Definitive therapy for ESBL-producers: life beyond carbapenems?

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Conflicts of interest

- Speaker: AstraZeneca, Astellas, Pfizer, Novartis, Merck
- Scientific advisory: Merck, AstraZeneca, Roche, Anchaogen
- Research grants:
  - Gilead, Novartis
  - Spanish Ministry of Economy, Andalusian Healthcare System
  - FP7, IMI (EU + EFPIA)

The betalactamases staircase

Carbapenemases
(MLB, KPC, OXA)

Cephalosporinases
(ESBLs, AmpCs)

Broad-spectrum penicillinases
(TEM-1, SHV-1)

Penicillinases

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Life beyond carbapenems?

- Yes, but endangered species!

- 74 yo female.
- Fever, right flank pain, dysuria (48h)
- Diabetes mellitus. Admitted because of CAP 2 months before, received ceftriaxone. Cystitis 4 months ago treated with cipro.
- Tª 39ºC, BP: 110/65, pulse 88 bpm, rest unremarkable.
- 15.000 WBC (87% leucocytes), creatinine 1.8 mg/dl, lactate normal, CRP 85 mg/l. Urine: leucocytes+++
- Urine and blood cultures performed
- Echography; mild right hydronephrosis – nephrostomy planned for next day

TABLE 2. Multivariate logistic regression analysis of risk factors for ESBL-producing *Enterobacteriaceae* isolation within 48 h of hospital admission in the derivation set, with corresponding point values

Parameter	Regression coefficient	*P*	OR (95% CI)	Score
Recent hospitalization[a]	1.73	<0.001	5.69 (2.94–10.99)	3
Admission from another healthcare facility	1.72	0.006	5.61 (1.65–19.08)	3
Charlson comorbidity index ≥ 4	1.33	<0.001	3.80 (1.90–7.59)	2
Previous therapy with β-lactams and/or fluoroquinolones[b]	1.30	<0.001	3.68 (1.96–6.91)	2
History of urinary catheterization[c]	1.25	<0.001	3.52 (1.96–6.91)	2
Age ≥70 years	1.16	<0.001	3.20 (1.79–5.70)	2

Score 7 →80% PPV

Tumbarello et al, AAC 2011

Table 2. Multivariate Analysis of Risk Factors for Community-Onset Bacteremia Due to Extended-Spectrum β-Lactamase (ESBL)-Producing *Escherichia coli*

Control group, model, risk factor	OR (95% CI)	*P*
Patients from the community-onset sepsis population		
General model		
Age >65 years	2.3 (1.2–4.3)	.005
Female sex	1.9 (1.07–3.5)	.02
Health care–associated bacteremia	2.1 (1.2–3.8)	.008
Cirrhosis of liver	4.7 (1.4–15.4)	.008
Obstructive urinary tract disease	3.5 (1.5–7.8)	.001
Urinary catheter use	2.3 (1.05–5.0)	.03
Recent antimicrobial use	1.9 (1.03–3.5)	.03
Model with specific types of health care contact[a]		
Resident in long-term care facility	8.6 (2.0–36.2)	.003
Model with specific antimicrobials[a]		
Fluoroquinolones	2.8 (1.2–6.5)	.01

Rodríguez-Baño et al, Clin Infect Dis 2010

Empirical therapy for community-onset urinary sepsis
Coverage against ESBL-producers

- Monotherapy
  - Cephalosporins
  - Fluoroquinolones
  - (Co-trimoxazole)
  - Aminoglycosides
  - Amox-clavulanate
  - Piperacillin-tazobactam
  - Carbapanems
- Combination therapy
  - Cephs/FQ/amox-clav + AG

Resistace rate >60%

Local differences in resistance rates

ESBL-producing *E. coli*

CTX-M-14-producer

Ampicillin	R
Amoxicillin/clavulante	S (MIC=4 mg/L)
Piperacillin/tazobactam	S (MIC=2 mg/L)
Ceftazidime	S (MIC=1 mg/L)
Cefotaxime	R
Cefoxitin	S
Temocillin	S
Meropenem	S
Ertapenem	S
Ciprofloxacin	R
Co-trimoxazole	R
Gentamicin	R
Amikacin	S
Tigecycline	S
Fosfomycin	S
Colistin	S

Meta-analysis available (non ESBLs)

- Aminoglycosides (monotherapy), compared to other drugs (mostly beta-lactams and quinolones)
  - Higher failure rate except in UTI
  - Higher rate of adverse events
    - Vidal et al, JAC 2007
- Tigecycline, compared to beta-lactams and quinolones
  - Higher failure[1-3] and mortality rate[2, 3]

    (1) Tasina et al, Lancet ID 2011. (2) Yahav et al, JAC 2011. (3) Prased et al CID 2012
  - **NOT FOR UTI!!**

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Fosfomycin disodium (IV)

- Lack of adequate PK/PD data (Parker, IJAA 2013)
- Risk of resistance development during therapy; probably much lower for *E. coli* (Karageorgopoulos, JAC 2012)
- Dosing? 2-8 g / 6-8h
- Well tolerated (hypokaliemia; sodium overload)
- Limited clinical expedience in MDR Enterobacteriaceae, always in combination
  - Karageorgopopulos JAC 2012, Dihn, SJID 2012, Navarro-San Francisco, CMI 2013, Michalopoulos CMI 2010, Pontikis IJAA 2014
- Ongoing RCT (FOREST: fosfomycin vs meropenem in bacteraemic UTI due to ESBL-producing *E. coli*)

