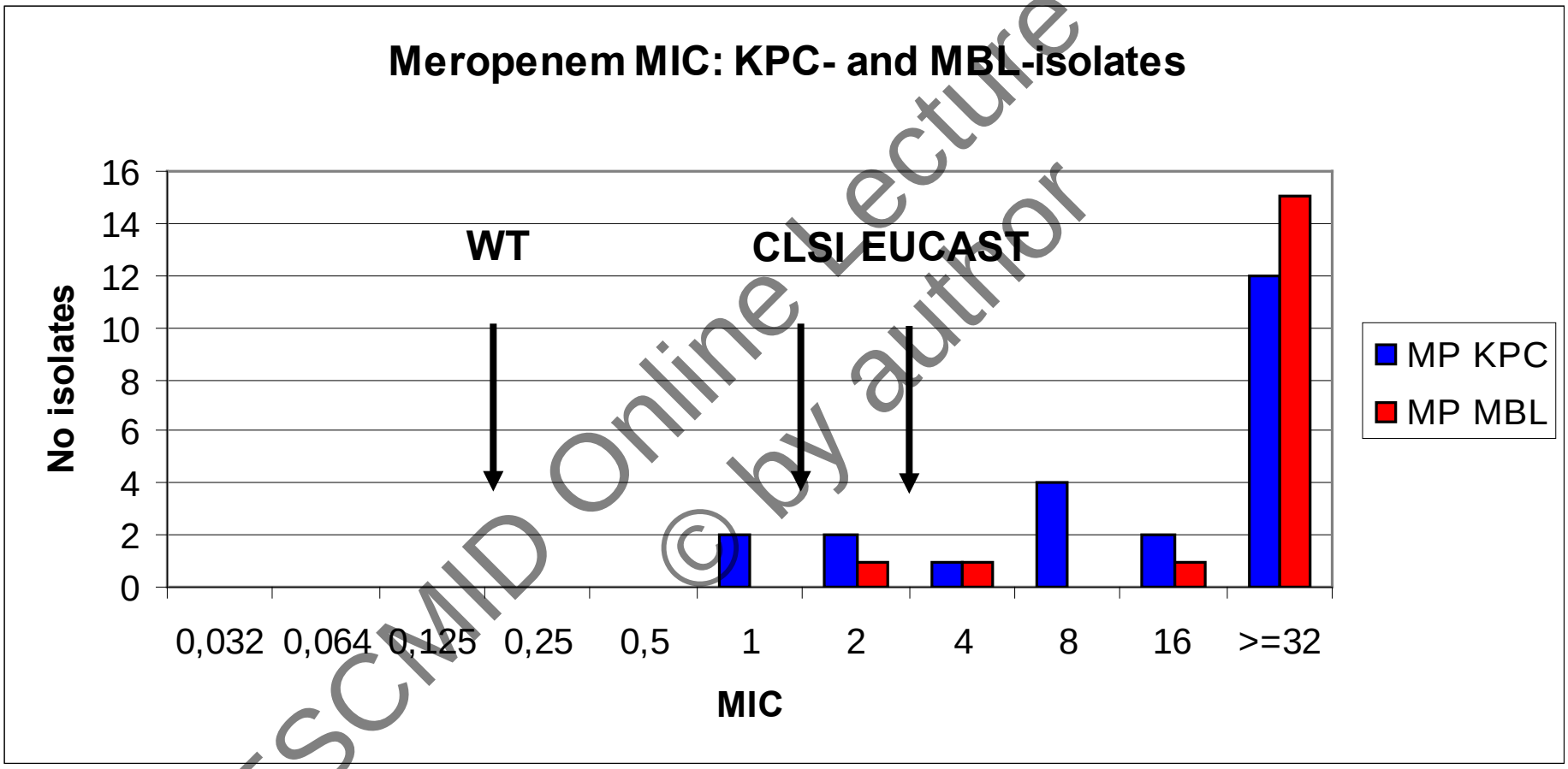
- Some initial words on therapeutic outcome
- Some carbapenemase-producers are susceptible to carbapenems (?) – the MIC paradigm
- PK/PD and carbapenemase-producers
- Clinical data for VIM-producers
- Clinical data for non-MBL-producers
- Critical voices
- What can we conclude?

Some words on therapeutic outcome

- Not all patients with susceptible strains respond
- Not all patients with resistant strains fail
- Co-morbidities and co-infections need to be taken into consideration
- Some patient populations are particularly difficult to judge in terms of therapeutic outcome

