

What role & indications for new β -lactams & β -lactamase inhibitor-combinations?

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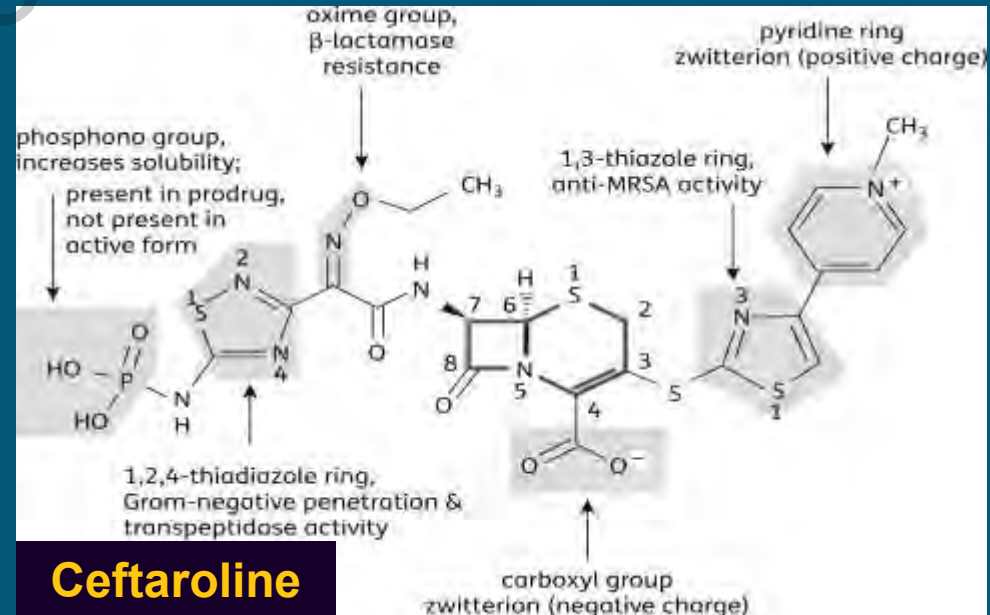
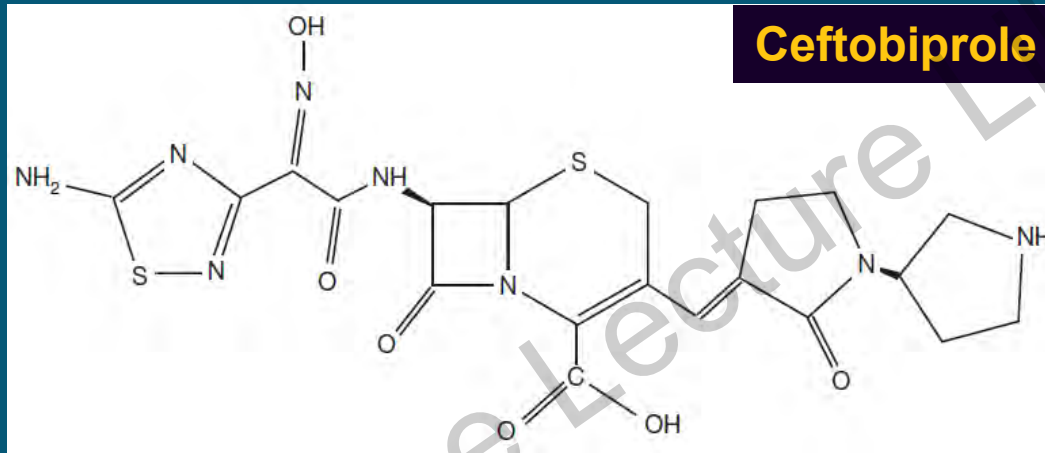
University of East Anglia &

Public Health England

New β -lactams & combinations

	Status	Indications/trials
Ceftobiprole	EU license	HAP, CAP
Ceftolozane-tazobactam	US license	cUTI, cIAI
Ceftazidime-avibactam	US license	cUTI, cIAI
Meropenem-Rpx7009	Phase III	Resistant pathogens
Imipenem-MK7655	Phase II	cIAI
Shionogi S-649266	Phase II	cUTI
Aztreonam-avibactam	Phase I	

Cephalosporins binding PBP-2'