Temocillin

- Stable against ESBL and AmpC enzymes
- PK/PD suggested breakpoint: S ≤8 mg/L
- Dosing: 2 gr/12h
  - Higher possible?
  - Continuous infusion 4-6 g/day

Livermore, JAC 2009; De Jongh, JAC 2008

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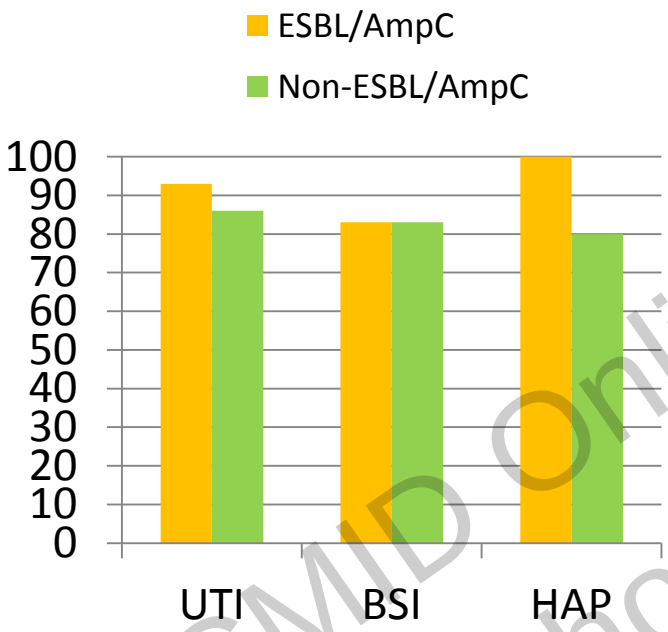
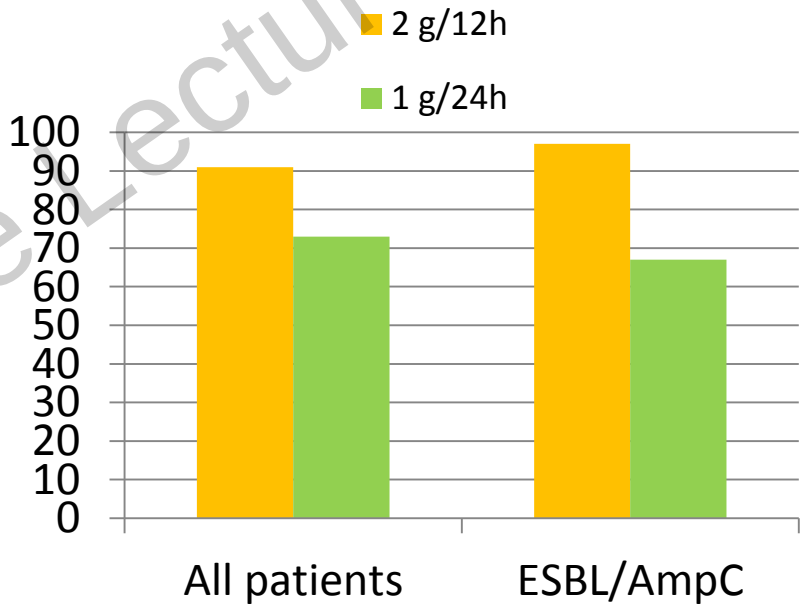
Temocillin

N=91 (43 UTI, 42 BSI, 8 HAP) 53 ESBL/AmpC producers)





Balakrishnan et al, JAC 2011

Oxy-imino-cephalosporins

- Cefotaxime, ceftriaxone, ceftazidime, cefepime
- Stochastic modelling suggest appropriate target attainment
  - MacGowan, CMI 2008, Nguyen, JAC 2014
- Doubts: inoculum effect, expression of beta-lactamases
- Breakpoints for susceptibility
  - EUCAST: ≤1 mg/L
  - CLSI: cefotaxime ≤1 mg/L; cefepime ≤2 mg/L (2014)
- Scarce clinical data
  - Good results: Goethaert, CMI 2006 (n=21); Bin, DMID 2006 (n=7)
  - Not so good results: Rodríguez-Baño, CMI 2012; Chopra, AAC 2012, Lee, CID 2013
- Interpretation
  - Probably OK for UTI if MIC ≤1 mg/L
  - Doubts for septic shock/non-UTI

Cephamycins

- Cefoxitin, cefotetan, ceftemazole, flomoxef

- Anecdotal cases of development of resistance due to porin loss
  - Pangon, J Infect Dis 1989; Lee, JAC 2007
- Flomoxef. Contradictory results
  - Lee, JAC 2006. Good results in 7 patients
  - Yang, BMD Infect Dis 2012. Higher mortality than carbapenems in haemodyalisis patients
- Cefmetazole.
  - Doi, IJID 2013. Good results in UTI (10 patients)

Beta-lactam/beta-lactam inhibitors

- Amox/clav, amp/sulb, tic/clav, pi/taz, sul/sulb

- Beta-lactam inhibitors typically inhibit ESBLs
- Resistance due to overproduction of beta-lactamases, additional mechanism (AmpC-type, OXA-1, porin loss, etc.)
- Vitek® may fail to detect pip/taz R in *E. coli* producing CTX-M-15 + OXA-1 (Pitout et al, Int J Antimicrob Agents 2008)

- No doubts for TEM-1, SHV-1 producers… why doubts for ESBLs?