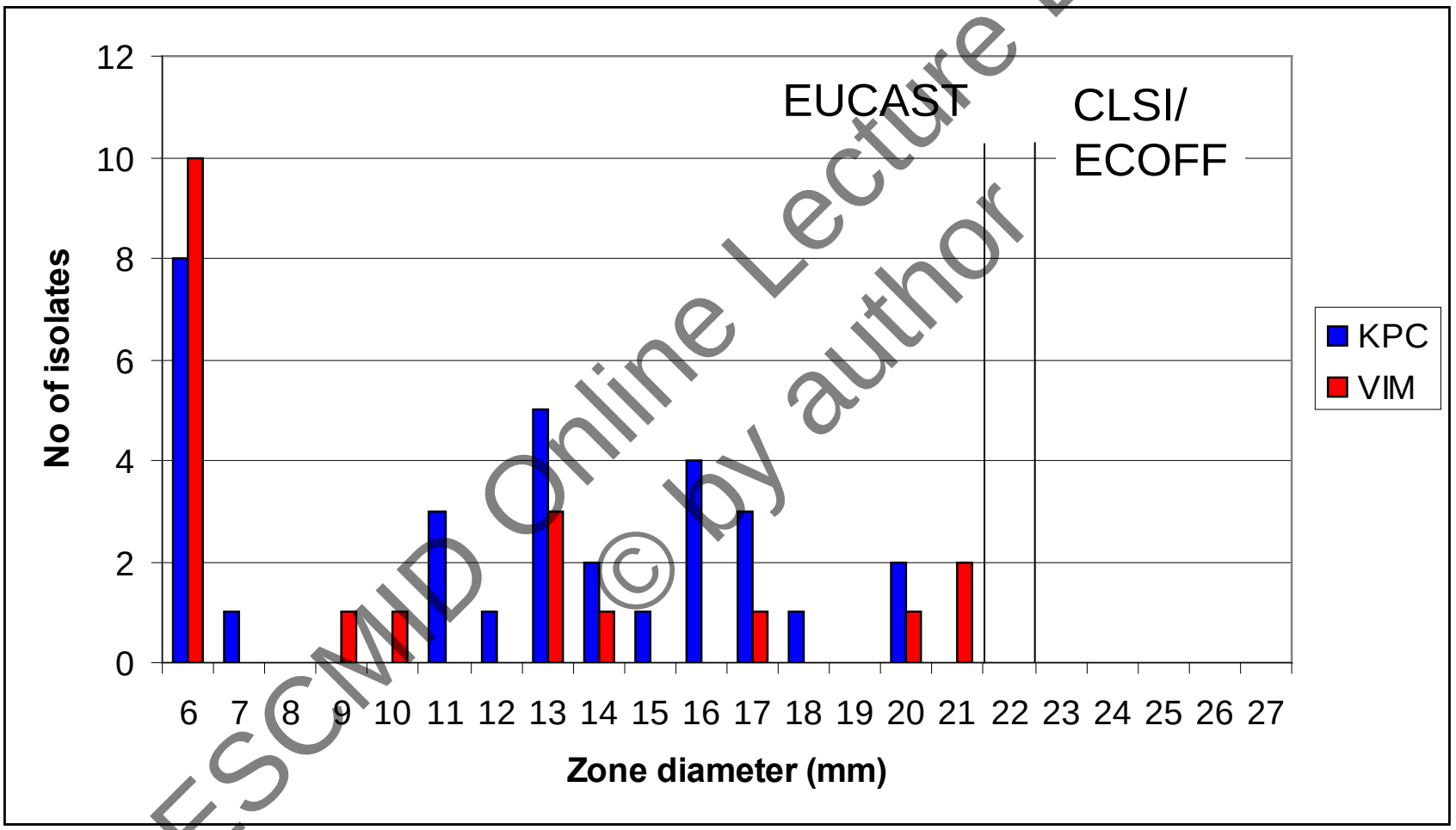


K. pneumoniae and meropenem



Vading et al. CMI; 2011: 5: 668

K. pneumoniae and meropenem



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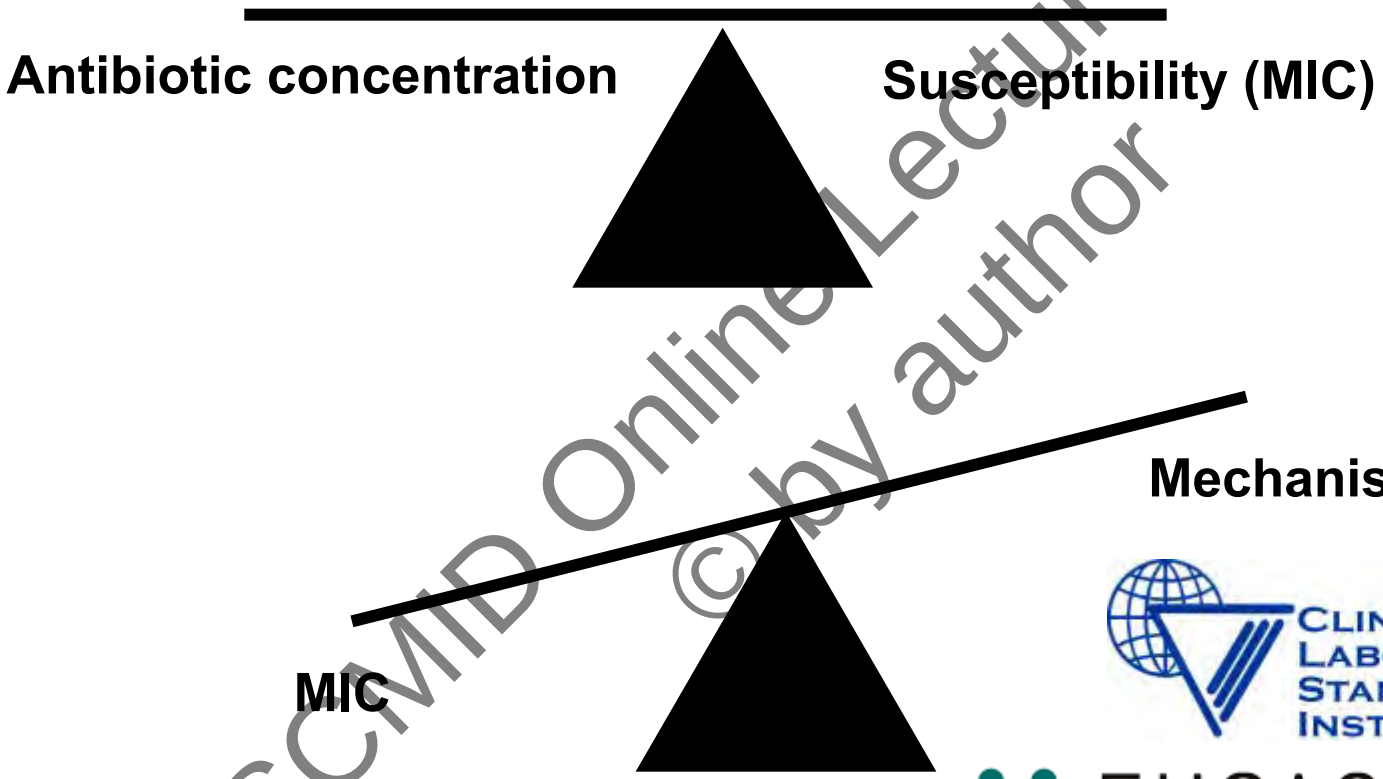
The MIC paradigm

