No, we can’t treat carbapenemase and ESBL producers based on MIC

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Lead on Antibiotic resistance PHE

What I’m going to argue

- **In-vitro/in-vivo correlation poorer than we like to think**
  - Patients are more variable
  - Susceptibility are less precise
- **Detecting mechanisms is**
  - A better guide to treatment
  - A safety check on susceptibility testing
  - Potentially faster than susceptibility testing

Typical MICs by β-lactamase type

	R-	TEM-1	TEM-12	TEM-10	CTX-M-15	CTX-M-14
Ceftazidime	0.12	0.12	8	128	32	2
Cefotaxime	0.03	0.03	0.12	1-2	256	128
Ceftriaxone	0.03	0.03	0.12	1-2	256	128

EUCAST bpts	mg/L
Ceftazidime, cefepime	≤1, >4
Cefotaxime & Ceftriaxone	≤1, >2

EUCAST proposed advice 'report as found; 'strong arguments to seek ESBLs infection control & epidemiological purposes'

What % of ESBL producers do you think are S to ≥1 cephalosporin on EUCAST criteria?

1) <1%
2) 1-5%
3) 5-10%
4) 10-25%
5) 25-50%
6) >50%
7) What's a cephalosporin?
8) Cephalosporins are a sort of poison that select for C. diff

BSAC Bacteraemia Surveillance, 2013; 105 ESBL producers, EUCAST criteria

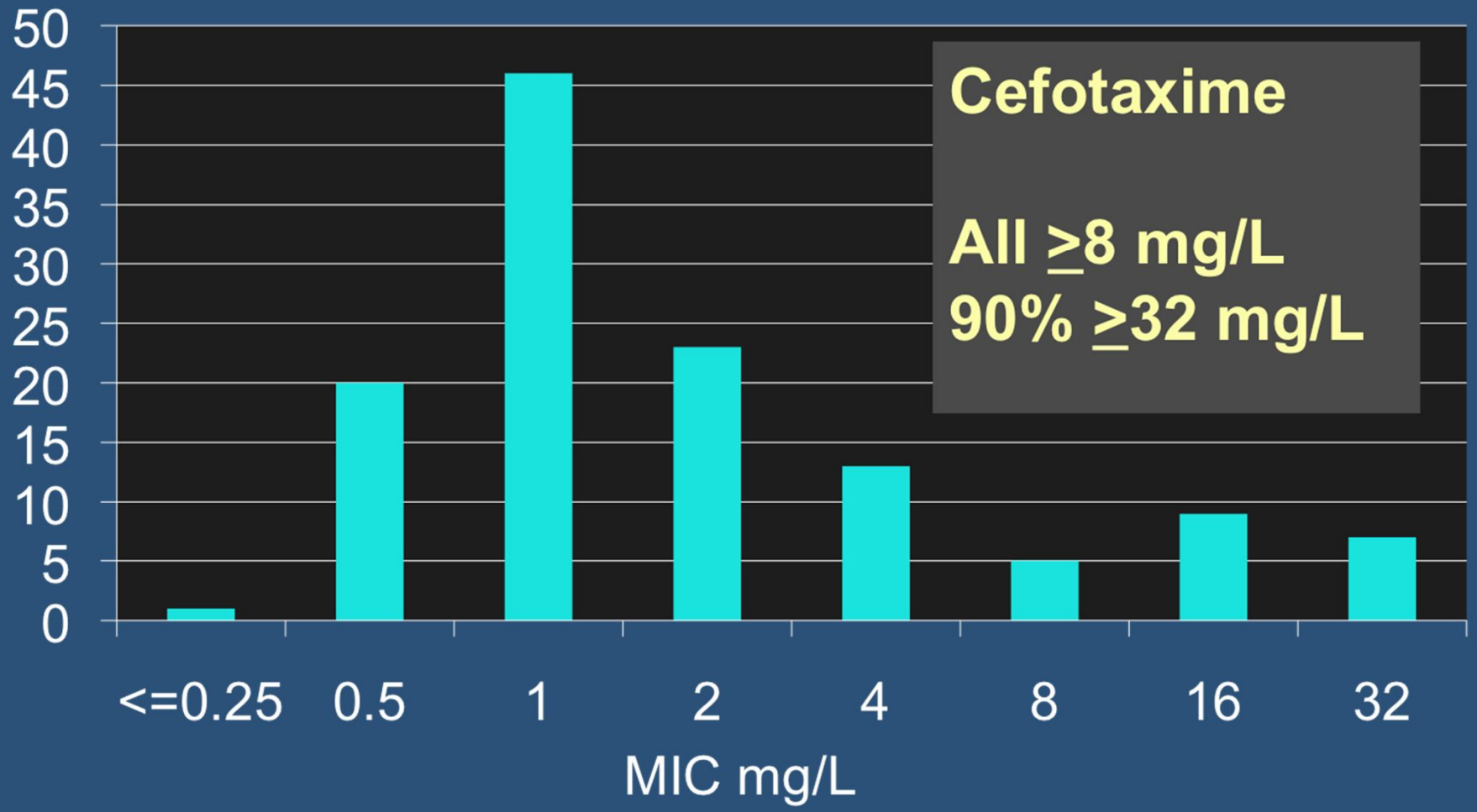
		Cefotaxime		Ceftazidime		Cefepime	
		S ≤1	I 2	S ≤1	I 2-4	S ≤1	I 2-4
CTX-M Gp1	78	0	0	2	14	9	11
CTX-M Other	14 (12=Gp9)	0	0	2	9	1	9
Non-CTX-M	13	6	0	1	5	10	2
Total	**105**	**6**	**0**	**5**	**28**	**20**	**22**