Ceftobiprole vs. ceftaroline

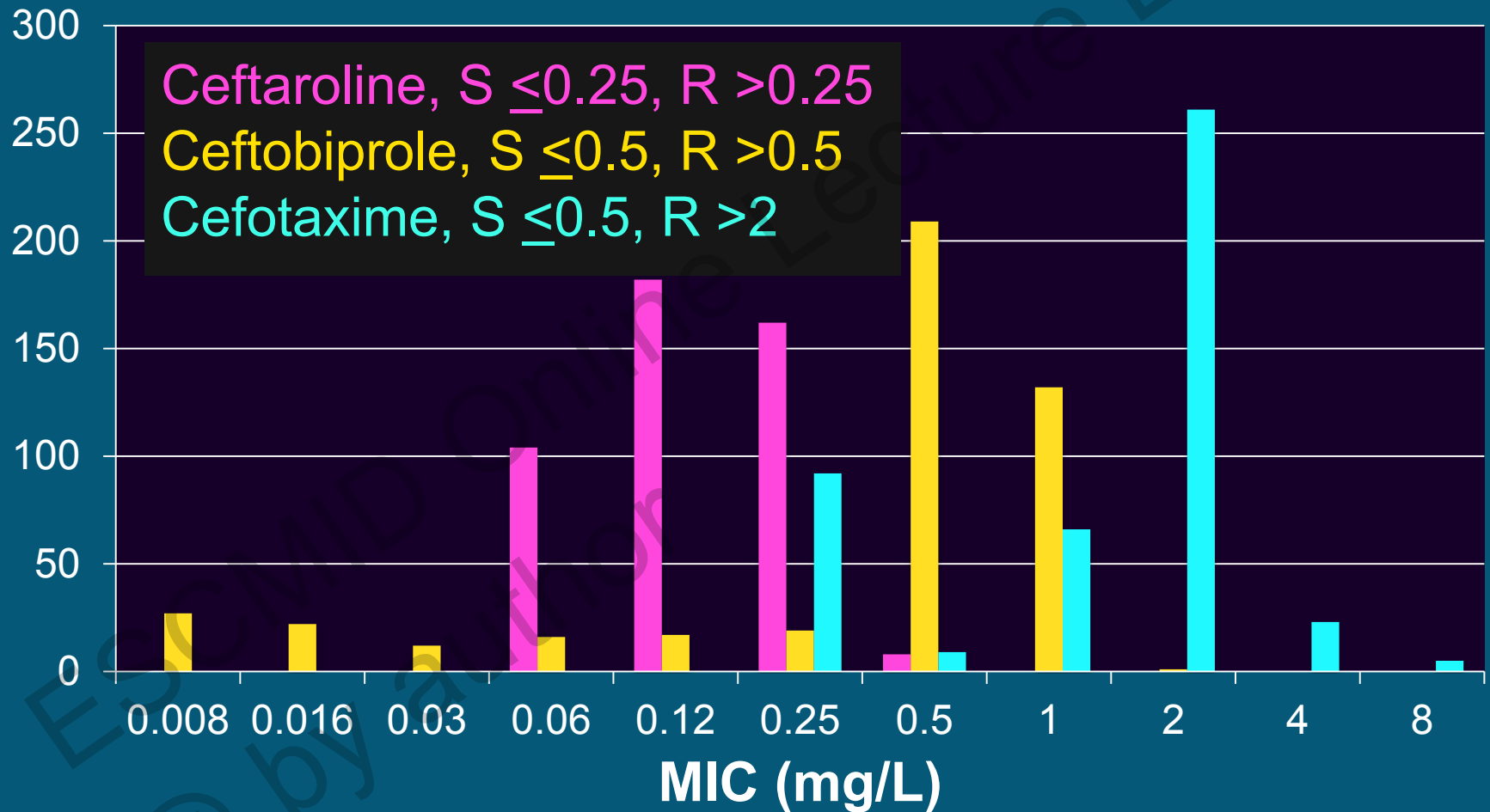
	Ceftobiprole	Ceftaroline
MRSA	MIC ₉₀ , 2 mg/L	MIC ₉₀ , 1 mg/L
<i>S. pneumoniae</i>	MICs ≤ cefotaxime	
Gram-ves <i>in vitro</i>	'Like cefepime' Labile to ESBLs not AmpC	'Like cefotaxime' Labile to ESBLs and AmpC
Indications	CAP + HAP	cSSSI, CAP
Dosage	500 mg q8h	600 mg q12h

Ceftaroline & ceftobiprole vs. *S. aureus* from Canada

	Range (mg/L)	MIC ₅₀	MIC ₉₀
Ceftaroline MSSA	≤0.012-0.5	0.25	0.25
Ceftaroline MRSA	0.5-1	0.5	1
Ceftobiprole MSSA	0.06-2	0.25	0.5
Ceftobiprole MRSA	0.5-2	1	2

Ceftaroline bpt S ≤1, R >1
Ceftobiprole bpt S ≤2, R >2

Cephalosporins vs. multiresistant pneumococci from Canada



Ceftobiprole & ceftaroline, where to use...?

???? Empirically

- in HAP, MRSA-risk patients are also *Pseudomonas* risk
- in CAP, ceftaroline superior to ceftriaxone in trials
- in SSTI (where MRSA may be present in mixed flora) ceftaroline licensed, ceftobiprole not licensed

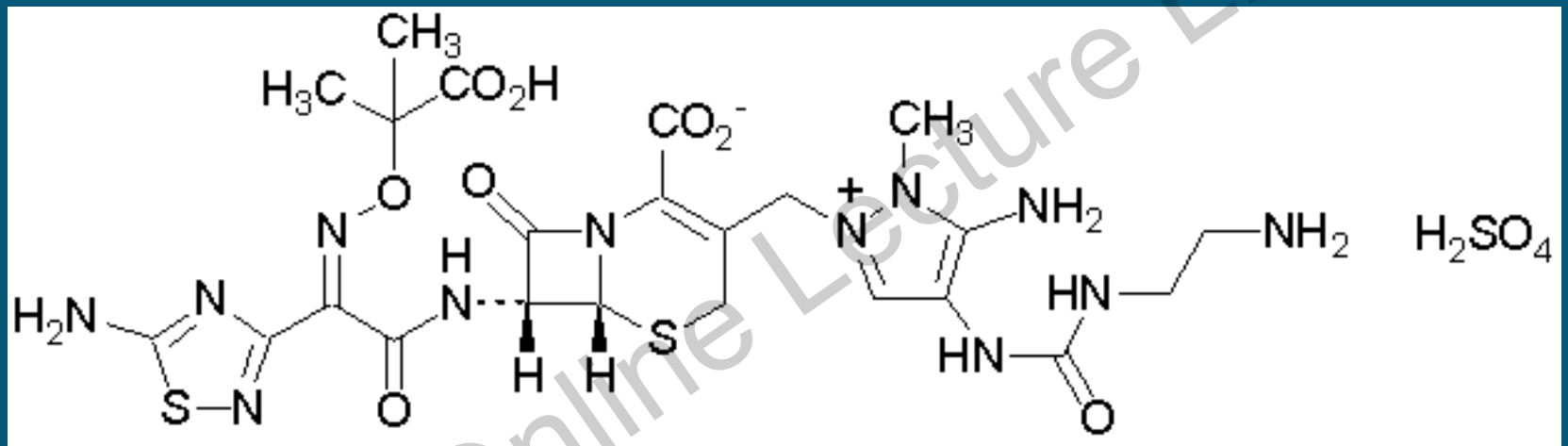
Microbiologically directed... where β -lactam preferred

- ?? couple with a diagnostic for MRSA
- Both need validation in endocarditis and bacteraemia

Vancomycin vs. β -lactams for MSSA bacteraemia

	Cohort, 7 years all cases		Case control matched for underlying status	
	Vanco	β -Lactam	Vanco	β -Lactam
No. cases	27	267	27	54
No. deaths	10	47	10	6
Deaths, %	37	18	37	11
<i>p</i>	0.02		<0.001	

