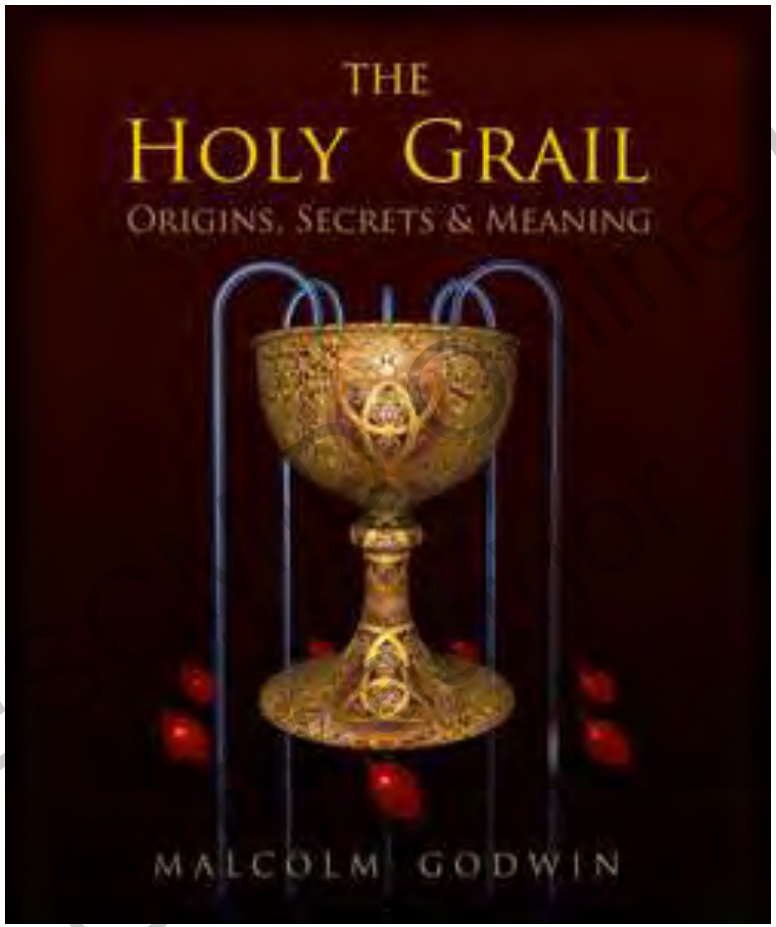
Sparing carbapenems by reviving old antibiotics

Mecillinam, Fosfomycin, Temocillin

John Turnidge

Carbapenem-sparing
The Holy Grail

THIS……



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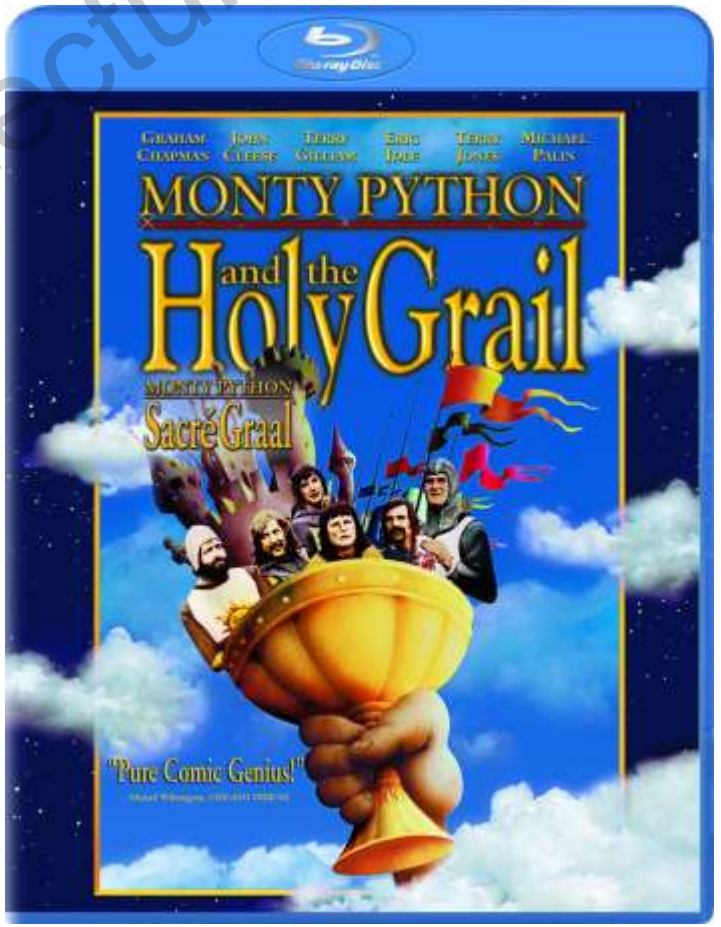

frontiers in
MICROBIOLOGY

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A new strategy to fight antimicrobial resistance: the revival of old antibiotics

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REVIE

Louis D. Saravola

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'Old' antibiotics for emerging multidrug-resistant bacteria

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Mecillinam	Niels Frimodt-Møller
Temocillin	Françoise van Bambeke
Fosfomycin	Angela Huttner

Carbapenem-sparing agents

- We still have choices…

Agent	Problem addressed
β-lactamase inhibitor combinations	ESBLs
Cefepime	AmpC producers
Nitrofurantoin	MDR E. coli mainly
Mecillinam	ESBLs
Temocillin	ESBLs
Fosfomycin	MDR Enterobacteriaceae

