increases in pH.\(^{14}\) It is know that the prostatic fluid may become markedly alkaline, a situation that should not influence the activity of daptomycin. All these data might support the rationale for the use of daptomycin in chronic bacterial prostatitis involving enterococci, particularly when antimicrobials included in primary regimens demonstrate inefficient in vitro activity due to resistance mechanisms. This is an area of clinical investigation that may improve the treatment of patients with chronic enterococcal prostatitis.

**Transparency declarations**

R. C. and A. P. J. have received honoraria for speaking from Novartis and Pfizer. P. R.-G. has no conflicts of interest to declare. R. L. C. is an employee of Novartis Pharma AG, and as such owns stock options with the company. R. L. C. has no other conflicts of interest to declare. The authors did not receive honoraria for writing this reply. A. P. J. is Editor-in-Chief of JAC, but took no part in, and did not influence, the editorial process.

**References**


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**Comment on: Newer antibacterial agents and their potential role in cystic fibrosis pulmonary exacerbation management**

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**Keywords:** glycylcyclines, *Mycobacterium abscessus*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*

Sir,

We read with great interest the article by Parkins et al.\(^1\) on the role of newer antibacterial agents in cystic fibrosis (CF) pulmonary exacerbation management. However, we would like to make some remarks on the authors’ statement that tigecycline may be a good candidate for the management of respiratory infections in CF patients.

Indeed, *Pseudomonas aeruginosa* remains the most commonly isolated pathogen from the sputum of CF patients. However, as *P. aeruginosa* is intrinsically resistant to tigecycline, this seems not to be the best treatment option in CF patients.\(^2\) Furthermore, in an observational and retrospective study, Garcia-Cabrera et al.\(^2\) showed that the superinfection rate during tigecycline treatment was 23.5%, with *P. aeruginosa* being responsible for 58.3% of the superinfections.

Concerning the two other Gram-negative pathogens that are increasingly being found in CF patients, namely *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*, resistance data do not fully support the use of tigecycline in pulmonary exacerbations in these patients. Reported MICs required to inhibit the growth of 90% of organisms (MIC\(_{90}\)) for *S. maltophilia* and *A. xylosoxidans* isolates are 2 mg/L\(^3\). In addition, the pharmacokinetic–pharmacodynamic (PK–PD) profile of tigecycline has to be taken into account when interpreting these resistance data.\(^4\) The ratio of AUC (AUC\(_{24}\)) to MIC (AUC\(_{24}/\text{MIC}\)) is the PK–PD index most likely to be predictive of efficacy.\(^5\) For instance, in patients with complicated skin and skin-structure infections, it was shown that an AUC\(_{24}/\text{MIC}\) of 17.9 was a statistically significant predictor of clinical and microbiological outcome.\(^6\) Recently, using an experimental *Acinetobacter baumannii* murine pneumonia model, it was shown that an AUC\(_{24}/\text{MIC}\) ratio in the lung of more than 4.37 was necessary for a good clinical and microbiological response.\(^7\) As the AUC\(_{24}\) in lung tissue and epithelial lining fluid is 9 mg/h/L and 2.28 mg/h/L, respectively, the AUC\(_{24}/\text{MIC}\) ratio for *S. maltophilia* and *A. xylosoxidans* would be 4.50 in lung tissue and 1.14 in epithelial lining fluid.\(^8\) Nevertheless, taking into account the risk of extrapolating the murine data to humans, we do think that these PK–PD figures should caution
against use of tigecycline to treat pulmonary exacerbations in CF patients. Besides, in poorly penetrated anatomic sites such as lung tissue, this may induce the development of resistance.

As Mycobacterium abscessus is increasingly involved in pulmonary infection in CF patients, we do agree with the authors that tigecycline offers exciting therapeutic potential for the rapidly growing mycobacteria (M. abscessus, Mycobacterium chelonae and Mycobacterium fortuitum). Although the clinical data are rather scarce, the susceptibility and PK–PD data seem promising. As the reported MIC90 for M. abscessus is 0.25 mg/L, the expected AUC24/MIC90 for this pathogen would be 36 in lung tissue and 9.12 in epithelial lining fluid, when calculated as mentioned above.1,6

However, we think that in order to make recommendations concerning tigecycline use in CF patients, human studies to define AUC24/MIC90 for the colonizing/infectious pathogens are needed. We therefore currently agree with the FDA drug safety communication of January 2010 that warned not to use tigecycline in pulmonary infections, especially hospital-acquired pneumonias, as mentioned above.1,6

The expected AUC24/MIC90 for this pathogen would be 36 in lung tissue and 9.12 in epithelial lining fluid, when calculated as

Transparency declarations
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References

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Newer antibacterial agents and their potential role in cystic fibrosis pulmonary exacerbation management—authors’ response

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Keywords: tigecycline, pharmacokinetics, pneumonia

Sir,

In response to the comments of Cooreman and Jeurissen1 on our recent article2 we would like to make several clarifications. Although Pseudomonas aeruginosa remains the most commonly isolated pathogen in cystic fibrosis (CF), this pattern is changing. The practice of early eradication of P. aeruginosa with aerosolized antibiotics has become the standard of care.3 In clinics in which this practice has been aggressively adopted, P. aeruginosa prevalence rates have dwindled to <5% in those CF patients <18 years of age.4 Accordingly, CF physicians are increasingly treating pulmonary exacerbations (PEx) caused by pathogens other than P. aeruginosa such as Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Staphylococcus aureus and so on. It is PEx with these pathogens, and not P. aeruginosa, for which we have advocated the use of tigecycline, as clearly indicated in our review.

The FDA has recently released a drug safety communication cautioning practitioners on the use of tigecycline in severe infections based on the pooled analysis of 13 trials involving >7000 patients where all-cause mortality was observed to be increased by 0.6% [95% confidence interval (CI) 0.1–1.2] relative to comparator antibiotics.5 However, the FDA did not warn that tigecycline should not be used in pulmonary infections as asserted by Cooreman and Jeurissen.1 Furthermore, community-acquired pneumonia remains an approved indication for the use of tigecycline. Most of the increased mortality in tigecycline-treated patients was attributable to hospital-acquired pneumonia, in particular, ventilator-associated pneumonia (VAP). This observation may not be relevant to CF PEx, a disease for which no antibiotic has an FDA-approved indication. PEx in CF are overwhelmingly caused by chronically colonizing pathogens and not through the new acquisition of pathogens,6,7 and as such the empirical provision of PEx antibacterials based on prior sputum results is commonplace and supported. The bacteriostatic nature of tigecycline, postulated to be a potential detractor in the management of respiratory infections, is not relevant in CF PEx as eradication of chronically infecting pathogens is generally not possible.3 The use of tigecycline in CF has been reported only rarely, but clinical outcomes have been favourable.8

CF-specific pharmacokinetic data for tigecycline (as well as for many antibiotics) continue to be lacking and the lower AUC data observed in patients in tigecycline trials with VAP and associated lower clinical cure rates9 emphasize the importance of understanding the pharmacokinetics of antimicrobials in disease-specific settings. With the increasing burden of multidrug-resistant pathogens in CF and their associated increased risk of mortality,10 new therapeutic options are desperately required.