European Journal of Clinical Pharmacology (2021) 77:197–205
https://doi.org/10.1007/s00228-020-02998-7

PHARMACOKINETICS AND DISPOSITION

Monte Carlo simulation evaluation of tigecycline dosing for bacteria with raised minimum inhibitory concentrations in non-critically ill adults

Brianna Kispal[1,2] · Sandra A. N. Walker[1,3]

Received: 17 July 2020 / Accepted: 14 September 2020 / Published online: 25 September 2020

Abstract

Purpose Tigecycline is one of few antibiotics active against multidrug-resistant bacteria; however, the assessment of dosing strategies to optimize its activity is needed. The purpose was to use Monte Carlo Simulation (MCS) to determine if safe tigecycline dosing options attaining breakpoints for pharmacokinetic/pharmacodynamic (PK-PD) targets in non-critically ill adults could be identified.

Methods Publications that evaluated tigecycline dosing regimens and provided mean PK variables of interest (minimum 2 of: elimination rate constant or half-life and volume of distribution or clearance), with SDs, were included. Weighted mean (±SDs) for each PK parameter were determined. Food and Drug Administration minimum inhibitory concentration (MIC) tigecycline breakpoints for susceptible (MIC ≤ 2 μg/mL), intermediate (MIC 4 μg/mL), and resistant (MIC ≥ 8 μg/mL) *Enterobacteriaceae* were used. MCS probability distributions for PK-PD target attainment of AUC for total tigecycline plasma concentration from 0 to 24 h following an intravenous dose ($AUC_{total,\ 0\text{-}24h}$) to MIC ratios of ≥ 18, 7, and 4.5 were generated, with success defined as ≥ 80% probability of target attainment at a given MIC.

Results Ten studies ($n = 442$) were eligible. Tigecycline 150 mg IV q12h for ward patients with resistant bacteria up to a MIC of 0.48, 1, and 2 μg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 18, 7, and 4.5, respectively, may be appropriate.

Conclusion Bacterial infections with tigecycline MICs ≥ 0.48–2 μg/mL, depending on $AUC_{total,\ 0\text{-}24h}$/MIC target, may require treatment with alternate antibiotics due to target attainment failure.

Keywords Tigecycline · Monte Carlo simulation · Resistant gram-negative bacteria · Non-critically ill patients · Pharmacokinetic(s) · Pharmacodynamic(s)

Introduction

Worldwide, over 700,000 patients die annually from infections caused by multidrug resistant (MDR) pathogens (resistance to 3 or more potentially useful antibiotics), with millions more suffering from serious complications [1]. By 2050, an estimated 10 million patients will die annually due to antimicrobial resistance [2], a number which will surpass deaths due to cancer, diabetes, and automobile accidents [1]. The most common resistant pathogens are *Enterococcus faecium*, *Staphylococcus aureus*, *Clostridium difficile*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae species* [3–5]. Several global strategies have been developed to combat the concerning trend of antimicrobial resistance, including increased epidemiological surveillance, appropriate antimicrobial use in human and animals, enhanced infection prevention, development of new therapies, and optimizing dose regimens using patient population pharmacokinetics and microbial pharmacodynamics [1].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-020-02998-7) contains supplementary material, which is available to authorized users.

✉ Sandra A. N. Walker
sandra.walker@sunnybrook.ca

Brianna Kispal
brianna.kispal@mail.utoronto.ca

[1] Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College St, Toronto, Ontario M5S 3M2, Canada

[2] Present address: Department of Pharmacy, Kingston General Hospital, 76 Stuart St, Kingston, Ontario K7L 2V7, Canada

[3] Department of Pharmacy Bayview Campus, Sunnybrook Health Sciences Center (SHSC), 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada

Clinicians are often confronted with the challenge of appropriately choosing and dosing antibiotics for extensive drug-resistant pathogens based on limited clinical data and/or significant toxic effects while trying to meet the pharmacokinetic/pharmacodynamic (PK-PD) targets that maximize bacterial killing and clinical cure [1, 6]. Monte Carlo simulation (MCS) is a recognized method for evaluating the probability of success with different antibiotic dosing strategies, where known PK-PD targets associated with improved clinical and microbiological outcomes are input as the surrogate marker for success [6].

