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A practice-based observational study identifying factors associated with the use of high-dose tigecycline in the treatment of secondary peritonitis in severely ill patients

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ABSTRACT

Introduction. Based on tigecycline linear pharmacokinetic/pharmacodynamics, dose increases have been advocated to maximise activity especially when severe infections with high bacterial load and/or multidrug resistance are suspected. This practice-based observational study explored factors associated with tigecycline administration (100 mg/12h, 200 mg loading dose) in severely ill patients with complicated intra-abdominal infection (cIAI) admitted to four Surgical Critical Care Units (SCCUs).

Methods. Medical records of all consecutive adult patients with cIAI and controlled infection source requiring surgery and admission for ≥48h to SCCU were reviewed and divided into patients treated with a regimen including tigecycline (tigecycline group) and those that not (control group). A logistic regression model was performed using "tigecycline administration" (dependent variable) and variables showing differences (p≤0.1) in bivariate analyses (independent variables).

Results. One hundred and twenty one patients were included. In the tigecycline group, higher percentage of patients (vs. controls) presented colon as surgical site (66.7% vs. 41.8%, p=0.006), nosocomial infection (55.6% vs. 26.9%, p=0.001), mechanical ventilation (48.1% vs. 28.4%, p=0.025), chronic renal replacement therapy (40.7% vs. 19.4%, p=0.008), septic shock (72.2% vs. 46.3%, p=0.004), and higher values of SAPS II (48.0±15.0 vs. 39.6±15.5, p=0.003), SOFA at admission (7.0±3.3 vs. 5.5±3.7, p=0.020), lactate-24h (2.5±2.8 vs. 1.6±0.9, p=0.029) and CRP-72h (207.4±87.9 vs. 163.7±76.8, p=0.021). In the multivariate analysis (R^2=0.187, p<0.001) nosocomial infection (OR=7.721; 95%CI=2.193, 27.179; p=0.001), colon as infection site (OR=4.338; 95%CI=1.432, 13.145; p=0.009) and CRP-72h (OR=1.009 per-unit; 95%CI=1.002, 1.016; p=0.012) were associated with tigecycline administration.

Conclusions. In severely ill patients with cIAI, high-dose tigecycline administration was associated with nosocomial origin of cIAI and colon as source infection site.

Key words: Secondary peritonitis; multidrug treatment regimen; post-surgical critical care; tigecycline; critically ill patients

Estudio observacional basado en la práctica diaria identificando factores asociados con la administración de dosis altas de tigeciclina en el tratamiento de la peritonitis secundaria en pacientes críticos

RESUMEN

Introducción. Se han postulado incrementos en la dosis de tigeciclina basándose en su farmacocinética/farmacodinamia lineal, especialmente en infecciones graves con sospecha de alta carga bacteriana o/y multirresistencia. El presente estudio observacional basado en la práctica diaria explora los factores asociados con la administración de tigeciclina (100 mg/12h, 200 mg dosis de carga) en pacientes críticos con infección intraabdominal complicada (cIIA) ingresados en 4 Unidades de Cuidados Críticos Quirúrgicos (UCCQ).

Métodos. Las historias clínicas de todos los pacientes adultos consecutivos con cIIA y foco de infección controlado que requerían cirugía e ingresaron en UCCQ durante ≥48h fueron revisadas y los pacientes fueron divididos en dos grupos: pacientes tratados con un régimen antibiótico que incluía tigeciclina (grupo tigeciclina) y aquellos que no (grupo control). Se realizó un modelo de regresión logística utilizando como variable dependiente la administración de tigeciclina y como independientes aquellas variables que mostraron diferencias (p≤0,1) en el análisis bivariado realizado.

