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REVIEW

Tigecycline antibacterial activity, clinical effectiveness, and mechanisms and epidemiology of resistance: narrative review

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Abstract

Tigecycline is unique glycylcycline class of semisynthetic antimicrobial agents developed for the treatment of polymicrobial infections caused by multidrug-resistant Gram-positive and Gram-negative pathogens. Tigecycline evades the main tetracycline resistance genetic mechanisms, such as tetracycline-specific efflux pump acquisition and ribosomal protection, via the addition of a glycyclamide moiety to the 9-position of minocycline. The use of the parenteral form of tigecycline is approved for complicated skin and skin structure infections (excluding diabetes foot infection), complicated intra-abdominal infections, and community-acquired bacterial pneumonia in adults. New evidence also suggests the effectiveness of tigecycline for the treatment of severe *Clostridioides difficile* infections. Tigecycline showed in vitro susceptibility to *Coxiella* spp., *Rickettsia* spp., and multidrug-resistant *Neisseria gonnorrhoeae* strains which indicate the possible use of tigecycline in the treatment of infections caused by these pathogens. Except for intrinsic, or often reported resistance in some Gram-negatives, tigecycline is effective against a wide range of multidrug-resistant nosocomial pathogens. Herein, we summarize the currently available data on tigecycline pharmacokinetics and pharmacodynamics, its mechanism of action, the epidemiology of tigecycline resistance, and its clinical effectiveness.

Keywords Tigecycline resistance · Tigecycline antibacterial activity · Tigecycline clinical Effectiveness

Introduction

The increasing incidence of multidrug-resistant (MDR) or extensively drug-resistant (XDR) bacterial pathogens is a major public health concern that poses an economic burden to healthcare system due to prolonged hospital stays and higher morbidity and mortality [1]. Tigecycline is a tetracycline-class antibacterial agent developed for the treatment of polymicrobial MDR infections [2] including both Gram-negative and Gram-positive bacteria. Tigecycline, known as

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GAR-936, or Tygacil, is the first, unique glycylcycline class of semisynthetic agents which is administered in a parenteral form [3] and was approved by the Food and Drugs Administration (FDA) in 2005 [4]. Later, in 2010, the FDA issued an alert that use of tigecycline in the treatment of severe infections and sepsis was significantly associated with an increased risk for all-cause mortality [5]. Currently, tigecycline has been approved as a monotherapy in adults for three indications including complicated skin and skin structures infections (cSSTI) with the exclusion of diabetes foot infection, complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CAP) [6, 7], and recent evidence suggests that tigecycline may be effective in the treatment of severe *Clostridioides difficile* infection [8]. The resistance to tigecycline includes chromosomally or accessory gene-encoded mechanisms. Herein, we summarize the currently available data on tigecycline pharmacokinetics and pharmacodynamics, its mechanism of action, the epidemiology of tigecycline resistance, and its clinical effectiveness.

Structural characterization

Tigecycline is chemically (4 S, 4 aS,5 aR,12aS)- 9- [2-(tert-butylamino) acetami do]- 4,7-bis(dimethylamino)-l,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-l, ll-dioxo-2-naphthacene-carboxamide [6, 9]. Its chemical formula is C29H39N508 with molecular weight of 585.65 Da [10]. Tigecycline is a chemically modified minocycline (9-t-butylglycylamido derivative of minocycline) [6, 9]. Compared with other tetracyclines, tigecycline's extended, wide-range antibiotic activity is due to a main backbone of minocycline with an N-alkyl-glycylamido side chain addition to the C9 carbon of the "D" tetracycline ring [6, 9].