Increased resistance to currently available antibiotics forces clinicians to treat highly resistant infections with relatively ineffective and/or toxic second-line agents, such as tigecycline or polymyxins [7, 8]. Tigecycline has been approved to treat various infections, including complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired pneumonia (CAP). Tigecycline is a bacteriostatic agent that exhibits time-dependent killing, where the ratio of the area under the concentration-time curve for total tigecycline concentration from 0 to 24 h ($AUC_{total,\ 0\text{-}24h}$) to minimum inhibitory concentration (MIC) ($AUC_{total,\ 0\text{-}24h}$ /MIC) is most predictive of clinical and microbiological cure [9]. The $AUC_{total,\ 0\text{-}24h}$ /MIC (or corresponding $AUC_{free,\ 0\text{-}24h}$ /MIC) targets for tigecycline vary depending on the type of infection, skin infections (≥ 17.9), intra-abdominal infections (≥ 6.96), and hospital-acquired pneumonia (HAP) (≥ 4.5 or with a free fraction of 0.2, area under the concentration-time curve for free tigecycline concentration from 0 to 24 h ($fAUC_{0\text{-}24h}$)/MIC ≥ 0.9) [9–11].

Tigecycline has activity against a broad range of antibiotic-susceptible and resistant gram-positive bacteria (GPB), anaerobes, atypical bacteria, and MDR gram-negative bacteria (GNB). It is one of the few available antibiotics with antimicrobial activity against MDR GNB; however, there are limitations with its use [12–17] and resistance rates as high as 50% have been reported [7]. Therefore, tigecycline is by no means an optimal antibiotic. Tigecycline is one of the few antibiotic alternatives for MDR bacteria; however, assessment of dosing strategies to optimize its antibiotic activity is needed.

Acinetobacter baumannii is one of the critical priority bacteria identified by the World Health Organization for which optimal antibiotic therapy is lacking and tigecycline may be an option for treatment [18]. For this reason, the tigecycline MIC profile for this species was selected in this study as the prototype to reflect MDR GNB susceptibility. Ward patients with no renal or hepatic impairment were selected for study, since this was the only patient population for which a reasonable number of tigecycline PK-PD studies have been published to allow determination of more robust weighted pharmacokinetic mean values to input into MCSs (Fig. 1).

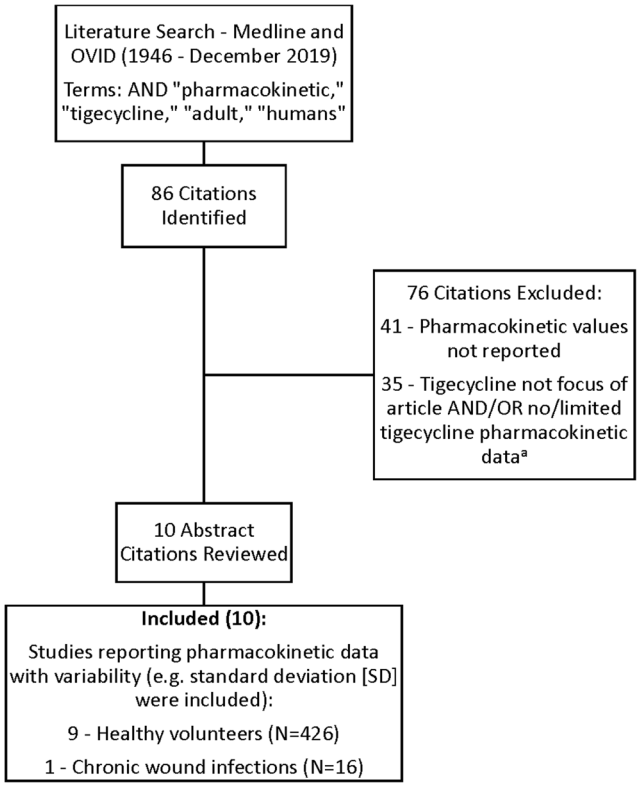

Fig. 1 Study Selection. [a]Tigecycline pharmacokinetic studies that were excluded because they did not contain a minimum of 2 required pharmacokinetic values to perform Monte Carlo simulations: healthy patients ($n = 3$), pneumonia ($n = 2$), liver impairment ($n = 2$), critically ill ($n = 1$), obesity ($n = 1$), intra-abdominal infection and skin and soft tissue infection ($n = 1$), skin and soft tissue infection ($n = 1$), and acute myeloid leukemia ($n = 1$); no pharmacokinetic studies in patient populations other than adult normal volunteer and ward patients who were not on any dialysis mode and did not have end-stage renal disease (ESRD) or hepatic dysfunction contained the required pharmacokinetic data

The objective of this study was to use MCS to evaluate different potential tigecycline dosing strategies to determine if safe dosing options could be identified that would attain practical numerical breakpoints for the tigecycline PK-PD targets ($AUC_{total,\ 0\text{-}24h}$ /MIC ≥ 18, 7, or 4.5) in adult normal volunteer and ward patients who were not on any dialysis mode and did not have end-stage renal disease (ESRD) or hepatic dysfunction.

