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EUCAST Expert Rules in AST

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

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REVIEW BACTERIOLOGY

EUCAST expert rules in antimicrobial susceptibility testing

R. Leclercq[1,2], R. Cantón[2,3,4], D. F. J. Brown[4], C. G. Giske[2,4,5], P. Heisig[2,6], A. P. MacGowan[4,7], J. W. Mouton[4,8], P. Nordmann[2,9], A. C. Rodloff[4,10], G. M. Rossolini[2,11], C.-J. Soussy[4,12], M. Steinbakk[4,13], T. G. Winstanley[2,14] and G. Kahlmeter[4,15]

Clin Microbiol Infect 2013; 19: 141–160
10.1111/j.1469-0691.2011.03703.x

Divided into:

- intrinsic resistance
- exceptional phenotypes
- interpretive rules.

Importance of these rules is to ensure:

- accurate identification/ AST
- clinically relevant use of agents

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Version 3…on its way!

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Consultation on proposals for a new version (v3) of EUCAST Expert Rules

Intrinsic Resistance and Exceptional Phenotypes Tables

EUCAST Expert Rules version 2.0 was published on 29 October 2011(http://www.eucast.org/expert_rules). The rules are currently under review and proposals for changes to the intrinsic resistance and exceptional phenotypes tables are presented here with a summary of changes and the revised tables 1-7.

The proposals are open for comment by 3rd December 2015. Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com).

Please use the attached form for your comments.

http://www.eucast.org/documents/discussion_documents/

Surveillance implications

1. Intrinsic rules are not an issue…perhaps could serve as a monitoring tool.
2. Interpretive rules will have an impact on surveillance data.
   - ß-lactam reporting are key areas relevant to our current surveillance data:
     1. ESBL/AmpC reporting
     2. CRE reporting

ESBL

EUCAST position

If isolate is an ESBL and is susceptible to amoxicillin-clavulanic acid or piperacillin-tazobactam then should be **reported as tested***

Using EUCAST breakpoints for *Enterobacteriaceae* the susceptibility of 3rd and 4th generation cephalosporins should be **reported as tested***

*same applies to plasmid-mediated AmpC

ESBL – the nuts and bolts

1. ESBL = Bush-Jacoby 2be
2. By definition “increased hydrolysis of oxyimino-ß-lactams (cefotaxime; ceftriaxone; ceftazidime; cefepime; aztreonam).
3. Inhibited by clavulanic acid and/or tazobactam
4. TEM/SHV/CTX-M: have different affinities for different antimicrobials.

ESBL

MIC data

1. Cefotaxime ECOFF*: 0.25µg/ml
2. Ceftriaxone ECOFF*: 0.125µg/ml
3. Ceftazidime ECOFF*: 0.5µg/ml
4. Cefepime ECOFF*: 0.125µg/ml
5. Aztreonam ECOFF†: 0.25µg/ml
6. Piperacillin-tazobactam ECOFF*: 8µg/ml

*only for *E. coli* and *K. pneumoniae*
† only for *E. coli*

mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=44&Specium=-1

New Tab | Google | VERB | Outlook Web App | MWEB- Sign Me In | Favs | Lumosity | CDC - Making Health | Sign in to your Micros | Dossier | Other book

imicrobial wild type distributions of microorganisms

ch

od: MIC Disk diffusion

Elements per page: 50

icrobial: Cefotaxime Species: Species... Disk content: Disk content...

nicrobial: **Cefotaxime** (Method: **MIC**)

distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

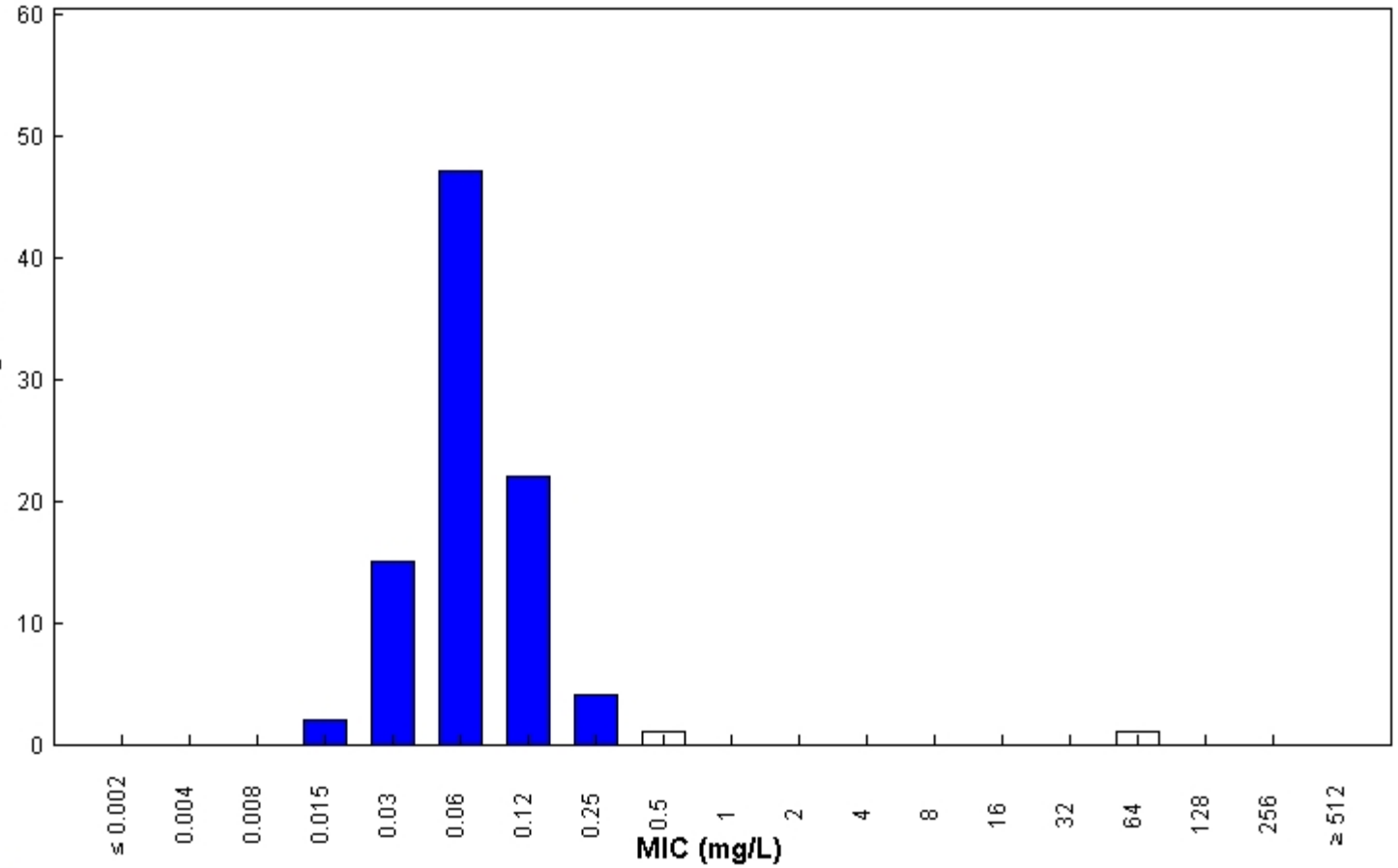
Show All Graph

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
obacter baumannii	0	0	0	0	1	2	0	25	6	11	24	92	359	389	161	217	26	125	5	ND
obacter calcoaceticus	0	0	0	0	0	0	0	0	0	1	0	0	3	1	0	1	0	0	0	ND
obacter lwoffii	0	0	0	0	0	0	0	31	23	45	64	38	65	35	9	7	0	0	15	ND
obacter spp	0	0	0	0	0	0	0	33	35	61	88	92	146	116	52	25	3	0	22	ND
olderia cepacia	0	0	0	0	0	0	0	0	0	7	4	5	9	5	4	6	0	1	0	ND
acter freundii	0	0	0	0	1	3	42	5	5	2	3	4	3	18	18	5	1	0	0	0.5
acter spp	0	0	0	0	17	35	19	11	10	9	2	4	3	4	4	3	0	0	0	0.5
bacter aerogenes	0	0	0	0	7	28	33	9	3	3	4	2	8	15	8	9	6	11	0	0.5
bacter cloacae	0	0	1	6	19	64	213	189	129	44	26	19	35	53	90	59	56	58	12	0.5
bacter spp	0	0	0	1	19	47	79	45	29	22	7	10	4	20	11	4	0	5	0	0.5
ichia coli	0	5	40	263	1638	4916	2338	469	188	81	52	37	38	50	68	131	22	33	28	0.25
ophilus influenzae	44	362	3540	6129	2539	833	153	45	20	17	1	2	0	0	0	0	0	0	0	0.064
ella pneumoniae	0	2	12	99	523	745	271	84	65	19	28	36	54	43	49	68	105	199	20	0.25
ella spp	0	5	21	86	103	73	34	13	16	11	4	1	2	1	0	1	1	0	0	0.125
ella pneumophila	0	0	0	2	10	51	56	40	23	1	0	0	0	0	0	0	0	0	0	ND
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
ella catarrhalis	0	0	0	27	108	483	430	275	907	517	9	1	0	0	0	0	0	0	0	ND
nella morganii	0	8	27	35	24	18	12	8	6	2	7	10	4	2	2	0	0	1	0	ND
ria gonorrhoeae	1022	1490	1466	1141	945	805	759	389	66	0	2	0	0	0	0	0	0	0	0	0.016
ria meningitidis	430	879	548	139	21	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0.016
rella multocida	1	15	103	35	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.032
s mirabilis	0	1	107	212	71	11	2	3	3	13	1	1	2	1	2	4	1	1	0	0.064
s vulgaris	0	0	14	22	27	23	20	11	3	0	0	0	4	2	1	0	0	4	0	0.125