Pharmacokinetics and pharmacodynamics

Due to insufficient absorption from the gut, tigecycline administration is intravenous; ~ 30–60 min every 12 h [6]. The in vitro plasma protein binding of tigecycline at 0.1, 1, and 15 ug/mL was reported as 71, 89, and 96, respectively, and showed nonlinear plasma-protein-binding behavior since the unbound fraction of tigecycline decreased with an increase in the total concentration of tigecycline [11]. Tigecycline has a systemic clearance (from 0.2 to 0.3 L/h/kg), a large volume of distribution (7–10 L/kg), and extensive distribution into various tissues [10]. The recommended standard dosage regimen for tigecycline is an initial dose of 100 mg followed by 50 mg every 12 hrs [12]. The recommended duration of treatment with tigecycline for cSSTI or cIAI and CAP is 5–14 and 7–14 days, respectively [13].

Tigecycline is excreted mainly unchanged in the bile [12] and has a very long half-life (t1/2) in humans (~ 27–42 h) [12]. Tigecycline achieves therapeutic concentrations by effectively and extensively penetrating body fluids and tissues, such as the lungs, skin, liver, heart, bone, and kidneys [14–16]. Tigecycline has relatively low mean steady-state serum concentrations of 0.403 mg/L and 0.633 mg/L in patients with cSSTI in the standard dosing [17]. The data on tigecycline pharmacokinetics showed that the ratio of tissue to serum tigecycline concentrations was 38-fold, 8.6-fold, 2.1-fold, 0.35-fold, and 0.58-fold higher in the gall bladder, lungs, colon, bone, and synovial fluid, measured at 4 h after administration of a single 100 mg dose [18]; a higher ratio of tissue to serum of tigecycline in skin and soft tissue was also found after 1–6 days of standard treatment [15]. The penetration of tigecycline into bones was reported by Bhattacharya et al. (bone: serum ratio; 4.77-fold) [19]. Data from several pharmacokinetic-pharmacodynamic (PK/PD) analyses and clinical trials showed that the ratio for the area under the concentration time curve and minimal inhibitory concentration (AUC/MIC) for serum tigecycline concentrations is a predictor of therapeutic response [20, 21]. Tigecycline does not readily cross the blood-brain barrier.

The experimental data suggested that tigecycline exhibits a time-dependent bactericidal activity and has a prolonged postantibiotic effect (PAE) against Gram-positive and Gram-negative pathogens following a 3 mg/kg dose [22–24]. In comparison to minocycline, tigecycline has a uniformly longer PAE for tested pathogens (3.4–4 h for *Staphylococcus aureus* and 1.8–2.9 h for *Escherichia coli*) [22, 23].

Tigecycline is eliminated from the body through biliary excretion in the feces (59%) and urine (22%). Age, sex, and renal function do not appear to interfere with the pharmacokinetics of tigecycline, and no dose adjustment is required for patients with renal impairment (including hemodialysis) [25–27]. However, clinical caution in the use of tigecycline is needed in patients who have severe hepatic dysfunction (Child Pugh C); an initial dose of 100 mg of tigecycline should be followed by reduced maintenance doses of 25 mg every 12 h [27–29].

Mechanism of Action

Tigecycline is a bacteriostatic, parenteral glycylcycline antibiotic with a stronger (5-fold) binding affinity and structural similarities to the tetracyclines [4, 14, 27]. The main mechanism of action of tigecycline is similar to other tetracyclines in that it acts an inhibitor of bacterial protein translation (i.e., elongation of the peptide chain) via reversible binding to a helical region (H34) on the 30S subunit of bacterial ribosomes. The binding of tigecycline prevents the incorporation of amino acid residues into the elongation of peptide chains and results in the loss of peptide formation and bacterial

growth [4, 14, 27] (Fig. 1). Tigecycline was developed to overcome the main molecular mechanisms of tetracycline resistance, such as tetracycline-specific efflux pump acquisition [e.g., *tet*(A)] and ribosomal protection [e.g., *tet*(M)], through the addition of a glycyclamide moiety to the 9-position of minocycline.

Antimicrobial susceptibility testing to tigecycline

Currently, several laboratory methods, including broth microdilution and disk diffusion, have been used for the determination of in vitro susceptibility to tigecycline [30, 31]. Broth microdilution is the reference method for the testing of in vitro susceptibility to tigecycline, though, according to the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [30, 31], the medium must be prepared fresh on the day of use and must be not more than 12 h old at the time the panels are made.

