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Comparative in vitro activity of temocillin and other β-lactams against *Pseudomonas aeruginosa* isolated from cystic fibrosis patients

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INTRODUCTION

❑ *Pseudomonas aeruginosa* is a major source of morbidity in Cystic Fibrosis (CF) patients. The recurrent character of these infections requires the frequent use of anti-pseudomonal antibiotics.

❑ As a result, multiresistance to anti-pseudomonal antibiotics is frequently observed in these strains [1].

❑ Reviving older antibiotics and optimizing their activity may help to alleviate this burden.

❑Temocillin (TMO) is the 6-α-methoxy derivative of ticarcillin (Fig.1). It is highly stable to AmpC-type cephalosporinases and most extended-spectrum β-lactamases (ESBLs). TMO was abandoned for a long time due to lack of activity against Gram-positive organisms, anaerobes and *P. aeruginosa*. Yet it was recently reintroduced because of its activity against ESBL-producing Enterobacteriaceae [2].

❑ Recent studies from our group showed that intrinsic resistance of *P. aeruginosa* to TMO was due to active efflux by the constitutively-expressed transporter MexAB-OprM and that natural mutations in the corresponding genes restored TMO activity [3].

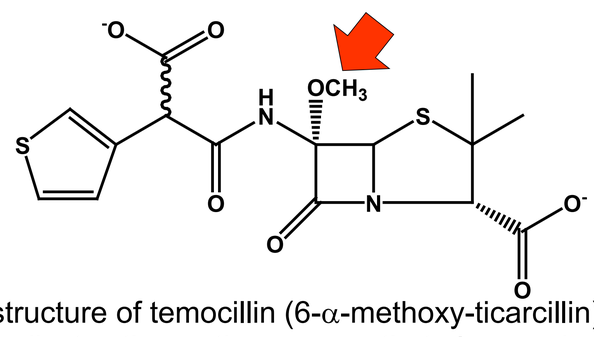


Fig.1 structure of temocillin (6-α-methoxy-ticarcillin). The red arrow indicates the methoxy group that plays an important role in resistance to hydrolysis by β-lactamases.

OBJECTIVES

to evaluate the activity of temocillin, in comparison with other antipseudomonal β-lactams, against *P. aeruginosa* collected in four CF centers across Europe.

METHODS

335 isolates of *P. aeruginosa* from CF patients

✓ 99 isolates provided by Dr M. Tunney, The Queen's University of Belfast, United Kingdom.

✓ 88 isolates provided by Drs A. Vergison / O. Denis from the Hôpital des Enfants Malades Reine Fabiola, Brussels, Belgium.

✓ 80 isolates provided by Prof. Patrick Plésiat, CHRU Besançon, Besançon, France.

✓ 68 isolates provided by Prof. Barbara Kahl, University of Münster, Münster, Germany.

✓Quality control strain ATCC ® 27853™.

Antibiotics used

Temocillin (TMO); ticarcillin (TIC); piperacillin / tazobactam (TZP); ceftazidime (CAZ); meropenem (MEM).