Cefotaxime / Escherichia coli

International MIC Distribution - Reference Database 2016-05-26

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

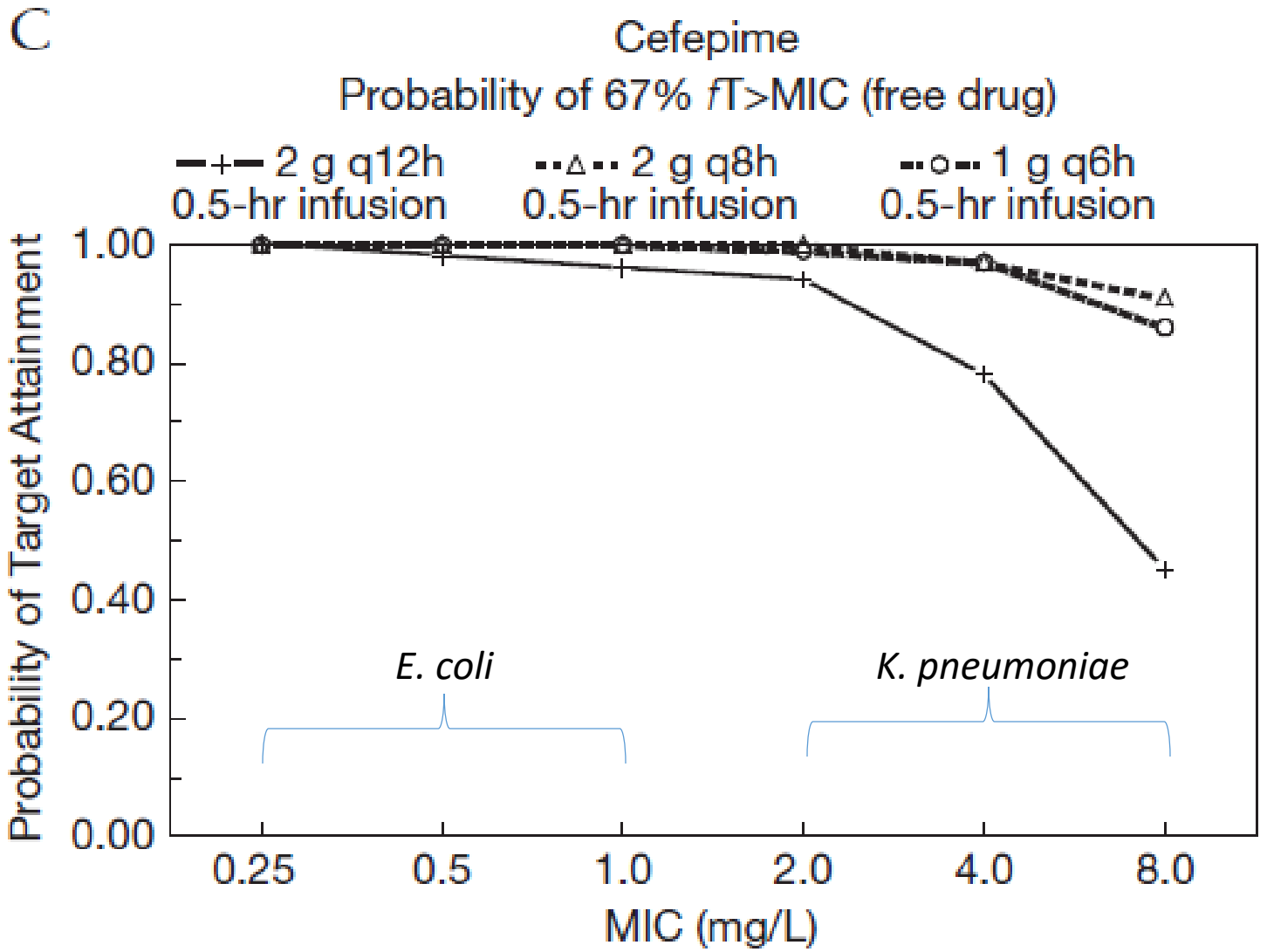


C
idemiological cut-off (ECOFF): 0.25 mg/L
ildtype (WT) organisms: ≤ 0.25 mg/L

10397 observations (41 data sources)

Histogram data | Save image as..