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Resultados. Se incluyeron 121 pacientes. En el grupo tigeciclina, un mayor porcentaje de pacientes (vs. control) presentaban el colon como sitio quirúrgico (66,7% vs. 41,8%, p=0,006), infección nosocomial (55,6% vs. 26,9%, p=0,001), ventilación mecánica (48,1% vs. 28,4%, p=0,025), terapia renal sustitutoria (40,7% vs. 19,4%, p=0,008), shock séptico (72,2% vs. 46,3%, p=0,025) y valores más altos de SAPS II (48,0±15,0 vs. 39,6±15,5, p=0,003), SOFA al ingreso (7,0±3,3 vs. 5,5±3,7, p=0,020), lactato-24h (2,5±2,8 vs. 1,6±0,9, p=0,029) y PCR-72h (207,4±87,9 vs. 163,7±76,8, p=0,021). En el análisis multivariado (R^2=0,187, p<0,001) la administración de tigeciclina se asoció con infección nosocomial (OR=7,721, 95%IC=2,193-27,179; p=0,001), colon como foco de infección (OR=4,338, 95%IC=1,432-13,145; p=0,009) y PCR-72h (OR=1,009 por unidad, 95%IC=1,002-1,016; p=0,012).

Conclusiones. En pacientes críticos con cIIA, la administración de tigeciclina a dosis alta se asoció con el origen nosocomial de la infección y con el colon como foco de la misma.

Palabras clave: Peritonitis secundaria; régimen antibiótico múltiple; cuidados críticos post-quirúrgicos; tigeciclina; paciente crítico

INTRODUCTION

Treatment of complicated intra-abdominal infections (cIAIs) in general consists in surgical source control, administration of antibiotics (often as a combination due to the polymicrobial nature of the infection) and intensive care[1-3]. Secondary peritonitis is the most frequent cIAI, and can be differentiated into community-acquired (about 70% of all) and post-operative (about 30%), the latter with an increased likelihood of being caused by antimicrobial resistant strains[2,4].

Classically, *Escherichia coli* and *Bacteroides fragilis* have been considered main responsible bacteria of intra-abdominal infections. In cIAIs other enterobacteria as *Klebsiella* spp., grampositives as staphylococci and streptococci, non-fermenters as *Pseudomonas aeruginosa*, other anaerobes belonging to the genera *Bacteroides*¸ *Clostridium* and *Fusobacterium*, together with yeasts as *Candida* spp. should be suspected[4]. In secondary peritonitis, enterococci are frequently co-isolated, and have been associated with presence of comorbidities[5]. The epidemiology towards drug-resistant pathogens, with increasing number of infections due to extended-spectrum β-lactamase (ESBL) and metallo-betalactamase producing bacteria among gramnegatives, methicillin-resistant staphylococci (MRSA) and vancomycin-resistant enterococci (VRE) in secondary peritonitis that occurs several days after admission calls for drugs that encompass this spectrum of bacteria[6].

Tigecycline has a broad spectrum of activity against multiple pathogens present in cIAIs including resistant strains that may be present, as ESBL-producers, metallo-betalactamase-producers, MRSA and VRE[7,8]. Recent guidelines recommend tigecycline for the treatment of hospital-acquired cIAIs in both stable non-critical patients and critically ill patients presenting risk factors for multidrug resistant pathogens[9]. Its use in post-operative peritonitis where the likelihood of resistant bacteria is higher than in community-acquired cIAIs of mild to moderate severity has been advocated[2,10]. In this sense, tigecycline is the only drug approved for the treatment of cIAIs due to resistant grampositive bacteria (MRSA, VRE)[6]. Clinical trials conducted in cIAIs with tigecycline included only small number of intensive care unit (ICU) patients that present higher disease severity than patients included in clinical trials[11], and evaluated tigecycline as monotherapy, not reflecting combined treatments used in daily practice for the treatment of cIAIs. A recent descriptive analysis[3,6] of five non-comparative observational studies reflecting real-life clinical practice supported the clinical value of tigecycline treatment, but only two of the five studies were conducted in ICUs with the standard tigecycline dose[12,13]. Nevertheless, based on linear pharmacokinetic and pharmacodynamics of tigecycline increases in doses have been advocated to maximise antibacterial activity especially when severe infections with high bacterial load and/or multidrug resistant bacteria are suspected[14]. In this sense, the use of 100 mg tigecycline every 12h has been reported in reduced number patients with different severe infections[15-17].