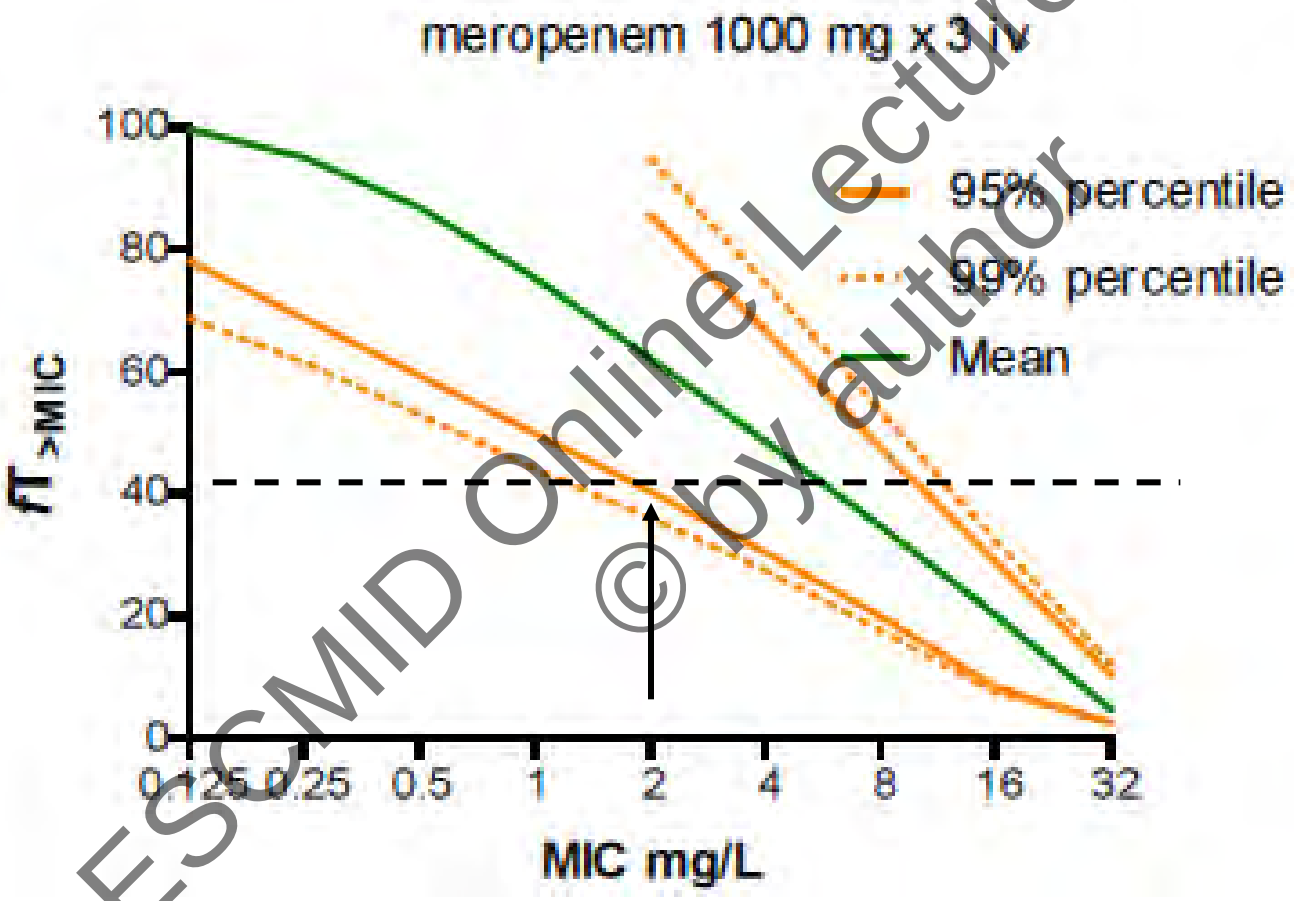


CLINICAL AND LABORATORY STANDARDS INSTITUTE

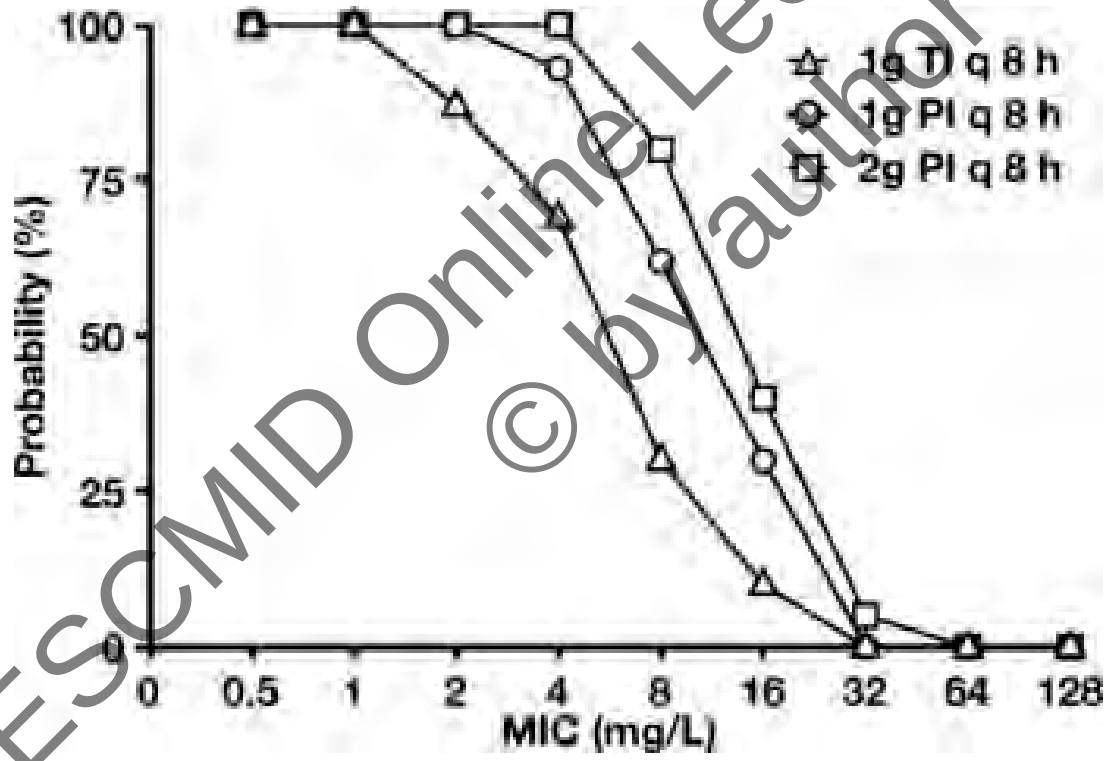
EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

PK/PD



Prolonged infusion or 2 g dosing (Kuti et al. J Clin Pharmacol 2003)



Current carbapenem breakpoints

	FDA	CLSI (2011)		EUCAST (EMA) (2011)		
	S	S	R	S	R	ECOFF
Imipenem	**≤4**	**≤1** (4)*	**≥4** (16)	**≤2**	**>8**	**≤0.5; ≤1****
Meropenem	**≤4**	**≤1** (4)	**≥4** (16)	**≤2**	**>8**	**≤0.125**
Ertapenem	**≤2**	**≤0.25** (2)	**≥1** (8)	**≤0.5**	**>1**	**≤0.06**
Doripenem	**≤0.5**	**≤1** (ND)	**≥4** (ND)	**≤1**	**>4**	**≤0.12**

