which have experienced the spread of OXA-23-producing \textit{A. baumannii}.\textsuperscript{12}

\section*{Funding}

The study was carried out as part of our routine work. A. C. G. is a researcher from the National Council for Science and Technological Development (CNPq), Ministry of Science and Technology, Brazil (Process number: 307816/2009-5).

\section*{Transparency declarations}

A. C. G. has received research funding and/or consultation fees from Janssen-Cilag, Wyeth/Pfizer, Novartis and Sanofi-Aventis. Other authors have nothing to declare.

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\section*{Tigecycline for severe infections: the gap between the warning and the necessity}

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\textbf{Keywords:} multidrug resistant, \textit{Acinetobacter} spp., ventilator-associated pneumonia

Sir,

I have received the US FDA warning describing an increased mortality risk associated with the use of tigecycline when compared with other drugs in the treatment of a variety of serious infections. The increased risk of mortality was determined using a pooled analysis of randomized clinical trials (RCTs) and was seen most clearly in patients treated for hospital-acquired pneumonia (HAP), especially ventilator-associated pneumonia (VAP), but was also seen in patients with complicated skin and skin structure infections (cSSSIs), complicated intra-abdominal infections (cIAIs), infections due to resistant pathogens and diabetic foot infections.\textsuperscript{1} Although for each indication the mortality difference was not statistically significant, trends were present and, when pooled, a statistically significant difference was observed. Based on these data, the FDA recommends that alternatives to tigecycline should be considered in patients with severe infections.

The FDA recommendation is thus based upon a combination of RCTs that were the scientific support for the FDA licensing approvals for tigecycline in cSSSI,\textsuperscript{2} cIAI\textsuperscript{3} and community-acquired bacterial pneumonia (CABP),\textsuperscript{4} as well as other studies in which tigecycline did not achieve outcomes suitable for such approvals (e.g. VAP).\textsuperscript{5} Clinicians are now faced with the conundrum that at present the FDA licensed approvals for tigecycline remain unaltered but an alert has been issued against severe sepsis, although tigecycline does not have an explicit licence for this indication. Understanding the context of both the alert and its relevance to the clinical circumstances facing doctors as they make decisions about severe sepsis management is therefore critical.

The context of the FDA alert is that it is based on RCTs where only a small percentage of patients with severe infections were included. No severity score was used in the cSSSI RCT (only 25.8% of patients required surgery/drainage),\textsuperscript{2} only 19.8% from the CABP RCT showed high pneumonia severity index (IV-V) values\textsuperscript{4} and the mean APACHE II score in patients from the cIAI and HAP RCTs was ≤15 (6.2 and 12.3, respectively).\textsuperscript{3,5} This lack of patients with severe sepsis in licensing studies is commonplace and not unique to tigecycline. For example the Infectious Diseases Society of America guidelines recommend
Acinetobacter

• Clinical efficacy in patients with severe infections with high APACHE II scores
• Pharmacological and clinical studies (efficacy and safety profile) using higher doses (i.e. 200 mg initial and 100 mg every 12 h)
• Use of concomitant antibiotic(s) with high serum concentration and activity against P. aeruginosa
• Propensity to develop resistance during the treatment (i.e. Acinetobacter spp), as well as superinfections (i.e. P. aeruginosa)

Figure 1. The most important tigecycline scientific issues to solve in the near future.

doripenem for the treatment of high-risk community-acquired and healthcare-acquired IAI in adults, although appendicitis without peritonitis was the diagnosis in nearly 50% of patients included in the RCT and 87.7% of the patients had an APACHE II score ≤10.6 Thus although RCTs are used extensively to characterize the efficacy and safety of new treatment options, the characteristics of the trial participants often do not reflect those of the wider patient population.

Notwithstanding the FDA approved indications for the drug, we have published data indicating that tigecycline’s pharmacological and microbiological profiles encourage its use for off-label indications in severely ill patients in intensive care units [e.g. VAP due to multidrug-resistant (MDR) Acinetobacter spp.].7–9 This practice is justified by the high regional resistance rates of MDR pathogens with limited therapeutic options [e.g. carbapenem-resistant Acinetobacter spp. and Klebsiella pneumoniae carbapenemase (KPC)-producing Enterobacteriaceae]. In addition, there is good evidence that early effective therapy for such infections in critically ill patients improves outcomes.10,11

Several authors have reported their experiences using polymyxins, fosfomycin, sulbactam and other antibiotics, alone or in combinations, for the treatment of infections due to these MDR pathogens.12 The comparative performance of these antibiotics relative to tigecycline is unknown. None of them has RCT studies published. Nevertheless, the epidemiological challenge facing physicians has forced them to incorporate these antibiotics into the hospital armamentarium. Hence there is a real risk that the FDA alert may promote a shift from tigecycline to these other antibiotics. This is despite the fact that these drugs have been relatively poorly evaluated both in terms of clinical efficacy, especially in severe sepsis, as well as in their comparative safety profile in the treatment of MDR pathogen infections.

Therefore, in this scenario of high rates of MDR pathogens, we need to reduce and rationalize the gap between the evidence from RCTs, which include non-severely ill patients for tigecycline, and our daily challenge of managing severely ill patients with few other therapeutic options and where these alternatives are not in themselves well investigated. Further work on tigecycline is needed to illuminate these questions and includes the need for well-controlled studies to evaluate its efficacy and safety profile in VAP using higher doses (i.e. 200 mg initial and then 100 mg twice daily). In addition, the role of tigecycline in combination with other antibiotics (e.g. carbapenems and polymyxins) and further understanding of tigecycline’s propensity to select resistant strains (e.g. Acinetobacter spp.) and to induce Pseudomonas aeruginosa or Proteae superinfections require further investigation (see Figure 1).

The FDA postulated that the bacteriostatic effect of tigecycline was a possible reason for the mortality difference observed in severe infections. No justification was given for this statement. The bulk of the evidence supports the concept that in treating endocarditis and meningitis, it is best to use agents with in vitro bactericidal activity. However, the data to support any superiority for bactericidal drugs over their bacteriostatic counterparts does not exist for most clinical situations, including severe sepsis.

Unfortunately the future antibiotic pipeline is not encouraging, and this is particularly true for agents against MDR Gram-negative pathogens. Clinical trials are indispensable tools to generate new knowledge and to test therapeutic options for the care of critically ill patients. Patients infected by MDR pathogens deserve healthcare professionals (physicians and regulatory authorities alike) who constantly search the best scientific evidence in order to improve their clinical outcomes. Presentation of such data must be clear and unconflicting and must reflect the real world of clinical care.

Acknowledgements
I acknowledge Danisa Campos for manuscript translation and development.

Funding
No funding of any kind has been received by the author.

Transparency declarations
D. C. is an adviser for Pfizer Laboratories Argentina regarding antibiotics and has received financial support from Wyeth Argentina SA to develop the observational studies that have been mentioned in this letter (references 7, 8 and 9).

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