ESBL – Pk/Pd

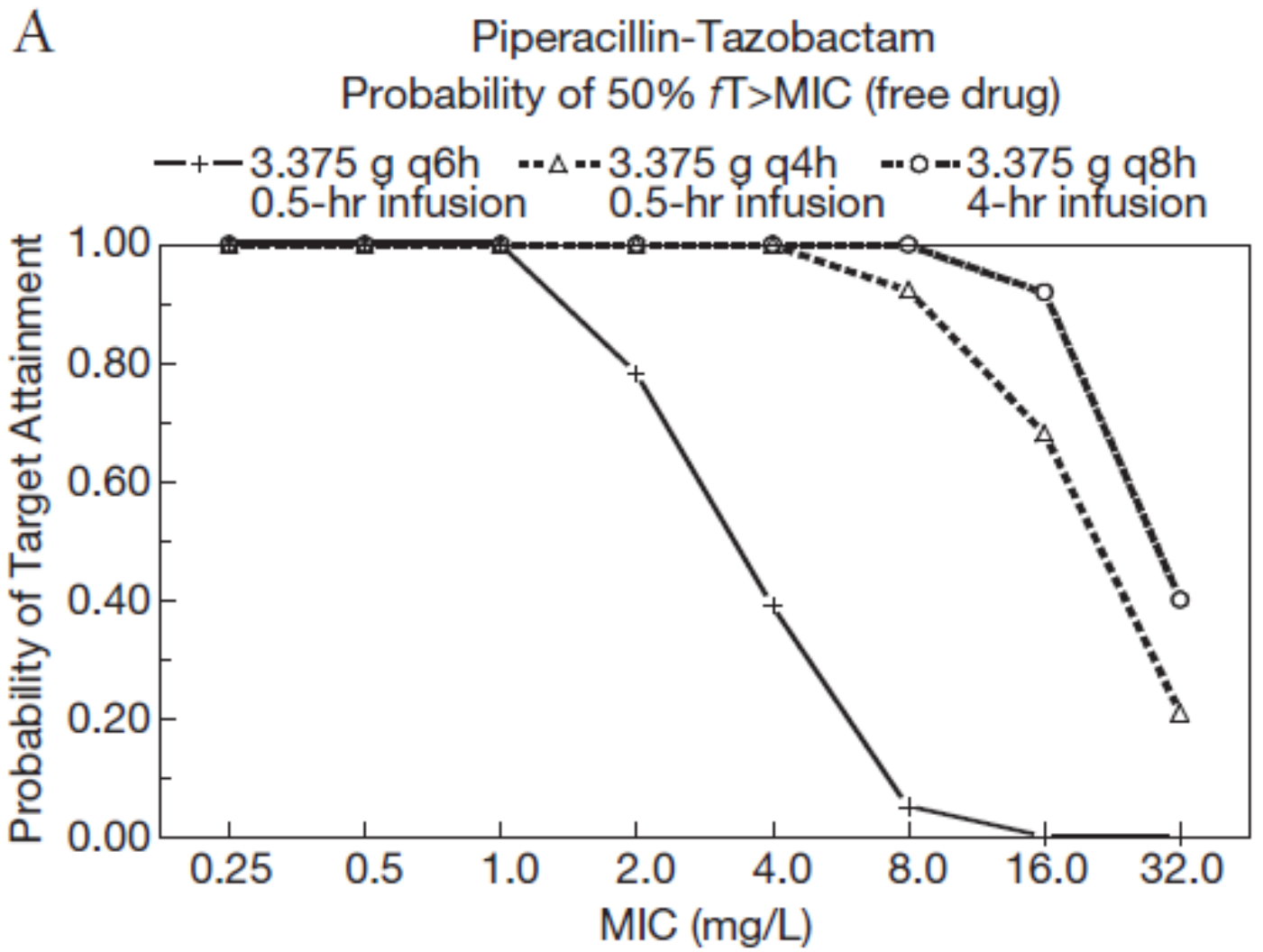


ECOFF = 0.125µg/ml

(Pharmacotherapy 2006;26(9):1320–1332)

ESBL – Pk/Pd

ECOFF = 8.0µg/ml



(Pharmacotherapy 2006;26(9):1320–1332)