*2009; ***E. coli* and *K. pneumoniae;* ND: not defined

Position of CLSI and EUCAST

CLSI

- New breakpoints published in June 2010 and January 2011*

  - to capture carbapenemase (mainly KPCs) producers

  - Rationale:
    - Pk/Pd tools avoiding PK subject variability (*inflated variance*)

- Modified Hodge test no longer necessary unless for infection control and epidemiological purposes

*Documents M100-S20-U; M100-S21

EUCAST

- Breakpoints published in 2006 and with doripenem in 2008*

  - define as “clinical breakpoints” not to detect carbapenemases

  - Rationale:
    - MIC distribution of wild-type isolates, MBL-KPC producers
    - Pk/Pd and clinical data

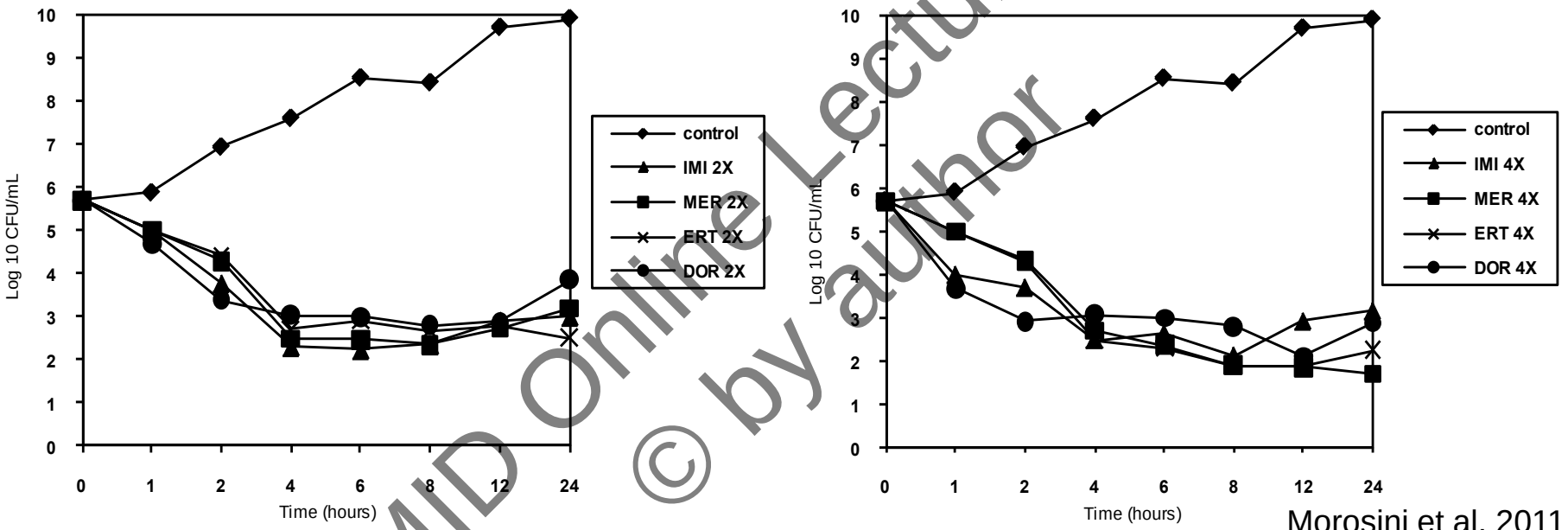
- Carbapenemase detection no longer necessary for clinical categorization unless for infection control purposes