The aim of the present study was to identify factors associated with tigecycline high-dose administration in our surgical critical care units (SCCUs) for the treatment of critically ill patients with secondary peritonitis.

METHODS

A multicentre observational comparative study was performed from June 2012 to June 2013 in four Spanish hospitals. A retrospective analysis was performed on prospectively acquired data recorded in medical records as part of daily routine care (practice-base analysis). Data of all consecutive adult patients with complicated intra-abdominal infection and controlled infection source requiring surgery and admission for ≥48h in the SCCU were reviewed. Patients with tertiary peritonitis were not considered. The informed consent was waived due to the observational nature of the study. The study protocol was approved by Ethics Committees of participating hospitals.

Patients were divided into two groups: Patients treated with a regimen including tigecycline (tigecycline group) and patients treated with a regimen not including tigecycline (control group). Demographic, clinical (comorbidities, need for mechanical ventilation, renal replacement therapy…) and microbiological data (results of intra-abdominal cultures and of periodical rectal swabs for colonization surveillance), antibiotic treatment, length of stay (intra-SCCU and in-hospital stay) and mortality (intra-SCCU, 28-day, and in-hospital mortality) were recorded. The Simplified Acute Physiology Score (SAPS II)[18] and The Sequential Organ Failure Assessment (SOFA)[19] were calculated with data in the first 24h and also with those 72h after admission in the case of the SOFA score. Daily determined values of C-reactive protein (CRP) and lactate were recorded. For each patient, the highest values of biomarkers in the first 72h were considered peak values.

Comparisons between proportions were performed by the Chi-square test and the Fisher's exact test, when necessary. For quantitative variables, since data did not show normality in the Kolmogorov –Smirnoff test, the Kruskal-Wallis and Mann -Whitney tests, when necessary, were used. All variables were compared between the tigecycline and the control group. Logistic regression models (step–wise procedure) were performed using as dependent variable "tigecycline administration" and as independent variables those showing differences ($p \leq 0.1$) in bivariate analyses comparing demographic, clinical data, and peak values of biomarkers between groups. Interactions and linear dependence between independent variables were previously controlled. The model showing the maximum parsimony (the lowest number of variables with no significant reduction in the value of the determination coefficient) and the highest R^2 was considered. Statistical analyses were performed using SPSS v 14 programme (SPSS Inc., Chicago IL).

Table 1 **Demographic and clinical data of patients by study group.**

	Total (n=121)	Tigecycline (n=54)	Control (n=67)	p value
Age, mean±SD	65.9±16.8	65.7±17.3	65.7±16.3	0.987
Males, n (%)	72 (59.5)	28 (51.9)	44 (65.7)	0.124
BMI[a], mean±SD	26.0±6.2	25.5±4.9	26.6±7.4	0.364
≥1 comorbidity, n (%)	36 (29.8)	14 (25.9)	22 (32.8)	0.409
Nosocomial-acquired infection, n (%)	48 (39.7)	30 (55.6)	18 (26.9)	0.001
Surgical site, n (%)				
Colon	64 (50.8)	36 (66.7)	28 (41.8)	0.006
Small bowel	23 (19.2)	11 (20.4)	12 (17.9)	0.731
Appendix	11 (9.2)	2 (3.7)	9 (13.4)	0.109
Biliary tract	10 (8.3)	1 (1.9)	9 (13.4)	0.041
Gastroduodenal tract	9 (7.5)	2 (3.7)	7 (10.4)	0.295
Others	4 (3.2)	2 (3.7)	2 (3.0)	1.000
Clinical scores				
SAPS II, mean±SD	43.4±15.8	48.0±15.0	39.6±15.5	0.003
SOFA, mean±SD				
0h	6.2±3.6	7.0±3.3	5.5±3.7	0.020
72h	4.7±3.8	5.5±3.7	4.2±3.8	0.056
>24h mechanical ventilation, n (%)	45 (37.2)	26 (48.1)	19 (28.4)	0.025
CRRT[b], n (%)	35 (28.9)	22 (40.7)	13 (19.4)	0.008
Septic shock, n (%)	70 (57.9)	39 (72.2)	31 (46.3)	0.004