Methods

Data collection

A literature search of Medline (Ovid; 1946 – December 2019) was conducted using the terms "tigecycline," "pharmacokinetic," "adult," and "human" to identify tigecycline

pharmacokinetic (PK) and pharmacodynamic (PD) parameters (Fig. 1). Studies were included if they evaluated clinically relevant tigecycline dosing regimens and provided mean PK variables of interest (at minimum 2 of: elimination rate constant (k^{-1}) or half-life ($t_{1/2}$) and volume of distribution (V_d) or clearance (CL)), with corresponding standard deviations (SD)). Of 86 identified studies, 9 studies in adult healthy volunteers ($n = 426$) [15, 16, 19–25] and one study in adult patients with chronic wound infection ($n = 16$) [26] provided relevant data for study inclusion (Fig. 1). Study characteristics and steady-state mean pharmacokinetic data (k^{-1}, $t_{1/2}$, V_d, CL, and $AUC_{total,\ 0\text{-}24h}$), along with SD around the values, were extracted from eligible studies into a Microsoft Excel 2010 Workbook (Appendix A), and weighted mean and SDs for each parameter were determined.

Data analysis

Since there are no Clinical and Laboratory Standards Institute (CLSI) *Acinetobacter spp.* MIC breakpoints for tigecycline [27], CLSI recommends that the Food and Drug Administration (FDA) [17, 28] breakpoints for susceptible (MIC ≤ 2 μg/mL), intermediate (MIC 4 μg/mL), and resistant (MIC ≥ 8 μg/mL) *Enterobacteriaceae* be used. Therefore, these were the MIC breakpoints used in this study. Institutional *Acinetobacter spp.* MICs at Sunnybrook Health Sciences Centre (SHSC) were not available at the time of the study for tigecycline; therefore, the percent of tigecycline resistant isolates at the study hospital could not be determined.

The weighted mean PK parameters (k^{-1}, V_d (L/kg) and patient weight (kg)) from the eligible studies and a range of MICs were input to perform MCSs (Crystal Ball v11.1.2.4.000). MCS probability distributions (1 million iterations) for PK-PD target attainments of $AUC_{total,\ 0\text{-}24h}$/MIC ratios of ≥ 18, 7, and 4.5 and the number of times the steady-state concentration (Css) was above the MIC were generated for several tigecycline dosing strategies. The MCS inputs were a log-normal distribution for the weighted means of the one compartment model tigecycline $k^{-1} \pm SD$ and $V_d \pm SD$, a normal distribution of the weighted mean ± SD for patient weight and MIC inputs ranging from 0.06 to 18 μg/mL (0.06 μg/mL, 0.12 μg/mL, 0.24 μg/mL, 0.48 μg/mL, 0.96 μg/mL, 1 μg/mL, 2 μg/mL, 4 μg/mL, 6 μg/mL, 8 μg/mL, 10 μg/mL, 12 μg/mL, 14 μg/mL, 16 μg/mL, and 18 μg/mL). Using these inputs, MCS probability distributions for the PK-PD targets were determined for intermittent infusion dosing regimens of 50 mg IV q12h, 75 mg IV q12h, 100 mg IV q12h, 125 mg IV q12h, and 150 mg IV q12h infused over 0.5 h and continuous infusion dosing regimens of 100 mg and 300 mg IV q24h infused over 24 h. The corresponding MCS probability of target attainment was determined for each aforementioned MIC value with each dosing regimen. A potentially successful regimen was defined as one in which the probability of attaining the target $AUC_{total,\ 0\text{-}24h}$/MIC was at least 80% at a given MIC for ward patients who were not on any dialysis mode and did not have ESRD or hepatic dysfunction.