Overall: 23 S to ≥1ceph; 49 S or I to ≥1ceph

E. coli 65; *Klebsiella* 24; *Enterobacter* 14; *Proteus 2*

http://www.bsacsurv.org

Ceftazidime MICs Enterobacteria with CTX-M-9/14 ESBLs



Effect of introducing new CLSI breakpoint for ceftazidime, Israel

ESBL producers (by Vitek) found susceptible:

- *E. coli,* 64% of 203
- *K. pneumoniae*, 8.6% of 85
- *P. mirabilis*, 100% of 21

CTX-M-2 is the prevalent ESBL

Yoram Keness' data in Livermore *et al.,* 2012

Outcome & MIC in bacteraemias with CTX-M-3/-14 *E. coli;* ceftazidime 2g q8h

Patient	Source	MIC (mg/L	Outcome
M62	UTI	8	Cure
F49	Peritonitis	1	Responded, but drainage needed
F36	UTI	2	Cure
M45	Biliary infection	2	Cure
M67	?	2	Cure
F76	HAP	8	Cure
F38	UTI	0.5	Cure

Bin *et al., DMID* 2006; **56:** 351

ESBL *E coli* infections treated with ceftazidime: all zones ≥18 mm

Patient	Infection	Ceftazidime MIC (mg/L)	Outcome
F70	Peritonitis	1	**Died,** Sepsis
F72	UTI	1	**Died,** Despite switch to imipenem
F69	UTI	0.75	**Fail,** Resolved on gentamicin
M49	Liver abscess	>16, not CTX-M	**Died,** Persistent infection
F82	UTI	0.06	**Cured**
M67	1º bacteraemia	0.5	**Cured**
F83	UTI	0.25	**Cured** Initial response to amox-clav