BLBI and ESBLs

- In vitro activity
  - Resistance
  - Inoculum effect
- Some animal model data
- Clinical data

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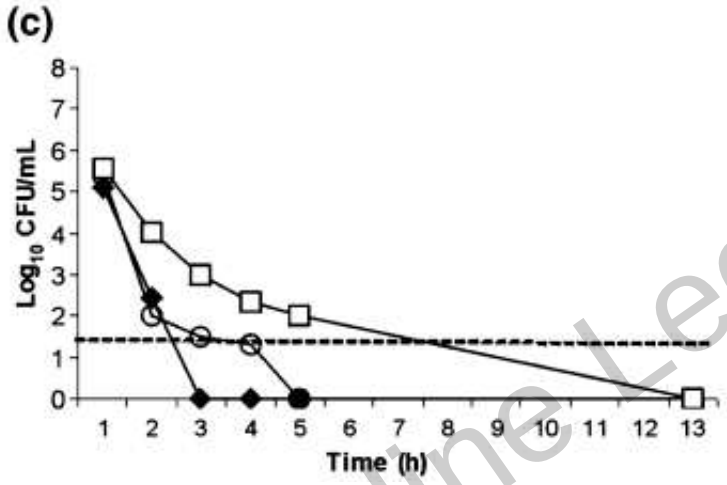
ESBL-producing *E. coli*

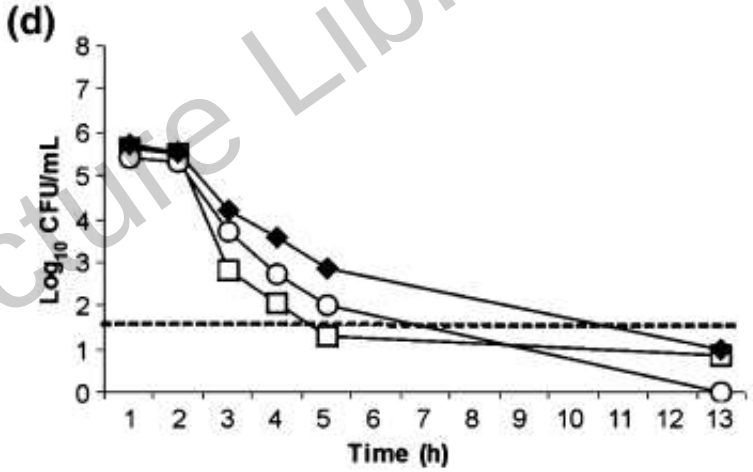
◆ CTX-M-14 ○ SHV-12 □ TEM-3

Low inoculum

Amox/clav (8xMIC)



Pip/taz (8xMIC)