Ceftolozane: more active than ceftazidime vs. *P. aeruginosa*



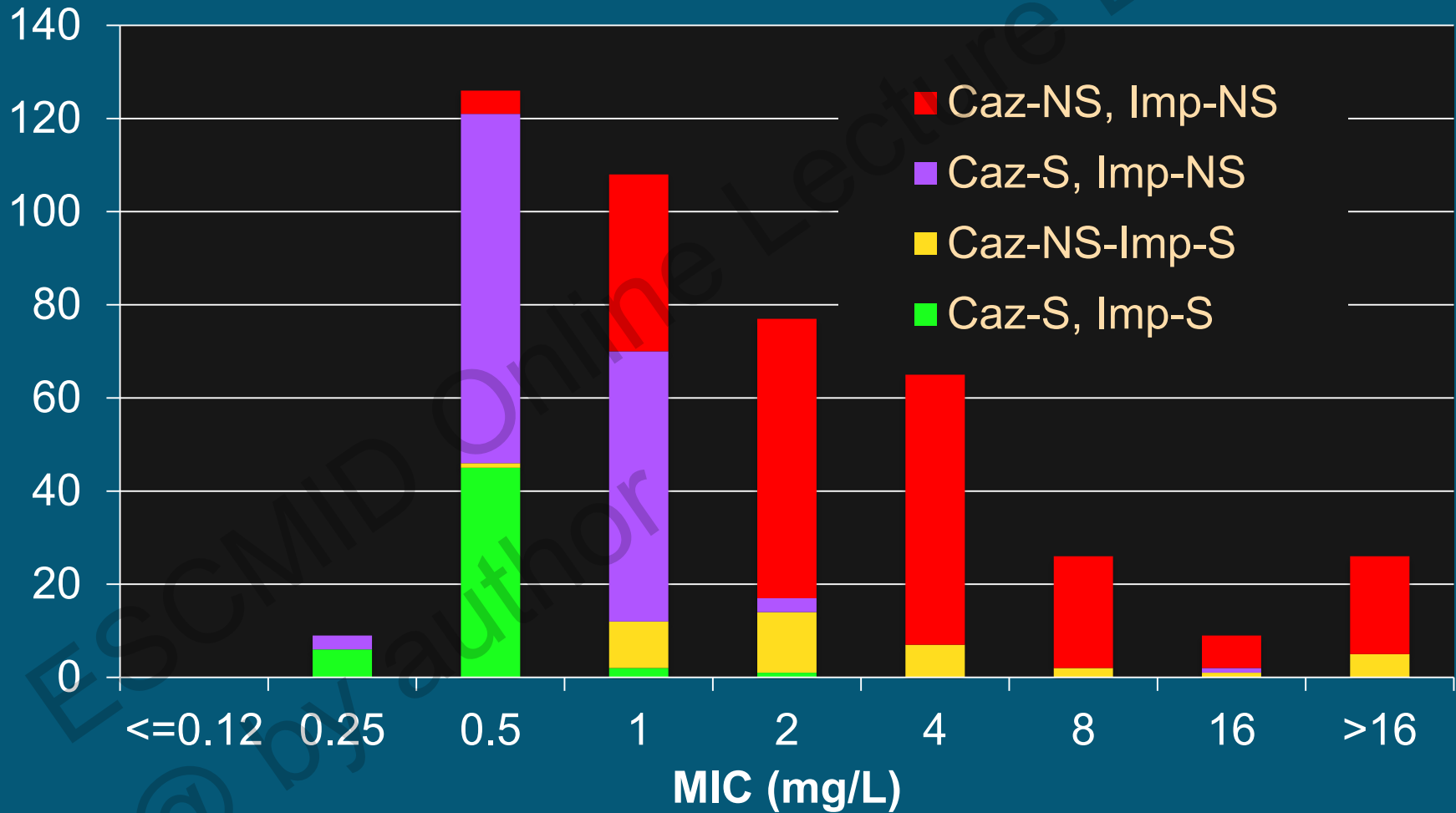
MICs

4 mg/L for AmpC⁺⁺⁺ *P. aeruginosa* vs. 16 mg/L ceftazidime

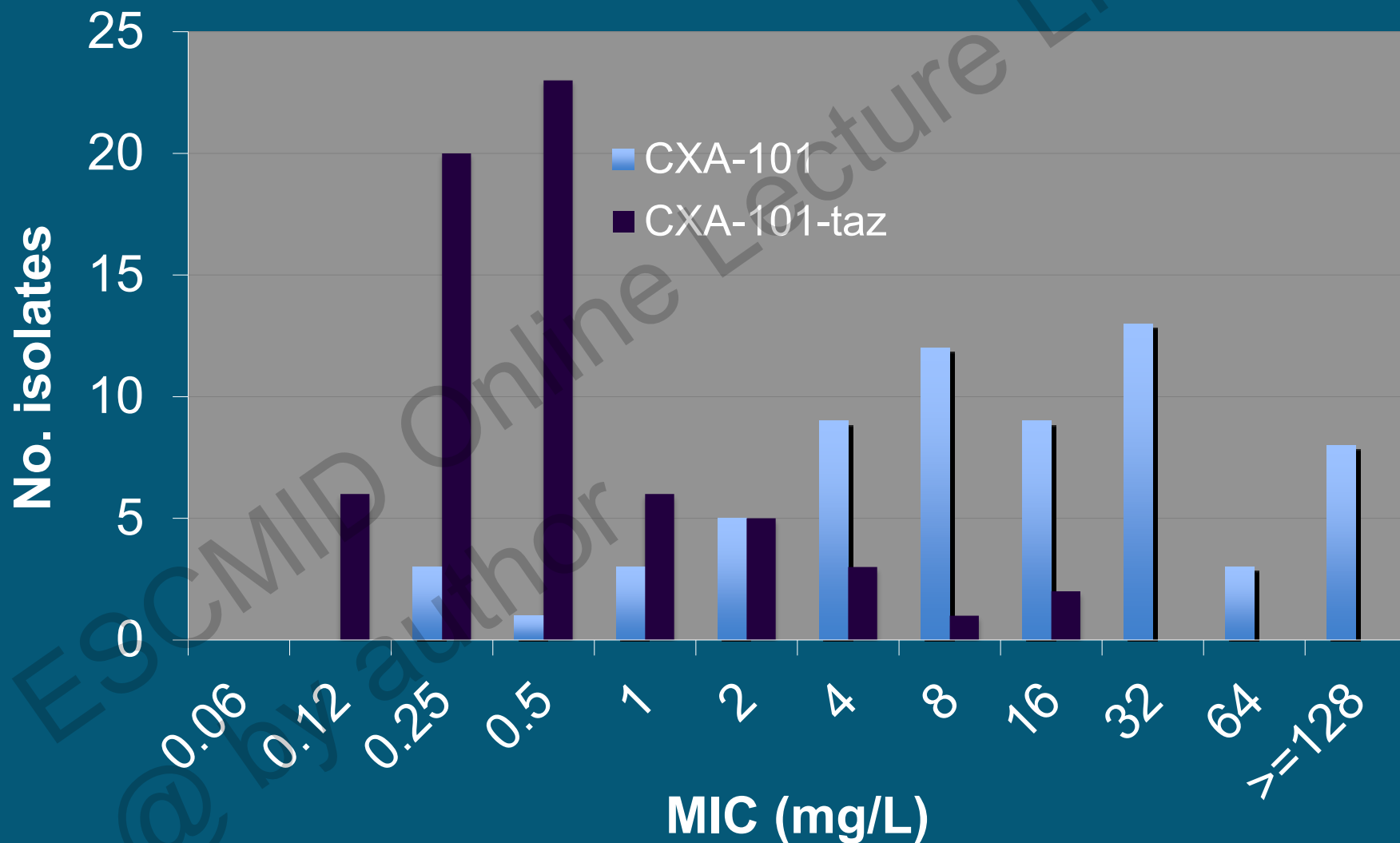
≤2 mg/L for efflux⁺⁺⁺ *P. aeruginosa* vs. 8-16 mg/L ceftazidime