Results

Pharmacokinetic data

Patient population-specific weighted means and SDs were determined from all studies in normal volunteer and ward patients who were not on any dialysis mode and did not have

Table 1 Summarized weighted pharmacokinetic parameters

Parameter	Healthy subjects ($N = 442$, # studies = 10)
Patient weight kg ($n = 199$)	80.37 ± 7.11
Elimination rate constant (k) h^{-1} ($n = 397$)	0.0296 ± 0.0150
Volume of distribution (V_d) L/kg ($n = 307$)	8.70 ± 3.44
Clearance (CL) L/h/kg (n = 307)	0.29 ± 0.06
Biliary Excretion (%) ($n = 12$)	58.60 ± 0.04
Urinary Excretion (%) ($n = 44$)	20.25 ± 0.03
Pharmacokinetic parameters for multiple dose tigecycline 50 mg iv q12h ($N = 171$, # studies = 6) [a]	
Peak concentration ($C_{max,ss}$) mg/L ($n = 163$)	3.40 ± 5.61
Trough concentration ($C_{min,ss}$) mg/L ($n = 60$)	3.25 ± 3.15
Peak time (T_{max}) h ($n = 110$)	2.46 ± 2.25
Mean Area Under the Concentration Curve ($AUC_{total,\ 0\text{-}24h}$) mg*h/L ($n = 144$)	59.77 ± 106.83

a: Data reflect total plasma or serum concentrations

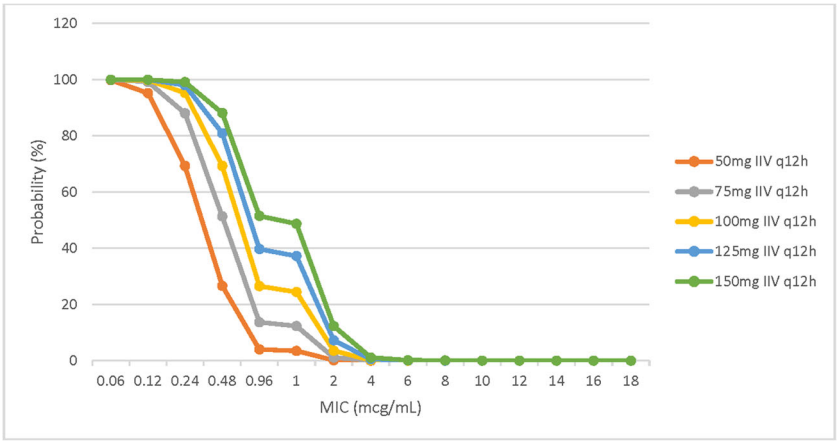

Fig. 2 Probability of $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of at least 18 relative to MIC with a variety of Tigecycline intermittent infusion dosing regimens. $AUC_{total,\ 0\text{-}24h}$, area under the total tigecycline concentration time profile from 0 to 24 h, IIV, intermittent infusion over 0.5 h, MIC, minimum inhibitory concentration

ESRD or hepatic dysfunction ($n = 442$, total of 10 studies) (Table 1). Weighted means and SDs for dose-dependent PK parameters (i.e. steady state peak and trough concentrations, time for peak concentration, and $AUC_{total,\ 0\text{-}24h}$) are also detailed in Table 1 for 50 mg IV q12h dosing ($n = 171$, total of 6 studies). All included studies provided only one compartment model pharmacokinetic data.

Monte Carlo simulation analyses

The probability of attaining a target $AUC_{total,\ 0\text{-}24h}$/MIC relative to a variety of MICs with different tigecycline intermittent infusion dosage regimens is shown for an $AUC_{total,\ 0\text{-}24h}$/MIC of 18 (Fig. 2), 7 (Fig. 3), and 4.5 (Fig. 4). All dosage regimens attained all three $AUC_{total,\ 0\text{-}24h}$/MIC targets up to a MIC of 0.12 μg/mL. Intermittent infusion dosing of 125 mg and 150 mg IV q12h both enabled an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of ≥ 18 with over 80% probability up to a MIC of 0.48 μg/mL (Fig. 2). When the $AUC_{total,\ 0\text{-}24h}$/MIC target was dropped to ≥ 7, the intermittent infusion dosing regimens of 100 mg, 125 mg, and 150 mg IV q12h achieved a ≥ 80% probability of target attainment up to a MIC of 1 μg/mL. When the $AUC_{total,\ 0\text{-}24h}$/MIC target was 4.5, 150 mg IV q12h achieved a ≥ 80% probability of target attainment up to a MIC of 2 μg/mL.