Carbapenem-sparing agents

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Agent	Problem addressed
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Mecillinam	ESBLs
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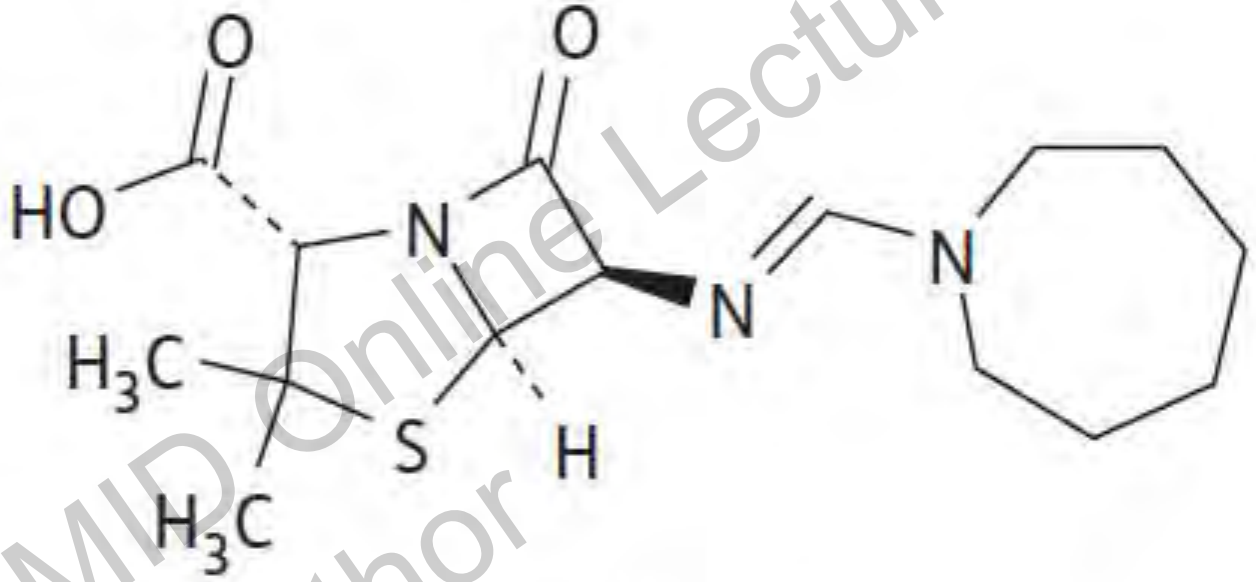
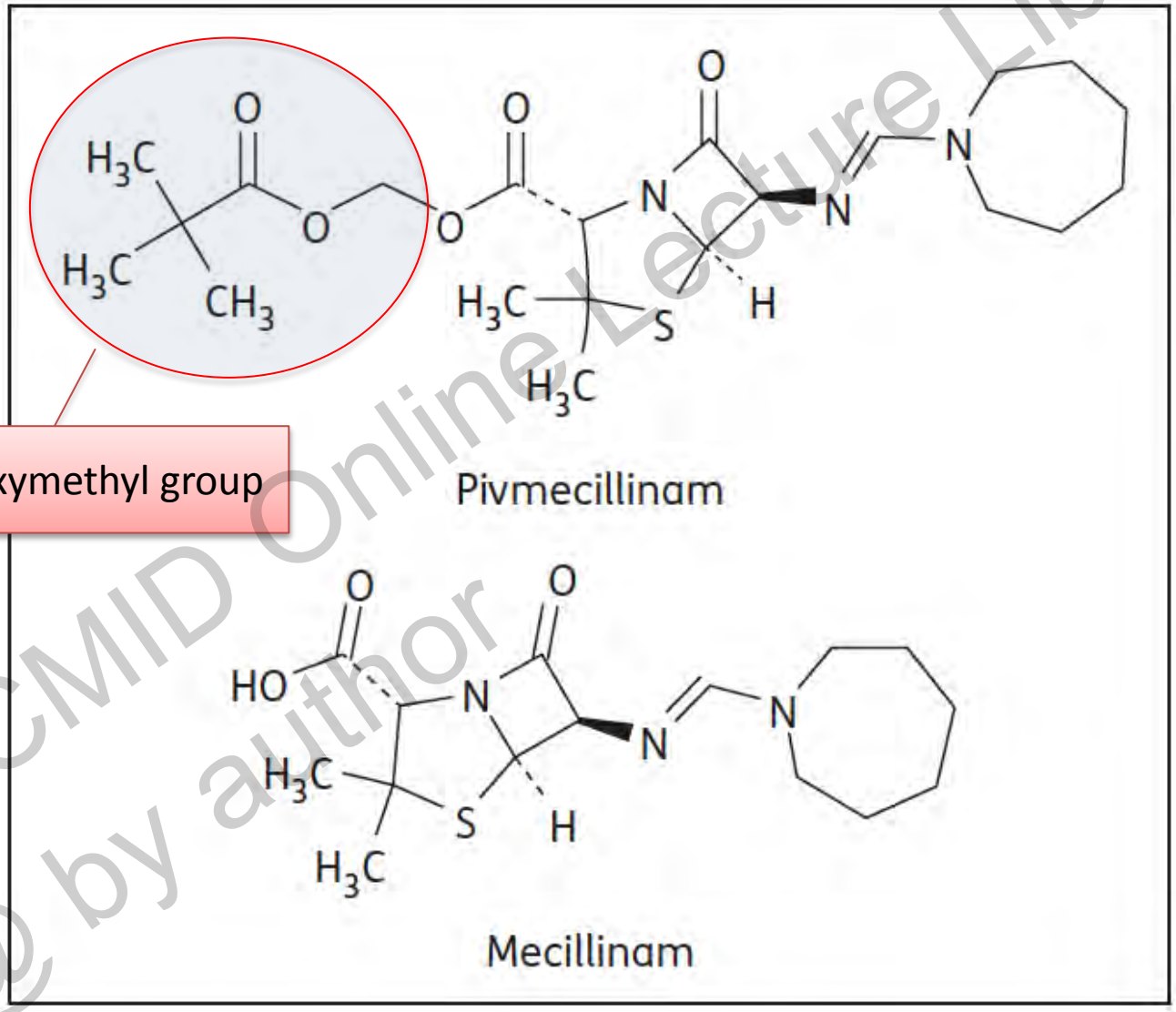
Mecillinam

a.k.a amdinocillin



Mecillinam

Mecillinam ← Pivmecillinam



Pivmecillinam

Current Registered Indications (UK)

Adults and children weighing more than 40 kg:

Urinary tract infections:

- Acute uncomplicated cystitis: 72 hour course of 2 tablets immediately followed by 1 tablet 3 times daily to a total of 10 tablets.
- Chronic or recurrent bacteriuria: 2 tablets 3 to 4 times daily.

Salmonellosis:

- Enteric fever: 1.2 - 2.4 g daily for 14 days.
- Salmonella carriers: 1.2 - 2.4 g daily for 2-4 weeks.

Mecillinam

Antibacterial properties

- High specificity against PBP-2 in the Gram-negative cell wall, unlike the majority of other β-lactam agents, which preferentially bind Gram-negative PBP-1A, -1B or -3.2
- Little or no Gram-positive activity
- Relative stability to common β-lactamases, including those of the CTX-M type.