López-Cerero et al, CMI 2010

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ESBL-producing *E. coli*

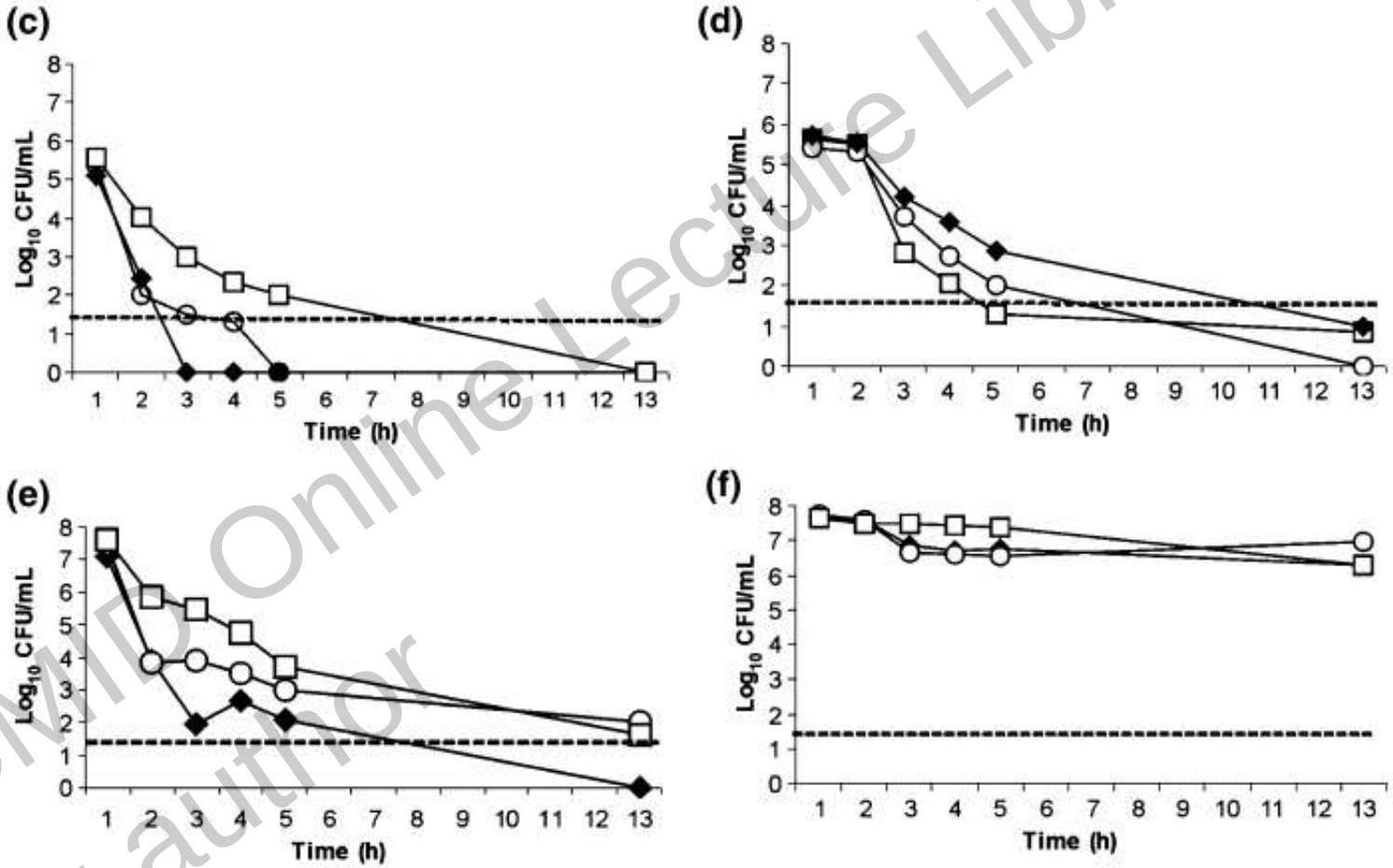
◆ CTX-M-14 ○ SHV-12 □ TEM-3

Amox/clav (8xMIC)

Pip/taz (8xMIC)

Low inoculum

High inoculum



López-Cerero et al, CMI 2010

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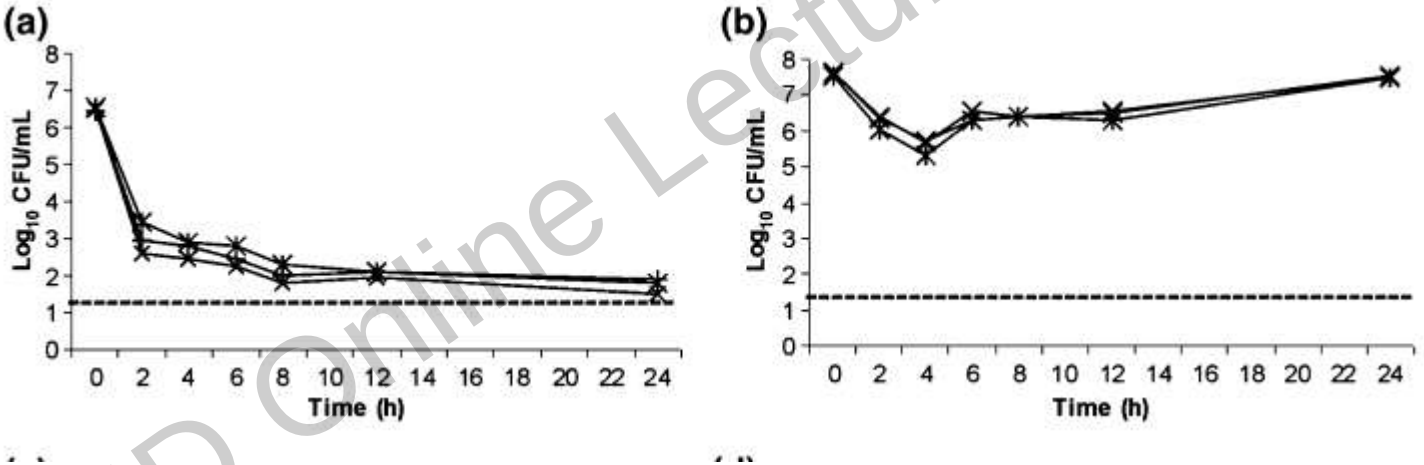
Non-ESBL-producing *E. coli* (ATCC 25922)

Amox/clav (8xMIC)

Pip/taz (8xMIC)