For other *Enterobacterales*, except for *E. coli*, the activity of tigecycline varies from insufficient in *Proteus* spp., *Morganella morganii*, and *Providencia* spp. to variable in other species [31]. The interpretative minimal inhibitory concentration breakpoints to tigecycline recommended by EUCAST [31], the Food and Drug Administration (FDA) [32], and the British Society for Antimicrobial Chemotherapy (BSAC) [33] to various bacteria are indicated in Table 1. The CLSI interpretative minimal inhibitory concentration breakpoints to tigecycline are not available.

Antibacterial activity

Alterations to the tetracycline structure resulted in an expansion of tigecycline's spectrum of an antibacterial activity against a wide spectrum of Gram-positive and Gram-negative pathogens [34]. Currently, due to its effectiveness, tigecycline is the last-line treatment option against MDR bacterial pathogens, especially carbapenem-resistant *Enterobacteriaceae* [35–40]. Tigecycline showed good activity against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, and penicillin-resistant *Streptococcus pneumoniae* [41].

In addition, tigecycline was highly active against *Stenotrophomonas maltophilia*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae* [42–44]. Blanton et al. [45] have indicated that tigecycline is effective against *Rickettsia rickettsii* [45].

Antibacterial activity was also observed against *Coxiella burnetii* derived from patients with acute Q fever [46]. The flow cytometry assay data suggest that tigecycline has antibacterial activity [(IC50) 0.71 × 10-3 μg/mL] against *Orientia tsutsugamushi* and that it may be a therapeutic option for the

