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Use of tigecycline at a teaching hospital

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ABSTRACT

Introduction: Tigecycline is an antimicrobial agent approved for the treatment of complicated skin and soft tissue infections, hospital-acquired and community-acquired pneumonia, intra-abdominal infections and anaerobic or atypical infections. **Objective:** To describe the use of tigecycline in a teaching hospital and to compare data from patients who had prescriptions audited by the hospital infection committee with those who received non-audited prescriptions. **Methods:** Retrospective observational cohort study conducted at a teaching hospital from April 2012 to March 2014 including patients who received tigecycline. Demographic variables, comorbidities, microbiological findings, prescribed antibiotics and technical reports issued by the Hospital Infection Control Service were collected. **Results:** 71 patients included, aged between 13 and 92 years, 63.4% were male and 56.3% were non-white. Tigecycline was the first antimicrobial choice in 19.7% (14/71) of the cases, while the use associated with other antibiotics was observed in 63.4% (45/71) of the prescriptions. with meropenem (28.9%). Empirical use was performed in 69.0% of cases, after culture and the antibiogram in 31.0% and off-label use in 81.7%. The microorganisms frequently identified by the culture tests were *Enterococcus faecalis* (27.2%), *Pseudomonas aeruginosa* (22.7%) and *Klebsiella pneumoniae* (18.1%). **Conclusion:** The study demonstrated that empirical and off-label use is common in clinical practice and few prescriptions guided by the results of the culture and the antibiogram, demonstrating the need for prescribers to evaluate the benefits/risks of using this antibiotic, risk of resistance, adverse effects and drug interactions, in addition to the cost.

Keywords: anti-bacterial agents; cross infection; off-label use; hospitals, teaching; drug misuse; tigecycline.

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INTRODUCTION

Tigecycline is the new member of a glycylcycline class of antimicrobial agents. It was developed to overcome two common tetracycline resistance mechanisms mediated by acquired efflux pumps and ribosomal protection[1]. Tigecycline has bacteriostatic in vitro activity against a wide range of multidrug-resistant Gram-positive and Gram-negative pathogens (such as vancomycin-resistant *Enterococcus spp*.; methicillin-resistant

Staphylococcus aureus; penicillin-resistant *Streptococcus pneumonia*; extended-spectrum ß-lactamase producing *Escherichia coli* and *Klebsiella pneumonia*; *Acinetobacter spp*. producing carbapenemase). Patients with anaerobic or atypical infections (*Mycoplasma, Legionella and Chlamydia spp*) can be treated with tigecycline. Besides the wide range spectrum, tigecycline does not have activity against *Pseudomonas aeruginosa, Proteus spp., Morganella spp.* and *Providencia spp.*[1-3]. Resistance cases were reported resulting from infections by *Acinetobacter baumannii*[4,5].

Food and Drug Administration (FDA), Brazilian National Agency for Sanitary Surveillance (ANVISA) and European Medicines Evaluation Agency approved tigecycline for the treatment of complicated infections in the skin and soft tissues, intra-abdominal and pneumonia, except community-acquired pneumonia[6,7], anaerobic or atypical infections (*Mycoplasma*, *Legionella* and *Chlamydia spp*).

In this meta-analysis, the authors correlated the use of tigecycline with increased clinical failure and septic shock at a higher rate when compared to similar drugs[8].

Studies on the use of medicines are essential for the detection, analysis of problems arising from the inappropriate use of medicines and the development of strategies to improve the quality of hospital care. Considering a few studies that are showing the aspects of tigecycline use, the objective of this study is to describe the use of tigecycline in a teaching hospital after its introduction as a standardized drug and compare data from patients who had their tigecycline prescriptions audited by the hospital infection committee with those who did not have their prescriptions audited.

METHODS

This retrospective cohort study was conducted in a tertiary teaching hospital in Campo Grande – MS, Brazil, over two years (2012 April 1st to 2014 March 31st). The inclusion criteria were to have a tigecycline prescription.

The hospital is a state reference in infectious diseases and complex procedures in the treatment of patients with HIV, renal therapy, cardiovascular surgery, hemodialysis and neurology, in addition to high-risk pregnancy, urology, tomography and lithotripsy treatment linked to the Brazilian healthcare system called SUS.

The data was collected from registers of the Hospital Pharmacy Service, from the medical records and the registers of Hospital Infection Control Service. These data included age, gender, comorbidities, inpatient clinic, patient clinical evolution, microorganisms isolated in culture results, bacterial susceptibility tests, antimicrobials in use, tigecycline monotherapy, clinical indication, tigecycline dose, time of tigecycline use and tigecycline consumption.

During the study period, Hospital Infection Control Service was evaluated by the sampling of the antimicrobials requisition. Patients were divided into two groups: E (E Group) - when Hospital Infection Control Service evaluated the prescriptions of tigecycline; and NE (NE Group) - when the provisions of tigecycline were not evaluated by Hospital Infection Control Service.