Antibiotic susceptibility testing

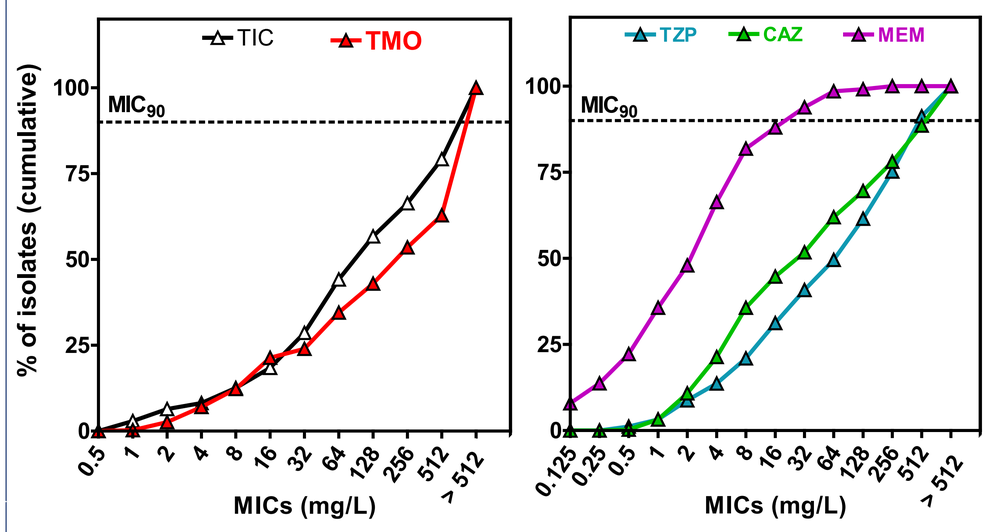
MICs were determined by microdilution in cation-adjusted Muller Hinton broth, according to CLSI guidelines [4] and susceptibility assessed using EUCAST interpretative criteria [5]. MICs of different antibiotics in individual strains were compared using quantile density contour analysis (JMP 10.0.2, SAS Institute Inc., Cary, NC).

REFERENCES

1. Llanes C et al., J Antimicrob Chemother. 2013 Aug;68(8):1763-71.
2. Livermore and Tulkens, J Antimicrob Chemother. 2009; 63:243-5.
3. Buyck et al., J Antimicrob Chemother. 2012; 67:771-5.
4. Performance Standards for Antimicrobial Susceptibility Testing; 23d Informational Supplement. CLSI document M100-S23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
5. European Committee on Antimicrobial Suscpetibility Testing. Breakpoint tables for interpretation of MICs and zone diameters – version 4.0. 2014 – http://www.eucast.org
6. De Jongh R et al., J Antimicrob Chemother. 2008; 61:382-8.

RESULTS

Fig. 2: MIC distribution (cumulative percentages) for temocillin (TMO) vs. ticarcillin (TIC), piperacillin/tazobactam (TZP), ceftazidime (CAZ) and meropenem (MEM) and corresponding percentages of susceptibility as assessed based on EUCAST susceptibility breakpoints for comparators and considering a provisional value of 16 mg/L for TMO.