[a]Body mass index; [b]Continuous renal replacement therapy

RESULTS

A total of 121 patients were included, 54 patients in the tigecycline group and 67 in the control group. Mean age was 65.9±16.8 years; 56.2% of patients were ≥65 years old and 38.0% ≥75 years, without differences between study groups. Table 1 shows demographics and clinical data by study group. Overall, the most frequent surgical site was the colon, with significantly higher percentage of patients with this surgical site in the tigecycline group and with the biliary tract as surgical site in the control group. Significantly higher percentage of nosocomial infections was found in the tigecycline group. Twenty-nine out of 121 (29.8%) patients presented ≥1 comorbidity, being the most frequent oncological metastasis (31.0%), chronic respiratory disease requiring domiciliary oxygen therapy (27.6%) and congestive heart disease (24.1%). No differences were found between groups in the percentage of patients presenting each comorbidity.

Patients in the tigecycline group showed significantly higher mean values of SAPS II, SOFA at admission (table 1), lactate values at 24h and CRP values at 72h (table 2). In addition, the percentage of patients requiring mechanical ventilation, chronic renal replacement therapy and the percentage of patients presenting septic shock was also significantly higher in the tigecycline group (table 1).

The multivariate analysis was significant (R^2=0.187, p<0.001) with nosocomial infection (OR=7.721; 95%CI=2.193, 27.179; p=0.001), colon as infection site (OR=4.338; 95%CI=1.432, 13.145; p=0.009) and CRP values at 72h (OR=1.009 per-unit; 95%CI=1.002, 1.016; p=0.012) being associated with tigecycline administration.

Table 3 shows details of antimicrobial treatments by study group. While single-drug therapy was significantly more common in the control group, multidrug therapy with ≥3 antimicrobials was significantly more frequently used in the tigecycline group, with significantly more frequent administration of piperacillin/tazobactam and antifungals concomitantly to tigecycline. On the contrary, carbapenems were significantly more frequently administered in the control group. No difference in mean length of antimicrobial administration was found between study groups (table 3) or between patients presenting septic shock and those that did not, both when analysing the whole study population and the tigecycline or the control group in separate. Mean length of treatment in patients with septic shock was similar in the tigecycline and the control groups (p=0.929).

Table 4 includes results of diagnostic microbiological cultures showing frequencies of isolates among the 121 study patients. A total of 70 (57.9%) patients had positive cultures, 74.3% of them polymicrobial, with significantly higher num-

Table 2 Values [as mean ± SD and median (interquartile range)] of biomarkers by study group.

	Total (n=121)	Tigecycline (n=54)	Control (n=67)	p value
CRP (mg/L)				
24h	220.6 ± 98.8	224.1 ± 85.5	217.2 ± 108.8	0.738
	214.0 (147.0, 284.0)	236.0 (148.0, 280.0)	196.5 (140.4, 295.1)	0.685
48h	234.9 ± 97.1	248.1 ± 96.8	222.2 ± 96.7	0.198
	229.5 (162.3, 305.9)	240.5 (165.3, 339.8)	206.0 (143.5, 290.8)	0.146
72h	185.3 ± 84.8	207.4 ± 87.9	163.7 ± 76.8	0.021
	170.1 (123.0, 256.0)	184.4 (143.0, 276.7)	146.5 (116.3, 228.5)	0.027
Peak	267.0 ± 105.3	286.1 ± 97.1	251.4 ± 109.8	0.072
	265.0 (201.4, 338.4)	282.0 (231.4, 355.5)	258.0 (182.0, 317.8)	0.128
Lactate (mmol/L)				
24h	2.1 ± 2.1	2.5 ± 2.8	1.6 ± 0.9	0.029
	1.5 (1.0, 2.1)	1.5 (1.1, 2.8)	1.5 (1.0, 1.9)	0.150
48h	1.6 ± 1.9	2.0 ± 2.6	1.3 ± 0.7	0.095
	1.2 (0.9, 1.7)	1.2 (0.9, 1.9)	1.1 (0.9, 1.5)	0.257
72h	1.7 ± 2.8	1.9 ± 3.2	1.5 ± 2.4	0.625
	1.1 (0.9, 1.5)	2.2 (1.3, 4.1)	1.9 (1.3, 3.0)	0.161
Peak	3.0 ± 3.9	3.1 ± 3.2	2.9 ± 4.5	0.740
	2.1 (1.3, 3.3)	2.2 (1.3, 4.1)	1.9 (1.3, 3.0)	0.217

Table 3 Details of antimicrobial treatment by study group.