*Version 1.3, January 2011

Preclinical data

- Bactericidal activity against VIM-1-producing *K. pneumoniae*

  MIC: imipenem, meropenem, doripenem = 8 mg/L, ertapenem = 1 mg/L

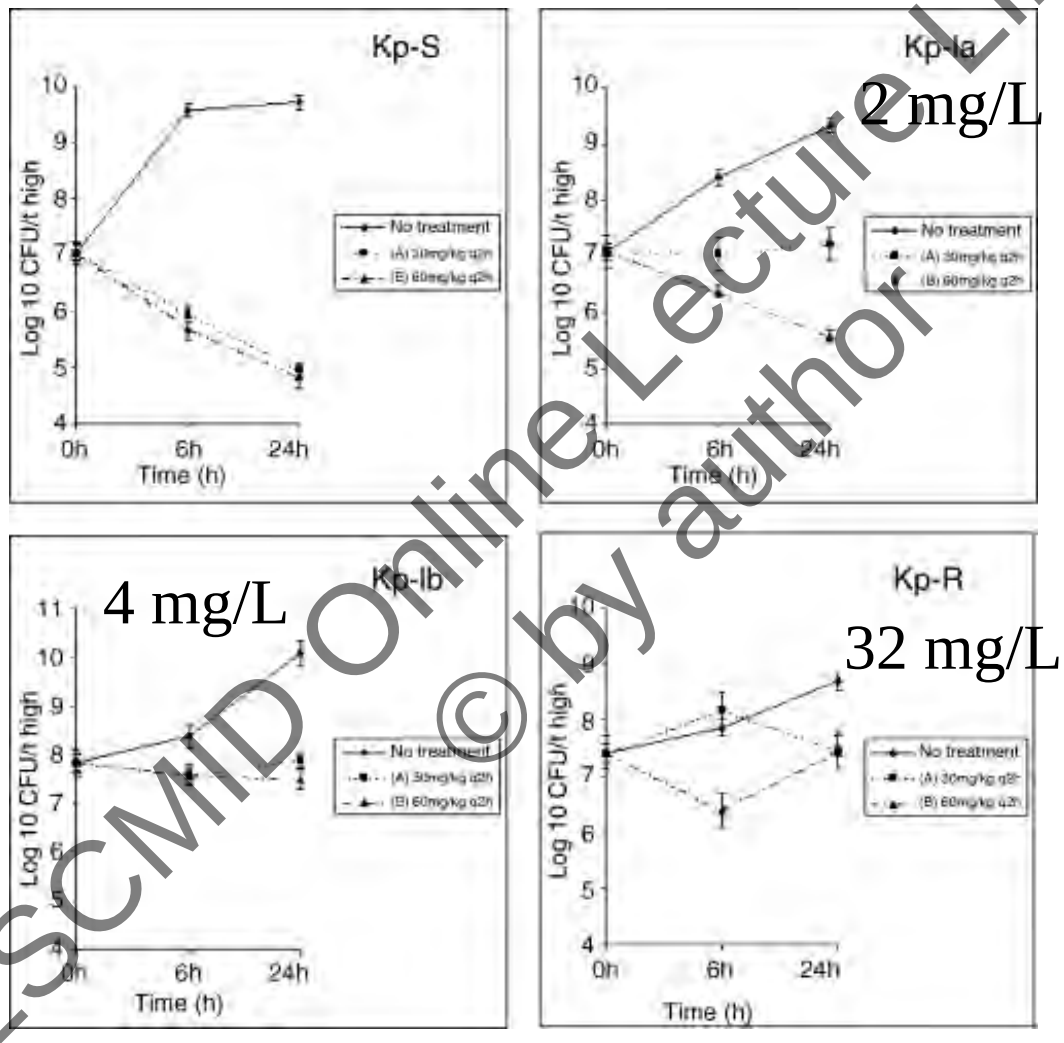


Morosini et al. 2011

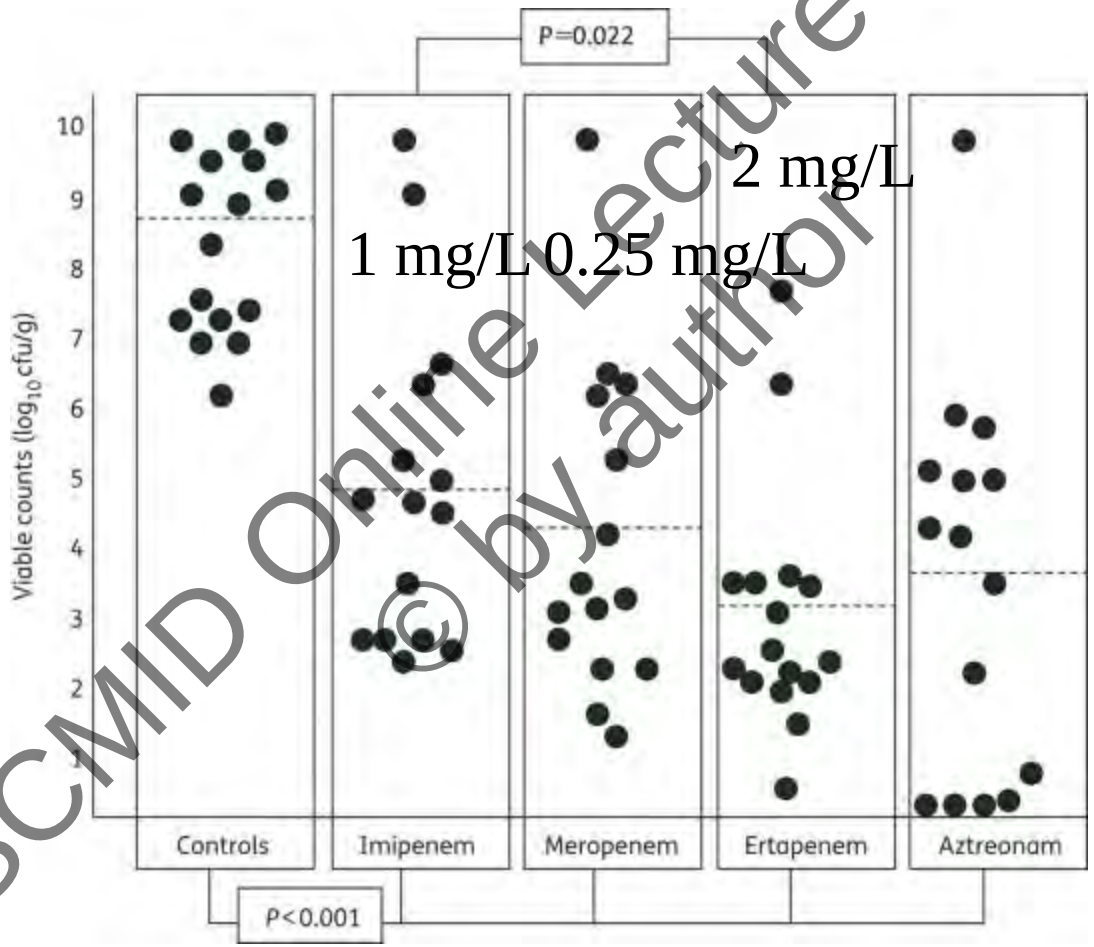
- Presence of KPC in Enterobacteriaceae exhibiting carbapenem MICs between 1-16 mg/L had no impact on the PD (%T > MIC) necessary for bacteriostasis by carbapenems

Craig et al. 48th ICAAC, 2008, abstract A-029

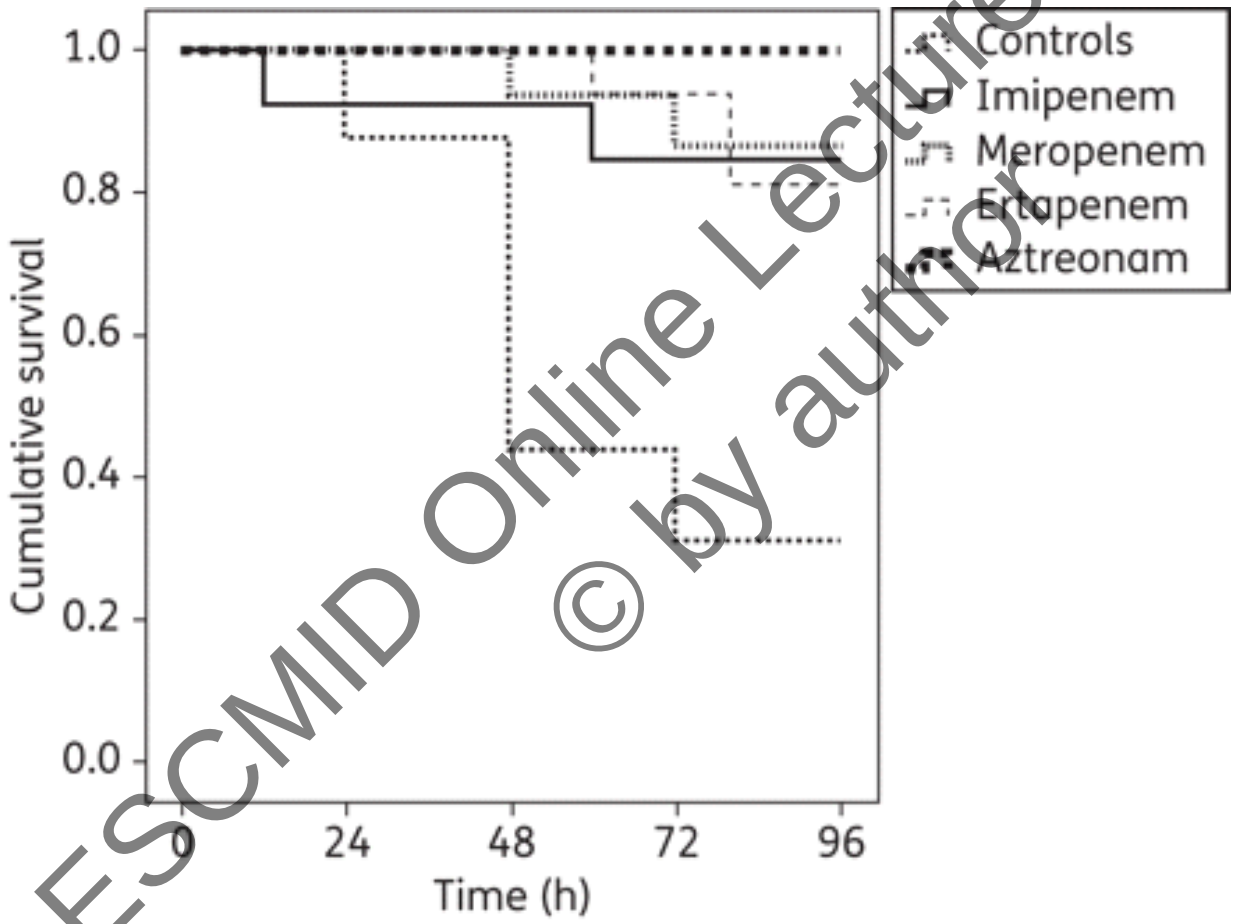
Daikos G et al. CMI 2007 (rat, neutropenic thigh)