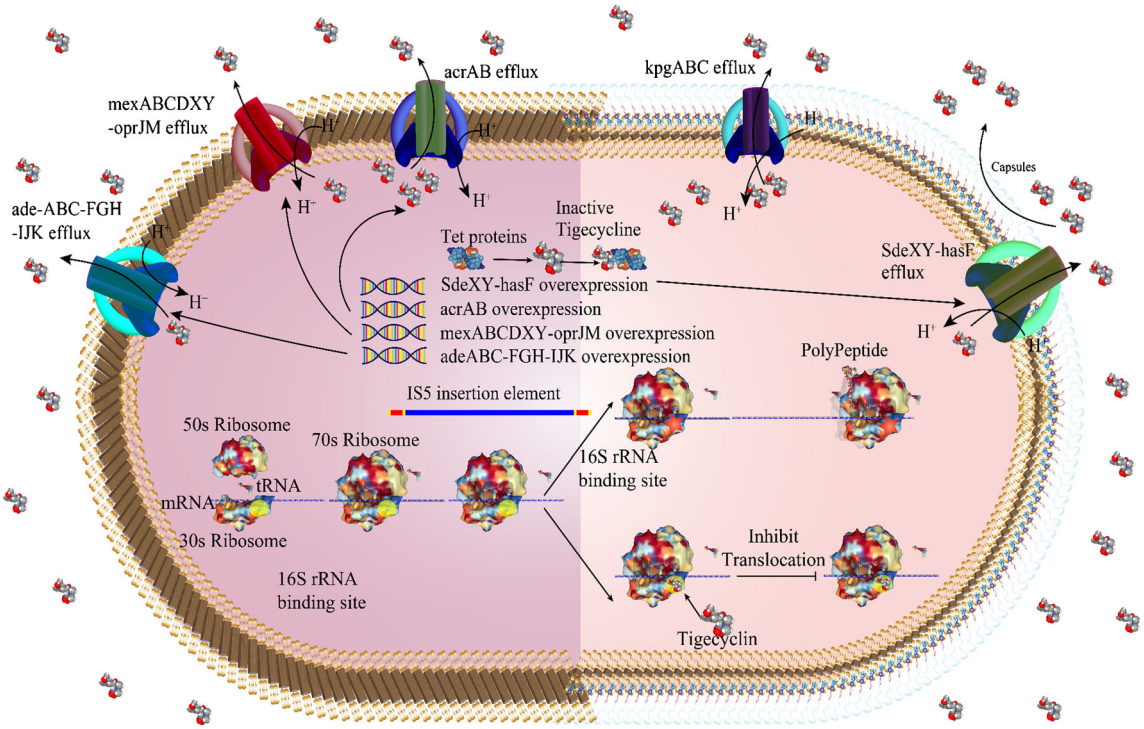

Fig. 1 Tigecycline mechanisms of action and resistance

Table 1 Tigecycline international *in vitro* susceptibility breakpoints.

Bacterial family/species	International breakpoints standard	Broth microdilution (mg/L)	Disk diffusion (mm)
Enterobacteriaceae	EUCAST	S ≤ 0.5, R > 0.5	S ≥ 18, R < 18
	FDA	S ≤ 2, R ≥ 8	S ≥ 19, R ≤ 14
	BSAC	S ≤ 1, R > 2	S ≥ 24, R ≤ 19
Staphylococcus spp.	EUCAST	S ≤ 0.5, R > 0.5	S ≥ 18, R < 18
	FDA	S ≤ 0.5	S ≥ 19
	BSAC	S ≤ 0.5, R > 0.5	S ≥ 26, R ≤ 25
Enterococcus spp.	EUCAST	S ≤ 0.25, R > 0.25	S ≥ 18, R < 18
	FDA	S ≤ 0.25	S ≥ 19
	BSAC	S ≤ 0.25, R > 0.5	S ≥ 21, R < 20
Streptococcus groups A, B, C and G	EUCAST	S ≤ 0.125, R > 125	S ≥ 19, R < 19
	FDA	S ≤ 0.25	S ≥ 19
	BSAC	S ≤ 0.25, R > 0.5	S ≥ 25, R < 19
Streptococcus pneumoniae	EUCAST	-	-
	FDA	S ≤ 0.06	S ≥ 19
	BSAC	-	-
Clostridioides difficile	EUCAST	S ≤ 0.25, R > 0.25	-
	FDA	S ≤ 4, R > 16	-
	BSAC	S ≤ 0.25	-
Acinetobacter spp.	EUCAST	-	-
	FDA	S ≤ 2, R ≥ 8	-
	BSAC	S ≤ 1, R > 2	S ≥ 20, R < 20
Pseudomonas spp.	EUCAST	-	-
	FDA	S ≤ 2, R ≥ 8	-
	BSAC	-	-

EUCAST European Committee on Antimicrobial Susceptibility Testing, *FDA* Food and Drug Administration, *BSAC* British Society for Antimicrobial Chemotherapy, *S* sensitive, *R*:Resistance

treatment of scrub typhus [47]. The susceptibility of C*lostridioides difficile* isolates was proved during pan-European, longitudinal surveillance [48]. In addition, clinical data on the use of tigecycline administered alone, or as a part of combination therapy of oral vancomycin and intravenous metronidazole, showed its efficiency in patients with a severe course of *Clostridium difficile* infection (CDI) [49]; however, randomized controlled trials are necessary before tigecycline can be recommended for routine use in the treatment of CDI [50].

Some pathogens, such as *P. aeruginosa*, *Proteus* spp. *Providencia* spp., and *Morganella* spp., are intrinsically resistant to tigecycline [51–53] and the development of acquired resistance to tigecycline has been described in several bacterial species such as A*cinetobacter baumannii*, *Klebsiella pneumonia*, *Enterobacter* spp., and *Bacteroides fragilis* [49].