MCS of continuous infusion dosing regimens of 100 mg IV q24h and 300 mg IV q24h infused over 24 h demonstrated that these regimens were able to attain at least a concentration equal to the MIC with a probability of ≥ 80% up to a MIC of 0.12 μg/mL and 0.24 μg/mL, respectively (Fig. 5). Figure 6 and Figure 7 show the probability of attaining a Css of 2 and 3 times above the MIC, respectively, with dosing of 100 mg and 300 mg IV q24h infused over 24 h at various MIC thresholds.

Discussion

Using a target probability of success of ≥ 80%, this MCS study supports the use of intermittent infusion tigecycline

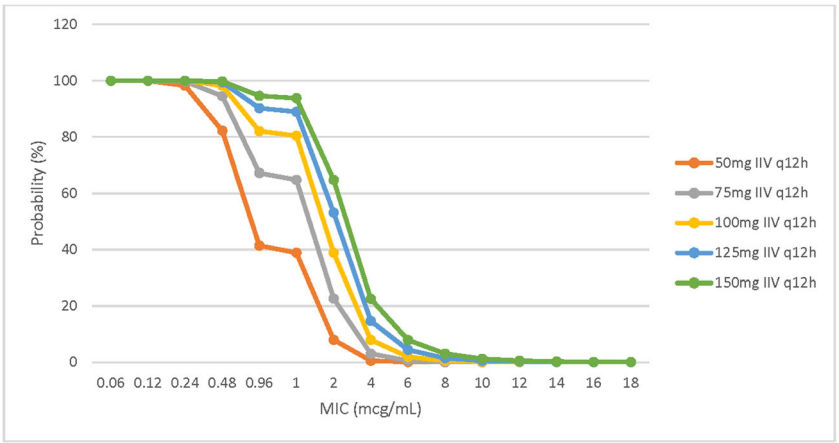

Fig. 3 Probability of $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of at least 7 relative to MIC with a variety of Tigecycline intermittent infusion dosing regimens. $AUC_{total,\ 0\text{-}24h}$, area under the total tigecycline concentration time profile from 0 to 24 h, IIV, intermittent infusion over 0.5 h, MIC, minimum inhibitory concentration

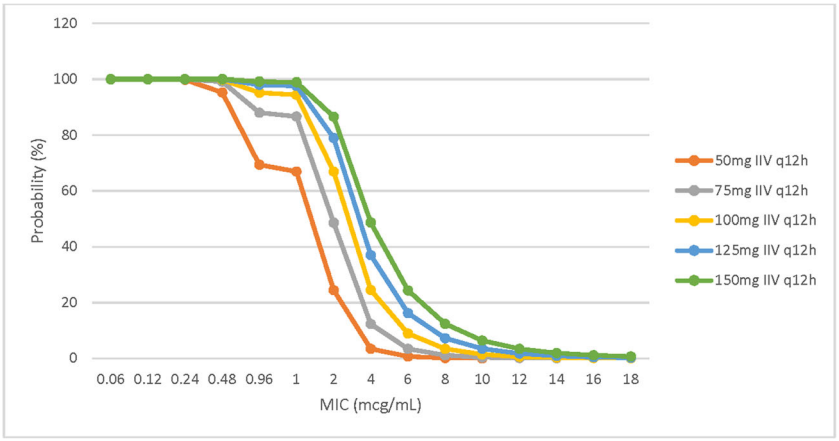

Fig. 4 Probability of $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of at least 4.5 relative to MIC with a variety of Tigecycline intermittent infusion dosing regimens. $AUC_{total,\ 0\text{-}24h}$, area under the total tigecycline concentration time profile from 0 to 24 h, IIV, intermittent infusion over 0.5 h, MIC, minimum inhibitory concentration

150 mg IV q12h for ward patients with resistant GNB up to a MIC of 0.48 μg/mL, 1 μg/mL, and 2 μg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 18, 7, and 4.5, respectively, in adult normal volunteer and ward patients. Continuous infusion dosage regimens were explored as an alternative to intermittent dosing to see if the $AUC_{total,\ 0\text{-}24h}$/MIC targets could be achieved at higher MIC values. Unfortunately, continuous infusion tigecycline 100 mg and 300 mg IV q24h only achieved a Css to just meet a MIC of 0.12 μg/mL and 0.24 μg/mL, respectively. Therefore, continuous infusion tigecycline does not provide any advantage in achieving necessary concentrations for higher MICs. In addition, tigecycline is only stable for 6h at room temperature in the vial and is relatively unstable after reconstitution, both of which make the use of continuous infusion tigecycline challenging [12].