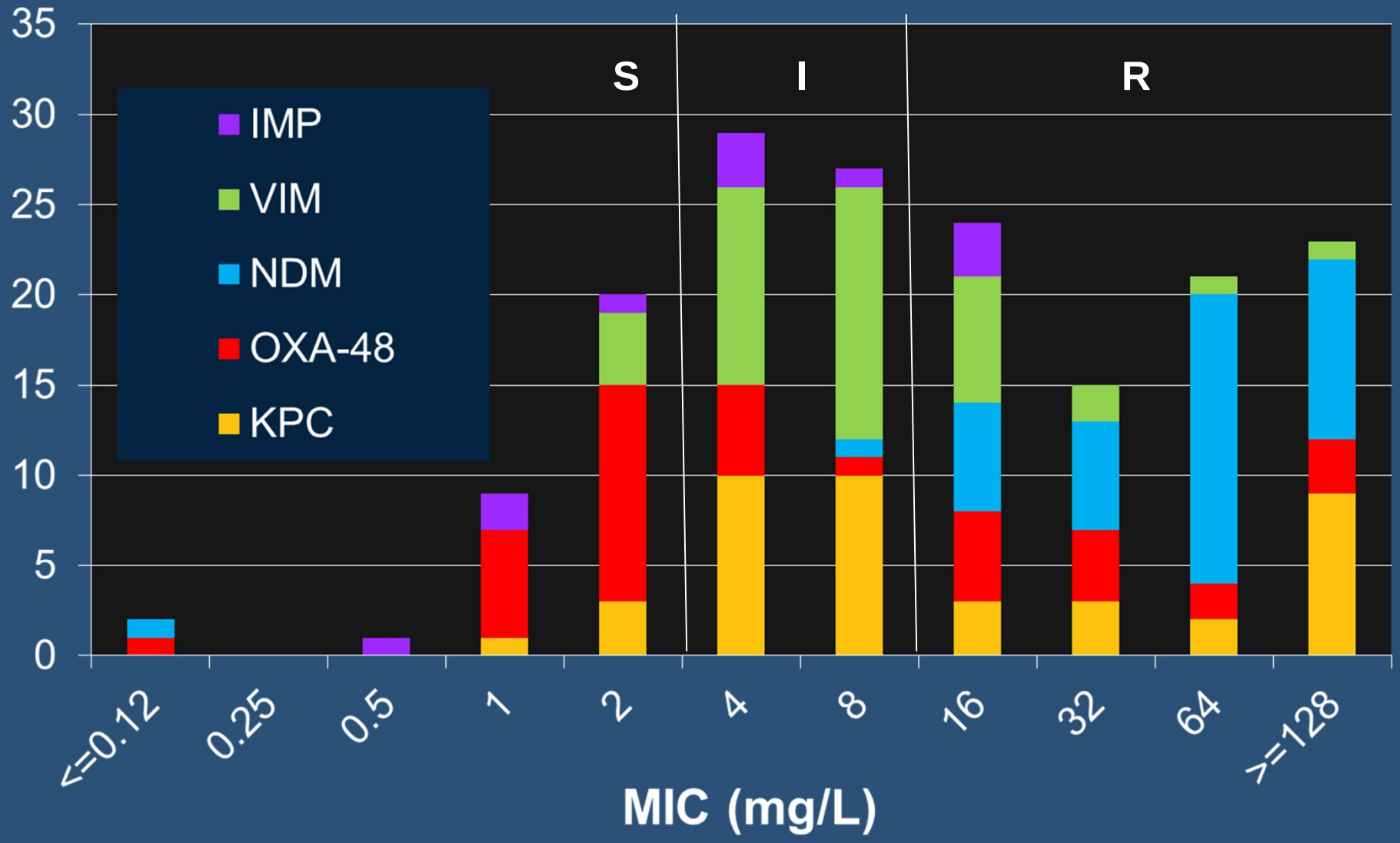
Hong Kong; CTX-M-14; MICs determined subsequently

Ho *et al., Scand JID* 2002; **34:**567
Livermore *et al., JAC* in press

Carbapenemase producers often appear susceptible to carbapenems

1) Agree
2) Disagree
3) What’s a carbapenemase

MICs of meropenem for carbapenemase-producing Enterobacteriaceae (n=174)



VIM-positive *K. pneumoniae*, Greece, 2001 onwards

- Mostly VIM-2, integron-borne on IncN plasmids
- In 25 of 40 surveillance hospitals
- Much resistance low level
  - If MIC >4 mg/L, 54% bacteraemia mortality,
  - 13% if MIC < 4 mg/L *vs.* 10.7% among controls

