

## Guideline summary: Appropriate use of tigecycline

**A. J. Brink**, M.B. Ch.B., M.Med. (Clin. Micro.)

*Ampath National Laboratory Services, Milpark Hospital, Johannesburg*

**D. Bizos**, M.B. B.Ch., F.C.S. (S.A.), M.Med., F.R.C.S. (Eng.) (Ad Eundem)

*Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg*

**K. D. Boffard**, M.B. B.Ch., B.Sc. Hons, F.R.C.S., F.R.C.S. (Edin.) F.R.C.P.S. (Glasg.), F.A.C. (S.A.), F.A.C.S

*Department of Surgery, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand*

**C. Feldman**, M.B. B.Ch., D.Sc., Ph.D., F.R.C.P., F.C.P. (S.A.)

*Division of Pulmonology, Department of Medicine, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand*

**D. C. Grolman**, M.B. B.Ch., F.C.S. (S.A.) Surg., F.C.S. (S.A.) Crit. Care

*Sandton Medi-Clinic, Life Fourways Hospital and Faculty of Health Sciences, University of the Witwatersrand*

**J. Pretorius**, M.B. Ch.B., M.Med. (Surg.), F.C.S. (S.A.)

*Department of Surgery, Steve Biko Academic Hospital and University of Pretoria*

**G. A. Richards**, M.B. B.Ch., Ph.D., F.C.P. (S.A.)

*Department of Medicine, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand*

**E. Steyn**, M.B. Ch.B., M.Med. (Surg.), F.C.S.S.A.

*Trauma and Emergency Service, Vincent Pallotti and Christiaan Barnard Hospitals, Cape Town, and President, Trauma Society of South Africa*

Tigecycline, the first of a new class of broad-spectrum antibiotics (the glycylicyclines), has been licensed in South Africa for the parenteral treatment of adult patients with complicated intra-abdominal infections (cIAIs) and complicated skin and soft-tissue infections (cSSTIs).

This article serves as a summary of the guideline on the appropriate use of tigecycline, published in mid-2010 as a collaborative effort by representatives of the Association of Surgeons of South Africa, the Critical Care Society of Southern Africa, the Federation of Infectious Diseases Societies of Southern Africa, the South African Thoracic Society and the Trauma Society of South Africa.<sup>1</sup>

The guideline addressed important aspects of the new agent, including details of its metabolism and pharmacokinetics, mode of action, antibacterial spectrum, and performance in key clinical trials including data regarding its safety and tolerability, and also highlights appropriate use of the drug. Other aspects that were considered included breakpoints for susceptibility testing, *in vitro* and *in vivo* data for its activity against multi-drug resistant (MDR) pathogens such as carbapenem-resistant *Acinetobacter baumannii*, *Enterobacteriaceae* and *Stenotrophomonas maltophilia*, and its use in bacteraemic patients and *Clostridium difficile* infections (CDIs).

The guideline and its summary were written because of concern regarding the widespread misuse of antibiotics. The primary intention of the current publication is to facilitate, through a brief summary published in several professional journals, the heterogeneous use of antibiotics as a component of antibiotic stewardship. The emphasis is on clinical profiles that could potentially benefit from empiric or directed tigecycline therapy.

### Appropriate use

Tigecycline has been studied as empiric monotherapy in cIAI, cSSTI and severe community-acquired pneumonia and would be an appropriate option as monotherapy for the treatment of patients with cIAI and cSSTI, which are the currently registered indications in South Africa, in the following circumstances:

### Empiric monotherapy

- in the elderly or patients with significant co-morbidity who have received frequent antibiotic therapy or are from long-term care facilities and, as such, are at risk for resistant bacteria such as extended spectrum beta-lactamase (ESBL)-producing strains or polymicrobial MDR infections (excluding *Pseudomonas* spp.)
- as an alternative in serious and complicated infections owing to methicillin-resistant *Staphylococcus aureus* (MRSA) infections in patients with established renal dysfunction and in those at risk of developing renal failure
- where there has been treatment failure with other broad-spectrum agents despite apparent source control and where pseudomonal infection is unlikely
- infections with organisms likely to be susceptible to tigecycline in patients with  $\beta$ -lactam allergy
- in the therapy of nosocomial and hospital-associated infections with MDR Gram-negative pathogens, where pseudomonal infection is unlikely and empiric cover for MRSA is also required
- to facilitate heterogeneous antibiotic use and reduce pressure on other agents currently in use as a component of antibiotic

stewardship. This is particularly relevant for the treatment of ESBL-producing Enterobacteriaceae, which has put significant pressure on carbapenems.