Mecillinam

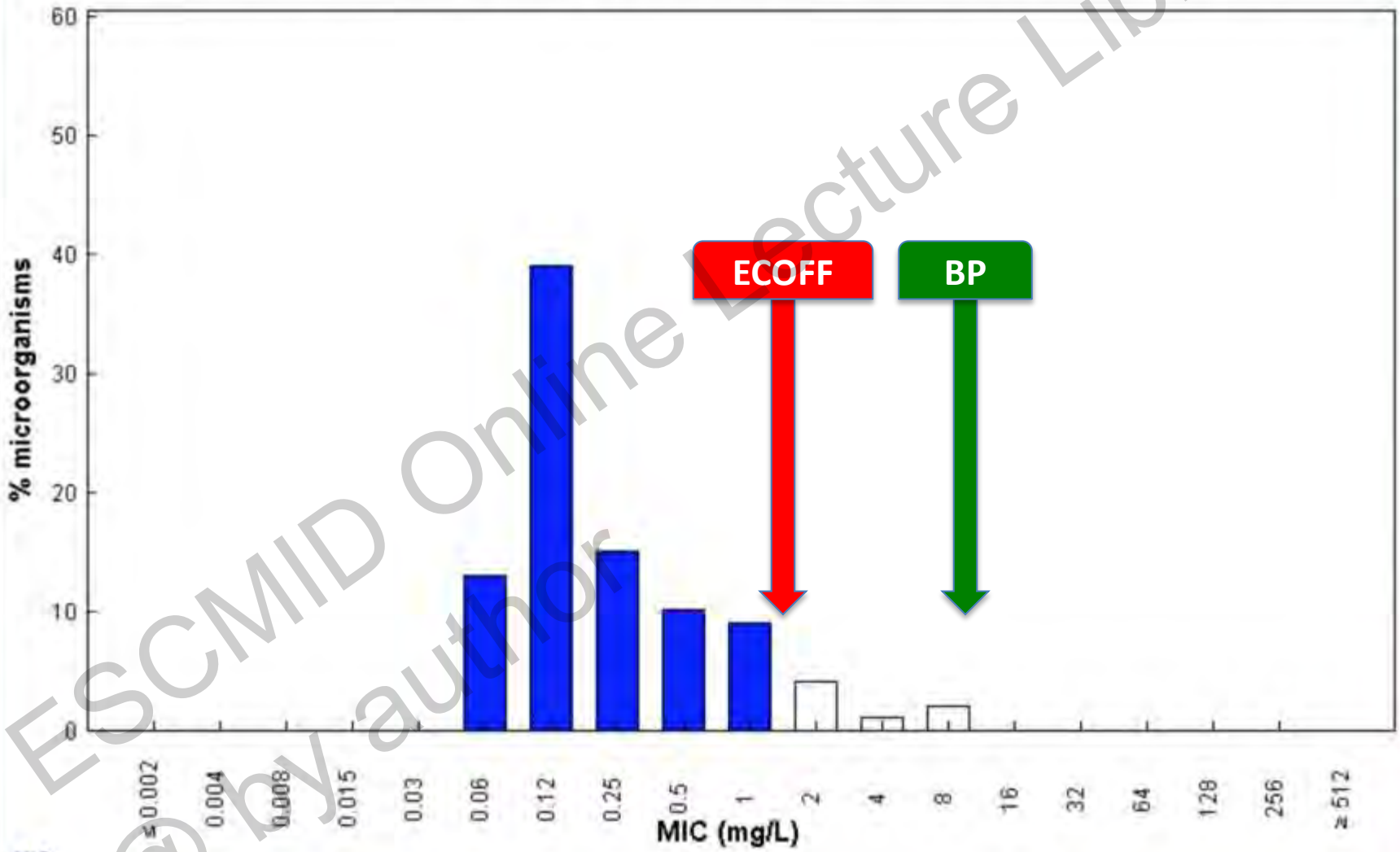
MIC Breakpoints

	S	I	R
EUCAST	≤ 8	--	> 8
CLSI	≤ 8	16	≥ 32

Mecillinam / Escherichia coli

International MIC Distribution - Reference Database 2015-04-19

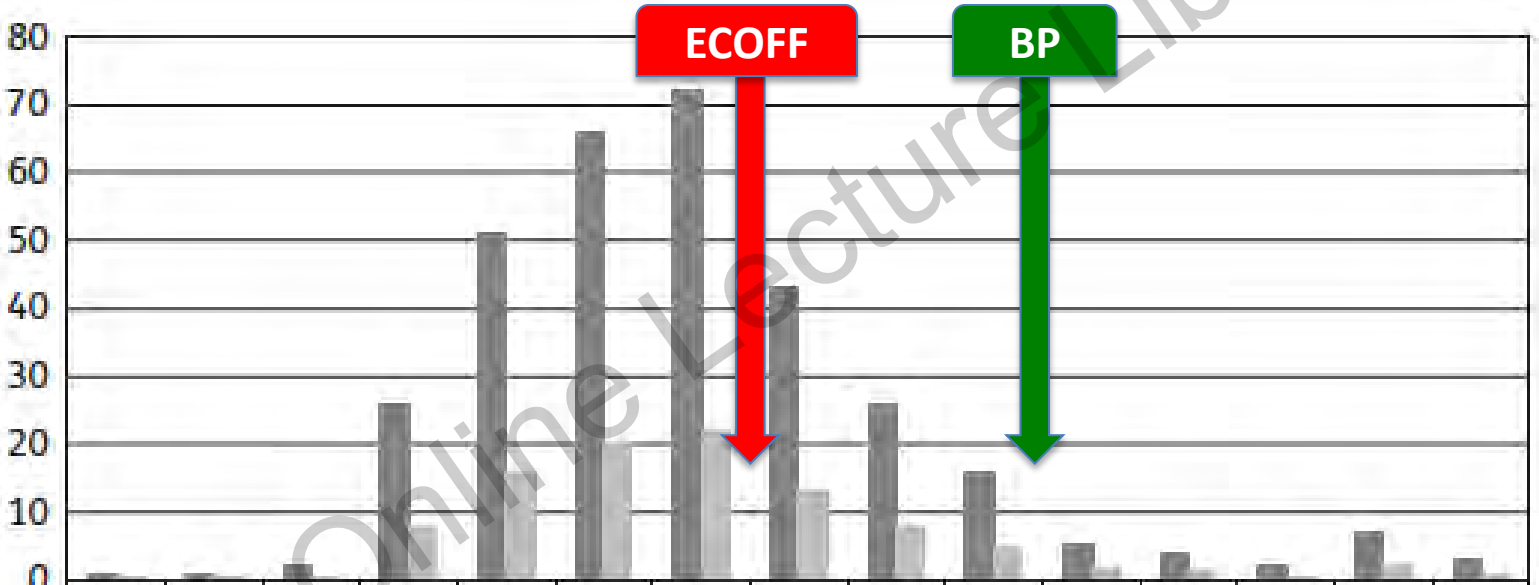
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 1 mg/L
Wildtype (WT) organisms: ≤ 1 mg/L

1636 observations (4 data sources)

Mecillinam MIC distribution of CPD-resistant *E. coli*



	0.02	0.03	0.06	0.13	0.25	0.5	1	2	4	8	16	32	64	128	256
No. of isolates	1	1	2	26	51	66	72	43	26	16	5	4	2	7	3
% of isolates	0.3	0.3	0.6	8	15.7	20.3	22.2	13.2	8	4.9	1.5	1.2	0.6	2.2	0.9

Mecillinam MIC (mg/L)

Wooton JAC 2010; 65:79-81

TEM-1 (2 isolates), hyperexpression of chromosomal AmpC (1 isolate), CTX-M (12 isolates), CTX-M/SHV (3 isolates), CMY-2 (3 isolates), CMY-2/CTX-M-1 (1 isolate), OXA (1 isolate), CTX-M/OXA-2 (1 isolate), TEM-1/CTX-M-1/CMY-2/OXA-1/OXA-2 (1 isolate), TEM/SHV/CTX-M (1 isolate), TEM/SHV/CTX-M/CMY/OXA-1/OXA-2 (1 isolate), TEM-1/CMY-2 (1 isolate), TEM/SHV/CTX-M-1 (1 isolate) and TEM/SHV/CTX-M-1/CTX-M-2/OXA-2 (1 isolate).

