International Journal of Antimicrobial Agents ■■ (2018) ■■–■■

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

# Differences in the rate of carbapenem-resistant Enterobacteriaceae colonisation or *Clostridium difficile* infection following frontline treatment with tigecycline vs. meropenem for intra-abdominal infections

Michele Bartoletti [a,*], Sara Tedeschi [a], Renato Pascale [a], Luigi Raumer [a], Alberto Enrico Maraolo [b], Giulia Palmiero [b], Fabio Tumietto [a], Francesco Cristini [a], Simone Ambretti [c], Maddalena Giannella [a], Russell Edward Lewis [a], Pierluigi Viale [a]

[a] *Infectious Diseases Unit, Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138, Bologna, Italy*
[b] *Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, via Sergio Pansini 5, 80131, Naples, Italy*
[c] *Operative Unit of Clinical Microbiology, S. Orsola-Malpighi Hospital, Via Massarenti 9, 40138, Bologna, Italy*

ARTICLE INFO

*Article history:*
Received 8 August 2017
Accepted 13 January 2018
Editor: J.-C. Lagier

*Keywords:*
Tigecycline
Intra-abdominal infection
*Clostridium difficile*
Carbapenem-resistant Enterobacteriaceae

ABSTRACT

**Objectives:** We hypothesised that treatment with a tigecycline-based antimicrobial regimen for intra–abdominal infection (IAI) could be associated with lower rates of subsequent carbapenem-resistant Enterobacteriaceae (CRE) colonisation or *Clostridium difficile* infection (CDI) compared with a meropenem-based regimen.

**Methods:** We performed a retrospective, single-centre, matched (1:1) cohort analysis of all patients who received at least 5 days of empirical or targeted tigecycline (TIG)- or meropenem (MER)-based treatment regimens for IAI over a 50-month period. Patients with previous CRE colonisation and CDI were excluded. Risk factors for CRE and CDI were assessed with a Cox regression model that included treatment duration as a time-dependent variable. Thirty-day mortality was assessed with Kaplan-Meier curves.

**Results:** We identified 168 TIG-treated and 168 MER-treated patients. The cumulative incidence rate ratio of CDI was 10-fold lower in TIG-treated vs. MER-treated patients (incidence rate ratio [IRR] 0.10/1000 patient-days, 95%CI 0.002–0.72, P = 0.007), but similar incidence rates were found for CRE colonisation (IRR 1.39/1000 patient-days, 95%CI 0.68–2.78, P = 0.36). In a multivariate Cox regression model, the receipt of a TIG- vs. MER-based regimen was associated with significantly lower rates of CDI (HR 0.07, 95%CI 0.03–0.71, P = 0.02), but not CRE (HR 1.12, 95% CI 0.45–2.83, P = 0.80). All-cause 30-day mortality was similar in the two groups (P = 0.46).

**Conclusion:** TIG-based regimens for IAI were associated with a 10-fold lower incidence of CDI compared with MER-based regimens, but there was no difference in the incidence of CRE colonisation.



## 1. Introduction

With the spread of extended spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae, empirical use of carbapenem-antibiotics for common healthcare-associated infections has increased dramatically in many institutions [1,2]. This increased carbapenem use, in turn, has been associated with higher rates of carbapenem–resistant Enterobacteriaceae (CRE) [3]. Carbapenems are also among the highest-risk group of antibiotics associated with *Clostridium difficile* infection (CDI) [4]. Consequently, carbapenem-sparing regimens are increasingly being promoted in institutions with higher rates of CRE or CDI [5].

Tigecycline is a potential alternative to carbapenems in patients with intra-abdominal infection (IAI) [6]. Tigecycline achieves high concentrations in the bile and gastrointestinal tract that may surpass the minimum inhibitory concentrations (MICs) of most CRE, and has been proposed as an alternative agent for reducing the selection of CRE [7]. Tigecycline treatment may also be associated with a lower rate of CDI. In fact, in animal models of CDI, tigecycline was effective in preventing overgrowth and toxin production by *C. difficile* [8] and anecdotal evidence indicates that tigecycline may be effective for the treatment of CDI in humans [9].

* Corresponding author. Infectious Diseases Unit, S. Orsola-Malpighi Hospital, Via Massarenti 9, 40138, Bologna, Italy.
*E-mail address:* michele.bartoletti4@unibo.it (M. Bartoletti).

https://doi.org/10.1016/j.ijantimicag.2018.01.010
0924-8579/

The aim of our study was to compare the cumulative 90-day risk for colonisation with CRE, and/or development of CDI in matched patients receiving tigecycline- vs. meropenem-based regimens for IAI. As a secondary endpoint, we compared the all-cause 30-day mortality in patients treated with meropenem-based regimens and tigecycline-based regimens.

## 2. Methods

### 2.1. Study design

We performed a retrospective, single-centre, cohort study of patients receiving tigecycline-based regimens, compared with patients treated with meropenem-based regimens, as empirical and/or definitive treatment for IAI from October 2011 to October 2015.

The study site was S. Orsola Malpighi Hospital, a 1400-bed tertiary teaching hospital. The study was approved by the local Institutional Review Board.

