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Use of tigecycline in critically ill patients with serious nosocomial intra-abdominal infections

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ABSTRACT

Intra-abdominal infection (IAI) is a frequent complication found in surgical intensive care unit (SICU) and continues to be associated with considerable mortality. Tigecycline, the first-in-class glycylcycline has demonstrated a broad spectrum of activity against a wide range of bacteria commonly found in IAI. This observational retrospective study aimed to describe the experience with tigecycline for serious nosocomial IAI in the SICU. Data were collected from 23 consecutive patients admitted to SICU with serious nococomial IAI who had received empirical treatment with tigecycline. In all cases, IAI was diagnosed via emergency surgery. Severe sepsis was found in 56.5% and 43.5% developed septic shock. Oncological disease was the most common comorbidity (60%). The mean Simplified Acute Physiology Score (SAPS) III within 24 hours from IAI diagnosis was 57.5±14.7, and 87% showed a McCabe score >1 (2 or 3). *Escherichia coli* was the most common pathogen (43.5%), followed by *Bacteroides* spp. and *Streptococcus* spp. (30.4%, respectively). All but one patient received tigecycline in combination (95.7%), particularly with fluconazole (52.2%), followed by piperacillin-tazobactam (43.5%). Empirical antibiotic therapy was considered adequate in 95%. The mean duration of treatment was 8.5±4.5 days. A favorable response was achieved in 78%. Failure of the antibiotic therapy was not observed in any patient. None of the patients discontinued tigecycline due to adverse reactions. SICU mortality was 13%, with no deaths attributable to tigecycline. These findings suggest that tigecycline combination therapy is an effective and well tolerated empirical treatment of serious nosocomial IAI in the SICU.

Keywords: intra-abdominal infections, critical patients, SICU, empirical treatment, tygecicline

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Uso de tigeciclina en pacientes críticos con infección intraabdominal nosocomial grave

RESUMEN

La infección intraabdominal (IIA) es una patología habitual en la unidad de cuidados intensivos quirúrgica (UCIQ) y se asocia a una considerable mortalidad. Tigeciclina es el primer antibiótico de la familia de las glicilciclinas que presenta un amplio espectro de actividad frente a las bacterias habituales responsables de la IIA. Este estudio observacional retrospectivo tiene como objetivo describir la experiencia con tigeciclina en los pacientes con IIA nosocomial grave ingresados en la UCIQ. Los datos fueron recogidos en 23 pacientes consecutivos admitidos en la UCIQ con IIA nosocomial grave que habían recibido tratamiento antibiótico empírico con tigeciclina. En todos los casos, la IIA fue diagnosticada mediante cirugía urgente. En el 56,5% de los pacientes se encontró sepsis grave y el 43,5% presentaron shock séptico. La enfermedad concomitante más frecuente fue la enfermedad oncológica (60%). El SAPS III (*Simplified Acute Physiology Score*) a las 24 h del diagnóstico de la IIA fue 57,5 ± 14,7 y un 87% de los pacientes presentaron un McCabe > 1 (2 o 3). El patógeno más frecuente fue *Escherichia coli* (43,5%), seguido de *Bacteroides* spp y *Streptococcus* spp (30,4%, respectivamente). Todos los pacientes excepto uno de ellos, recibieron tigeciclina en combinación con otros antimicrobianos (95,7%), con más frecuencia fluconazol (52,2%), seguido de piperacilina-tazobactam (43,5%). El tratamiento antibiótico empírico fue considerado adecuado en el 95% de los pacientes. La duración media del tratamiento antibiótico fue 8,5 ± 4,5 días. Se consiguió una respuesta favorable en el 78% de los pacientes. No se observó fracaso del tratamiento antibiótico en ningún paciente. Tampoco en ningún caso hubo que suspender el tratamiento con tigeciclina debido a la presencia de reacciones adversas. La mortalidad en la UCIQ fue del 13%, y ninguna muerte fue atribuible a tigeciclina. Estos hallazgos sugieren que la utilización de tigeciclina en combinación con otros antimicrobianos es un tratamiento eficaz y bien tolerado en los pacientes con IIA nosocomial grave ingresados en la UCIQ.

Palabras clave: infección intraabdominal, pacientes críticos, UCIQ, tratamiento empírico, tigeciclina.