Mecillinam Pharmacokinetics

- Kerrn et al., 2004
  - 400mg pivmecillinam dose = 296 mg mecillinam

	Mecillinam ($n = 9$)	
Collection interval (h)	Urine concentration (mg/L) (range)	Accumulated excreted (mg) (range)
Control (0 sample)	0	0
0–3	296 (84–1324)	81 (27–139)
3–6	47 (12–432)	109 (82–154)
6–12	5 (0[a]–17)	114 (86–156)
12–24	0 (0[a]–1)	114 (86–156)

Mecillinam

Clinical Efficacy

J Antimicrob Chemother 2014; **69**: 303–308
doi:10.1093/jac/dkt368 Advance Access publication 25 September 2013

Journal of Antimicrobial Chemotherapy

Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria

Simon Dewar*, Lee C. Reed and Roland J. Koerner

Pivmecillinam

Clinical Efficacy against ESBL+ UTIs

Authors (Design)	Year	N	% Efficacy ESBL
Jansåker et al. (Prospective observational; *E. coli* and K . *pneumoniae*)	2014	30 - 400mg tid 9 - 200mg tid	84% 'clinical cure' 79% microbiological 5/39 relapsed
Søraas et al. (Population-based study; ESBL+ve E. coli)	2104	41	44% failure – defined by repeat prescription

Pivmecillinam

Clinical Efficacy against ESBL+ UTIs

Søraas et al 201

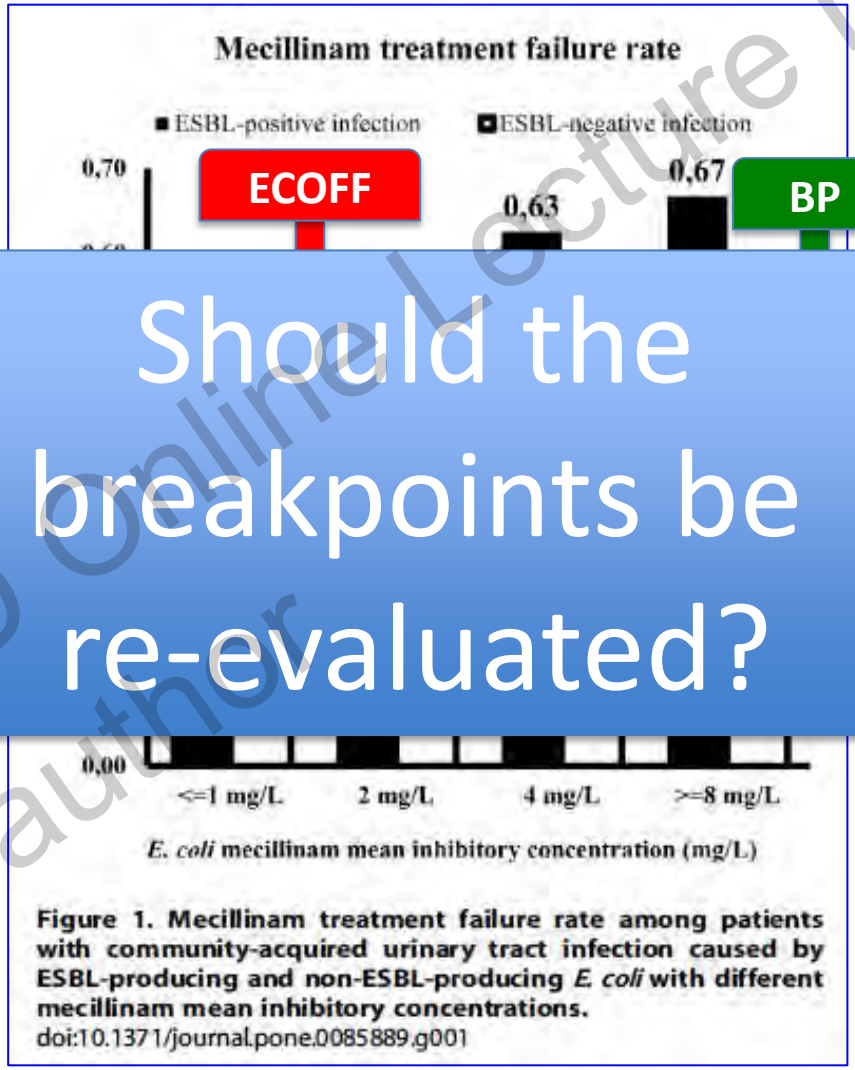


Figure 1. Mecillinam treatment failure rate among patients with community-acquired urinary tract infection caused by ESBL-producing and non-ESBL-producing *E. coli* with different mecillinam mean inhibitory concentrations.
doi:10.1371/journal.pone.0085889.g001

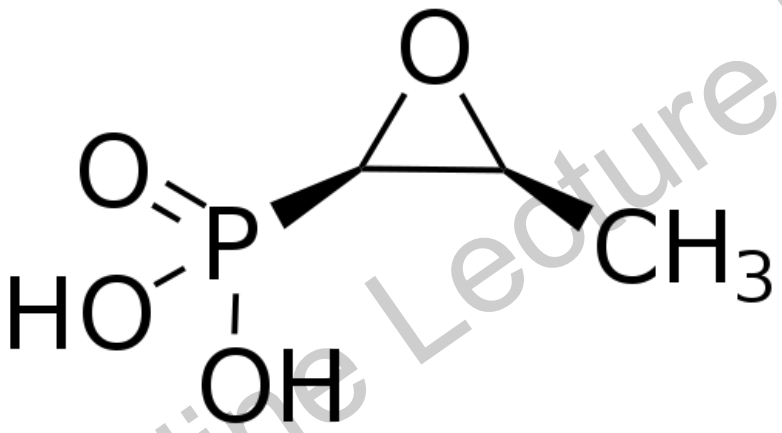
Should the breakpoints be re-evaluated?