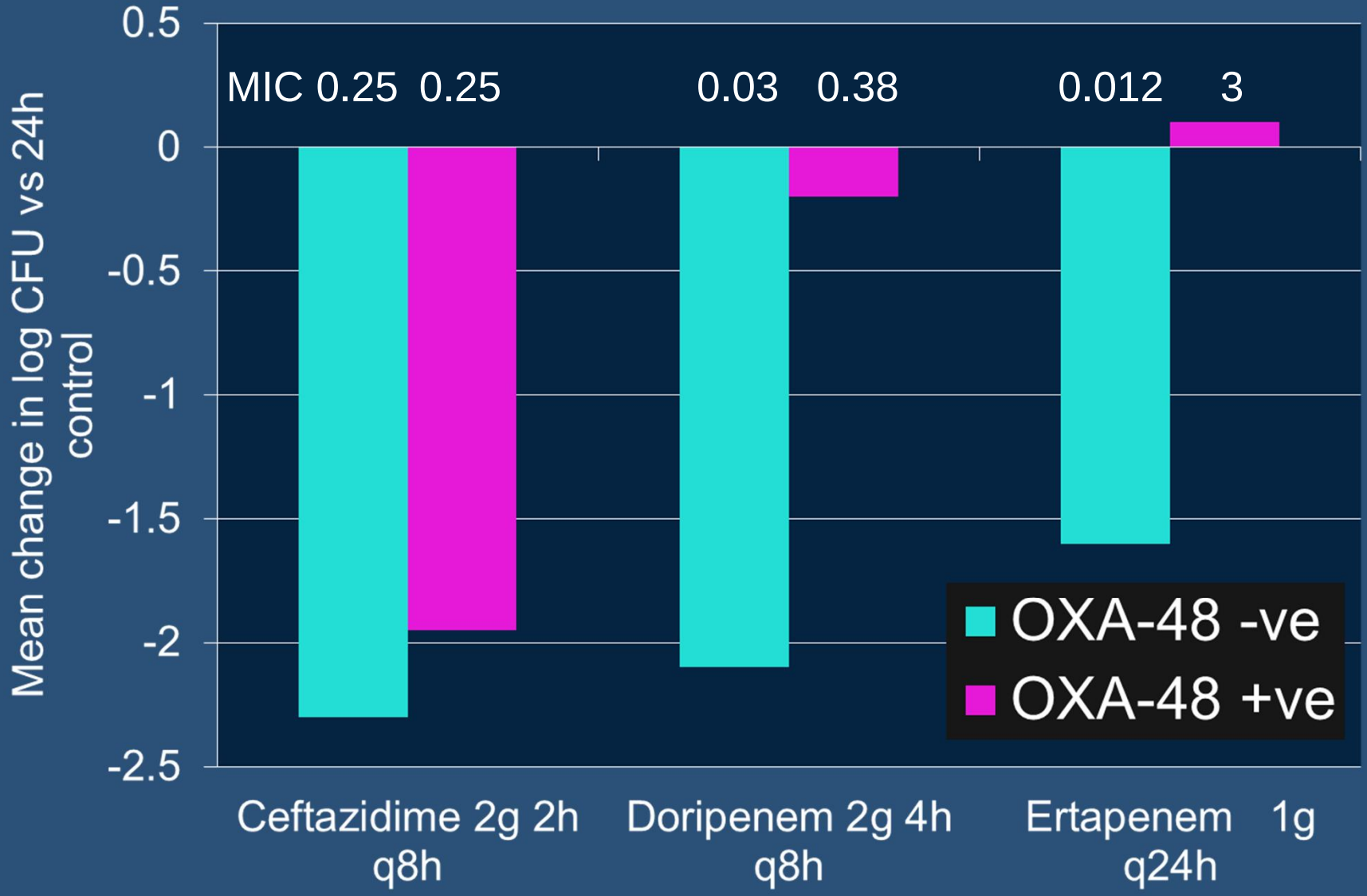
Vatopoulos *Eurosurv* 2008, 13 pii 8023

Carbapenem R_x in infections with KPC *Klebsiella*

Patient	Site	MIC imipenem		Days imipenem	Outcome
		Vitek	Etest		
M76	Respiratory	2	0.25	7-mero	Failed
M82	Blood	4	2	14	Cure
M92	Respiratory	4	2	3	Cure
F64	Respiratory	4	2	12	Failed
F69	Respiratory	4	8	6	Failed
F46	Blood	4	8	7	Cure
M77	Respiratory	4	≥32	7	Failed
F61	UTI	2	≥32	7	Cure
M52	UTI	4	16	14	Failed
F60	Blood	≥16	8	10-mero	Failed
M60	Respiratory	≥16	8	7-mero	Cure