INTRODUCTION

Intra-abdominal infection (IAI) is one to the most frequent complications treated in the surgical area. At present, a high proportion of patients with IAI require admission to an intensive care unit (ICU) and mortality continues to be above 20%[1]. Increased bacterial resistance[2], inadequate empirical treatment[3], and poor control of the infectious focus[4], may be, among others, the factors responsible for failure of its management.

In recent years we have witnessed a significant increase in the incidence of multiresistant microorganisms both in the community and hospital setting[5], particularly in ICUs[6,7]. This scenario has created an urgent need to develop new antibiotics with a broad antimicrobial spectrum that overcome the usual mechanisms of resistance. Moreover, given the polymicrobial aerobic and anaerobic etiology of IAIs, optimizing the spectrum of antibiotic therapy is crucial to the approach to their treatment.

Tigecycline is the first agent in a new class of antibiotics belonging to the glycylcycline group, structurally similar to the tetracyclines whose structure confers a broader antimicrobial spectrum and a decreased susceptibility to the development of resistance than tetracycline antibiotics. Thus, this antimicrobial agent is not affected by the main mechanisms of bacterial resistance of the tetracyclines, based on the activity of efflux pumps that reduce that the intracellular concentration of the antibiotic and ribosomal protection[8]. The broad spectrum of action of tigecycline covers gram-positive, gram-negative, anaerobic and atypical pathogens, including microorganisms resistant to multiple antimicrobial agents[9,10]. In this regard, tigecycline has been reported to have microbiological efficacy against a large number of multiresistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant *Enterococcus* spp.[11]. In addition, it has been reported to possess a broad spectrum of action against multiresistant gram-negative bacteria such as extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* or carbapenamase-producing *Acinetobacter* spp.[12,13]. However, resistance to tigecycline has been shown in *Pseudomonas aeruginosa* and decreased sensitivity in *Proteus* spp.[14].

The broad spectrum of action against multidrug resistant bacteria, its wide tissue distribution[15], and the lack of adjustments for hepatic or renal impairment, make tigecycline an especially useful antibiotic agent for early treatment of IAIs in the ICU setting[13,16,17]. However, available experience on the use of tigecycline in critical patients is scarce and the studies conducted have evaluated its use in different hospital settings and in different infections and microorganisms against which it is applied[16,18-20]. There are limited observational studies available describing the use of tigecycline in the ICU, and furthermore they consist of heterogeneous reports in terms of the indication for treatment with tigecycline[16,20].

The present study describes the experience with tigecycline in patients with serious nosocomial IAIs in the surgical ICU (SICU) of a University hospital and their clinical outcome in routine clinical practice.

PATIENTS AND METHODS

Study population and design. All consecutive patients admitted for serious nosocomial IAI to the SICU of a University hospital were retrospectively analyzed. The study population included patients of both sexes and 18 years or older who had received at least one dose of tigecycline for treatment of IAI.

This was a non-interventional retrospective registry limited to collecting the information recorded in the data base of patients with IAI, which reflects the experience with tigecycline in the SICU in routine clinical practice. The data collected for each patient included: demographic data (age, gender), anthropometric data (weight, height, BMI), co-morbidity, data on IAI, microbiological data, treatment related data (tigecycline therapy, previous and concomitant antibiotic treatment, adequacy of antibiotic treatment in the first hours of infection), and data on patient outcome (clinical efficacy, death).

Assessment of severity of underlying disease at 24 hours from diagnosis of infection was performed using the following severity scores: Simplified Acute Physiology Score III (SAPS III)[21], Sequential Organ Failure Assessment (SOFA)[22], McCabe score[23] and serum lactate levels.

Identification of microorganisms was performed according to the standard microbiological procedures of our institution.

Definitions

a) Treatment adequacy.

Empirical antibiotic treatment in the first 6 hours in the SICU was considered adequate or inadequate in terms of coverage of the antimicrobial agents used against the microorganisms isolated, and based on the clinical improvement of the patient.

b) Clinical outcome of patients.

The clinical outcome of patients was analyzed by assessing whether they showed a favorable clinical response, suffered a treatment failure, experienced a new suture failure, or if they died.