ß-lactam/ß-lactamase inhibitors

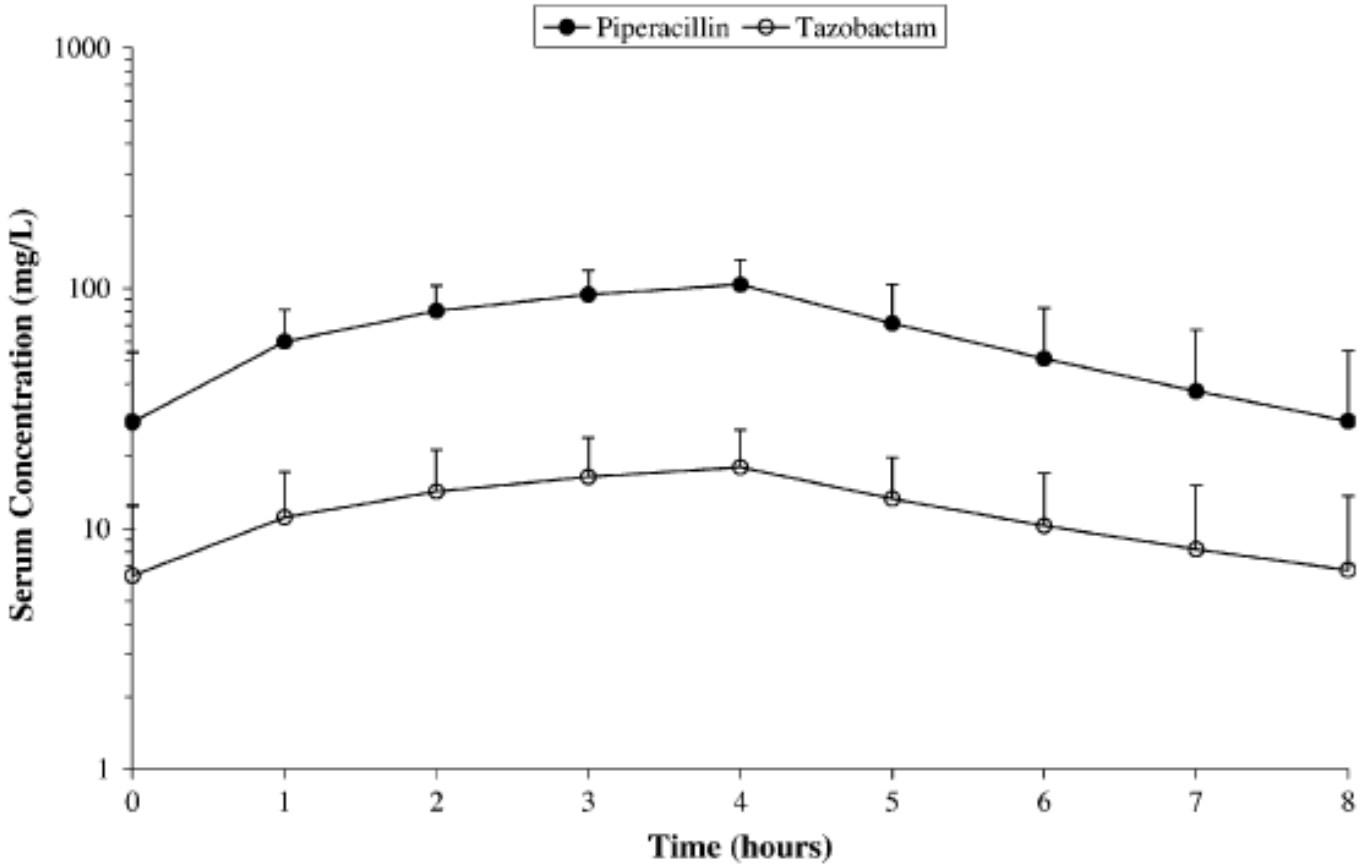


Fig. 1. Steady-state serum concentrations (mean ± standard deviation) of piperacillin and tazobactam following prolonged infusions of 4.5 g every 8 h.

K.M. Shea et al. / International Journal of Antimicrobial Agents 34 (2009) 429–433