Mecillinam

Conclusions

- Long history of safe and effective use in UTI
- Based on current breakpoints, seems like a reasonable option for ESBL-producing Enterobacteriae
- Clinical experience is limited
- Findings of Søraas et al. raise important questions

Fosfomycin

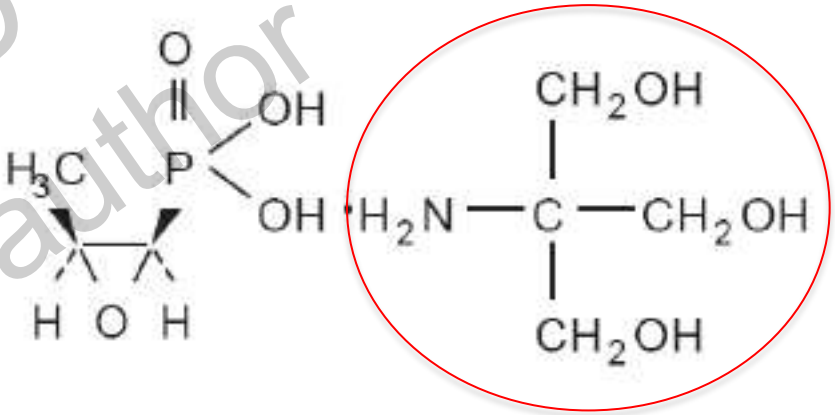


- Natural product
  - From *Streptomyces fradiae*
- Mechanism of action
  - inhibits bacterial cell wall biogenesis by inactivating the enzyme UDP-*N*-acetylglucosamine-3-enolpyruvyltransferase, also known as MurA

Fosfomycin

Three formulations

- Fosfomycin disodium
  - For intravenous use
- Fosfomycin calcium
  - For oral use
- Fosfomycin trometamol (or tromethamine)
  - 5.6 g ora



Fosfomycin trometamol

Approved indications (US)

INDICATIONS

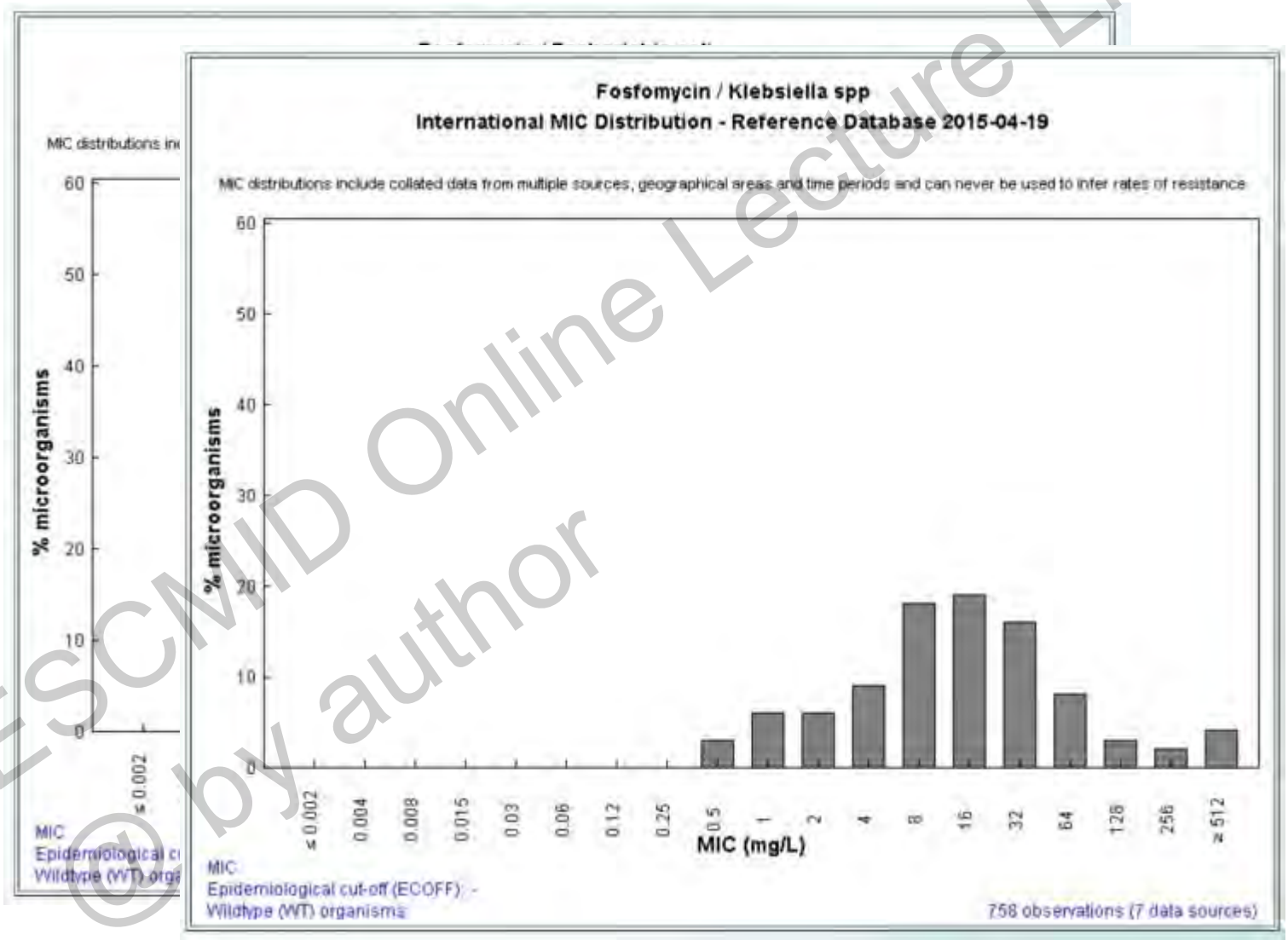
MONUROL is indicated only for the treatment of uncomplicated urinary tract infections (acute cystitis) in women due to susceptible strains of Escherichia coli and Enterococcus faecalis. MONUROL is not indicated for the treatment of pyelonephritis or perinephric abscess.

If persistence or reappearance of bacteriuria occurs after treatment with MONUROL, other therapeutic agents should be selected. (See **PRECAUTIONS** and **Clinical Studies** section)

Fosfomycin trometamol

- Most experience:
  - For the treatment of uncomplicated UTI
    - Single dose therapy!
  - Since the early 1970s
- Greatest current interest:
  - Treatment of lower UTI caused by ESBL-producing Enterobacteriaceae
  - Role for other pathogens less clear

Fosfomycin trometamol
MIC distributions



Fosfomycin trometamol
MIC Breakpoints

	S	I	R
EUCAST	≤ 32	--	> 32
CLSI	≤ 64	128	≥ 256

Fosfomycin trometamol

- Pharmacokinetics
  - Bioavailability = 37%, little food effect
  - Plasma C_{max} = 26 mg/L
  - V_{ss} = 136 L
  - 38% excreted in urine
  - Mean urinary levels 706 ± 466 mg/L
    2-4 hours post-dose
- Pharmacodynamics
  - ?????