Clinical response was determined based on the investigator's judgment as a favorable clinical response or treatment failure according to usual clinical practice criteria. A favorable clinical response was considered when the clinical outcome of the patient was assessed as cure or improvement based on resolution or improvement of signs and symptoms; so that the patient did not require new antibiotic treatment, or there were no serious adverse effects requiring discontinuation of tigecycline-based therapy. Treatment failure was defined as persistence or worsening of clinical signs and symptoms of IAI or appearance of new signs or symptoms associated with infection, requirement of additional antibiotic treatment, or replacement of tigecycline for an alternative antibiotic treatment.

Table 1 Demographic and clinical characteristics of patients and IAI-related data at SICU admission

Demographics and clinical characteristics	No. patients (%)
Demographic and anthropometric data	
Gender: men, n (%)	16 (69.6%)
Age (yr, mean ± SD)	63.6±16,6
BMI (Kg/m2, mean ± SD)	24.9±5,1
Comorbidity[a]	
Cancer	14 (60.9)
Neutropenia	4 (17.4)
Diabetes mellitus	4 (17.4)
Corticotherapy	3 (13.0)
Cardiovascular disease	3 (13.0)
Health care setting within last year	3 (13.0)
Chronic kidney disease	2 (8.7)
COPD	2 (8.7)

IAI related data	No. patients (%)
IAI non preceded by surgery	4 (17.4)
Nosocomial infection	2 (8.7)
Community-acquired infection	2 (8.7)
Postoperatory IAI	19 (82.6)
Type of surgical intervention	
Programmed	11 (55.0)
Emergency	9 (45.0)
Type of surgical procedure[b]	
Hemicolectomy	3 (15.0)
Esophagectomy	2 (10.0)
Subtotal gastrectomy	2 (10.0)
LAR	2 (10.0)
SB resection + Anastomosis	2 (10.0)
Sigmoidectomy	2 (10.0)
ASA classification for patients who underwent surgery[c]	
Healthy	2 (10.0)
Mild-moderate systemic disease	10 (50.0)
Severe systemic disease not associated to disability	8 (40.0)
Diagnosis of IAI	
Septic shock	13 (56.5)
Emergency surgery	23 (100.0)
Location	
Colon	11 (47.8)
Stomach-duodenum	4 (17.4)
Small bowel	2 (8.7)
Complicated cholecystitis-cholangitis	1 (4.3)
Pancreas	1 (4.3)
Severity score within 24h from diagnosis of IAI (mean ± SD)	
SAPS III scored	57.5 ± 14,7
Predicted mortality according to SAPS III (%)	30
SOFA score	7.0 ± 2,2
Serum lactate	1.8 ± 1.3
McCabe score >1; n (%)	20 (87.0)
Measures taken for management of infectious process	
Mechanic ventilation ≥24h	8 (34.8)
CVV-HDF	6 (27.3)

ASA: American Society Anesthesiology; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CVV-HDF: Continous Veno-Venous Hemodiafiltration; IAI: Intra-abdominal Infection; LAR: Low Anterior Resection; SAPS III: Simplified Acute Physiology Score; SB: Small Bowel; SICU: Surgical Intensive Care Unit; III; SOFA: Sequential Organ Failure Assessment.

[a]Patients may suffer more than one comorbid condition (multiple response variable). Comorbidities present in at least 5% of patients are presented.

[b]Most frequent surgical procedures used in at least 10% of patients are presented. Data have been calculated over 20 patients.

[c]Data have been calculated over 20 patients.

[d]Two (8.7%) patients showed SAPS III score between 1% and 10%, 10 (43.5%) patients between 10% and 20% and the 3 patients remaining (13.0%) between 30% and 40%.

Statistical analysis. To describe the clinical outcome of patients admitted for severe IAI and treated with tigecycline, a descriptive analysis was carried out on all qualitative and quantitative variables. Qualitative variables were analyzed using absolute and relative frequencies and quantitative variables using the main measures of central tendency and dispersion (mean, median, standard deviation[5], minimum, maximum, first quartile and third quartile). The results were expressed as mean ± SD and median (range).

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 statistical software (SPSS, Chicago, IL, USA).