>128 mg/L for metallo-β-lactamase producers

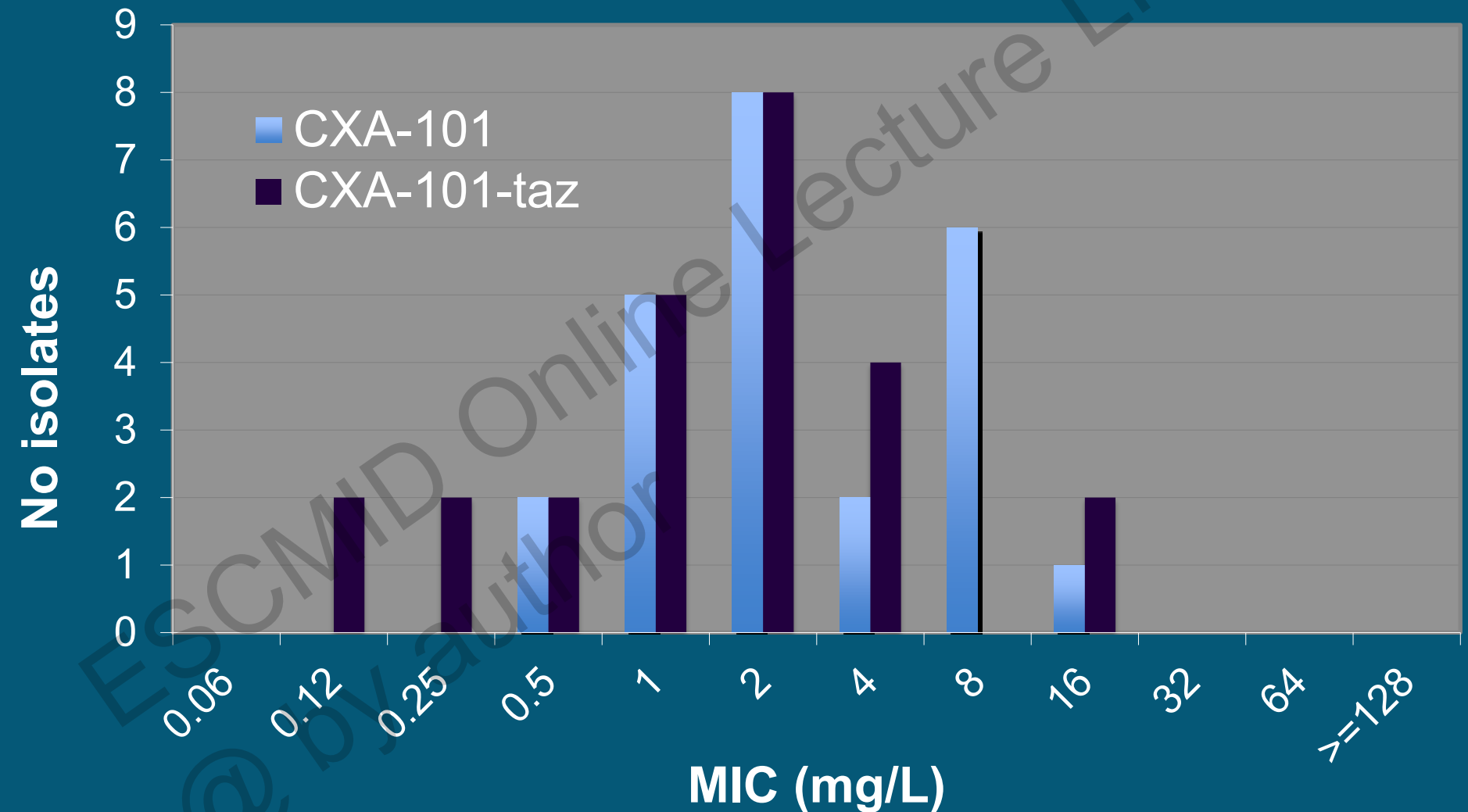
Ceftolozane-tazobactam vs. *P. aeruginosa*