Tigecycline is approved for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections[9]. All prescriptions for different situations from that considered off-label use as well as those in different dosages of the recommended in the literature and the use in patients younger than 18 years.

Measures of central tendency (mean and median) and Chi-square test (χ^2) with Yates correction were used as appropriate. The significance level was considered as $p<0.05$. Statistical analysis was performed using the software StatCalc in Epi 7.

The Ethics Committee on Human Research at the Universidade Federal de Mato Grosso do Sul approved the study (Process 30172014.6.0000.0021).

RESULTS

A total of 71 patients received tigecycline during the study specified period. They admitted to the emergency room (24/71, 33.8%), medical clinic (5/71, 7.1%), surgical clinics (31/71, 43.6%) and intensive care unit (11/71, 15.5%). The mean age of patients was 58 years (range 13-92). There was no statistically significant difference between the groups E and NE (Table 1). From 71 patients, only 26 patients (36.6%) had their antibiotic prescription evaluated by the Hospital Infection Control Service. There was no dose adjustment for Child-Pugh class C patients.

More than half of the patients (40/71; 56.3%) were discharged from the hospital, 43.7% (31/71) died before discharge while 22.6% (07/31) of them were in the Intensive Care Unit (ICU).

It observed that tigecycline therapy was prescribed as an empirical treatment (49/71; 69.0%), culture-directed prescription (22/71; 31.0%) and off-label use (58/71; 81.7%). In only 19.7% (14/71) of the prescriptions, the therapeutic indication complied with that recommended by the regulatory authorities. Tigecycline was the first antimicrobial choice in 19.7% (14/71) of the cases while the associated use was observed in 63.4% (45/71) of the prescriptions.

Although 22 patients had culture-directed prescriptions, 34 isolates were identified because the cultures had more than one microorganism. *Enterococcus faecalis* (27.2%), *Pseudomonas aeruginosa* (22.7%) and *Klebsiella pneumoniae* (18.1%) were the most frequently isolated microorganisms (Table 2).

The antimicrobials used in combination with tigecycline are shown in Table 3. Some patients had more than one microorganism isolated.

Table 1: Characteristics of patients treated with tigecycline, Campo Grande, MS, Brazil, 2012-2014.

	Total n (%) n=71	Group E n (%) n=26	Group NE n (%) n=45	*p*
Age				
<18 years	5 (7.0)	2 (7.7)	3 (6.7)	0.4338
18–59 years	33 (46.5)	15 (57.7)	18 (40.0)	
≤60 years	33 (46.5)	9 (34.6)	24 (53.3)	
Gender				
Male	45 (63.4)	20 (76.9)	25 (55.6)	0.3295
Female	26 (36.6)	6 (23.1)	20 (44.4)	
Culture and Sensitivity				
Present	22 (31.0)	5 (19.2)	17 (37.8)	0.4310
Not present	49 (69.0)	21 (80.8)	28 (62.2)	
Off-label Usage				
Yes	58 (81.7)	22 (84.6)	36 (80.0)	0.6175
No	13 (18.3)	4 (15.4)	9 (20.0)	
Therapeutic Indication				
Recommended	14 (19.7)	5 (19.2)	9 (20.0)	0.6064
Not Recommended	57 (80.3)	21 (80.8)	36 (80.0)	
Dosage				
Recommended	54 (76.1)	20 (76.9)	34 (75.6)	0.5535
Not Recommended	17 (23.9)	6 (23.1)	11 (24.4)	
First pharmacological choice				
Yes	14 (19.7)	4 (15.4)	10 (22.2)	0.6002
No	57 (80.3)	22 (84.6)	35 (77.8)	
Monotherapy				
Yes	26 (36.6)	13 (50.0)	13 (28.9)	0.4310
No	45 (63.4)	13 (50.0)	32 (71.1)	

Group E - patients with requirements evaluated by the Hospital Infection Control Service; Group NE - patients with prescriptions not evaluated by the Hospital Infection Control Service.

Table 2: Identification of microorganisms in 22 patients treated with tigecycline, Campo Grande, MS, Brazil, 2012-2014.

Microorganisms	n	%
Enterococcus faecalis	6	27.2
Pseudomonas aeruginosa	5	22.7
Klebsiella pneumoniae	4	18.1
Morganella morganii	3	13.6
Acinetobacter baumannii	2	9.1
Proteus mirabilis	2	9.1
Staphylococcus epidermidis	2	9.1
Staphylococcus aureus	2	9.1
Enterobacter cloacae	1	4.5
Escherichia coli	1	4.5
Proteus penneri	1	4.5
Enterococcus faecium	1	4.5
Enterobacter cloacae	1	4.5
Staphylococcus capitis	1	4.5
Streptococcus agalactiae	1	4.5
Burkholderia Cepacia	1	4.5

Table 3: Antimicrobials used in combination with tigecycline, Campo Grande, MS, Brazil, 2012-2014.