RESULTS

Clinical and demographic characteristics of patients. A total of 23 patients with serious nosocomial IAI who had

Table 2 Microbiology of IAI

Microorganisms	No. patients (%)
Gram negatives	
Escherichia coli	10 (43.5)
Bacteroides spp.	7 (30.4)
Bacteroides fragilis	4 (17.4)
Klebsiella spp.	3 (13.0)
Pseudomonas aeruginosa[a]	3 (13.0)
Prevotella spp.	3 (13.0)
Gram positives	
Streptococcus spp.	7 (30.4)
Enterococcus faecalis	5 (21.7)
Enterococcus faecium	3 (13.0)
Clostridium spp.	2 (8.7)
Staphylococcus aureus	2 (8.7)
Candida albicans	3 (13.0)
Candida tropicalis	2 (8.7)

Most frequent pathogens identified in microbiologic cultures in more than 5% of patients are presented in the table.

[a] ***Pseudomonas aeruginosa* is found as a part of the polymicrobial flora of infection focus.**

received empirical treatment with tigecycline were retrospectively analyzed.

The main clinical and demographical characteristics of the patients at admission and during their stay in the SICU are shown in table 1. Sixteen (69.6%) patients were men and the mean age was 63.6 ± 16.6 years. Cancer was the most frequent underlying co-morbidity recorded in the medical history, affecting 14 (60.9%) patients. Other underlying diseases among patients with IAI were neutropenia and diabetes mellitus in 4 (17.4%) patients respectively.

Thirteen (56.5%) patients presented severe sepsis and 10 (43.5%) developed septic shock. In 19 (82.6%) patients, IAI was postoperative in origin. Among patients who developed an IAI after a surgical operation, the most frequent procedure was hemicolectomy, carried out in 4 (20.0%) patients. In all cases, infection was diagnosed via emergency surgery.

The mean SAPS III score in the first 24 hours since IAI diagnosis was 57.5±14.7. Twenty one (87.0%) patients showed a McCabe score of more than 1 (2 or 3).

Eight (34.8%) patients required mechanical ventilation for at least 48 hours during their stay in the SICU, while 6 (27.3%) required continuous veno-venous hemodiafiltration (CVV-HDF).

Microbiology. The most frequent microorganisms in IAIs, identified with a frequency higher than 15%, were mainly gram-negative pathogens. *E. coli* was the microorganism most frequently identified in cultures, present in 10 (43.5%) patients. Anaerobes and gram-positive cocci ranked second in frequency among microbiological cultures of the patients. *Bacteroides* spp. and *Streptococcus* spp. were detected in the microbiological cultures of 7 (30.4%) patients, respectively. *Enterococcus faecalis* was identified in 5 (21.7%) patients and *Bacteroides fragilis* in 4 (17.4%). The remaining microorganisms were identified with a frequency less than 15%. Only 2 patients had *P. aeruginosa* in their infectious diagnosis as part of their polymicrobial flora (tables 2 and 4).

Prior antibiotic therapy and tigecycline treatment

a) Prior antibiotic therapy.

Only 2 (8.7%) patients had received more than two cycles of antibiotic therapy within the year previous to diagnosis of IAI, whereas 17 (73.9%) patients had received antibiotic therapy within the 2 previous months, and 3 (13.0%) had been treated with fluconazole (table 3).

b) Tigecycline therapy and concomitant antibiotic treatment.

Tigecycline was used as monotherapy in only one patient, whereas in the remaining 22 (95.7%) patients tigecycline was administered in combination with other antibiotic agents. Together with tigecycline, the most frequently selected treatment for management of IAI was the antifungal agent fluconazole, received by 12 (52.2%) patients, followed by the antibiotic combination piperacillin-tazobactam, given to 10 (43.5%) patients. Caspofungin and anidulafungin were administered in 7 (30.4%) patients, respectively, and 4 (17.4%) received cefepime (tables 3 and 4).

The mean duration of antibiotic therapy with tigecycline was 8.5 ± 4.5 days. With regard to the drugs used in combination with tigecycline, mean duration was 6.6 ± 4.1 and 5.9 ± 2.4 days for fluconazole and piperacillin-tazobactam, respectively (table 3).

Among the 21 patients in whom adequacy of treatment was known, empirical antibiotic therapy administered in the first 6 hours from diagnosis of infection was adequate in 20 (95.2%) patients. Treatment was considered inadequate in only 1 patient (table 3).

Clinical outcome. Five (21.7%) patients died prior to discharge from the hospital. In no case was death attributable to treatment of IAI with tigecycline. Three (13.0%) patients died during their stay in the SICU, whereas the remaining 20 (87.0%) patients continued in the hospital ward after discharge from the SICU. The median total duration of hospitalization was 43 days (range 37-84 days) (table 4).