Weisenberg *et al.*, *DMID* 2009;**64**:233

Human-simulated regimens *vs.* OXA-48+/- *K. pneumoniae* 454 in immunocompetent mouse thigh infection



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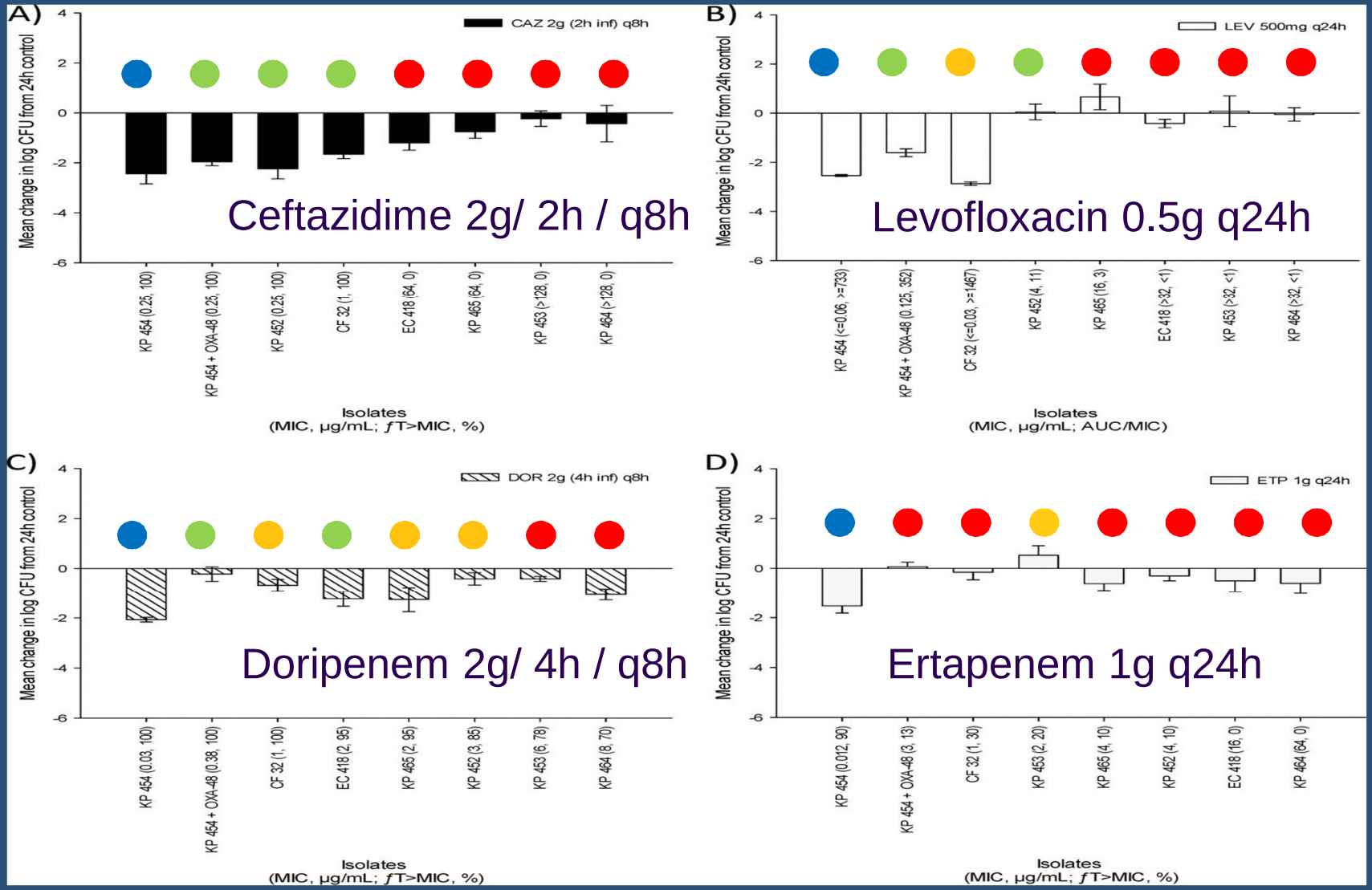
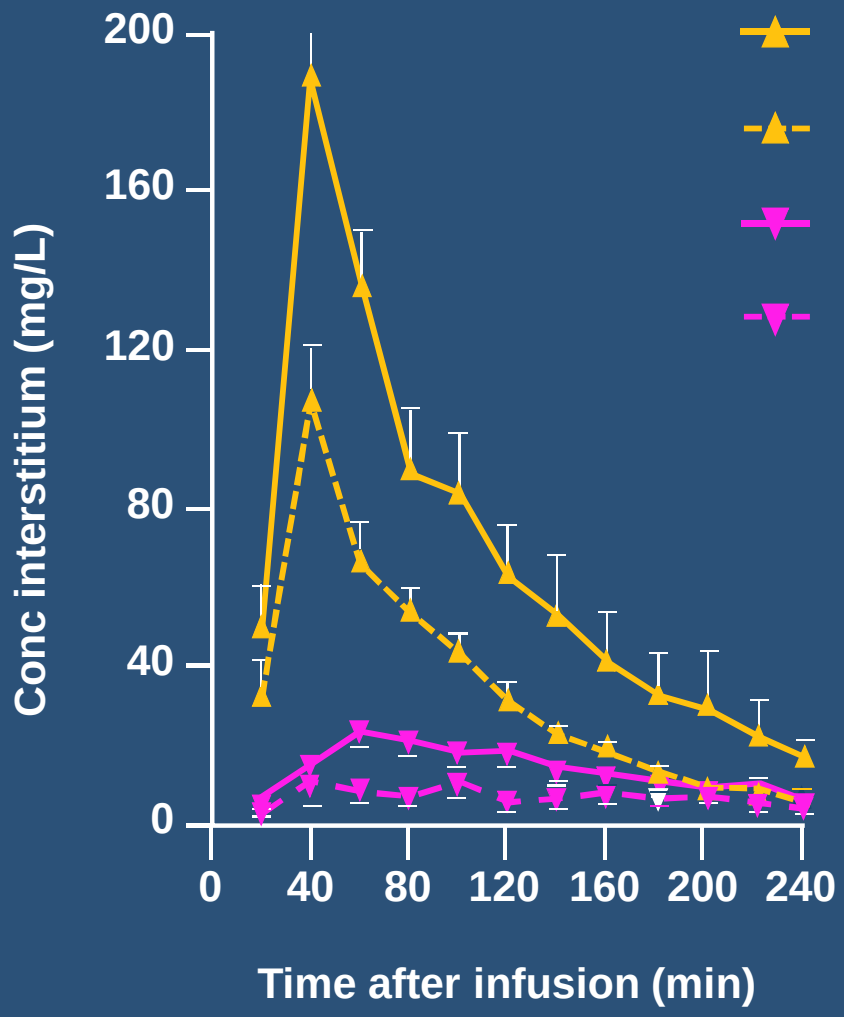


