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ARTICLE

Superinfection during treatment of nosocomial infections with tigecycline

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Abstract We performed a retrospective and observational study of 51 patients treated with tigecycline, as the treatment for nosocomial infections due to multidrug-resistant microorganisms, to evaluate the superinfection rate and their etiologies. Superinfections were diagnosed in 12 (23.5%) patients (seven due to *Pseudomonas aeruginosa*, 13.7%) and one patient had *P. aeruginosa* colonization. Five patients with superinfection died (41.6%), three due to superinfections and two to underlying diseases. The superinfection rate observed during tigecycline treatment is higher than that previously reported. *Pseudomonas aeruginosa* is the most frequent agent, being the cause of 58.5% of all superinfections.

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Introduction

Tigecycline has a broad-spectrum in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus* spp., and against most Enterobacteriaceae, including extended-spectrum β-lactamase (ESBL)-producing strains [1]. Tigecycline is also active against *Acinetobacter baumannii*, including multidrug-resistant (MDR) strains [2]. However, *Pseudomonas aeruginosa* is intrinsically resistant, and some species of the genera *Proteus* have reduced susceptibility. Clinical trials did not show higher superinfection rates than comparators [3–5] in patients with tigecycline treatment. However, the lack of activity of tigecycline against *P. aeruginosa* is important because of the fact that it is a relevant nosocomial agent, and it is currently a growing health problem on account of the increase of imipenem-resistant strains [6]. The aim of this study was to evaluate the superinfection rates, including by *P. aeruginosa*, during tigecycline treatment.

Patients and methods

We performed an observational and retrospective study of all adult patients admitted to the University Hospital Virgen del Rocío, Southwest Spain, a 1,251-bed terciary center with two intensive care units (ICU) for adults, who received tigecycline as the treatment for nosocomial infections between November 1, 2007 and October 31, 2008. All

Table 1 Patients with superinfection during the treatment of nosocomial infections with tigecycline

Sex/age	Underlying disease	Previous antibiotics	Infection treated with tigecycline	Tigecycline alone or combination therapy	Clinical cure/ microbial eradication[a]	Duration of treatment with tigecycline	Bacteria causing superinfection. Clinical syndrome	Clinical cure/ microbial eradication[b]	Final Outcome
F/55	Burn 40% TBSA[c] *A. baumannii* VAP[d]	Colistin	*A. baumannii* VAP	Alone	Yes/yes	7 days	*Pseudomonas aeruginosa* Nosocomial pneumonia	Yes/yes	Cure
M/71	Burn 28% TBSA[c] *A. baumannii* VAP[d]	Colistin	*A. baumannii* VAP	Alone	Yes/yes	10 days	*Pseudomonas aeruginosa* Burn infection	Yes/yes	Cure
M/30	Pancreatitis	Piperacillin/ tazobactam	*A. baumannii* intra-abdominal abscess	Alone	Yes/yes	14 days	*Pseudomonas aeruginosa* Intra-abdominal abscess	Yes/yes	Cure
F/23	CT[e] *E. faecium* *E. faecium* surgical site infection	Ampicillin Gentamicin	*E. faecium* surgical site infection	Alone	Yes/yes	8 days	*Pseudomonas aeruginosa* Surgical site infection	Yes/yes	Cure
M/23	CT[e], *A. baumannii* *A. baumannii* pneumonia	Colistin Rifampin	*A. baumannii* pneumonia	Associated to rifampin iv	Yes/yes	8 days	*Pseudomonas aeruginosa* Nosocomial pneumonia	Yes/ yes	Cure
F/56	Cholangiocarcinoma *A. baumannii* intra-abdominal abscess after surgery	Colistin	*A. baumannii* intra-abdominal abscess	Associated to rifampin iv	No/yes	26 days	*Pseudomonas aeruginosa* Intra-abdominal abscess	No/no	Death
M/32	CT[e], *A. baumannii* *A. baumannii* pneumonia	Colistin	*A. baumannii* pneumonia	Associated to rifampin iv	Yes/yes	7 days	*Pseudomonas aeruginosa* Nosocomial pneumonia	No/yes	Death
F/60	CT[e], *A. baumannii* *A. baumannii* pneumonia	Colistin	*A. baumannii* pneumonia	Associated to rifampin iv	Yes/yes	7 days	*Providencia stuartii* Pleural empyema	Yes/yes	Cured
M/72	Duodenal ulcer perforation ESBL-*E. coli* surgical site infection, candidemia	Metronidazole Gentamicin Ertapenem Caspofungin	*A. baumannii* intra-abdominal abscess after surgery	Alone	No/yes	7 days	*Morganella morganii* Intra-abdominal infection	No/no	Death
M/35	CT[e], *A. baumannii* *A. baumannii* surgical site infection	Colistin	*A. baumannii* surgical site infection	Associated to rifampin iv	Yes/yes	12 days	*Enterococcus faecalis* Surgical site infection	Yes/yes	Cured
M/63	Insulinoma surgical intervention	None	*A. baumannii* surgical site infection	Alone	Yes/yes	7 days	*Proteus mirabilis* intra-abdominal infection	Yes/yes	Non-related death
M/71	Stroke *A. baumannii* pneumonia	Colistin	*A. baumannii* pneumonia	Alone	Yes/yes	14 days	*Enterobacter cloacae* Tracheobronchitis	No/no	Non-related death