### 2.2. Population

All consecutive patients receiving tigecycline as empirical or targeted treatment alone or in combination with other antibiotics for IAI for at least 5 days were screened from January 2011 to October 2015 using pharmacy records for inclusion in the study. The inclusion criteria were: i) age over 18 years; ii) minimum follow-up of 3 months (for survived patients); and iii) rectal swab performed within 3 months of therapy (only for CRE evaluation). Patients were excluded from the analysis if they had any of the following: i) previous CRE colonisation; ii) previous episode of CDI; iii) had previously received gentamicin, colistin or CDI-active therapy (i.e. metronidazole, oral vancomycin); iv) had no evidence of IAI; v) received combination therapy of tigecycline plus carbapenems; or vi) died within 5 days of the start of the tigecycline- or meropenem-based regimen.

The cohort of patients meeting inclusion criteria and treated with a tigecycline-based regimen (TIG group) were matched (1:1) with a cohort of similar patients meeting the study criteria who received a meropenem-based regimen (MER group) for at least 5 days. Patients in each treatment group were matched with respect to: i) admission to the same hospital ward in the same month and year; ii) length of in-hospital stay (range ± 5 days); iii) duration of antibiotic administration; iv) acute physiology and chronic health evaluation (APACHE) II score at time of infection onset (range ± 2); v) age (range ± 5 years); and vi) immunocompromising condition.

### 2.3. Definitions

IAI was defined as new onset of fever and/or abdominal pain plus new or worsening radiological images of abscess, bowel perforation, appendicitis, diverticulitis and post–surgical effusion with or without peritonitis. Different subtypes of IAI were defined as previously described [10]. IAI was classified as community-acquired or healthcare–associated. Healthcare-associated IAI was defined as an infection that developed at least 48 h after hospital admission or in patients with post-operative IAI [11].

CDI was diagnosed in patients who had unformed stools associated with a positive *C. difficile* glutamate dehydrogenase (GDH) antigen plus positive toxin A/B. Comorbidities were identified according to the Charlson comorbidity score. A patient was considered to have an immunocompromising condition if the following were present: neutropenia (<500 cells/mm$^3$); haematopoietic stem cell and solid organ transplantation; receipt of steroids (dose ≥0.3 mg/kg/day of prednisone equivalent for >3 weeks); or treatment with other recognised T-cell immunosuppressing agents, such as calcineurin inhibitors, TNF-α blockers, monoclonal antibodies, or nucleoside analogues, in the previous 90 days.

### 2.4. Patient management and data collection

Every prescription of tigecycline and meropenem was reviewed by an infectious disease specialist and confirmed if deemed appropriate in accordance with the antimicrobial stewardship programme. Every case of hospital-onset diarrhoea was screened for CDI. In case of discharge before the pre-established 90-day follow-up, every emergency room access and any follow-up visit were reviewed to collect additional cases of home-onset diarrhoea. Every patient was screened for CRE with rectal swab at hospital admission and once per week until discharge. After discharge the rectal swab was performed during an outpatient visit or at admission, in case of re-admission. Contact precautions were applied for all cases of CRE colonisation and CDI [12,13]. Data were collected using a standardised form. Variables included: patient demographics, date and ward of hospitalisation, underlying diseases and concomitant treatments. IAI data were also collected, including the date of diagnosis, epidemiological classification, causative pathogens and cause. Infection severity and underlying condition were assessed at the time of IAI diagnosis with Bone score and APACHE II score, respectively. We also recorded data of source control of the infection, ICU admission and in-hospital or 30-day mortality. To minimise the risk of underdiagnosed CRE or CDI after discharge, we also reviewed all cases of CRE rectal colonisation and CDI from centralised microbiology records for the entire province of Bologna, an urban area with more than 1 million inhabitants.

### 2.5. Microbiology

*Clostridium difficile* GDH antigen was detected with ELISA Enzyme immunoassay (Wampole *C. difficile* Check-Techlab®) and positive toxin A/B was detected with immunoenzymatic membrane test (Wampole Tox A/B quick check Techlab®).

Blood cultures and intraoperative sampling were performed according to routine clinical care. Identification and susceptibility test of the isolated pathogens were carried out using the Vitek 2 system (bioMérieux Italia). Antibiotic MICs were classified according to EUCAST breakpoints.

Rectal swabs were inoculated on to a chromogenic plate containing a carbapenem drug as selective agent. Bacterial growth was evaluated after overnight incubation at 35 °C, (Biomerieux, France). Furthermore, carbapenemase production was confirmed by disc–diffusion synergy test (RoscoDiagnostica, Denmark).

### 2.6. Statistical analysis

Categorical variables were presented as absolute numbers and their relative frequencies and were compared using the chi-square test. Quantitative variables were presented as mean and standard deviation (SD) if normally distributed or as median and interquartile range (IQR) if non-normally distributed.

The association of non-antibiotic related demographic or clinical variables with the risk for CRE colonisation or CDI were analysed by Fischer's exact test for categorical independent variables, or Wilcoxon signed-rank test for continuous variables. Candidate independent variables ($\alpha = 0.1$) were then entered into a Cox-proportional hazard regression model to identify independent risk factors affecting the cumulative rate of CRE colonisation or CDI risk within 90 days in the two study cohorts. The time period of patient treatment (month, year) was included in the model to account for possible infection outbreaks. The proportional hazards assumption was tested graphically by examining scaled Schoenfeld residuals from the model vs. time, and overall model fit evaluated using the

Please cite this article in press as: Michele Bartoletti, et al., Differences in the rate of carbapenem-resistant Enterobacteriaceae colonisation or *Clostridium difficile* infection following frontline treatment with tigecycline vs. meropenem for intra-abdominal infections, International Journal of Antimicrobial Agents (2018), doi: 10.1016/j.ijantimicag.2018.01.010