	Total	Tigecycline	Control	p value
No. antimicrobials/patient [median (IQR)]	2 (1, 3)	3 (2, 4)	1 (1, 3)	<0.010
Therapy with: [no. patients (%)]				
1 antimicrobial	42 (34.7)	5 (9.3)	37 (55.2)	<0.001
2 antimicrobials	24 (19.8)	14 (25.9)	10 (14.9)	0.131
≥3 antimicrobials	55 (45.5)	35 (64.8)	20 (29.9)	<0.001
Antibiotics administered [no. treatments (%)]				
Tigecycline	54 (44.6)	54 (100)	0 (0.0)	
Carbapenems	76 (62.8)	21 (38.9)	51 (76.1)	<0.001
Piperacillin/tazobactam	45 (37.2)	31 (57.4)	14 (20.9)	<0.001
Other β-lactams	8 (6.6)	2 (3.7)	6 (9.0)	0.295
Daptomycin	16 (13.2)	6 (11.1)	10 (14.9)	0.538
Glycopeptides	5 (4.1)	1 (1.9)	4 (6.0)	0.223
Aminoglycosides	6 (5.0)	3 (5.6)	3 (4.5)	1.000
Metronidazole	4 (3.3)	1 (1.9)	3 (4.5)	0.627
Other antibiotics	24 (19.8)	10 (18.5)	14 (20.9)	0.744
Antifungals [no. treatments (%)]	48 (39.7)	30 (55.6)	18 (26.9)	0.001
Length of treatment (days; mean±SD)	8.0±4.0	8.4±4.7	7.7±3.4	0.262

ber of species per sample and significantly more frequent isolation of *Enterococcus* spp. in the tigecycline group. Cultures of rectal swabs for colonization surveillance yielded growth of multidrug resistant bacteria in 17 out of 121 patients (14.0%): 13 out of 54 (24.1%) in the tigecycline group and 4 out of 67 (6.0%) in the control group (p=0.007). A total of 14 ESBL-producing enterobacteria were isolated, 11 (20.4%) in the tigecycline and 3 (4.5%) in the control group (p=0.007). In addition, 2 *Stenotrophomonas* spp. (one in each group) and one *Acinetobacter* spp. (in the tigecycline group) were isolated.

Complications as persistence or recurrence of intra-abdominal infection was found in 6 out of 121 (5.0%) patients in global, 4.5% patients in the tigecycline group and 3.0% in the control group (p=0.265). Overall, surgical wound infection occurred in 24.0% patients, 33.3% in the tigecycline group and 16.4% in the control group (p=0.034). Table 5 shows length of stay and mortality by study group. Both length of intra-SCCU and in-hospital stay were significantly longer in the tigecycline group, without significant differences in mortality rates by study group (table 5). Overall, mortality rates were significantly higher in the 70 patients developing septic shock (vs. patients that did not) for intra-SCCU (20.0% vs. 0.0%, p<0.001), 28-day (30.0% vs. 2.0%, p<0.001) and in-hospital mortality (38.6% vs. 5.9%, p<0.001). In both study groups, mortality was higher among patients with septic shock (vs. patients that did not): tigecycline (intra-SCCU: 23.1% vs. 0.0%, p=0.049; 28-day: 33.3% vs. 0.0%, p=0.011; and in-hospital mortality: 41.0% vs. 0.0%, p=0.002); control group (intra-SCCU: 16.1% vs. 0.0%, p=0.018; 28-day: 25.8% vs. 2.8%, p=0.009; and in-hospital mortality: 35.5% vs. 8.3%, p=0.014). Nevertheless, no significant differences in mortality (intra-SCCU, 28-day or in-hospital) were found comparing patients with septic shock in the tigecycline group versus in the control group.