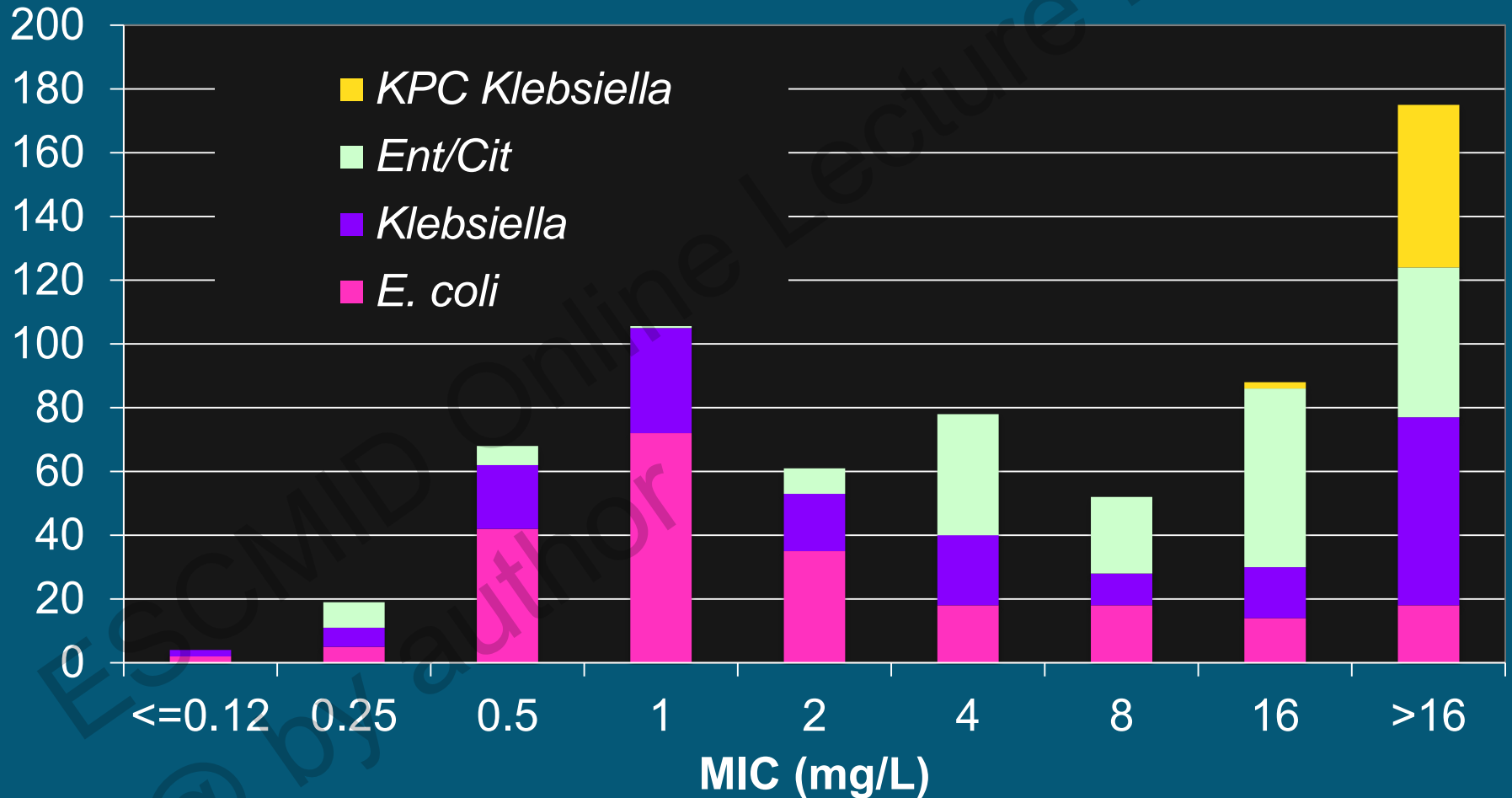
Ceftolozane +/- tazobactam vs. ESBL Enterobacteriaceae



Ceftolozane +/- tazobactam vs. AmpC Enterobacteriaceae



Ceftolozane-tazobactam (4 mg/L) vs. ceftazidime-R Enterobacteria



Ceftolozane-tazobactam cUTI, Phase III

	Ceftol-tazo 1+0.5g q8h 7days	Levofloxacin 0.75g q24h 7days
Clinical cure	95.9%	93.2%
Microbiological eradication (ME)	84.7%	75.1%*
ME Enterobacteriaceae	278/313=88.8%	253/325=77.8%*
ME <i>P. aeruginosa</i>	6/7=85.7%	7/12=58.3%

* P < 0.05

Ceftolozane-tazobactam cIAI, Phase III, 993 patients

	Ceftol-tazo 1+0.5g q8h 4-10 days + metronidazole	Meropenem 1g q8h 4-10 days
Clinical cure (Clinically evaluable)	94.1%	94.0%
Microbiologically evaluable	94.2%	94.7%

Ceftolozane-tazobactam vs. ESBL isolates from pairs of cUTI & cIAI trials

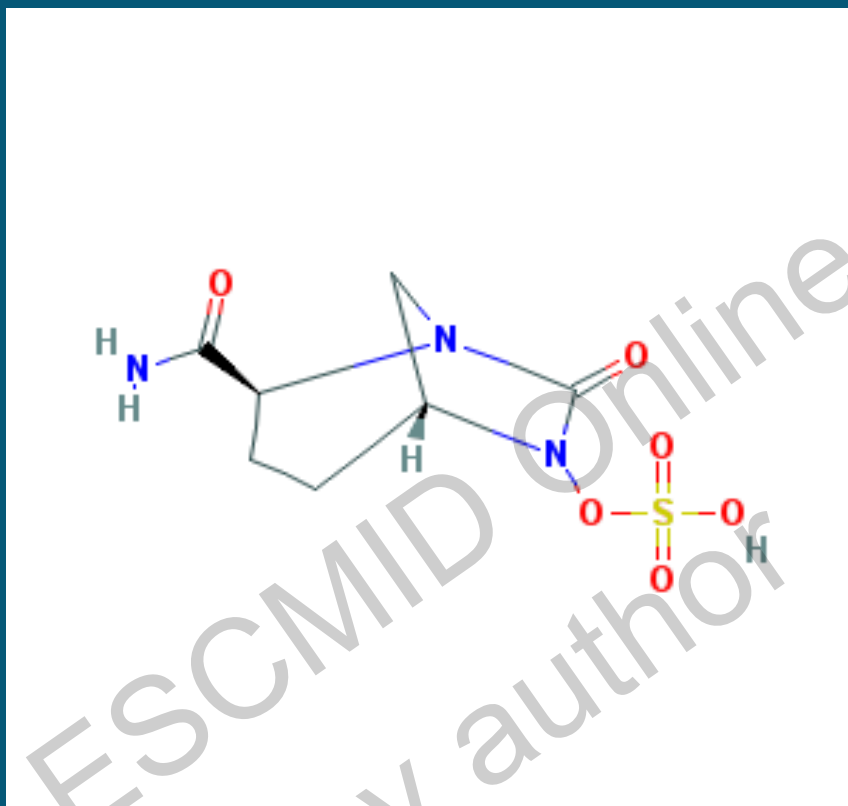
- 153 patients (11%) had ESBLs: 103 cUTI, 50 cIAI
- More were older (31% vs 21% aged >65 & renally impaired)
- UTI comparator, levofloxacin; cIAI, meropenem