Eighteen (78.3%) patients achieved a favorable response with tigecycline therapy. Failure of the antibiotic therapy for IAI was not observed in any patient. None of the patients needed to discontinue tigecycline treatment due to adverse reactions. Three (13.0%) patients suffered a new suture failure (table 4).

Table 3 Tigecycline treatment and previous and concomitant therapy

Antibiotic treatment	No. patients (%)
Antbiotic treatment prior to tigecycline	
>2 cycles of antibiotics within the year prior to tigecycline	2 (8.7)
Antibiotic therapy within the 2 previous months[a]	17 (73.9)
Tigecycline treatment	
Combined therapy	22 (95.7)
Concomitant treatment with tigecycline[b]	
Fluconazole	12 (52.2)
Piperacillin-tazobactam	10 (43.5)
Caspofungin	7 (30.4)
Anidulafungin	7 (30.4)
Cefepime	4 (17.4)
Voriconazole	2 (17.4)
Amikacin	1 (8.7)
Treatment duration[c] (days, mean ± SD)	
Tigecycline	8.5±4,5
Fluconazol	6.6±4,1
Piperaciline-Tazobactam	5.9±2,4
Adequate treatment within the first 6 h[d]	
Adequate	20 (95.2)
Inadequate	1 (4.8)

[a]Three patients received antifungal treatment with fluconazole within the 2 previous months before the start of treatment with tigecycline.
[b]Multiple response variable.
[c]Duration of antibiotic treatments administered to more than 40% of patients are presented.
[d]Adequacy of empiric treatment administered within the first 6h of IAI. Adequacy of treatment was unknown in 2 patients.

DISCUSSION

The findings of the present investigation demonstrated that tigecycline combination therapy is an effective and well tolerated empirical treatment for critical patients with serious nosocomial IAIs. Although these were critically ill patients with severe sepsis and septic shock, 78% achieved a favorable response with tigecycline therapy. None of the patients showed failure of the antibiotic therapy for IAI. The mortality rate in this series was 21.7%, and there were no deaths attributable to tigecycline therapy.

Available experience on the use of tigecycline in critically ill patients is scant and the studies conducted to date differ with regard to its use (empirical or rescue therapy), types of infection treated and microorganisms against which it is used[16,18-20]. To our knowledge, this is the first homogeneous series of critically ill patients describing experience with tigecycline in the SICU setting in which the specific indication of this antibiotic for the treatment of complicated IAI was assessed.

The study population comprised patients with severe sepsis and septic shock (57%), who underwent emergency abdominal surgery. Most patients had some relevant comorbidity, and 60% were oncological patients. The severely ill patient population analyzed in the present study is underrepresented or even excluded from pivotal clinical trials of tigecycline, since the number of patients with severe underlying disease, such as immunosuppressed patient, those with an acute Physiology and Chronic Health Evaluation II (APACHE II) score> 15 (4%), or with multiple intraabdominal abscesses (10%), was very limited in these trials[24].

The pivotal trials on which approval of the use of tigecycline in IAIs was based are part of a pooled analysis of the randomized trials that were the basis for the recent United States Food and Drug Administration (FDA) alert describing the increased mortality risk associated with the use of tigecycline compared to other drugs in the treatment of a variety of serious infections, including complicated IAIs[25]. In this scenario, there are discrepancies between the evidence of the clinical trials, which generally exclude severely ill patients treated with tigecycline, and the situation the clinician must face in daily management of critically ill patients as a result of the high rate of multiresistant pathogens and the few available treatment options evaluated for this type of patients, especially in sepsis[26]. In this regard, clinical studies are needed to evaluate the efficacy of tigecycline in critically ill patients.

Morbidity and mortality for severe IAI is high, particularly in patients with more severe infections and greater comorbidity[1]. The mortality rate (21.7%) for the population of critically ill patients was lower than the predicted mortality according to SAPS III severity score shown within the 24h from diagnosis of IAI based on their baseline comorbidity (30%). Even though they were critically ill patients with relevant associated comorbidities, the mortality rate was relatively low (21.7%). Furthermore, the mortality seen in the current series was even lower than that reported in a German study in patients with severe sepsis and septic shock in the SICU setting (30%)[20].