High inoculum



López-Cerero et al, CMI 2010

Similar results for pip/taz in Thomson et al, AAC 2001

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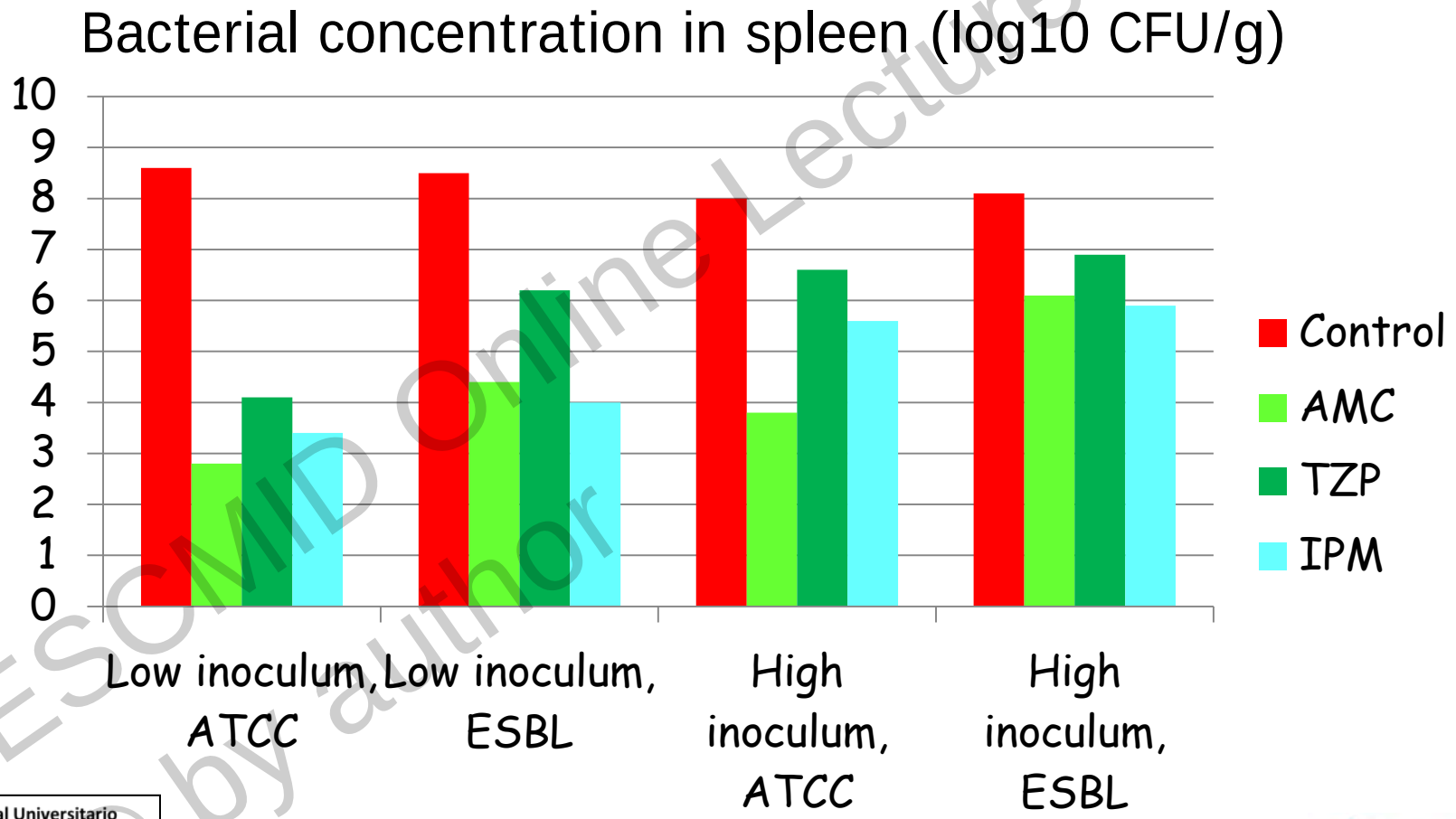
BLBI-ESBLs: animal models

- Rats, IAI, *K. pneumoniae* TEM-26
  - Pip/taz: dose-dependent efficacy
    - Rice et al, AAC 1994
    - Thauvin-Eliopoulos et al, AAC 1997
- Rabbits, endocarditis, *K. pneumoniae* TEM-3
- Rabbits, meningitis, *K. pneumoniae* TEM-3
  - Pip/taz: good results
    - Mentec et al, AAC 1992
    - Leleu et al, AAC 1994

Inoculum Effect on the Efficacies of Amoxicillin-Clavulanate, Piperacillin-Tazobactam, and Imipenem against Extended-Spectrum β-Lactamase (ESBL)-Producing and Non-ESBL-Producing *Escherichia coli* in an Experimental Murine Sepsis Model

F. Docobo-Pérez,[a] L. López-Cerero,[b] R. López-Rojas,[a] P. Egea,[b] J. Domínguez-Herrera,[a] J. Rodríguez-Baño,[b] A. Pascual,[b,c] J. Pachón[a]