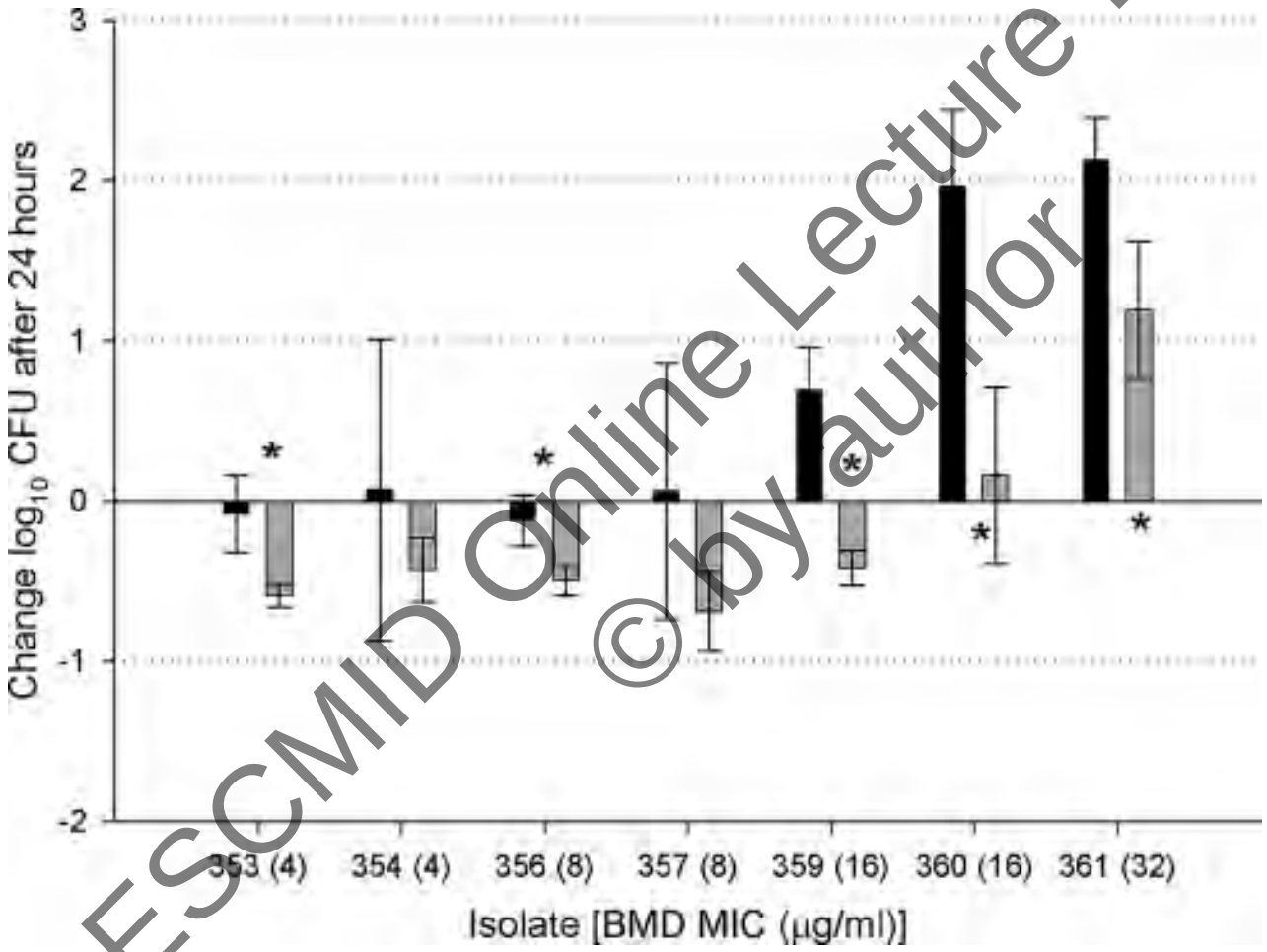
Souli et al. JAC 2011 (Rabbit, intraperitoneal infection)