[a] Respect to infection treated with tigecycline

[b] Respect to superinfection

[c] TBSA: total body surface area

[d] VAP: ventilator-associated pneumonia

[e] CT: cranial trauma

patients received 100 mg of tigecycline as the loading dose, followed by 50 mg every 12 h. The duration of treatments was a decision of the physicians in charge of the patients and was related to the clinical conditions. In each patient, we analyzed all cultures made until hospital discharge or death. Patients without follow up cultures during or after tigecycline treatment and those with prior or concomitant isolation of *P. aeruginosa* at the beginning of the treatment were excluded.

The following data were analyzed: sex, age, underlying diseases, infections, treatments with tigecycline and other concomitant antibiotics, and clinical and microbiological outcomes. Established criteria were used to define clinical infections [4, 5, 7]. We defined colonization and superinfection as the isolation of bacterial strains different to those causing the primary infection, in the absence or presence of the above criteria of infection, respectively, without any other possible cause when the superinfection was diagnosed. Clinical cure was considered as the disappearance of all signs and symptoms attributable to infection after the completion of antibiotic and surgical treatment if necessary, and microbial eradication as negative cultures in the follow up.

Microbial identification and antibiotic susceptibility were performed with the MicroScan system (Siemens, Healthcare, Spain). To determine susceptibility, all microorganisms were cultured on Mueller–Hilton agar plates (Francisco Soria Melguizo, Madrid, Spain). Minimum inhibitory concentration (MIC) breakpoints for tigecycline were determined by the E-test method (AB Biodisk, Solna, Sweden). US FDA-approved guidelines for interpreting tigecycline susceptibility test results for Enterobacteriaceae and *A. baumannii* (susceptible MIC ≤ 2 μg/mL; intermediate MIC > 2 or <8 μg/mL; resistant MIC ≥ 8 μg/mL) were applied in this study [8].

Results

Tigecycline was prescribed as the treatment for nosocomial infections in 51 patients, 23 (45.1%) with hospital-acquired pneumonia (HAP), 15 (29.4%) with complicated intra-abdominal infections (CIAIs), and 13 (25.5%) with skin and soft tissue infections (SSTIs). Sixteen out of 51 tigecycline prescriptions (31.3%) were made in medical and surgical wards and the rest in the ICU. Etiological agents (all susceptible to tigecycline) were as follows: 29 *A. baumannii*