AAC 2013



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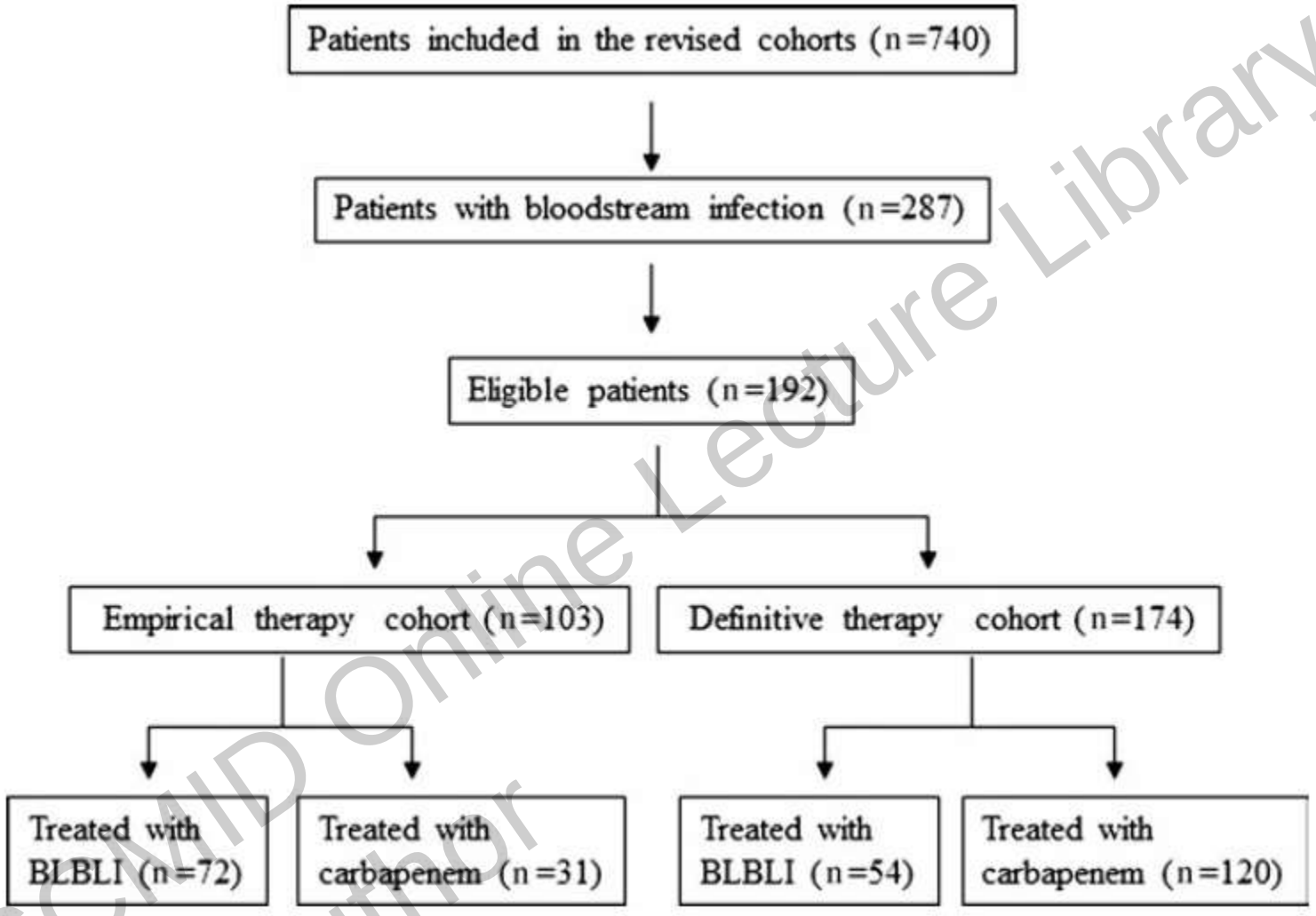
Development of R during therapy

- One case of prosthetic valve endocarditis (*K. pneumoniae* CTX-M-2 + OXA-2) treated with pip/taz
- Mechanism not identified
  - Zimhony et al, AAC 2006

β-Lactam/β-Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum β-Lactamase–Producing *Escherichia coli*: A Post Hoc Analysis of Prospective Cohorts

Jesús Rodríguez-Baño,[1,2] María Dolores Navarro,[1] Pilar Retamar,[1] Encarnación Picón,[1] Álvaro Pascual,[1,3] and the Extended-Spectrum Beta-Lactamases–Red Española de Investigación en Patología Infecciosa/Grupo de Estudio de Infección Hospitalaria Group[a]

Clin Infect Dis 2012; 54: 167-74



Rodríguez-Baño et al, Clin Infect Dis 2012

Bias control

- Classification
  - Strict criteria for assigning BLBLI or carbapenem groups
- Confounding
  - Separated analysis for empirical and definitive therapy
  - Propensity score for receiving BLBLI
  - Multivariate analyses (Cox regression), multiple modelling
    - Mortality up to 30 days
    - Length of stay after bactereaemia