#### Directed monotherapy (based on culture results)

- polymicrobial infections with MDR organisms (excluding *Pseudomonas* spp., *Proteus* spp., *Providencia* spp. and *Morganella* spp.) such as serious and complicated infections owing to mixed infections of MRSA or ESBL-producing organisms
- selected MRSA infections in the presence of renal dysfunction
- Tigecycline may also be an alternative for the treatment of recurrent or refractory CDI. Minimum inhibitory concentrations (MICs) for tigecycline are low in this organism, and the achieved faecal drug levels are more than adequate with standard intravenous dosaging. In addition, tigecycline would appear to have a low propensity to select for CDIs.
- Tigecycline may be a treatment option for staphylococcal and enterococcal infections that have resistance or intermediate sensitivity to vancomycin/teicoplanin (h-VISA, VISA, VRSA, VRE).

#### Directed combination therapy (based on culture results)

- In the absence of conclusive evidence, it is the authors' opinion that tigecycline may be effective as a salvage therapy for serious and life-threatening infections with MDR *A. baumannii*, if no other antibiotic is available according to susceptibility testing. In this scenario, combinations with polymyxin and/or fosfomycin and/or rifampicin may be appropriate. If used in this circumstance, unpublished pharmacokinetic/pharmacodynamic data suggest that it should be used at higher than the registered dose (at a dose of 100 - 150 mg 12-hourly).
- Similarly, tigecycline may be used as salvage therapy on life-threatening *S. maltophilia* infections. In this scenario, standard dosing might be appropriate but consideration should be given to combination therapy with trimethoprim/sulphamethoxazole.
- It is envisaged that tigecycline will be used in South Africa for directed therapy, particularly for carbapenem-resistant (ertapenem and/or imipenem-cilastatin and/or meropenem and/or doripenem) strains where, besides polymyxin and possibly fosfomycin, no alternative Gram-negative antibiotics are available. In this circumstance, tigecycline therapy should be combined with polymyxin in life-threatening infections.

#### Inappropriate use

Tigecycline is not an appropriate empiric option as monotherapy for the treatment of patients with cIAI at risk of infection with *P. aeruginosa*, and in particular in those with recurrent infection (tertiary peritonitis).

Other important risk factors for pseudomonal infections in this setting, in which tigecycline use would be inappropriate, include:

- inadequate and/or initial source control failure
- malnutrition
- advanced age (>90 years)
- high APACHE II score
- immuno-suppression and use of corticosteroid therapy.

It is also not an appropriate empiric option as monotherapy for the treatment of patients with cSSTI where *P. aeruginosa* is a prevalent organism, such as in chronic diabetic foot infection and particularly in those patients with macerated, non-healing ulcers or wounds of long duration on prolonged broad-spectrum antibiotic therapy.

#### Conclusion

In summary, tigecycline would be an appropriate empiric option as monotherapy for the treatment of cIAIs and cSSSIs in patients when:

- resistant organisms are suspected (excluding pseudomonal infections)
- patients have received prior antibiotics (within the past 3 months)
- early treatment failure has occurred
- patients are allergic to  $\beta$ -lactams
- there is concern about tolerance to vancomycin
- patients are elderly and/or are from long-term care facilities
- co-morbidities such as renal impairment are present.

**Endorsement.** Endorsed by the Association of Surgeons of South Africa, Trauma Society of South Africa, Federation of Infectious Diseases Societies of Southern Africa, the Critical Care Society of Southern Africa and the South African Thoracic Society.

**Disclaimer.** This statement is published for educational purposes only. The recommendations are based on currently available scientific evidence together with the consensus opinion of the authors.

#### REFERENCE

1. Brink AJ, Bizos D, Boffard KD, et al. Guideline: Appropriate use of tigecycline. *S Afr Med J* 2010;100:388-394.