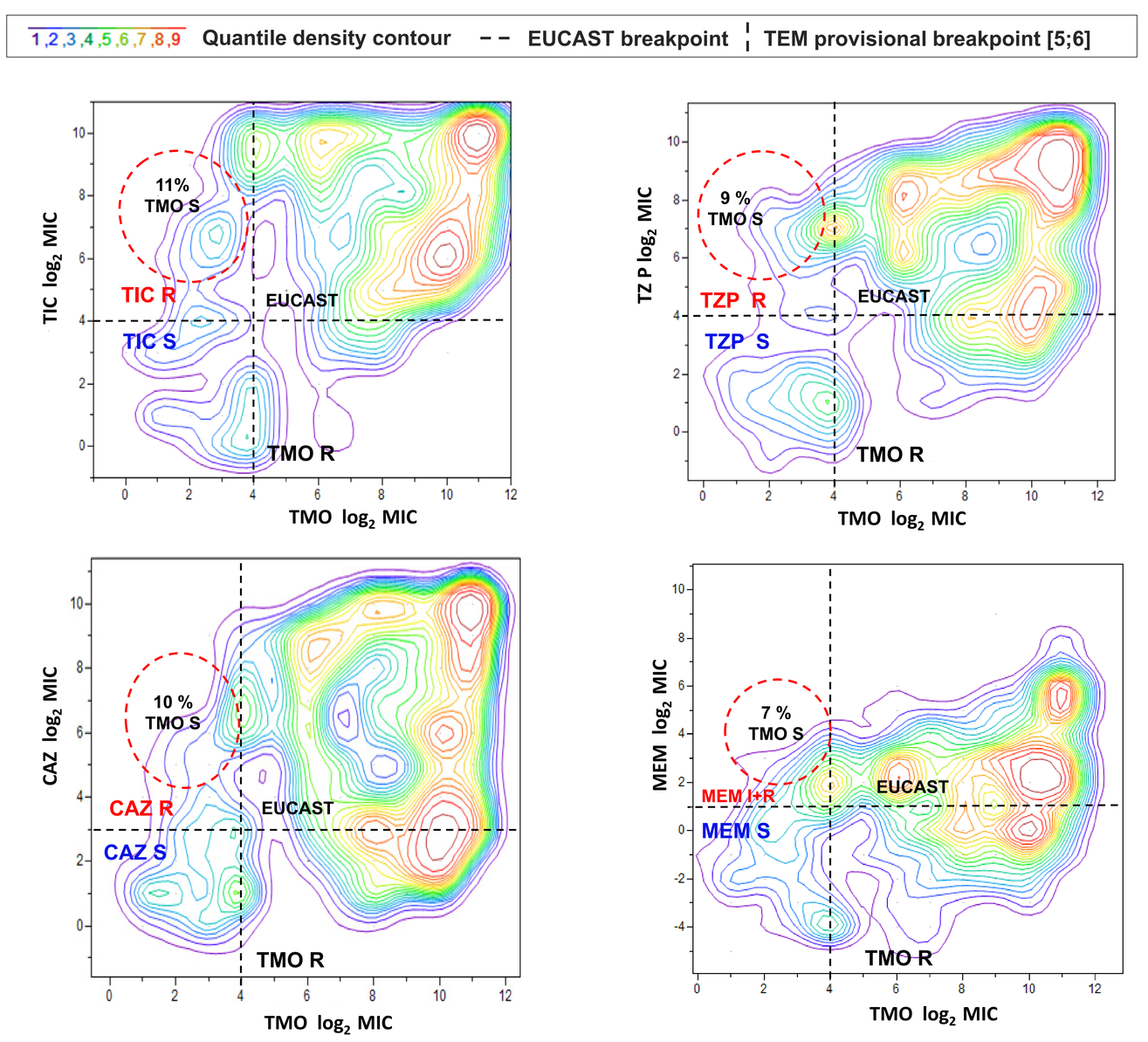


Drug	MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S [a,b]
MEM	2	16	48
TZP	64	512	32
CAZ	32	512	36
TIC	128	>512	19
TMO	256	>512	**22**

[a] EUCAST breakpoints in mg/L: **TIC** R>16; **TZP** R>16; **CAZ** R>8 ; **MEM** R>8.
[b] **TMO** provisional breakpoint R>16 mg/L [6].

→One fifth of the strains have MICs ≤ 16 mg/L for TMO and TIC
→Half of the strains were susceptible to MEM, and one third to TZP and CAZ

Fig. 3: Correlation between MICs of TMO vs. TIC, TZP, CAZ and MEM for individual strains using quantile density contour analysis (MIC expressed in log_2 scale). The red circle indicates on each figure the percentage of strains remaining susceptible to TMO while resistant to comparator (using EUCAST susceptibility breakpoints).



➔ ~10% of strains that were resistant to TIC, TZP, CAZ, or MEM remained susceptible to temocillin

CONCLUSIONS

- **According to EUCAST susceptibility breakpoints, half of the strains were susceptible to MEM, and one third to TZP and CAZ in this collection.**
- **Interestingly, temocillin was as active as its parent compound TIC against *P. aeruginosa* isolated from cystic fibrosis patients, with 22 % of the strains displaying an MIC ≤ 16 mg/L.**
- **A subset of strains that were resistant to TIC, TZP, CAZ, or MEM remained susceptible to temocillin possibly due to the expression of ESBL(s), carbapenemase(s) or other resistance mechanisms that do not affect temocillin.**
- **Temocillin may therefore offer a useful alternative in the treatment of *Pa* exacerbations in CF patients and should be included in susceptibility testing.**

Acknowledgments

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