INCREMENT - Study design

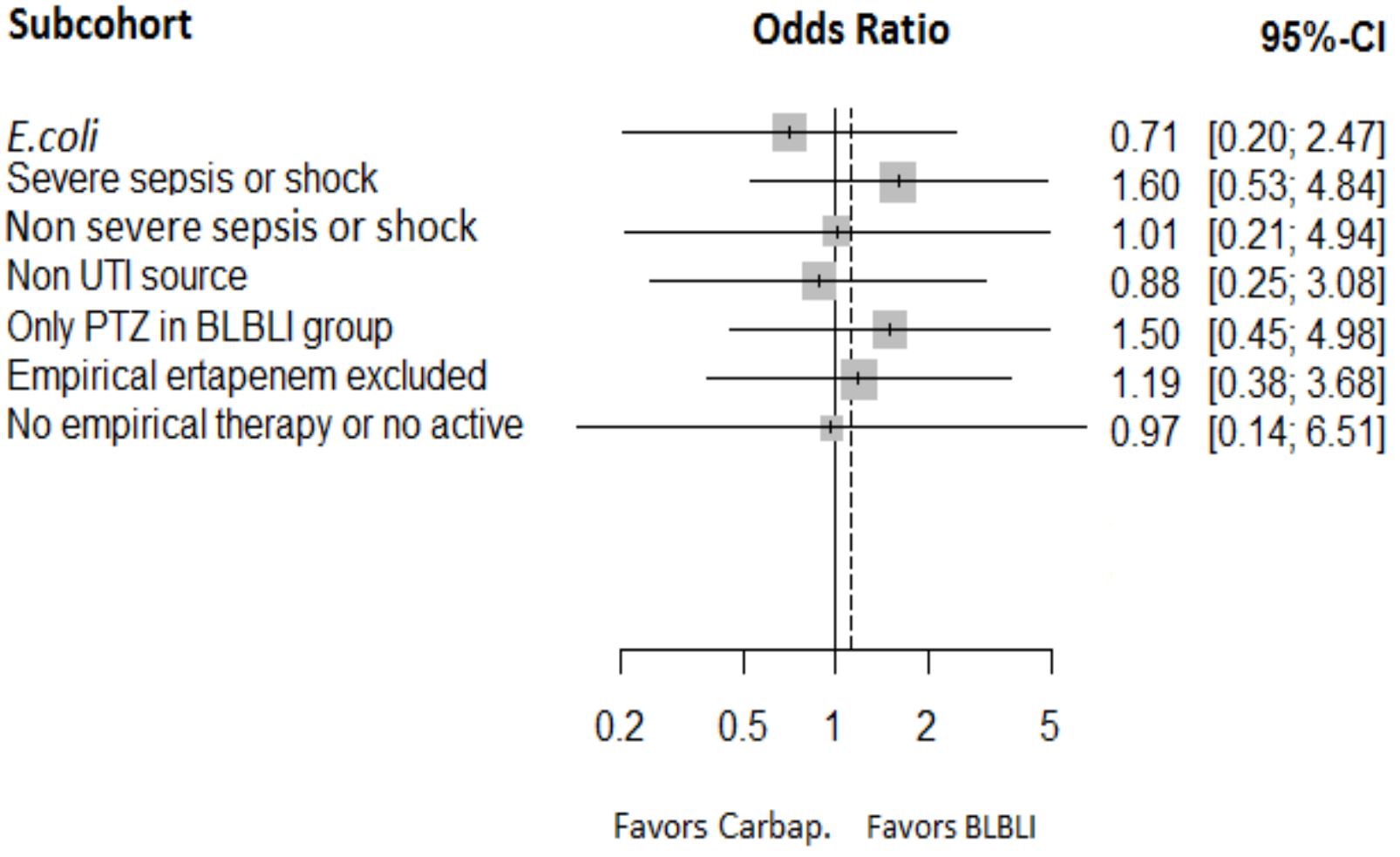
1. Multinational, retrospective cohort study.
2. Registered Clinicaltrials.gov: NCT01764490
3. Reported according to STROBE guidelines
4. Patients with monomicrobial BSI due to ESBL-E or CPE
5. Monotherapy:
   - BLBLI or carbapenem (any)
6. Outcomes:
   - 14-day clinical cure/response rate
   - 30-day all-cause mortality
7. Analysis: statistically sound

Antimicrob Agents Chemother **2016**

AOR for outcomes

	Empirical therapy cohort	Targeted therapy cohort	Global cohort
Cure/improvement day 14	0.68 (0.20-2.21)	1.59 (0.55-5.2)	1.17 (0.38-3.91)*
14-day mortality	0.73 (0.31-1.70)	0.46 (0.10-1.69)	0.57 (0.08-2.78)*
30-day mortality	0.59 (0.26-1.31)	0.34 (0.16-1.68)	0.93 (0.26-3.02)*

Empirical therapy group – D14 clinical cure



ESBL - EUCAST vs CLSI

	ZONES		MICs			
Cephalosporins	**EUCAST**	**CLSI**	**EUCAST**	**CLSI**		
Cefepime	24/21	25/18	1/4	2/16		CLSI: No intermediate but a S-DD
Cefotaxime	20/17	23/19	1/2	1/4		CLSI: ceftriaxone = or
Cefoxitin	19/19	18/14	NA	3/32		EUCAST: cefoxitin is a screen (ECOFF high sens but poor spec for AmpC)
Ceftazidime	22/19	21/17	1/4	4/16		
Piperacillin-tazobactam	**20/17**	**21/17**	**16/8**	**128/16**		**Disc content: different CLSI: 100_10µg EUCAST: 30_6µg**

ESBL – How to report…

1. Interpretive rules as per EUCAST is to report as is for oxyimino-cephs and BLBLI.
2. Important caveats here:
    1. CLSI vs EUCAST CBP
    2. Testing modality being used
    3. Dosing optimized