Antibiotic	n	%
Meropenem	13	28.9
Polymyxin E	12	26.7
Fluconazole	10	22.2
Teicoplanin	6	13.3
Anidulafungin	6	13.3
Polymyxin B	6	13.3
Amikacin	5	11.1
Azithromycin	4	8.9
Ceftriaxone	3	6.7
Metronidazole	3	6.7
Imipenen + Cilastatin	3	6.7
Ceftazidime	3	6.7
Linezolid	2	4.4
Clindamycin	2	4.4
Piperacilin + Tazobactan	2	4.4
Micafungin	2	4.4
Gentamicin	1	2.2
Levofloxacin	1	2.2
Cefepime	1	2.2
Ciprofloxacin	1	2.2
Sulfamethoxazole + Trimethoprim	1	2.2

DISCUSSION

Our study demonstrated that empiric and off-label use are common in clinical practice and few prescriptions guided by culture and antibiogram results, demonstrating the need for prescribers to evaluate the benefits/risks of using this antibiotic.

Increased bacterial resistance and lack of perspectives to new antimicrobial agents lead to the use of tigecycline in situations other than its main official indication. Thus, it is necessary to discuss not only the use but also the best ways to optimize the required performance, the risk of resistance, the occurrence of adverse events and drug interactions besides the cost.

It is also important to consider that tigecycline should be used cautiously, considering that. Tigecycline achieves very low serum levels to be considered a safe drug in severe patients. Moreover, lung concentrations are not well known, even with perfect conditions of serum levels.

The off-label use of tigecycline is a frequent practice in the hospital studied (81.7%) and a similar result was also observed in a Latin America multicenter study (68.5%)[10] and in studies conducted in Argentina[11,12]. On the other hand, there is a great difference in tigecycline prescription between Europe and Latin America. In Europe, more frequently, prescribers follow the recommendations of regulatory agencies[13-15], while in Latin America the off-label prescription is the most common practice[10-12].

Off-label prescription is legal and often appropriate, but it may raise several clinical, safety and ethics issues. The off-label prescription may be justified if there is a risk-benefit ratio with enough evidence[9], during the presence of a multidrug-resistant microorganisms infection[1-3], and no other available option[16].

To promote the rational and correct use of antimicrobials, it is necessary to improve the prescription pattern, to identify the etiologic agent and its sensitivity. However, the use of antimicrobials in clinical practice begins before culture results and performance of sensitivity tests, and in this way, several studies have demonstrated empiric use of tigecycline[10-13,17]. In our study, 69.0% of the treatments started without the culture and sensitivity results and this fact. It is usual in the tigecycline treatment even when the culture results are not available[18]. Any empiric antibiotic regimen should be reassessed and tailored as soon as culture and sensitivity results become available. This practice serves to reduce costs, decrease the incidence of superinfection and minimize the development of antimicrobial resistance. It has been proven that maintaining inappropriate empirical prescriptions causes an increase in hospitalization time, unnecessarily burdening the health system[19].

The use of tigecycline in 12 institutions evaluated in Argentina and the administration of previous antibiotic therapy was not associated with significant differences in the proportion of clinical success. Patients receiving concurrent antibiotic treatment showed a significantly lower clinical success rate than patients receiving tigecycline as monotherapy[12]. Monotherapy can be used in official indications for patients with community infections or related care health in selected cases, as presented by Montravers *et al.*[20], which obtained good results in more than half of the patients, while the combination therapy should be used in a variety of patients with nosocomial infections[3,21].

In this study, we observed a high frequency of patients who used concurrent antibiotics (63.4%). The associated administration of tigecycline to other antimicrobials, either empirically or targeted use explained by the possibility of covering the presence of *P. aeruginosa*[18].

The indication of tigecycline against *Enterococcus faecalis* was the most frequent because this was the main isolated microorganism (27.2%) in this study, different from that found by other authors[10,20,22]. The use of tigecycline in sectors of high hospital complexity indicates the differences in the predominant *flora* in these environments. Although tigecycline is used for the treatment of severe infections both in critically ill patients and patients with less severe clinical conditions[18].

The FDA issued a warning about the increased risk of mortality associated with the use of tigecycline when compared to other drugs for the treatment of several infections[23]. The present study did not assess the risk of mortality in patients who received tigecycline, it recommended judicious use with an evaluation of the risks and benefits[3,24].

The damage caused by failures in the process of using this medication can be individual or collective. From an individual point of view, extensive use is associated with exposure to a greater number of drug interactions, microbial resistance, adverse reactions, prolonged hospitalization and incomplete therapeutic regimen. From the collective point of view, there is an increase in direct and indirect costs of assistance and an increase in microbial resistance. Thus, it is recommended to implement an antimicrobial control program, also known as stewardship.

The authors themselves note that this small number of patients is a potential study limitation, although all hospital patients who used tigecycline during the study were included. Also, a common limitation in this type of study is the incomplete information in medical records. To minimize these limitations, the authors included other information obtained from the hospital pharmacy, laboratory, and infection control services.

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