Rodríguez-Baño et al, Clin Infect Dis 2012

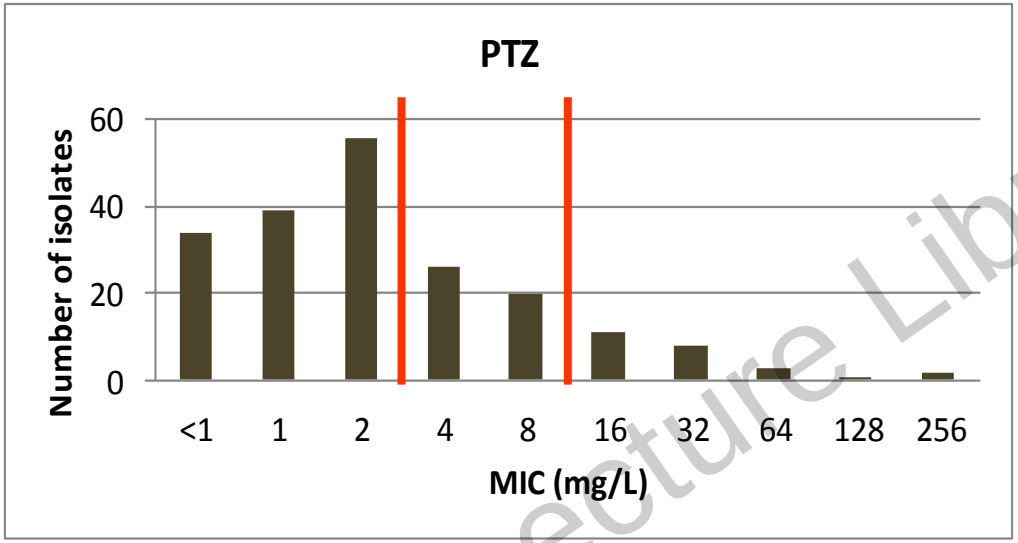
Characteristic	Empirical Therapy Cohort			Definitive Therapy Cohort		
	BLBLI (n = 72)	Carbapenem (n = 31)	*P*	BLBLI (n = 54)	Carbapenem (n = 120)	*P*
Age, median y (IQR)	69 (59–80)	60 (52–78)	.1[b]	67 (56–83)	70 (55–78)	.3[b]
Male sex	29 (40.3)	11 (35.5)	.6	34 (63)	70 (58.3)	.5
Nosocomial acquisition	26 (36.1)	24 (77.4)	<.001	18 (33.3)	67 (55.8)	.006
Charlson index, median, (IQR)	2 (1–5)	2 (1–5)	.6[b]	2.5 (1–5)	3 (1–5)	.5[b]
Cancer	21 (31.9)	11 (35.5)	.7	15 (27.8)	43 (35.8)	.2
Immunosuppression	5 (6.9)	5 (16.1)	.1[c]	3 (5.6)	15 (12.5)	.1
Neutropenia	2 (2.8)	3 (9.7)	.1[c]	0	7 (5.8)	.1[c]
Urinary or biliary tract as source	52 (72.2)	18 (58.1)	.1	42 (77.8)	79 (65.8)	.1
ICU admission	7 (9.9)	2 (6.7)	.7[c]	4 (7.4)	18 (15.4)	.1
Severe sepsis or shock at presentation	14 (19.4)	9 (29.0)	.2	8 (14.8)	32 (26.7)	.08
Pitt score, median (IQR)	1 (0–2)	1 (0–2)	.7[b]	1 (0–2)	1 (1–2)	.04[b]
CTX-M enzyme	57 (80.3)	25 (86.2)	.4	43 (82.7)	95 (81.2)	.8
Definitive therapy						
Carbapenem	32 (44.4)	30 (93.7)	<.001	…	…	…
BLBLI	34[d] (47.2)	0	<.001	…	…	…
Empirical therapy						
Carbapenem	…	…	…	0	30 (25)	<.001
BLBLI	…	…	…	45[d] (83.3)	38 (31.7)	<.001
Cephalosporins	…	…	…	7 (13)	39 (32.5)	.006
Fluoroquinolones	…	…	…	2 (3.7)	13 (10.8)	.1[c]
Appropriate empirical therapy	…	…	…	34 (63)	64 (53.3)	.2
Mortality, no. of deaths						
Day 7	2 (2.8)	3 (9.7)	.1[c]	1 (1.9)	5 (4.2)	.6[c]
Day 14	7 (9.7)	5 (16.1)	.3	3 (5.6)	14 (11.7)	.2
Day 30	7 (9.7)	6 (19.4)	.1	5 (9.3)	20 (16.7)	.1
Hospital stay after BSI, median (IQR), d	12 (8–28)	13 (9–25)	.7[b]	13 (8–22)	13 (10–25)	.04[b]

BLBLI vs carbapenems	Empirical therapy cohort	Definitive therapy cohort
Death (HR,adjusted)*	0.93 (0.25-3.51)	0.76 (0.28-2.07)
Hospital stay (HR, adjusted)*	1.07 (0.3-3.0)	1.32 (0.91-1.90)

*Including propensity score

Rodríguez-Baño et al, Clin Infect Dis 2012

MIC distribution



Bacteraemia due to ESBLEC treated with PTZ
N=39

- Urinary tract N=11
  - Low MIC Mortality 0/7[a]
  - Intermediate MIC Mortality 0/2
  - High MIC Mortality 0/2
- Other source N=28
  - Low MIC Mortality 0/11[b]
  - Intermediate MIC Mortality 3/8 (37.5%)[c]
  - High MIC Mortality 4/9 (44.4%)[d]

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Retamar et al. AAC 2013

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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 2013

Carbapenems		Pooled RR (95% CI)
vs. non-BLBLI	Empirical	0.50 (0.33-0.77)
	Definitive	0.65 (0.47-0.91)
vs. BLBLI	Empirical	0.91 (0.66-1.25)
	Definitive	0.52 (0.23-1.13)

Merino trial ongoing in Australia/New Zeeland!!