The favorable clinical response achieved with tigecycline therapy in our study was consistent regardless of the etiology of the infections. Among the most common pathogens treated were *E. coli* and *B. fragilis*, two enterobacteria strains that typically colonize the gastrointestinal tract. After the Enterobacteriaceae family, the next most common infection was that caused by enterococci, with a greater presence of *E. faecalis* and to a lesser extent *E. faecium*. Accordingly, piperacillin-tazobactam in combination with tigecycline was the predominant regimen used in order to provide adequate enterococcal coverage due to the worse prognosis of patients infected with *Enterococcus* spp.[27].

An incidence of *Candida* spp. infection of around 6% has been reported In the ICU setting, with a higher mortality rate

Table 4 Main characteristics of patients, antibiotic treatment and clinical outcome

No.	Age (yr)	Comorbidity[a]	SAPS III[b]	Microbiology	Tigecycline treatment duration (days)	Combination treatments	Clinical outcome
1	69	Cancer, DM	52	*Bacteroides* spp. *E. faecium*, other	9	piperacilline-tazobactam anidulafungin, fluconazole	Favorable
2	67	NR	38	*P. aeruginosa, B. fragilis, Prevotella, E. faecalis, Streptococcus* spp.	4	caspofungin, fluconazole	Favorable
3	27	NR	49	NA[c]	6	piperacilline-tazobactam, fluconazole	Favorable
4	75	Cancer	71	*E. coli* AMCR, E-coli TZPR, *E. coli* CIPR	10	caspofungin	Favorable
5	57	Cancer	46	*E.coli, B.fragilis, Clostridium, C. tropicalis*	8	fluconazole	Favorable
6	82	Cancer, COPD, neutropenia, DM, CVD	60	*E. coli* BLEE, *E. coli* AMCR, *E. coli* TZPR, *E. coli* CIPR, *Bacteroides* spp., *Clostridium, Prevotella, E. faecalis*, other	23	caspofungin	Favorable
7	46	Cancer, neutropenia	50	*Bacteroides* spp.	7	cefepime, caspofungin	Favorable
8	66	NR	25	*E. coli, B.fragilis, Bacteroides* spp., *Clostridium, Veionella, Streptococcus* spp.	8	piperacilline-tazobactam, voriconazole	Favorable; new suture failure
9	82	Cancer	48	*E. coli* BLEE	8	none	Favorable
10	84	Cancer	70	*E. faecalis*	7	piperacilline-tazobactam, caspofungin, fluconazole	Éxitus
11	70	Cancer, neutropenia, corticotherapy	83	*Enterobacter* BLEE, *C. tropicalis*	8	piperacilline-tazobactam, anidulafungin	Éxitus
12	40	NR	70	NA[c]	9	piperacilline-tazobactam, voriconazole	Favorable
13	73	Cancer	50	*E. faecalis*, other	8	piperacilline-tazobactam, caspofungin,	Favorable
14	81	Cancer, CKD	72	*Streptococcus* spp.	8	fluconazole	New suture failure; deathd
15	64	Cancer	50	*E. coli, Streptococcus* spp.	9	fluconazole	Favorable; new suture failure
16	83	CVD	58	*Kleibsella* spp.	8	anidulafungin	Death
17	51	Cancer, neutropenia, corticotherapy	80	*Acinetobacter* spp., *P. aeruginosa, E. faecium, Candida* spp.	11	cefepime, caspofungina, fluconazole	Death
18	64	NR	58	*E. coli, Kleibsella* spp., *P. aeruginosa, Bacteroides* spp., *E. faecalis, C. albicans*	19	piperacilline-tazobactam, anidulafungin, fluconazole	Favorable
19	26	Corticotherapy	50	*E. coli, Proteus* spp., *Streptococcus* spp., *S. aureus*	6	anidulafungin, fluconazole, amikacine	Favorable
20	71	Cancer	74	*E. faecium*	8	cefepime, anidulafungin	Favorable
21	59	COPD, DM, CVD, surgery within last yr	76	*E. coli, Prevotella, S. aureus*	4	cefepime, anidulafungin	Favorable
22	58	DM, CKD	46	*Kleibsella* spp., *Streptococcus* spp.	6	piperacilline-tazobactam, fluconazole	Favorable
23	68	Cancer	46	*E. coli, B. fragilis, Bacteroides* spp., *Peptostreptococcus* spp., *Streptococcus* spp.	2	piperacilline-tazobactam	Favorable

AMCR: amoxiclav-resistant (amoxicillin + clavulanic acid), CIPR: ciprofloxacin-resistant; CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, CVD: Cardiovascular Disease, DM: Diabetes Mellitus, NA: non available, NR: none reported. SAPS III: Simplified Acute Physiology Score III; TZPR: piperacilline-tazobactam-resistant.