Studies have demonstrated that the theoretical tigecycline MIC breakpoint increases with increasing tigecycline dose [9, 10, 29]. Ni et al. [29] observed that with a target of $fAUC_{0\text{-}24h}$/MIC > 0.90 (equivalent to $AUC_{total,\ 0\text{-}24h}$/MIC > 4.5), the probability of target attainment with tigecycline 50 mg IV q12h was > 99% at a MIC of 0.5 μg/mL and decreased to < 10% at a MIC of 2 μg/mL. At the PK/PD target of $fAUC_{0\text{-}24h}$/MIC > 0.90 (equivalent to $AUC_{total,\ 0\text{-}24h}$/MIC > 4.5), we similarly found that the probability of target attainment with tigecycline 50 mg IV q12h was > 95% up to a MIC of 0.5 μg/mL and decreased to < 25% at a MIC of 2 μg/mL (Fig. 4). Xie et al. [9] assessed a range of MIC breakpoints (0.004–16 μg/mL) and found that the target attainment was $AUC_{total,\ 0\text{-}24h}$/MIC ≥ 18, tigecycline achieved >99% attainment with both 50 mg and 100 mg IV q12h at a MIC of ≤ 0.25 μg/mL that decreased to 0% and 67.98%, respectively, for a MIC of 0.5 mg/L. When the target attainment was $AUC_{total,\ 0\text{-}24h}$/MIC of 7, while both tigecycline 50 mg IV q12h and 100 mg IV q12h were able to achieve 100% attainment at a MIC of ≤ 0.5 μg/mL, target attainment decreased to 96.6% and 12.93%, respectively, for tigecycline 100 mg IV q12h and 50 mg IV q12h for a MIC of 1 μg/mL and 0% target attainment with both regimens for a MIC ≥ 2 μg/mL. This study [9] used the same $AUC_{total,\ 0\text{-}24h}$/MIC targets and MIC breakpoints as we explored. Similarly, we found that tigecycline 100 mg IV q12h at a MIC of 0.48 μg/mL only had a 69% probability of target attainment for an $AUC_{total,\ 0\text{-}24h}$/MIC

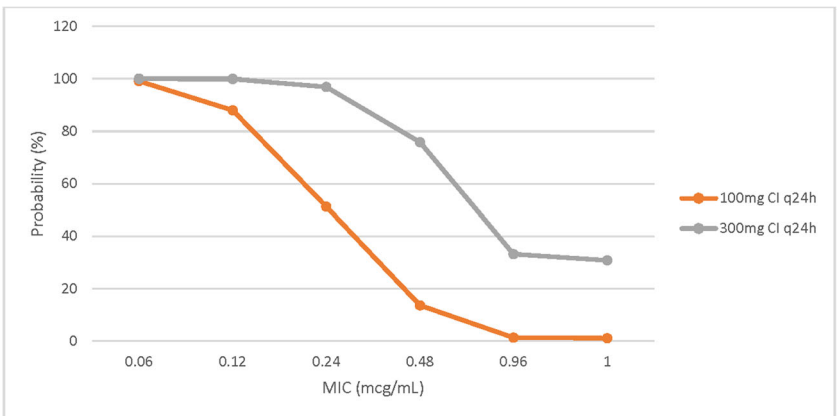

Fig. 5 Probability the Css is at least equal to the MIC with continuous infusion dosing. *CI* continuous infusion without a loading dose, *Css* steady-state concentration, *MIC* minimum inhibitory concentration

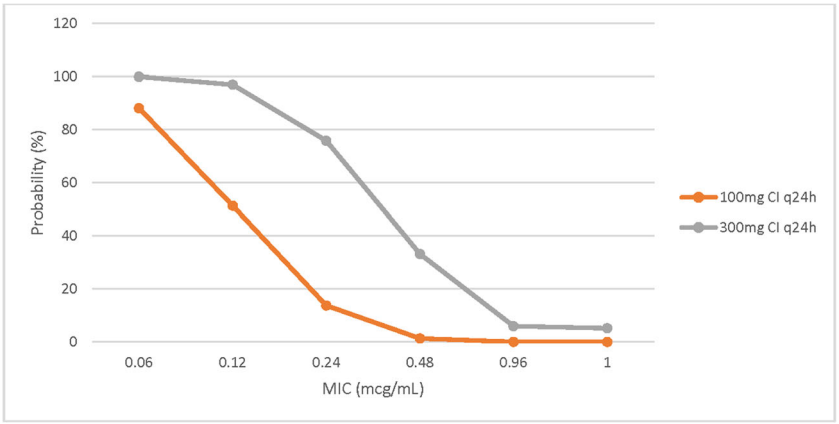

Fig. 6 Probability the C_{ss} is 2 times above the MIC with continuous infusion dosing. *CI* continuous infusion without a loading dose, *Css* steady-state concentration, *MIC* minimum inhibitory concentration