DISCUSSION

This study exploring variables associated with empirical tigecycline administration for the treatment of secondary peritonitis in SCCUs identified in the multivariate

Table 4 **Species isolated from intraabdominal samples by study group. Data are expressed as n (%) except where indicated.**

	Total (n=121)	Tigecycline (n=54)	Control (n=67)	p value
Patients with positive samples	70 (57.9)	35 (64.8)	35 (52.2)	0.164
Species per sample, median (IQR)	2 (1, 4)	3 (2, 4)	2 (1, 3)	0.001
Enterococcus spp.	34 (28.1)[a]	22 (40.7)	12 (17.9)	0.005
Streptococcus spp.	22 (18.2)	11 (20.4)	11 (16.4)	0.575
S. aureus	4 (3.3)	3 (5.6)	1 (1.5)	0.323
P. aeruginosa	5 (4.1)	2 (3.7)	3 (4.5)	1.000
E. coli[b]	37 (30.6)	18 (33.3)	19 (28.4)	0.464
Klebsiella spp.[c]	8 (6.6)	6 (11.1)	2 (3.0)	0.137
Other Enterobacteria	7 (5.8)	5 (9.3)	2 (3.0)	0.249
Anaerobes	29 (24.0)	7 (13.0)	22 (32.8)	0.011
Candida spp.	13 (10.7)	5 (9.3)	8 (11.9)	0.639

[a]*E. faecium* (n=14), *E. faecalis* (n=11) and *Enterococcus* spp. (n=9); [b]Four ESBL-producer isolates, three in the tigecycline group and 1 in the control group; [c]Two ESBL-producer isolates in the tigecycline group

Table 5 **Outcome by study group.**

	Total (n=121)	Tigecycline (n=54)	Control (n=67)	p value
Length of stay (days), median (IQR)				
SCCU	5.0 (2.0, 10.0)	6.0 (4.0, 14.8)	4.0 (2.0, 8.0)	0.005
In-hospital	19.5 (11.0, 32.0)	27.5 (15.3, 33.8)	15.0 (10.0, 27.3)	0.005
Mortality [n (%)]				
SCCU	14 (11.6)	9 (16.7)	5 (7.5)	0.116
28-day	22 (18.2)	13 (24.1)	9 (13.4)	0.131
In-hospital	30 (24.8)	16 (29.6)	14 (20.9)	0.269

analysis nosocomial origin and colon as source infection site as factors associated with inclusion of tigecycline in antibiotic regimens. These determinants, being more specific, are related to those of a previous analysis showing that main reasons for tigecycline use were the need of broad-spectrum coverage, failure of previous antibacterial therapy and suspicion of resistant pathogens[6].

Increase in tigecycline dosing appears to be an interesting therapeutic option to maximise antibacterial activity especially when facing severe infections with high bacterial load and/or multidrug resistant bacteria[14]. Recent studies in critically ill patients with severe infections have concluded that tigecycline at high doses can be administered without relevant toxicity to improve outcome in patients infected by multidrug resistant pathogens[15-17]. In contrast to these studies including different severe infections, this study evaluated this high-dose exclusively in critically ill patients with cIAIs where multidrug resistant bacteria and high bacterial load should be suspected.

Nosocomial infections represent 30% of all secondary peritonitis, increasing the risk of resistant pathogens and worsening the prognosis[2]. In the present study, the overall percentage of nosocomial infections was similar (39.7%), however, this percentage increased to 55.6% in the tigecycline group, being significantly higher than in controls. Another factor increasing risk of patients is the infection site, with perforations of the biliary system or jejunum producing intermediate bacterial counts and those of the colon origin, high bacterial counts[2]. From this perspective, in the present study patients in the tigecycline group showed significantly higher frequency of colon as source of infection (vs. biliary tract in controls), higher number of species per sample and higher isolation of *Enterococcus* spp. Presence of isolates from this genera has been associated with higher Charlson comorbidity index and presence of chronic obstruction pulmonary disease (COPD) as main comorbidity[5]. In our study, although frequency of COPD was similar in both groups, significantly higher number of patients requiring mechanical ventilation was found in the tigecycline group. In addition, severity (SAPS II and SOFA scores) and percentage of septic shock were significantly higher among patients in the tigecycline group.