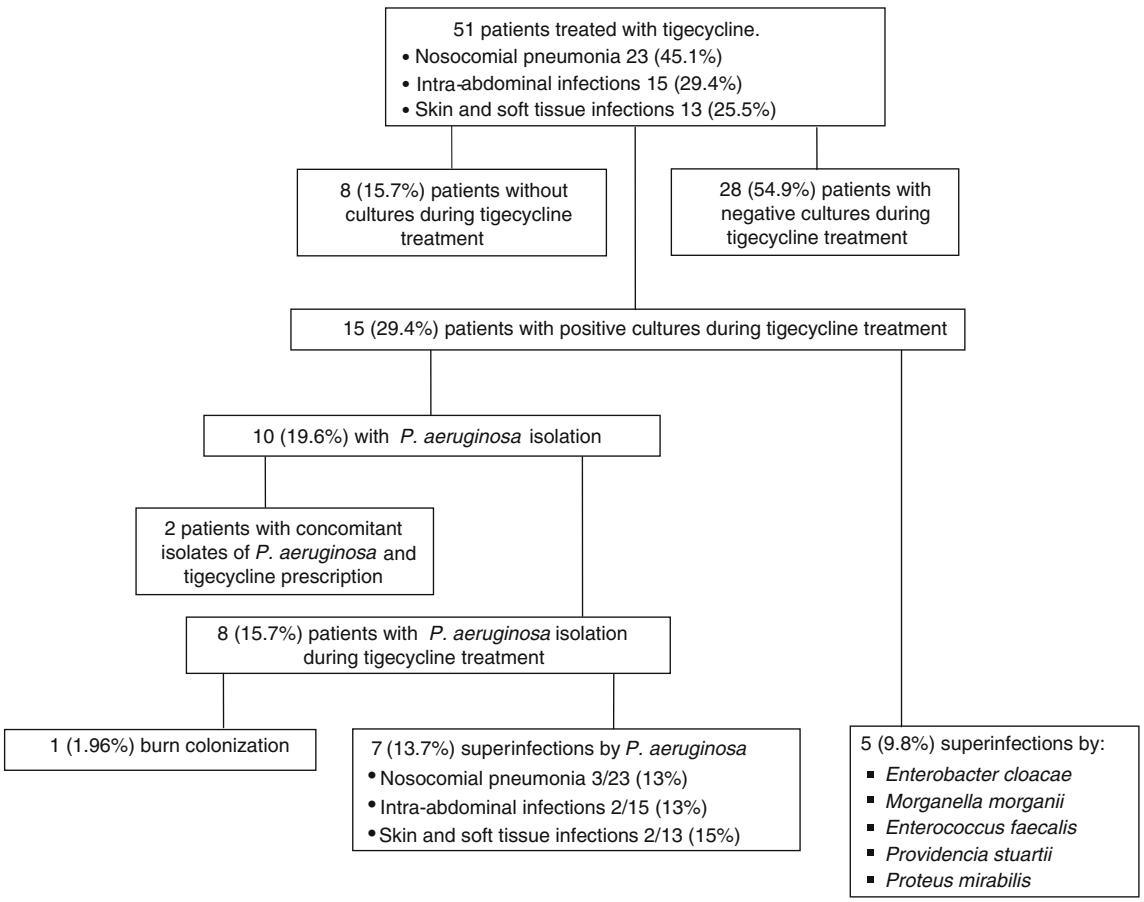

Fig. 1 Superinfection and colonization outcomes of 51 patients treated with tigecicline

(56.8%), 19 (37.2%) Enterobacteriaceae (10 [19.6%] ESBL-producing: six *Escherichia coli* and four *Klebsiella pneumoniae*), and 11 others (21.5%) (8 [15.6%] of them were polymicrobial infection).

Eight patients (15.7%) had no follow up cultures and were excluded from the study. Twenty-eight patients (54.9%) had no positive cultures during tigecycline treatment. Finally, 15 patients (29.4%) had at least one positive culture, with isolates different to those causing the infection, during tigecycline treatment. In these patients, tigecycline was indicated for infections by MDR *A. baumannii* (n=13), *Enterococcus faecium* (n=1), and *Stenotrophomonas maltophilia* (n=1).