of 18. Our study examined higher tigecycline dosage regimens than Xie et al. [9], enabling provision of PK-PD target attainment data for other tigecycline dosing regimens at higher MICs. In another study by Xie et al. [10], it was observed that tigecycline 150 mg q12h, tigecycline was able to achieve 96.6% target attainment of $AUC_{total,\ 0\text{-}24h}$ /MIC of 7 at a MIC of 4 μg/mL. They recommended the standard dose of tigecycline 50 mg IV q12h as this was able to achieve 97.3% target attainment of $AUC_{total,\ 0\text{-}24h}$ /MIC of 4.5. When the target was an $AUC_{total,\ 0\text{-}24h}$ /MIC of 18, > 90% target attainment was achieved with tigecycline 200 mg IV q12h, 100 mg IV q12h, and 50 mg IV q12h for MICs of 2, 1, and 0.5 μg/mL, respectively. Patients in this study were critically ill patients with severe infections [10]. When using an $AUC_{total,\ 0\text{-}24h}$/MIC attainment of 18, and a dosing regimen of tigecycline 150 mg IV q12h, Xie et al. [10] demonstrated that tigecycline was effective up to a MIC of 4 μg/mL. This was different from our results, which demonstrated that when using an $AUC_{total,\ 0\text{-}24h}$/MIC target of 18, tigecycline 150 mg IV q12h was only effective up to a MIC of 0.48 μg/mL in non-critically ill patients. Of note, Xie et al. [10] also observed that target attainment was significantly lower for obese patients. The patients had a mean weight of 69.1 kg in the study by Xie et al. [10], whereas the patients in our study had a mean weight of 80.37 kg. The differences in patient weight and population (non-critically ill vs critically ill) between our study and that of Xie et al. [10] likely account for the differences in target attainment with the different tigecycline dosing regimens evaluated.

As the dose of tigecycline increased, the theoretical MIC breakpoint for which tigecycline treatment is effective improved. Although increasing the dose of tigecycline would likely increase the success of the regimen, there are gastrointestinal dose-limiting side effects that prevent increasing the dose beyond 300 mg/day, even with the use of an anti-emetic, such as ondansetron [14–16]. This was a crucial factor when determining the maximal tigecycline dosing evaluated in this study.

The FDA tigecycline susceptibility breakpoint against *Enterobacteriaceae* is a MIC ≤ 2 μg/mL. However, the dosage regimens examined in this study only met the $AUC_{total,\ 0\text{-}24h}$/MIC target of ≥ 18 up to a MIC of 0.48 μg/mL, which is significantly lower than the FDA breakpoint. The failure to meet the PK-PD target for tigecycline at safe and tolerated dosing regimens up to 150 mg iv q12h in our MCS study

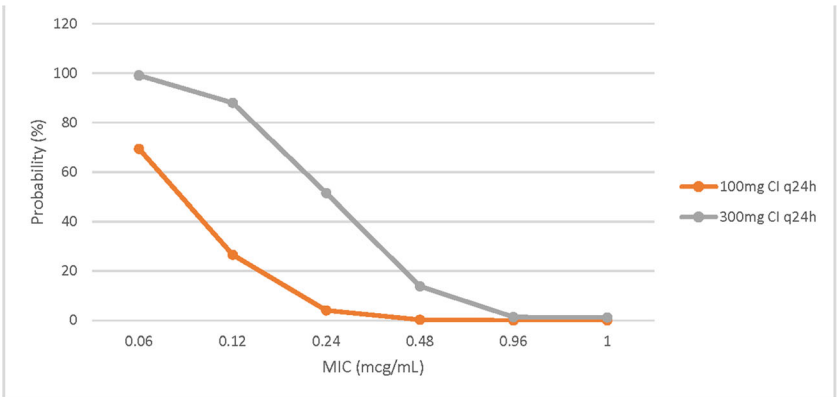

Fig. 7 Probability the C_{ss} is 3 times above the MIC with continuous infusion dosing. *CI* continuous infusion without a loading dose, *Css* steady-state concentration, *MIC* minimum inhibitory concentration

may provide evidence of limited clinical success against pathogens with MICs above 0.48 μg/mL.