[a]Comorbid conditions recorded in the medical history are described

[b]SAPS III score within the 24h of infection

[c]A sample for microbiologic culture was not taken from this patient.

[d]For this patient, death was attributable to a second suturing procedure.

being found in patients with nosocomial fungal infection[28]. In addition, Candida spp. infection is frequent when broad-spectrum antibiotics are used in patients with ICU stays longer than 7 days[28]. In this context, most patients in this series received antifungal treatment with tigecycline, mainly fluconazole. Almost all patients received tygecycline combined with other antibiotics, with only one patient being given tigecycline as a single-agent. Considering the risk of tigecycline-resistant infection with *P. aeruginosa* and *Proteus spp.*, tigecycline was used in combination with other antibiotics that adequately cover the presence of tigecycline-resistant bacteria such as *P. aeruginosa*. The use of tigecycline mostly in combined regimens is in agreement with studies published recently in critically ill patients with IAIs[18,20]. However, discordant data have been documented in tigecycline use patterns in critically ill patients. Thus, in an Italian study of mostly critically ill patients with nosocomial infections, treatment with tigecycline was administered mainly as monotherapy[19], whereas half of patients with complicated IAI received tigecycline as a single-agent in a French study conducted in the ICU setting[16].

Empirical therapy was considered adequate in 95% of the cases analyzed in this study. It should be noted that the only patient in whom empirical treatment was not considered adequate had a favorable response to tigecycline therapy. Despite the fact that this patient had a *P. aeruginosa* infection and was treated with tigecycline combined only with antifungal treatment, the patient achieved a favorable response to therapy. Accordingly, previous studies have documented a reduced rate of treatment failure with tigecycline associated with the presence of baseline *P. aeruginosa* infection[29].

The mean duration of tigecycline therapy was 9 days, which is in agreement with period considered by most surgeons of 7 days as the minimum treatment duration that patients with IAIs should receive. Nevertheless, optimal duration of antibiotic therapy in IAIs remains controversial, primarily because of the lack of controlled studies providing adequate scientific support[30].

The main limitations of the study arise from to its retrospective nature, the small number of cases included in the series and its conduct in a single center, which limits the extrapolation of the conclusions to other hospitals. Despite these limitations, homogeneity of the series in terms of the approved indication of tigecycline for the treatment of IAIs in critically ill patients makes the results obtained for efficacy and clinical outcome attain greater consistency. Hence, considering the lack of data on the use of tigecycline in IAIs in critically ill patients, the findings obtained in this study, although they should be viewed as purely descriptive, could provide useful information for clinicians on management of these patients. Furthermore, this type of study can collect clinical information in a population of patients urgently requiring treatment and who would have been excluded from clinical trials due to their baseline conditions of disease severity and comorbidity.

The findings of this observational study suggest that tigecycline is an effective and well tolerated empirical treatment of serious nosocomial IAI in the SICU setting, representing an effective alternative that may overcome the increasing problem of bacterial resistance in critical care.

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None declared

REFERENCES

1. Barie PS, Hydo LJ, Eachempati SR. Longitudinal outcomes of intra-abdominal infection complicated by critical illness. Surg Infect (Larchmt) 2004; 5:365-73.
2. Fish DN, Ohlinger MJ. Antimicrobial resistance: factors and outcomes. Crit Care Clin 2006; 22:291-311.
3. Krobot K, Yin D, Zhang Q, Sen S, Altendorf-Hofmann A, Scheele J, et al. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis 2004; 23:682-7.
4. Chromik AM, Meiser A, Holling J, Sulberg D, Daigeler A, Meurer K, et al. Identification of patients at risk for development of tertiary peritonitis on a surgical intensive care unit. J Gastrointest Surg 2009; 13:1358-67.
5. Livermore DM. Bacterial resistance: origins, epidemiology, and impact. Clin Infect Dis 2003; 36(Suppl 1):S11-S23.
6. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med 2001; 134:298-314.
7. Smith MA, McInnis LA. Antimicrobial resistance in critical care. Crit Care Nurs Clin North Am 2007; 19:53-60.
8. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev 2001; 65:232-60.
9. Hoban DJ, Bouchillon SK, Johnson BM, Johnson JL, Dowzicky MJ. In vitro activity of tigecycline against 6792 Gram-negative and Gram-positive clinical isolates from the global Tigecycline Evaluation and Surveillance Trial (TEST Program, 2004). Diagn Microbiol Infect Dis 2005; 52:215-27.
10. Draghi DC, Tench S, Dowzicky MJ, Sahm DF. Baseline in vitro activity of tigecycline among key bacterial pathogens exhibiting multidrug resistance. Chemotherapy 2008; 54:91-100.
11. Garrison MW, Nuemiller JJ. In vitro activity of tigecycline against quinolone-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. Int J Antimicrob Agents 2007; 29:191-6.