P. aeruginosa was isolated in 10 patients (19.6%) during tigecycline treatment. Seven patients (13.7%) had superinfections (3 HAP, 2 CIAIs, and 2 SSTIs) (Table 1) and one had surgical wound colonization. Two patients with polymicrobial infection, including *P. aeruginosa* isolated at the beginning of the treatment, were excluded. The median time elapsed between the prescription of tigecycline and *P. aeruginosa* isolation was 8 days (range 7–26). Five other superinfections (9.8%) were caused by *Proteus mirabilis*, *Morganella morganii*, *Providencia stuartii*, *Enterobacter cloacae*, and *E. faecalis*. These 12 superinfections (Fig. 1) were caused by tigecycline non-susceptible bacteria.

There was no difference between superinfection/colonization rates in the different nosocomial infections treated with tigecycline: HAP (5/23, 21.7%), CIAIs (5/15, 33.3%), and SSTIs (4/13, 30.7%).

Five out of the 12 patients died (41.6%), two due to CIAIs by *P. aeruginosa* and *M. morganii*, one due to nosocomial pneumonia by *P. aeruginosa*, and two due to underlying diseases. In Table 1, the characteristics and outcomes of the 12 patients with superinfections are detailed.

Discussion

In our observation, the superinfection rate during tigecycline treatment was 23.5% (12 of 51). *Pseudomonas aeruginosa* was the most frequent agent, being responsible for 58.3% of superinfections. This rate of superinfections is higher than previously described, in spite of the exclusion of 8 out of 51 patients because of the absence of follow up cultures. In a clinical trial in patients with SSTIs, patients treated with tigecycline showed an incidence of superinfections of 2.4%, with 0.7% being in the arm treated with vancomycin plus aztreonam [3]. Other studies showed superinfection rates ranging from 2.4% [9] to 4.3% [4, 5]. These studies did not specify the etiological agents responsible for causing these superinfections.

We used tigecycline to treat a variety of infections, some not indicated in official FDA and EMEA labeling for tigecycline, such as HAP, but the patients were critically ill and there were no other alternative treatments. Moreover, tigecycline has demonstrated to be effective to treat HAP by MDR *A. baumannii* [10].

Tigecycline is highly effective against most Gram-positive, Gram-negative, and anaerobic bacteria, including MDR strains. *Pseudomonas aeruginosa* is intrinsically resistant [11], and *Proteus* spp., *Klebsiella pneumoniae*, *Providencia* spp., *M. morganii*, *Enterobacter* spp., and *E. coli* may show reduced tigecycline susceptibility. Tigecycline administered in healthy subjects significantly reduced the numbers of enterococci, *E. coli*, lactobacilli, and bifidobacteria, and increased *Candida albicans*, *K. pneumoniae*, and *E. cloacae*, and some patients (7/12) presented colonization by resistant strains to tigecycline on day 8 [12]. Also, an increase in tigecycline MIC during tigecycline treatment against *A. baumannii* and *K. pneumoniae* infections, and bloodstream infections and other infections caused by tigecycline-non-susceptible *A. baumannii* have been observed [13–15].

P. aeruginosa is an emerging health problem due to nosocomial infections caused by carbapenem-resistant strains [6]. The use of ineffective antibiotics against *P. aeruginosa* could increase the risk of colonization or infection. However, clinical trials did not refer superinfections by intrinsically resistant microorganisms [3, 4], like *P. aeruginosa*, as noted in the present study.

In summary, the superinfection rate during treatment with tigecycline may be higher than previously reported. In our knowledge, this is the first study documenting superinfection by *P. aeruginosa* during tigecycline treatment. Considering the potential risk of infection with *P. aeruginosa* and other resistant bacteria, a tight surveillance in the follow up of patients treated with tigecycline must be performed in order to disregard or confirm this potential risk.

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