Wiskirchen *et al. AAC* 2014;**58**:1678-1683

Sepsis & antibiotic pK



- Muscle of healthy volunteers
- Adipose tissue of healthy volunteers
- Muscle of septic patients
- Adipose tissue of septic patients

- **Piperacillin 4 g in 10 min**
- **APACHE II score (36-66)**

Joukhadar *et al. Crit Care Med* 2001;**29:**385

How accurate are your clinical lab's MICs

1) We are accredited lab and run controls on all MICs
2) We only accept results if S control is at exact reference value
3) We only accept if S & R controls are at exact reference values
4) The textbooks say MICs are OK +/- 1 doubling dilution
5) We have a Vitek / Phoenix. We trust it
6) Honestly, our MICs are a bit ‘iffy’
7) We do disc tests, not MICs
8) I don’t know, ask the lab tech

Susceptibilities of 5 VIM +ve *Klebsiella* by 5 methods

	Broth	Etest	Vitek	Phoe-nix	Micro-scan
Imipenem	2-4	2-8	8-≥16	≥16	≤ 4
Meropenem	1-4	1-4	1-2	≥16	≤ 4

Authors overlap with those who said patients respond if carbapenem MIC <4 mg/L…..

S ≤2 mg/L; R >8 mg/L

Giakkoupi *et al.* *JCM* 2005;**43:**494

Carbapenem R_x in infections with KPC *Klebsiella*

Patient	Site	MIC imipenem		Days imipenem	Outcome
		Vitek	Etest		
M76	Respiratory	2	0.25	7-mero	Failed
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E. coli NCTC13352. K-12 derivative with TEM-10, a ceftazidimase

	MIC mg/L
Ceftazidime	>128
Cefotaxime	1-2
Ceftriaxone	1-2
Cefepime	2-4

4 labs each did disc tests 10 times…

NCTC13352: ceftazidime 30 μg discs: 10 tests/lab

	Mean zone (mm)	SD (mm)	S ≥30	I 26-29	R ≤25
Lab 1	8.1	0.57	0	0	10
Lab 2	6.8	1.75	0	0	10
Lab 3	6.0	0	0	0	10
Lab 4	6.0	0	0	0	10

Data courtesy Jenny Andrews, Birmingham

NCTC13352: cefotaxime 30 μg discs: 10 tests/lab

	Mean zone (mm)	SD (mm)	S ≥30	I 24-29	R ≤23
Lab 1	28.7	0.82	1	9	0
Lab 2	29.4	0.97	6	4	0
Lab 3	25.9	1.29	0	10	0
Lab 4	31.3	1.06	10	0	0

Data courtesy Jenny Andrews, Birmingham

NCTC13352: cefepime 30 μg discs: 10 tests/lab

	Mean zone (mm)	SD (mm)	S ≥32	I 27-31	R ≤26
Lab 1	26.4	0.52	0	4	6
Lab 2	28.1	0.74	0	10	0
Lab 3	23.0	1.55	0	0	10
Lab 4	29.1	1.00	0	10	0

Data courtesy Jenny Andrews, Birmingham

Which is more useful?

1) 48 h post-specimen

‘It’s a *Kleb. pneumoniae*. Very resistant. We’ve found an MIC of 2 mg/L for meropenem, though. It might be okay at high dose. Or prolonged infusion. Otherwise there’s colistin.’

‘Yes, of course; our lab is fully accredited!’