Fosfomycin trometamol

ESBL UTI Efficacy

Authors (Dosing regimen)	Year	N	% Efficacy ESBL
Pullukcu et al. (3g 2nd-daily x 3)	2007	52 *E. coli*	94% clinical 79% microbiological
Rodriguez-Baño et al. (1 x 3g dose)	2008	28 *E. coli*	93% clinical
Neuner et al. (at least 1 x 3g dose)	2012	7 *E. coli* and *Klebsiella*	71% microbiological

Fosfomycin Issues

- Susceptibility testing
  - No Broth Microdilution standard
  - Requirement for glucose-6-phosphate in the medium
- How long should UTI be treated??
  - No-one currently recommends a single dose
  - Possibly 3g 2nd-daily for 3 doses
- Doubtful fficacy against other MDR pathogens

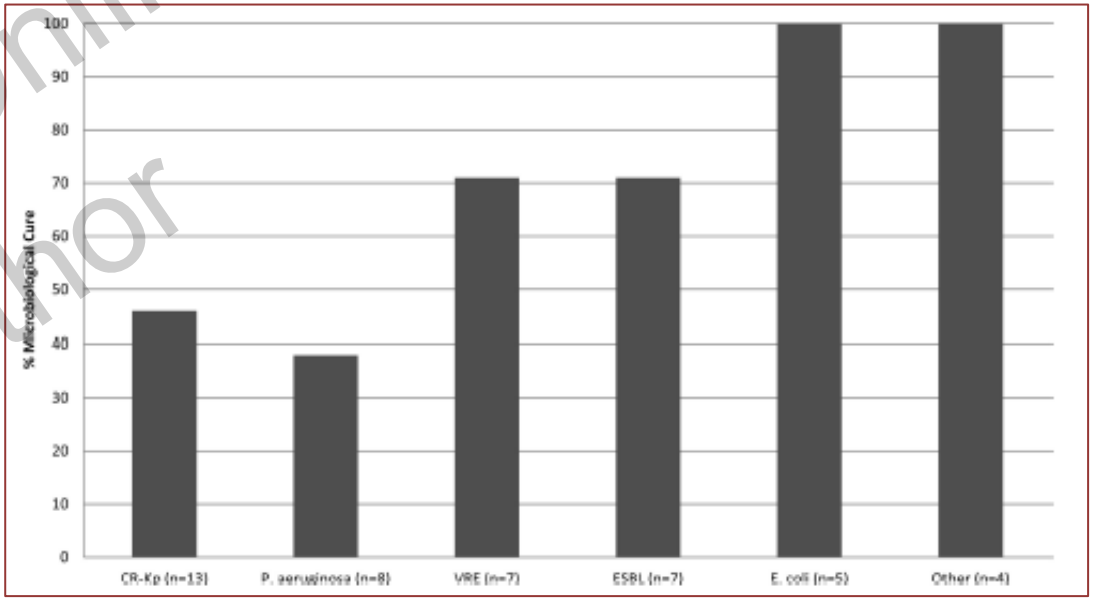
Fosfomycin Issues

Efficacy against other MDR pathogens

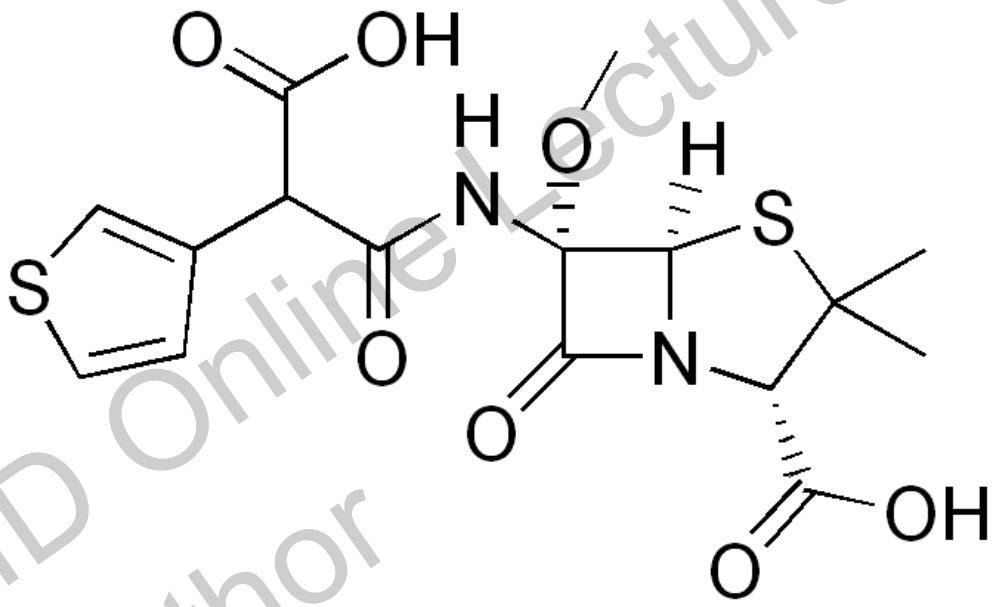
Livermore et al., 2011

Fosfomycin	2	4	8	16	32	64	128	≥256
IMP	1[a]	3	4	1	1			3
NDM	5[b]	1	3	1	2	2	1	1
VIM			1	1	1	1		1
KPC			1	4	1	4		1
SME-1				1				
OXA-48	2[b]	1	2	1	5	3	5	
Impermeability + ESBL					2	1	1	5
Impermeability + AmpC	1			1	1	2	1	

Neuner et al., 2012



Temocillin



Temocillin

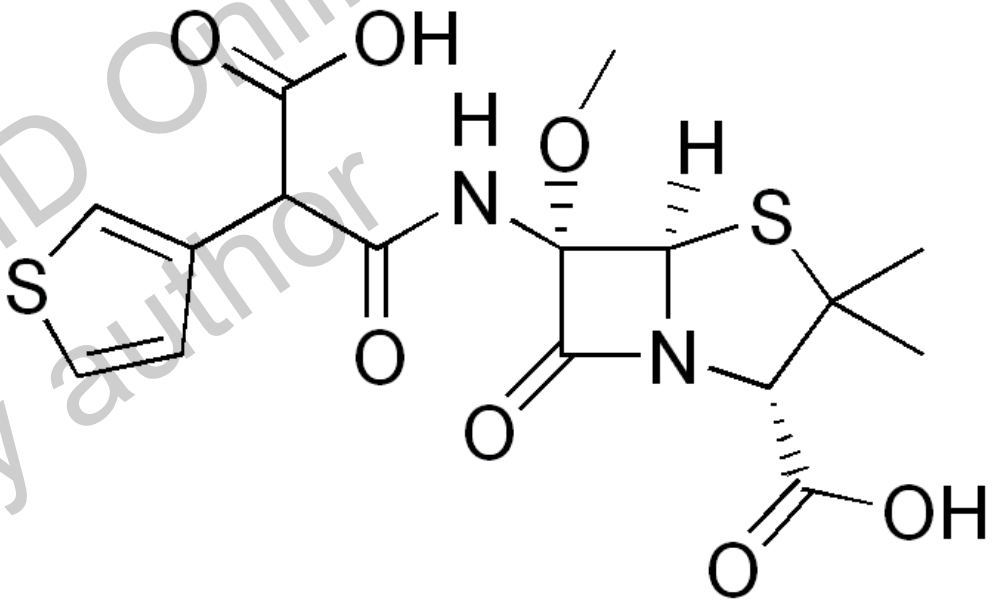
Journal of Antimicrobial Chemotherapy (2009) **63**, 243–245
doi:10.1093/jac/dkn511
Advance Access publication 18 December 2008

JAC

Temocillin revived

David M. Livermore[1]* and Paul M. Tulkens[2]

[1]Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK; [2]Unité de Pharmacologie Cellulaire et Moléculaire & Centre de Pharmacie Clinique, Université Catholique de Louvain, Bruxelles, Belgium



Temocillin

- Mechanism of action
  - Targets PBP3 >> PBP1
- Spectrum
  - Gram-negatives except *P. aeruginosa* or anaerobes
- Redeeming features
  - Stability to extended-spectrum and AmpC β-lactamases, as most metallo-β-lactamases
  - Does not select for stably-derpressed AmpC mutants

Temocillin

Approved Indications (UK)

4.1 Therapeutic indications

Negaban is indicated for the treatment of septicaemia, urinary tract infection and lower respiratory tract infection where susceptible gram-negative bacilli are suspected or confirmed.