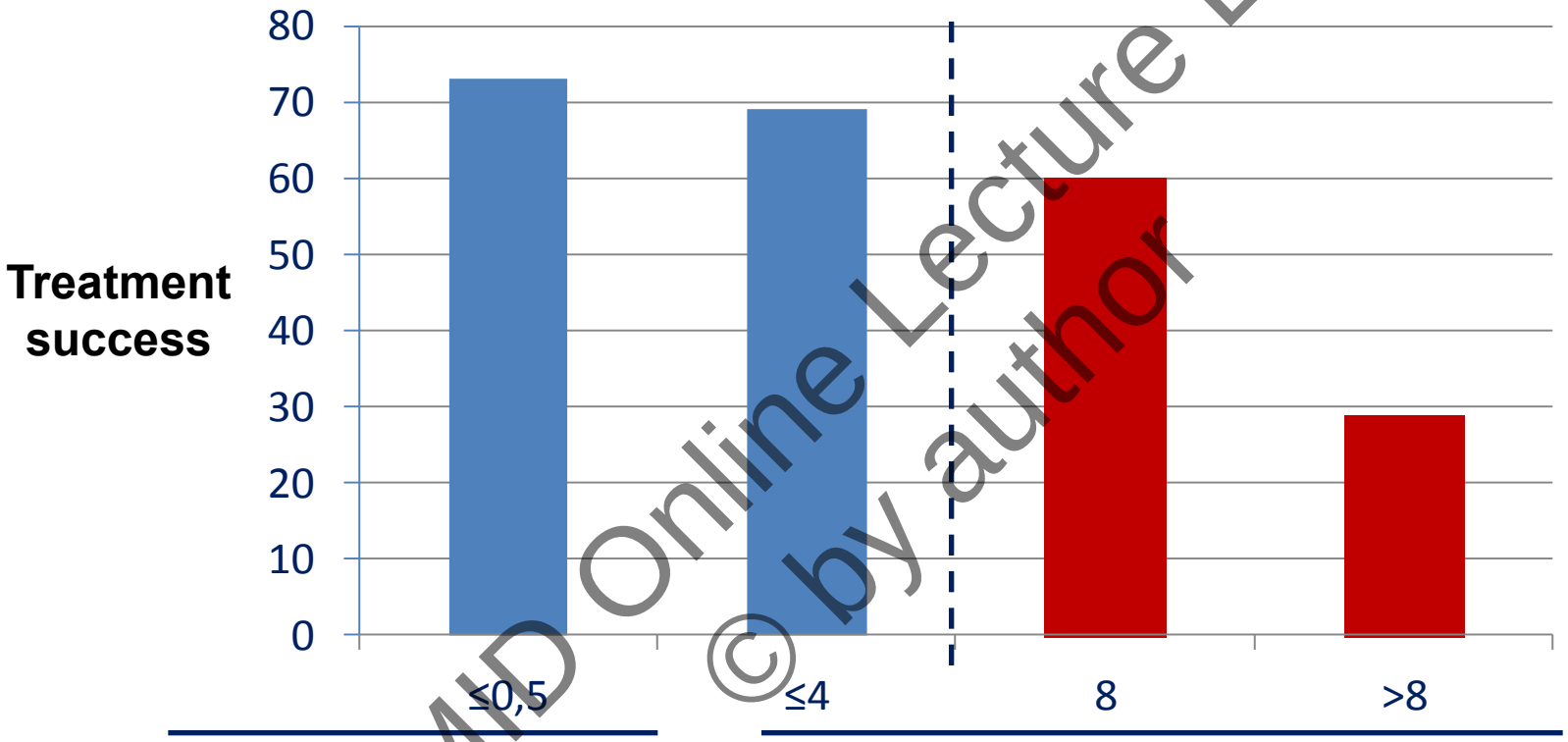
Souli et al (cont): survival of animals



Bulik et al. AAC 2010



Clinical outcomes of carbapenem monotherapy



22 patients with non-carbapenemase-producing *K. pneumoniae* isolates

44 patients with VIM, NDM or KPC producing *K. pneumoniae* isolates

Daikos et al.Clin Microbiol Infect 2011; 17: 1135-41

Weisenberg et al (KPC) DMID 2009

Age (year)/sex	Underlying condition	Acute illness (tested isolate site)	Apache II	MIC (Vitek/Etest)	Treatment (days)	Response
46/F	Skin graft	Bacteremia (blood)	6	4/8	Imipenem (7), port removal	Microbiologic and clinical success
61/F	CHF	Pyelonephritis (urine)	21	2/≥32	Imipenem (7)	Microbiologic and clinical success
82/M	None	Urosepsis (blood)	25	4/2	Imipenem (14)	Microbiologic and clinical success
92/M	Dementia	Pneumonia (resp)	12	4/2	Imipenem (3)	Clinical success
64/F	Esophageal cancer	Tracheobronchitis (resp)	15	4/2	Imipenem (12)	Microbiologic failure
76/M	Cerebral hemorrhage	Tracheobronchitis (resp)	21	2/0.25	Meropenem (7)	Clinical and microbiologic failure
69/F	Metastatic cancer	Pneumonia (resp)	36	4/8	Imipenem (6)	Clinical failure/death
77/M	MRSA 1 abscess	Tracheobronchitis (resp)	23	4/≥32	Imipenem (7)	Microbiologic failure
52/M	Melanoma	UTI (urine)	17	4/12	Imipenem (14)	Microbiologic failure
67/M	Polyneuropathy	Urosepsis (blood)	21	4/≥32	Tigecycline (7)	Clinical and microbiologic failure
65/M	Lung mass	Tracheobronchitis (resp)	15	4/1	Tigecycline (7)	Clinical and microbiologic success
83/F	Laryngeal cancer	Pneumonia (blood)	14	≥16/≥32	Tigecycline (7)	Clinical success
39/F	Stem cell transplant	Urosepsis (urine)	12	8/8	Tigecycline (14)	Clinical success
79/M	None	Pneumonia (resp)	27	8/32	Tigecycline (14)	Clinical success
19/M	Trauma, craniotomy	Shunt associated meningitis (CSF)	18	N/A	Tigecycline/gentamicin[a]	Clinical and microbiologic success
79/F	s/p CABG	Bacteremia (blood)	29	8/2	Tigecycline/imipenem	Clinical failure/death
0/M	Seizures	Pneumonia (resp)	n/a	≥16/≥32	Gentamicin (7)	Clinical success
60/F	Metastatic cancer	Wound (wound)	25	8/≥32	Amikacin (7)	Clinical success
59/F	ESRD	Line infection (blood)	22	≥16/≥32	Gentamicin (10)	Clinical and microbiologic success
60/F	Pelvic infection	Bacteremia (blood)	24	≥16/8	Meropenem (10)	Clinical and microbiologic failure
50/M	Liver transplant	Bacteremia	9	≥16/8	Meropenem (7)	Clinical and microbiologic success

The first 11 isolates yielded imipenem-susceptible results by Vitek 2 testing (MIC ≤4); the remainder of isolates yielded imipenem-resistant results on routine testing.