2) 4 h post-specimen

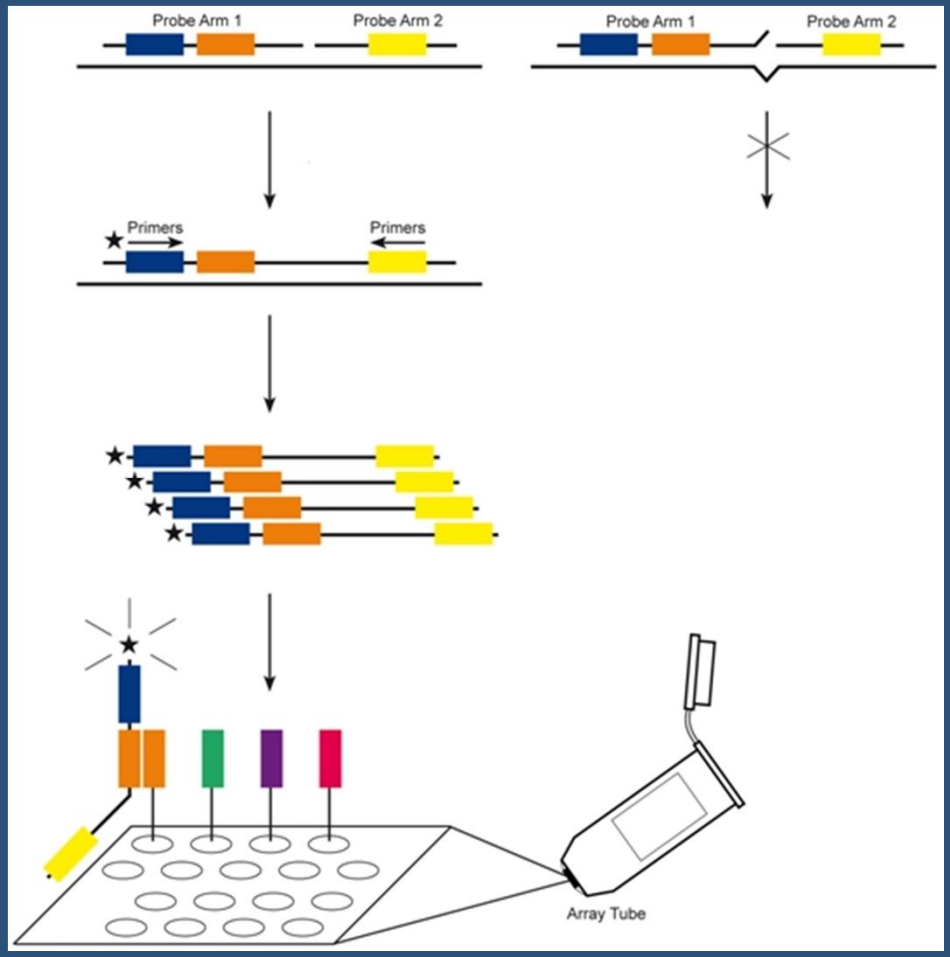
‘There is something with a KPC gene in this sputum from Mr X with the ventilator pneumonia’

‘It’s likely to be resistant to everything except colistin’

Rapid molecular detection of resistance

- PCR or gene chip technology on overnight culture... or directly from specimen
- Identify gene and predict resistance
  - But not MIC / direct measure of susceptibility
- Would be available if all ESBLs were *bla*$_{CTX-M}$ variants
  - Has been slow for ESBLs because many are sequence variants of *bla*$_{TEM/SHV}$
- Feasible for carbapenemase genes

Checkpoints array for carbapenemases, ESBLs & AmpC



	Array +ve	Array -ve
OXA-48 (11)	11	0
KPC (8)	8	0
IMP (12)	12	0
VIM (3)	3	0
NDM (7)	7	0
Imperm (16)	0	16
-ve Controls (7)	1	6

http://www.check-points.com

Zhang *et al. ECCMID* 2011

Useful tests that give a result at 24h…… 24h ahead of susceptibility data

- Chromogenic selective media to detect ESBL or carbapenemase producers
- Chromogenic cephalosporin HMRZ-86 (Cica β-Test)
- ➢ Use with inhibitors to predict β-lactamase type
- Acidimetric (CarbaNP) / Iodometric test to detect carbapenemase activity
- MALDI-ToF based carbapenemase detection
- **BUT THEY DON'T GIVE AN MIC**

Wilkinson *et al., JCM* 2012;**50:**3102
Livermore *et al., JAC* 2007; **60:** 1375
Dortet *et al. JMM* 2014;**63:**772
Hrabák *Methods Mol Biol* 2015;**1237:**91-6

ESBL Report by mechanism

- Ceph MICs of 1-4 mg/L don’t reliably predict cure
- Routine susceptibility testing not so precise as we suppose
- Finding a mechanism is faster than measuring an MIC
  - It is going to become a lot faster
- Thinking mechanisms enables the unusual to be spotted

Carbapenems may still be useful in combination vs carbapenemase producers

- 38 articles, 105 cases; mostly *K. pneumoniae* (89%) blood (52%) or RTI (30%).
- 47% monotherapy 53% combinations: more failure in monotherapy 49% vs 25%; p= 0.01)
  - True for polymyxin or carbapenem based combination
- Failure rates insignificantly different for 3 main combinations:
  - Polymyxin + carbapenem (30%)
  - Polymyxin + tigecycline (29%)
  - Polymyxin + aminoglycoside (25%)

Lee & Burgess AAC 2012 epub