	Ceftolozane-tazo	Comparator
Clin Cure, cUTI	98.1	82.6
Micro erad, cUTI	72.2	45.7
Clin Cure, cIAI	95.8	88.5
Micro erad, cIAI	95.8	88.5

Issues with ceftolozane-tazobactam

- Fear of cephalosporins re. *C. difficile*
- Carbapenems now generic
- Uncertain coverage vs. AmpC *Enterobacter*
- cUTI & cIAI not best sites to test anti-pseudomonas role
 - Ventilator pneumonia trial in progress using 2+1g q8h
 - Trials vs. chronic respiratory *P. aeruginosa* needed

Avibactam, an diazabicyclooctane

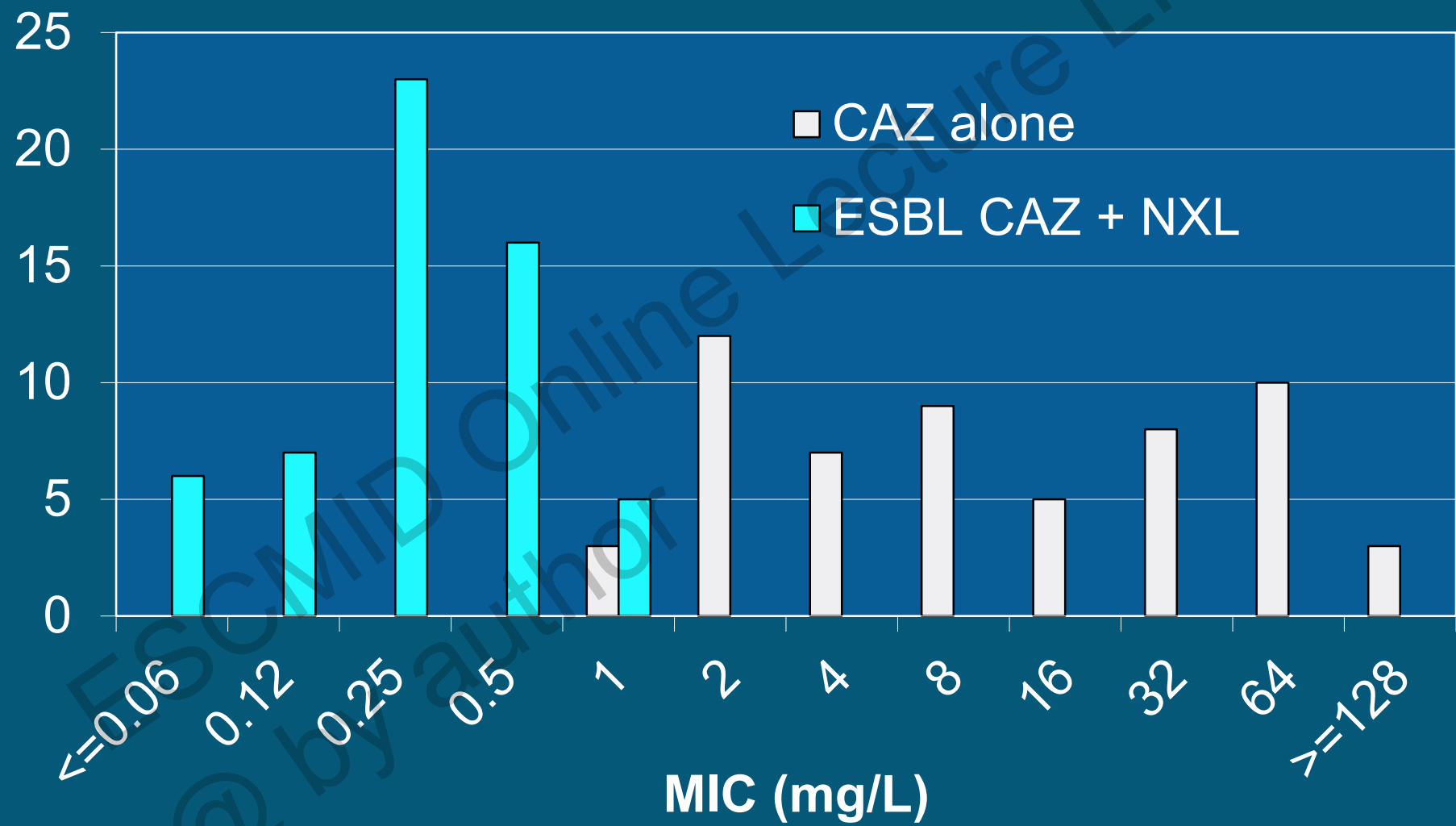


Avibactam

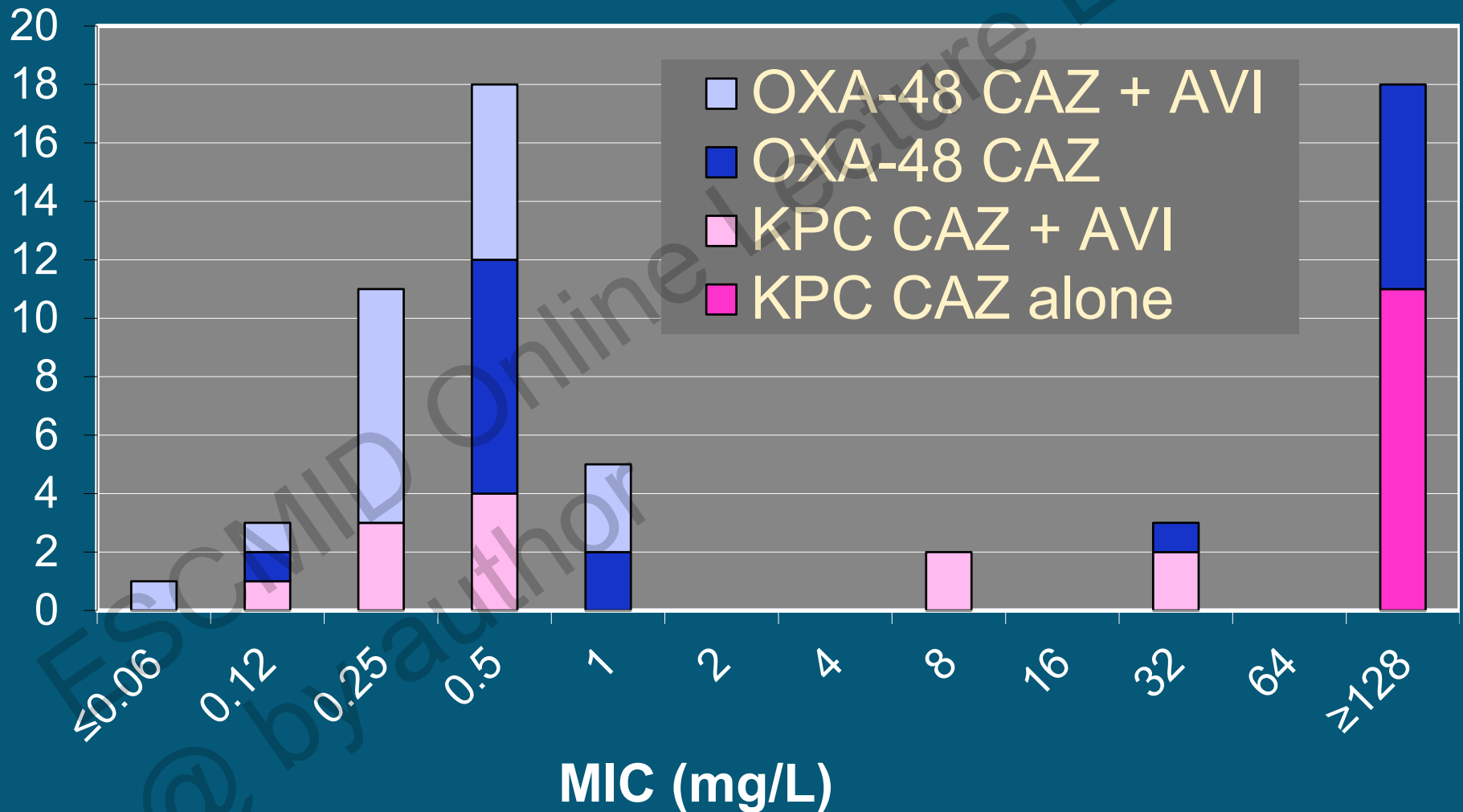
Inhibits:

- Class A, inc. KPC
- Class C / AmpC
- Some class D
- NOT Class B

Ceftazidime + avibactam (4 mg/L) Enterobacteria with CTX-M ESBLs



Ceftazidime + avibactam (4 mg/L) Enterobacteria with KPC or OXA-48

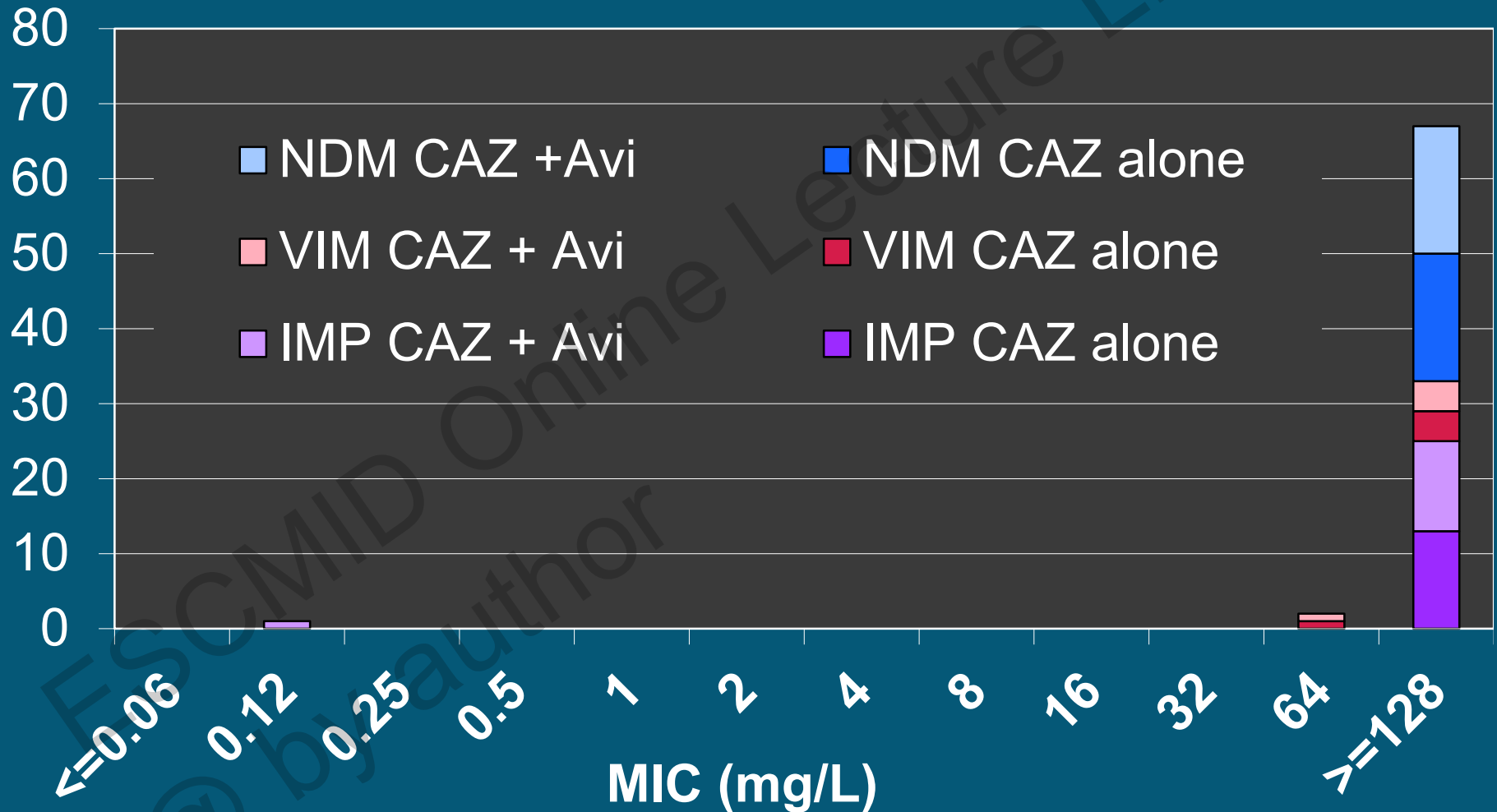


Ceftazidime-avibactam

Mouse sepsis, KPC *Klebsiella*

	ED ₅₀ (mg/kg) with ceftazidime : avibactam				
	Ceftaz alone	2:1	4:1	8:1	16:1
Control	1.9	1.0	1.1	0.62	NT
KPC Kleb VA361	1578	8.1	15.1	15.9	29.5
KPC Kleb VA406	709	3.5	3.8	7.2	12.1

Avibactam (4 mg/L) + ceftazidime vs. Enterobacteria with MBLs



Where might ceftazidime-avibactam be used?