In mixed infections where gram-positive or anaerobic bacteria are also liable to be implicated, co-administration with other appropriate antibacterial agents should be considered.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Adults (including the elderly): The usual dosage is 1-2 g every 12 hours.

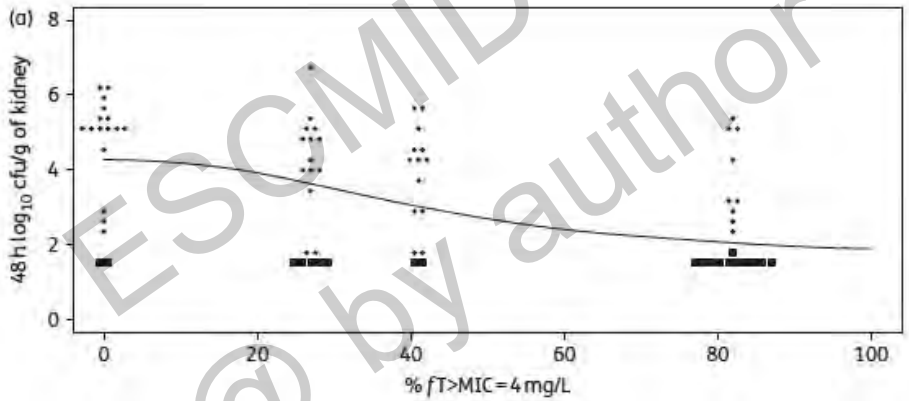
Children: Insufficient data are available to recommend an appropriate dosage regime.

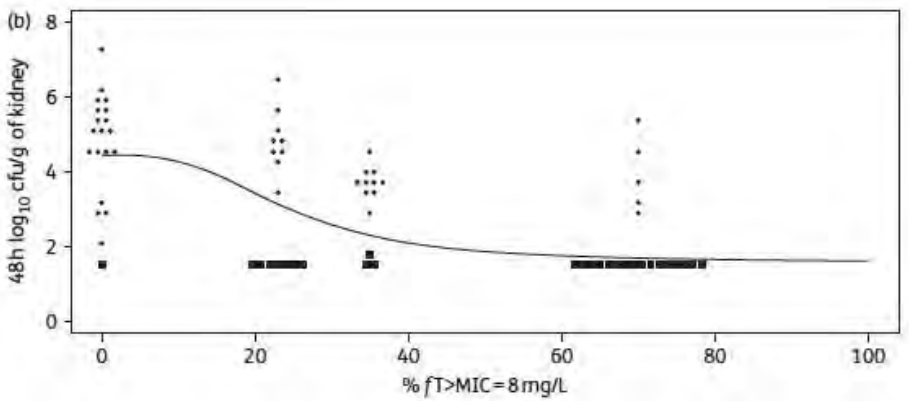
Dosage in patients with impaired renal or hepatic functions (adults): Temocillin is mainly excreted renally and unchanged. Excretion is reduced in renal impairment and half-life is increased according to the severity of renal failure. In moderate and severe renal failure, dose adjustments are necessary in accordance with the following regimen:

Temocillin

PK/PD

- Reasonable favourable with an adult dosing schedule of 2g 12-hourly, at a breakpoint of 8 -16 mg/L (40% *f*T>MIC)
  - ESBLs and hyper-AmpCs: MIC_{90} = 16 mg/L
- UTI mouse model (Soubirou et al., JAC 2015;70:1466-72)