AmpC

EUCAST position

"Discourages use of cefotaxime, ceftriaxone or ceftazidime in *E. cloacae* (A), *C. freundii, M. morganii & Serratia spp* (B), because of risk of selection for resistance"

AmpC – MIC data

1. ECOFFs:
    1. *E. cloacae:* 0.5µg/ml
    2. Rest = ND

Link to EUCAST MIC tables

AmpC – the nuts and bolts

1. AmpC = Bush-Jacoby 1/1e
2. By definition “greater hydrolysis of cephs than benzylpenicillin; hydrolysis of cephamycins.
3. No inhibition by clavulanic acid and/or tazobactam
4. ACT/CMY/FOX/MIR: have different affinities for different antimicrobials.
5. Inducibility: dependent on the ß-lactam (strong vs weak inducers)

AmpC – EUCAST rule 9.2

9.2	*Enterobacter* spp., *Citrobacter freundii*, *Serratia* spp., and *Morganella morganii*	Cefotaxime, ceftriaxone, and ceftazidime	Cefotaxime, ceftriaxone, and ceftazidime	IF susceptible *in vitro* to cefotaxime, ceftriaxone or ceftazidime, THEN note that the use in monotherapy of cefotaxime, ceftriaxone or ceftazidime should be discouraged, owing to the risk of selecting resistance, or suppress the susceptibility testing results for these agents	published Selection of AmpC-derepressed cephalosporin-resistant mutants may occur during therapy. The use of a third-generation cephalosporin in combination with an aminoglycoside may also lead to failure by selection of resistant mutants. Combination with quinolones has, however, been found to be protective. The selection risk is absent or much diminished for cefepime and cefpirome

Enterobacter spp graded A, others graded B evidence.

Reference is the Chow study.

Chow landmark study

1. 1991 prospective observational study
2. 6 centres collected consecutive *Enterobacter* isolates from blood over a period of 18 months
3. 129 patients in total; 118 received appropriate empiric Rx; 11 (9%) isolated a 2nd R isolate.
4. 7 patients (6%) had identical isolates = emergence of resistance
5. 6 patients (5%) had cephalosporin resistance
6. **19%** (6/31) emergence of resistance following 3GC Rx.

Considerations…

Table 3. Emergence of Resistance during Antibiotic Therapy for *Enterobacter* Bacteremia*

Patient	Antibiotics Used	Emergence of Resistance to Drug	MIC before Therapy	MIC after Therapy	Duration of Therapy when Resistance Was Seen	Source of Second Positive Culture	*Enterobacter* spp.	Outcome
			μg/mL		*d*			
1	Cefotaxime	Cefotaxime	≤ 4	> 32	16	Intra-abdominal abscess	*E. cloacae*	Survived
2	Ceftazidime, tobramycin	Ceftazidime	≤ 2	> 16	18	Blood	*E. cloacae*	Survived
3	Ceftazidime, gentamicin	Ceftazidime	≤ 2	> 16	5	Blood	*E. cloacae*	Survived
4	Cefotaxime, amikacin	Cefotaxime	≤ 4	> 32	6	Blood	*E. aerogenes*	Died
5	Ceftizoxime	Ceftizoxime	8	32	4	Blood	*E. cloacae*	Survived
6	Cefotaxime, gentamicin	Cefotaxime	8	32	7	Blood	*E. aerogenes*	Survived
7	Piperacillin, tobramycin	Tobramycin	≤ 0.25	8	8	Two central venous catheters	*E. cloacae*	Survived

* MIC = minimal inhibitory concentration.

Our most important finding was that administration of a third-generation cephalosporin within 14 days of *Enterobacter* bacteremia was more likely to be associated with a multiresistant *Enterobacter* sp. in the initial positive blood culture ($P < 0.001$, Table 2). This finding

AmpC – How to report…

1. The case for suppression or changing susceptible to resistant is weak (*Enterobacter* spp > others).
2. As per EUCAST, **DO NOT** modify but rather add a comment.

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Thank you

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