Combination antibiotic regimens are preferred in patients with poor risk profiles and higher severity scores[6] as those admitted in SCCU units who require immediate antibiotic therapy (prior to availability of microbiological results). In the published analysis of five observational studies while tigecycline was used in combination in 24% patients in one study not including critically ill patients, combined therapy with tigecycline represented 84% in the Spanish study carried out in the ICU[6]. In the present study, single drug treatment was significantly more frequent in the control group, mainly with carbapenems. Notably, combination therapy in the tigecycline group, in addition to reducing the use of carbapenems, included more frequently an antifungal drug. The presence of *Candida* spp. infections in the ICU has increased in the last 20 years, with 18% of all severe septic infections caused by them and 25% of these cases being invasive intra-abdominal infections[20]. High-risk collectives include patients with postoperative peritonitis[21]. Nevertheless, once available, results of intra-abdominal cultures in the present study did not show differences in *Candida* isolation.

In addition to patient's factors influencing antibiotic election, in secondary peritonitis of nosocomial origin

the presence of multidrug-resistant bacteria and coverage of enterococci should always be considered[1]. Despite the higher recovery of enterococci in the tigecycline group, no differences in multidrug-resistant bacteria from intra-abdominal cultures were found in the present series; however, isolation of resistant bacteria from rectal swabs was significantly higher in the tigecycline group. In addition to clinical scores and development of septic shock, the threat of antimicrobial resistance is one of the major challenges in the management of cIAIs, and insufficient/inadequate antimicrobial regimens have been identified as one of the variables most strongly associated with unfavourable outcomes[9]. In the present study, >50% regimens including tigecycline also included piperacillin/tazobactam covering *P. aeruginosa*. This species is isolated in about 0 to 20% of cIAIs, with great variability among studies[6, 22]. Considering the high selection of critically ill patients in published studies, coverage of this species may be necessary in some institutions[23] despite that its pathogenic role in cIAIs remains to be clarified[6]. Isolation of *P. aeruginosa* in the present study represented 4.1% of all isolates.

In real life, patients with cIAIs are critically ill, suffer from comorbid conditions and have higher disease severity than those treated in clinical trials. SAPS II[24,25] and SOFA[26,27] scores have demonstrated to be good prognostic tools in previous cIAI studies. In the tigecycline group, significantly higher percentage of patients presented severe infection (higher SAPS II and SOFA values), colon as source infection site, nosocomial infection and septic shock. With this imbalance between study groups, it is not surprising that the frequency of wound site infection, length of intra-SCCU and of in-hospital stay were significantly higher in the tigecycline group, and that early mortality (intra-SCCU) was also higher (although not significantly) in this group. Nevertheless, no difference between groups in in-hospital mortality was found. The overall in-hospital mortality was similar to the percentage of non-responders in the previous analysis of five tigecycline non-comparative observational studies (only 2 of them in the ICU)[6].

The present practice-based comparative observational study showed that main reasons for tigecycline inclusion in combined treatment regimens for the treatment of cIAI in critically ill patients were nosocomial origin of cIAI and colon as source infection site. Despite the markedly higher severity of patients in the tigecycline group, no differences in in-hospital mortality were observed. Although the observational non-interventional nature of the study limits our conclusions, the results support the use of high-dose tigecycline in combined regimens for the treatment of cIAIs in critically ill patients.

ACKNOWLEDGEMENTS

Data entry and analysis of this study was supported by Pfizer S.L.U. (Madrid, Spain) that has no role in study design, collection, analysis and interpretation of data, in writing of the report or in the decision to submit the article.

E. Maseda has received payments for lectures from Astellas Pharma, Pfizer and Merck Sharp & Dohme. Maria-Jose Gimenez has received travel grants from Pfizer for ECCMID attendance. The remaining authors have no conflicts of interest.

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