Continuous infusion of meropenem (Ho et al. Surg Inf 2011)

	Initial urine culture	*Initial blood culture*	*Re-emergence blood culture 2 months later*
Amikacin	16	16	16
Ampicillin	≥32	≥32	≥32
Ampicillin/sulbactam	≥32	≥32	≥32
Aztreonam	≥64	≥64	≥64
Cefazolin	≥64	≥64	≥64
Cefepime	≥8	Resistant (no value given)	≥8
Ceftazidime	≥64	≥64	≥64
Ceftriaxone	≥64	≥64	≥64
Gentamicin	≥16	≥16	≥16
Levofloxacin	≥8	≥8	≥8
Meropenem	2	8	8
Piperacillin/tazobactam	≥128	≥128	≥128
Tigecycline	≥8	≥8	≥8
Trimethoprim-sulfamethoxazole	≥320	≥320	≥320
Polymyxin B	Not tested	1	32

Definitive treatment: meropenem 6 g/day (continuous infusion)
HPLC: 19-29 mg/L meropenem

Critical voices

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Journal of Antimicrobial Chemotherapy

Are susceptibility tests enough, or should laboratories still seek ESBLs and carbapenemases directly?

David M. Livermore[1,2*], Jenny M. Andrews[3], Peter M. Hawkey[4], Pak-Leung Ho[5], Yoram Keness[6], Yohei Doi[7], David Paterson[8] and Neil Woodford[2]

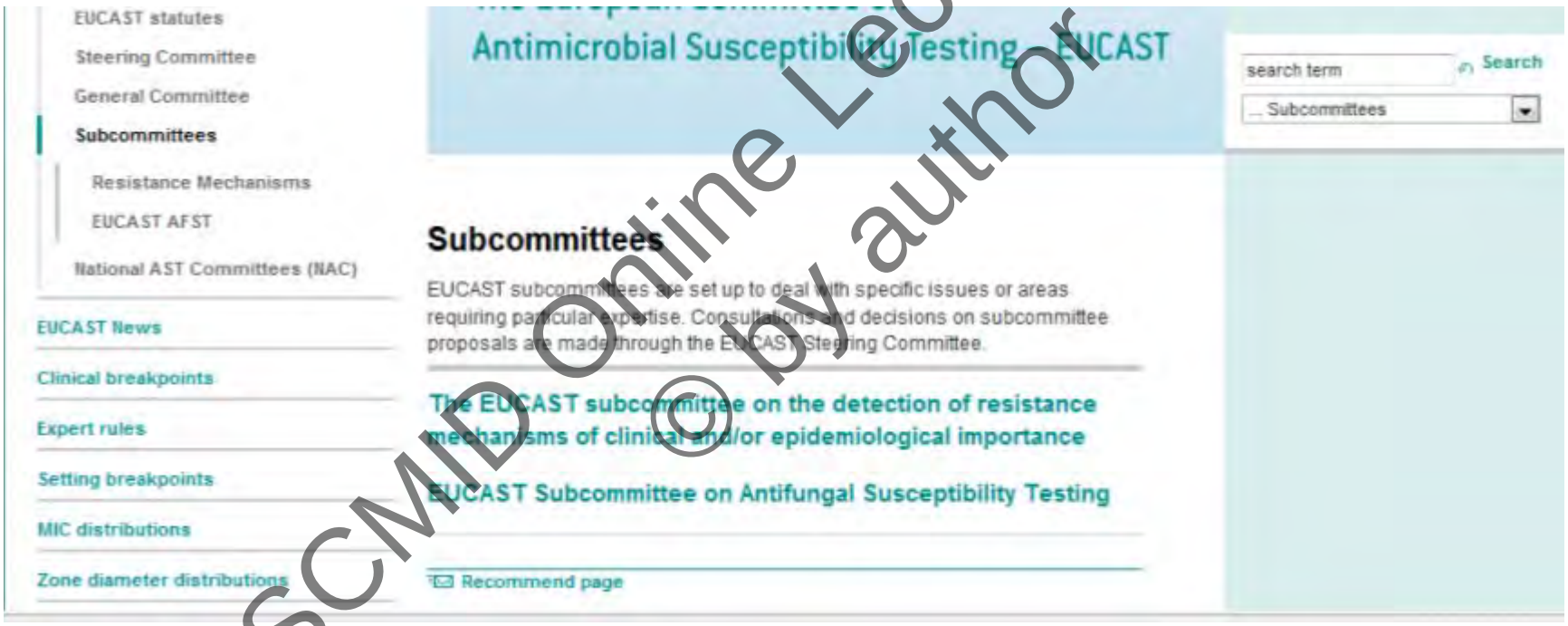
[1]Norwich Medical School, University of East Anglia, Norwich, UK; [2]Antibiotic Resistance Monitoring & Reference Laboratory, Health Protection Agency—Colindale, London, UK; [3]Department of Microbiology, Sandwell and West Birmingham NHS Trust, City Hospital, Birmingham, UK; [4]School of Immunity and Infection, The Medical School, University of Birmingham, Edgbaston, Birmingham, UK; [5]Department of Microbiology and Carol Yu Centre for Infection, The University of Hong Kong, Queen Mary Hospital, Hong Kong SAR, China; [6]Clinical Microbiology Laboratory, Emek Medical Center, Afula, Israel; [7]Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [8]University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital Campus, Brisbane, Australia

- Failures occur with carbapenemase-producers
- MICs are not reproducible
- People will stop testing for carbapenemases (and for regular ESBLs) – infection control will not be a strong enough argument

Personal comments regarding these concerns

- The data that exist (and have been reviewed here) are scarce, but if anything supports reporting as found
  → Zero failures can never be expected
- MIC-testing is not an easy task
  → Different methods should be systematically compared with ”difficult” organisms
  → Such organisms should be evaluated in vitro kinetic models to gather more data on what is the most appropriate estimate of the MIC (keeping in mind that broth microdilution is the gold standard)
  → NEQAS: some organisms may travel less well than others
- **EUCAST has not discouraged labs from carbapenemase testing**

EUCAST subcommittee for detection of resistance mechanisms



Should the breakpoints be changed?

- Breakpoints should mainly predict clinical outcomes
  → Epidemiological (microbiological) cut-offs can be used for the purpose of detecting epidemiologically significant resistance
- At present no evidence indicates therapeutic failure if carbapenem producers have low MICs
  → CLSI and EUCAST have both decided to abandon interpretive reading both for classical ESBL- and carbapenemase-producers
- Overcalling resistance can be a significant problem when treatment options are very few

So what should we finally do?

- Combination therapy is probably a good idea when facing strains with carbapenems MIC > ECOFF
  - → Treatment options are few and the consequences of further development of resistance are high
- Reporting carbapenemase-producers routinely as resistance does not make sense based on the available data in the literature
- We need to collaborate on gathering high quality outcome data – especially it is important to record MIC determined with gold standard methodology
- MIC-testing with carbapenemase-producers may be challenging and should be studied closely
- Carbapenemase-testing is extremely important from a public health point of view and should not under any circumstance be discontinued