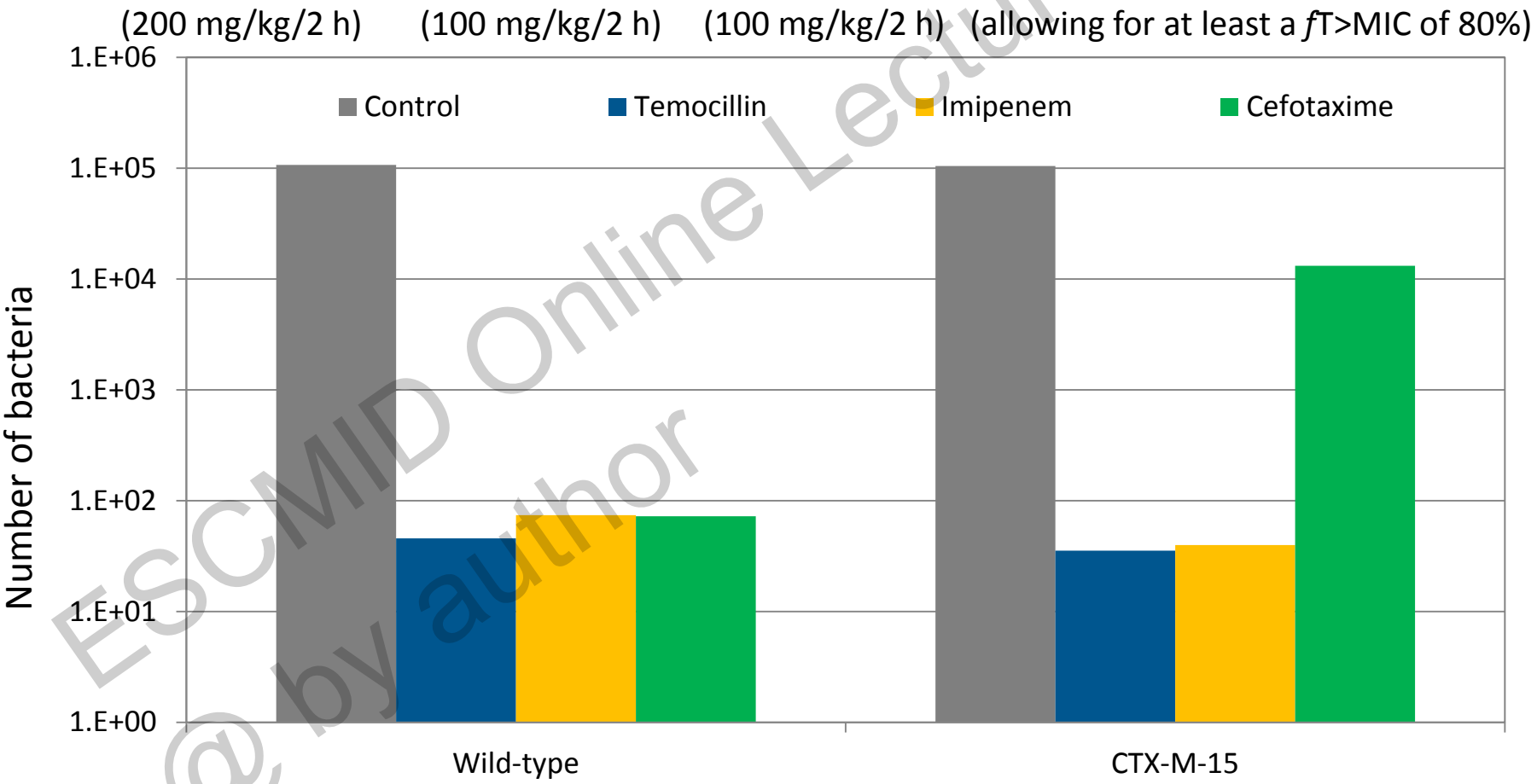


Temocillin

- Clinical experience
  - Published experience is old
  - In regular use in Belgium for ~30 years
- Gupta et al., JAC 2009; 64:431-3
  - 6 cases of ESBL or AmpC sepsis – good outcomes
- Balakrishnan et al., JAC 2011; 66: 2628–2631
  - 92 ESBL+ infections, mainly UTI and BSI

UTI due to ESBL-producing *E. coli*
A murine model

Temocillin *vs* imipenem *vs* cefotaxime



Soubirou et al., JAC 2015;70(5):1466-72

Temocillin

Clinical efficacy against ESBL+ strains

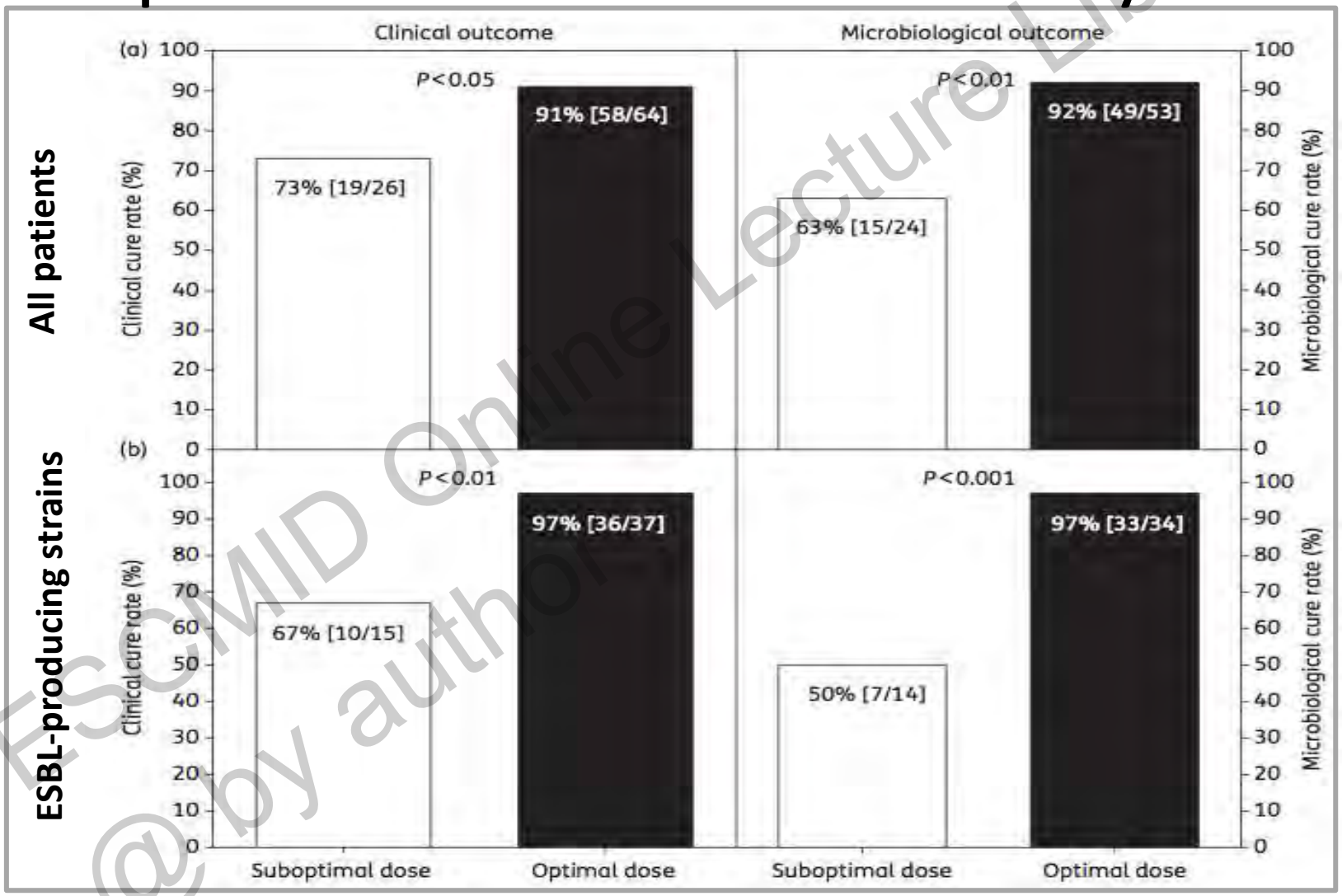
- Retrospective analysis of 92 infections among which 58% were due to ESBL-producing strains

Variable	UTI	BSI	HAP	Total
Clinical cure[a]				
ESBL/dAmpC negative	6/7 (86%)	15/18 (83%)	4/5 (80%)	25/30 (83%)
ESBL/dAmpC positive	26/28 (93%)	19/23 (83%)	2/2 (100%)	47/53 (89%)
Total[b]	38/42 (90%)	35/42 (83%)	6/8 (75%)	79/92 (86%)
Microbiological cure[a]				
ESBL/dAmpC negative	6/7 (86%)	9/11 (82%)	4/5 (80%)	19/23 (83%)
ESBL/dAmpC positive	23/27 (85%)	18/22 (82%)	no data	41/49 (84%)
Total[b]	34/39 (87%)	28/34 (82%)	4/6 (67%)	66/79 (84%)

Balakrishnan et al., JAC 2011;66:2628-2631

Temocillin

Importance of the correct daily dose



Balakrishnan et al., JAC 2011;66:2628-2631

Temocillin Issues

- No published breakpoints
  - ? Susceptible ≤ 16 mg/L
- Higher Doses than 4g per day needed in sepsis patients?
  - ?Continuous infusion (De Jongh et al., JAC 2008)

Summary

- As carbapenem-sparing agents
  - Fosfomycin trometamol YES
  - Temocillin YES
  - Mecillinam MAYBE