Although no clinical data for tigecycline MICs against *Acinetobacter spp.* at SHSC were available at the time of the study, a North American study [30] showed that the prevalence of *Acinetobacter spp.* in North America is still low and that tigecycline-resistant MIC breakpoints are rarely encountered. Nicolau et al. [30] identified 17 patients with intra-abdominal infections due to *A. baumannii*, with tigecycline MICs ranging from ≤ 0.06 to 2 μg/mL; no isolates had a MIC ≥ 2 μg/mL and only 2 of 17 (11.8%) patients had a MIC of 2 μg/mL. Given that IAIs need the highest target $AUC_{total,\ 0\text{-}24h}$/MIC attainment value of 18, the fact that no MICs were ≥ 2 μg/mL is encouraging for the use of tigecycline in North America, for at least the near future.

This study used the largest available dataset of tigecycline PK values, which was that of normal, healthy patients. Although other tigecycline MCS studies have been published [9, 10, 31–34], they were completed in different populations or in relation to different bacteria and used PK values that were obtained from a single published study. This study used weighted PK parameters obtained from the inclusion of 10 eligible studies. Given that the study excluded other patient populations (e.g., critically ill and burn patients), the results of the study may not be generalizable to other patient populations. Selection of a single standard tigecycline dosing regimen to optimize PK-PD target attainment is not possible for all of its therapeutic indications, given the broad range of $AUC_{total,\ 0\text{-}24h}$/MIC target values for different types of infection. Although the sample size was large ($n = 442$), interpatient variability in the pharmacokinetic values existed, which may increase the risk of error and variability in the weighted PK values that were established for adult ward patients lacking renal or hepatic dysfunction. No data were available for tigecycline MICs for *Enterobacteriaceae* or *Acinetobacter spp.* at SHSC; therefore, North American data were relied on to estimate encountered *Acinetobacter spp.* at our hospital. However, we modeled a large range of MICs and provided data for the probability of target attainment with different dosing regimens at specific MICs. Therefore, if the microbial MIC distribution is known, hospitals could use the data provided in this study to identify the probability of target attainment with a given dose of tigecycline. Finally, these results assume that you must meet the target $AUC_{total,\ 0\text{-}24h}$/MIC attainment value for clinical cure or microbiological eradication and does not account for alternative factors or interventions that may influence patient outcomes, such as source control or combination therapy [35].

This study focused on otherwise healthy patients, since data was lacking in other patient populations. Studies evaluating tigecycline PK-PD target attainment with different dosage regimens in other populations (e.g. critically ill and burn patients) are needed. Based on our study observations, further research focusing on alternative therapeutic options to tigecycline when the MIC is > 0.48 μg/mL are needed. Finally, as the dose of tigecycline increased, the theoretical MIC breakpoint for which tigecycline treatment is effective improved. Therefore, further research should focus on ways to overcome gastrointestinal dose-limiting side effects to increase the likelihood of treatment success.

Conclusion

The results of this MCS study support the use of intermittent infusion tigecycline 150 mg IV q12h for ward patients with resistant GNB up to a MIC of 0.48 μg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 18, up to a MIC of 1 μg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 7, and up to a MIC of 2 μg/mL for an $AUC_{total,\ 0\text{-}24h}$/MIC target attainment of 4.5. Continuous infusion tigecycline regimens did not offer an advantage over intermittent infusion tigecycline against bacteria with higher MICs (> 0.12–0.24 μg/mL). Resistant GNB infections that are associated with a tigecycline MIC ≥0.48 μg/mL may require treatment with alternate antibiotics, based on the failure to attain PK-PD tigecycline targets.

Author's contributions Brianna Kispal: data collection, data analysis, manuscript development; Sandra Walker: project supervisor, study conceptualization, methods development, data analysis, manuscript development.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability The data that supports the findings of this study are available in the supplementary material of this article.

Compliance with ethical standards

Conflict of interest All authors attest that they have no competing interests to declare.

Code availability Not applicable.

Ethics approval Not required.

Consent to participate Not applicable.

Consent for publication Not applicable

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