12. Leclerc T, Perez JP, Debien B, Clapson P, Lenoir B. [Treatment of a septic shock due to multiresistant Acinetobacter baumannii with tigecycline in combination]. Ann Fr Anesth Reanim 2007; 26:1056-8.
13. Vasilev K, Reshedko G, Orasan R, Sanchez M, Teras J, Babinchak T, et al. A Phase 3, open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant Gram-negative organisms including Enterobacter species, Acinetobacter baumannii and Klebsiella pneumoniae. J Antimicrob Chemother 2008; 62 Suppl 1:i29-i40.
14. Slover CM, Rodvold KA, Danziger LH. Tigecycline: a novel broad-spectrum antimicrobial. Ann Pharmacother 2007; 41:965-72.
15. Meagher AK, Ambrose PG, Grasela TH, Ellis-Grosse EJ. The pharmacokinetic and pharmacodynamic profile of tigecycline. Clin Infect Dis 2005; 41 Suppl 5:S333-S340.
16. Jung B, Chanques G, Ghiba M, Cisse M, Rossel N, Perrigault PF, et al. Tigecycline for treatment of severe infections in intensive care: a drug use evaluation. Ann Fr Anesth Reanim 2010;29(5):354-60.
17. Stein GE, Craig WA. Tigecycline: a critical analysis. Clin Infect Dis 2006; 43:518-24.
18. Alvarez-Lerma F, Blanco L, Rodriguez JA, Grau S, Conde-Estevez D, Luque S. Differences in the use of tigecycline between ICU patients and non-ICU patients. Rev Esp Quimioter 2010; 23:63-71.
19. Bassetti M, Nicolini L, Repetto E, Righi E, Del B, V, Viscoli C. Tigecycline use in serious nosocomial infections: a drug use evaluation. BMC Infect Dis 2010; 10:287.
20. Swoboda S, Ober M, Hainer C, Lichtenstern C, Seiler C, Wendt C, et al. Tigecycline for the treatment of patients with severe sepsis or septic shock: a drug use evaluation in a surgical intensive care unit. J Antimicrob Chemother 2008; 61:729-33.
21. Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, et al. SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 2005; 31:1345-55.
22. Vincent JL, de MA, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998; 26:1793-800.
23. McCabe WR, Jackson GG. Arch Intern MedGram-negative bacteremia. I. Etiology and ecology. Arch Intern Med 1962;110:847-64.
24. Babinchak T, Ellis-Grosse E, Dartois N, Rose GM, Loh E. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. Clin Infect Dis 2005; 41 Suppl 5:S354-S367.
25. Food and Drug Administration. FDA Drug Safety Communication: Increased Risk of Death with Tygacil (Tigecycline) Compared to Other Antibiotics Used to Treat Similar Infections. http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm. 1-9-2010.
26. Curcio D. Tigecycline for severe infections: the gap between the warning and the necessity. J Antimicrob Chemother 2011; 66:454-6.
27. Montravers P, Lepape A, Dubreuil L, Gauzit R, Pean Y, Benchimol D, et al. Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. J Antimicrob Chemother 2009; 63:785-94.
28. Leon C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lerma F, et al. A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care Med 2006; 34:730-7.
29. Passarell JA, Meagher AK, Liolios K, Cirincione BB, Van Wart SA, Babinchak T, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. Antimicrob Agents Chemother 2008; 52:204-10.
30. Maseda E, Gilsanz F. Duration of antibiotic therapy in intraabdominal infections. Enferm Infecc Microbiol Clin 2010; 28 Suppl 2:49-52.