- Initial FDA license for cIAI and cUTI, based on Phase II data;
- Phase III now complete for these; HAP/VAP in progress
- Obvious use is microbiologically directed
 - Use where KPC or OXA-48 proven or likely
 - Link to diagnostics to seek producers
- ????? Use as 'carbapenem sparing vs. ESBL producers
 - BUT only if ecological studies show less collateral effect than carbapenems

Developmental β -lactamase inhibitor combinations

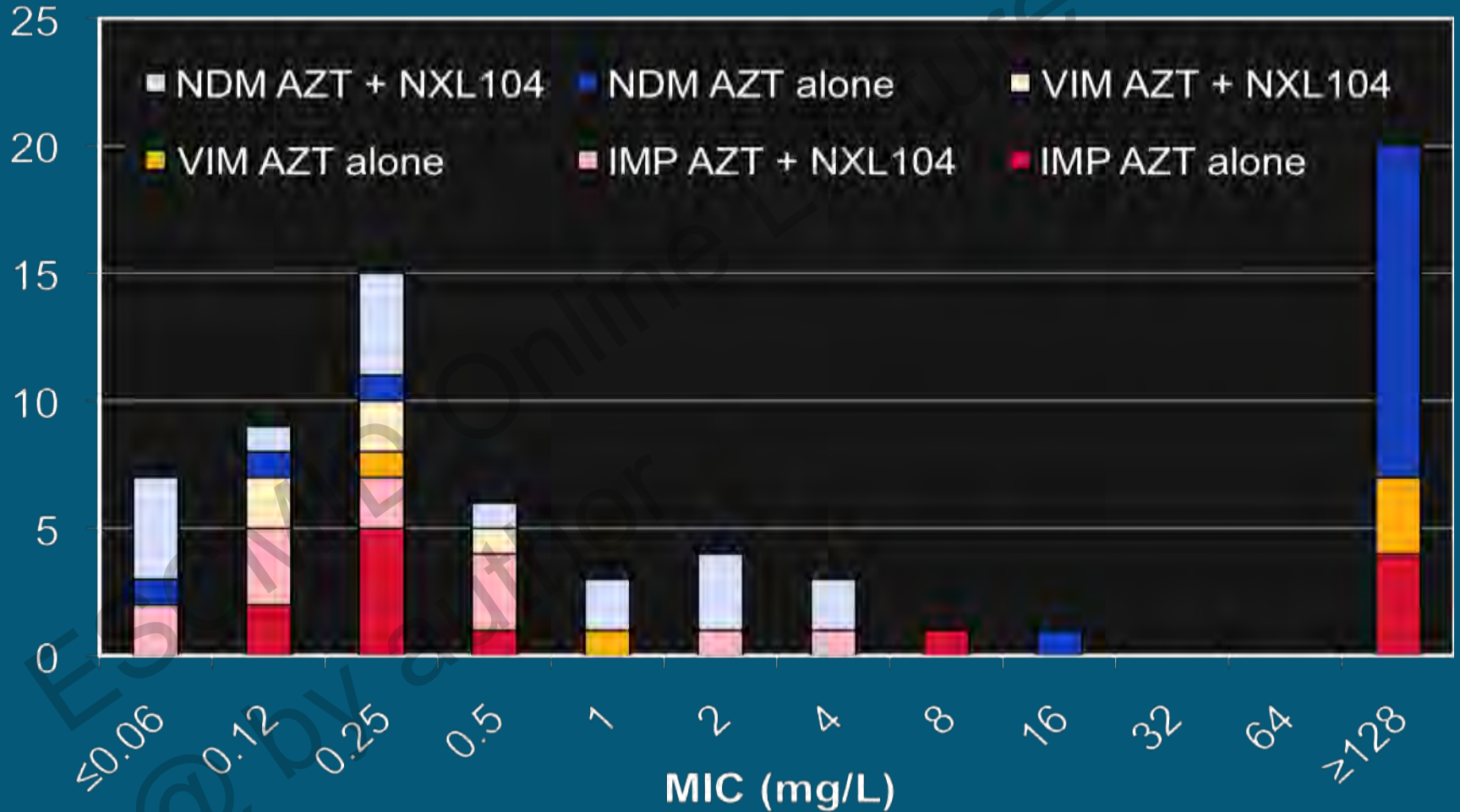
Meropenem-Rpx7009; imipenem-MK-7655

- Main gain over base carbapenem = KPC coverage
- Imipenem-MK-7655, some general gain vs. *P. aeruginosa*
- No gain vs metallo carbapenemases or OXA-48
- Meropenem-Rpx7009 2g+2g q8h, 3h infusion

??? Couple with a PCR for *bla*_{KPC}

- ??? Step down to carbapenem alone in *bla*_{KPC} excluded

Aztreonam + avibactam 4 mg/L vs. Enterobacteriaceae with MBLs



Shionogi S-649266, catechol cephalosporin

- Exploits ferric iron uptake pathway of Gram –vs bacteria
- MICs lower under iron starvation
 - Generally ≤ 1 mg/L for Gram-negatives,
 - ≤ 2 mg/L *Acinetobacter* & carbapenemase producers
- No toxicity with 14 days at 2g q8h
- Phase II cUTI trial now recruiting

<http://www.clinicaltrials.gov>

Ito *et al.* ICAAC 2014 Poster F-1562

Shimada *et al.* ICAAC 2014 Poster F-1564

Summary

Ceftobiprole (& ceftaroline)

- Need evaluation in MRSA bacteraemia & endocarditis

Ceftolozane-tazobactam

- Unique feature is anti-*P. aeruginosa* activity
- Needs evaluation where *P. aeruginosa* predominates!

Ceftazidime-avibactam

- Unique feature is coverage of OXA-48 and KPC
- Few good alternatives vs. bacteria with these enzymes...

All could be linked to diagnostics to optimise stewardship