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- 78 yo female, admitted because of stroke 10 days ago. Receiving cipro for nosocomial UTI due to *Proteus mirabilis* day 5
- New Fever, cough, dyspnoea
- Tª 39ºC, BP:95/65, pulse 90 bpm, rest unremarkable.
- 17.000 WBC (85% leucocytes), creatinine 1.2 mg/dl, lactate 2.5 mmol/L
- Chest X-ray: right lower lobe infiltrate
- Urine and blood cultures performed
- Support therapy

ESBL-producing *K. pneumoniae*

Ampicillin	R
Amoxicillin/clavulante	R
Piperacillin/tazobactam	R
Ceftazidime	R
Cefotaxime	R
Cefoxitin	R
Temocillin	R
Meropenem	S
Ertapenem	S
Ciprofloxacin	R
Co-trimoxazole	R
Gentamicin	R
Amikacin	S
Tigecycline	S
Fosfomycin	S
Colistin	S

CTX-M-15
SHV-1
OXA-1

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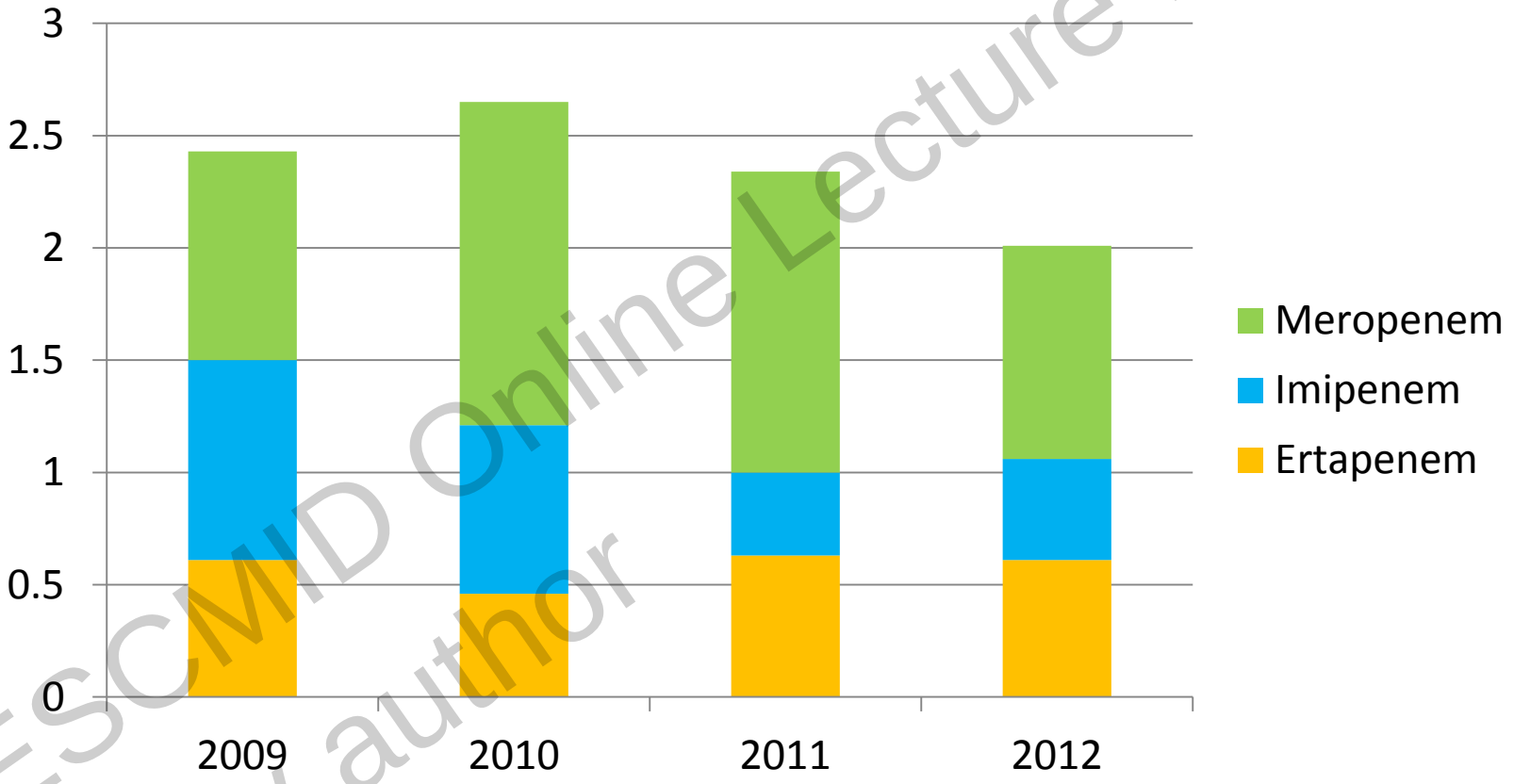
Carbapenems, DDD / 100 patient-days



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Carbapenem-sparing regimens for ESBLs: Conclusions

- Empirical therapy
  - Community-onset infections: ceph or amox/clav + AG
  - Nosocomial infections
    - UTI or non-severe infections: CAZ or FEP or pip/taz + AG
    - Other infections: carbapenem
- Definitive therapy
  - UTI, biliary tract infections, *E. coli*: amox/clav, pip/taz if susceptible
  - Other microorganisms, infections: temocillin?
- Research
  - RCT empirical therapy for UTI in high risk patients: beta-lactam + AG vs carbapenem
  - RCT definitive therapy temocillin vs carbapenem
  - RCT definitive therapy cephamycin vs carbapenem

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