Mechanisms of tigecycline resistance

In the last decades, the emergence of tigecycline resistance has been reported worldwide [49, 54, 55] though there are relatively few data available regarding the molecular basis for resistance to tigecycline. As shown in vitro, the Tet proteins [e.g., Tet(X), Tet(A), Tet(K) and Tet(M)] have the potential to acquire mutations leading to a reduced susceptibility (i.e,. increased MICs) to tigecycline [56] possibly through the horizontal transfer of mobile genetic elements carrying several resistance genes. In addition, the mobile tigecycline-resistance *tet*(X) gene variants are newly emerging tigecycline resistance mechanisms in humans and animals [57]. The Tet(X) is a flavin-dependent monooxygenase that originated from *Bacteroides* spp. and was detected in *Enterobacteriaceae* and some *Acinetobacter* spp. isolates [58–60].

In Gram-negative bacteria, the chromosomally encoded, overexpression of resistance-nodulation division (RND) efflux pumps such as AdeABC, AdeFGH, AdeIJK, MexXY, and AcrAB are important molecular mechanisms in the resistance of bacteria to tigecycline [61–63].

Acinetobacter baumannii

The occurrence of increased MICs and resistance to tigecycline among *Acinetobacter* spp. was associated with the

upregulation of AdeABC, AdeFGH, AdeIJK, AbeM, and AdeDE pumps and also the presence of the *tetX* gene [64, 65] although some studies noted that additional efflux pumps or different molecular mechanisms might contribute to tigecycline resistance [58, 66, 67]. The nucleotide and amino acid alterations in the AdeRS two-component system may lead to adeABC overexpression and tigecycline resistance [68]. Besides it was found that the BaeSR system positively regulates the expression of adeA and adeB and stimulated tigecycline-resistant strains [69].

Additional mechanisms of decreased susceptibility to tigecycline, such as a novel RND pump, the presence of *tet*(X1) or *tet*A genes, a mutation in the *trm* gene encoding S-adenosyl-L-methionine (SAM)-dependent methyltransferase, and a frameshift mutation in the *plsC* gene that encodes for 1-acyl-sn-glycerol-3-phosphate acyltransferase, have been detected in the clinical *A. baumannii* isolates[69–71].

Enterobacteriaceae

The intrinsic resistance to tigecycline in *Enterobacteriaceae* has been described in *Morganella morganii* and *Proteus mirabilis* and was attributed to the constitutive upregulation of the multidrug AcrAB efflux pump [50]. The AcrAB efflux pumps and their regulatory genes also play a role in the decreased susceptibility to tigecycline in *E. coli* and *Klebsiella* spp. [55, 62, 72–74].

Currently, SoxS, MarA, RamA, and Rob have been characterized as global regulators of the AcrAB pump in *Enterobacteriaceae* [75] although the exact mechanism of AcrAB pump overexpression has not been clarified [76, 77].

Escherichia coli

Tigecycline is a possible substrate for the AcrAB and AcrEF pumps in *E. coli* [78]. The physiological role of the AcrAB pump in *E. coli* is critical, and it excretes a diversity of lipophilic and amphiphilic antibiotics as substrates [79]. MarA, SoxS, and Rob have been suggested as regulators involved in the MDR phenotype in *E. coli* [80]. One of the major mechanisms involved in the *E. coli* MDR phenotype is mediated by the *mar* regulon that stimulates the downregulation of the OmpF outer membrane porin and also stimulates the upregulation of the AcrAB efflux pump [81, 82]. In *E. coli*, MarA (controlled by the local repressor MarR) acts as a positive regulator of the AcrAB–TolC efflux pump [83]. Additionally, in some *E. coli* strains that have high tigecycline MICs, a frameshift mutation (insertion of a cytosine at position 355) has been described in *marR* (one of the targets for reduced susceptibility to tigecycline) that led to the overexpression of MarA and AcrAB pumps [83]. Linkevicius et al. [84] selected tigecycline-resistant *E. coli* mutants in vitro and evaluated their biological fitness and cross-resistance.

A relatively low-level resistance and a high fitness cost were identified in isolates with mutations of efflux regulatory network genes (*lon*, *acrR*, and *marR*) and related lipopolysaccharide core biosynthesis pathway genes (*lpcA*, *rfaE*, *rfaD*, *rfaC*, and *rfaF*). Remarkably, the fitness cost of mutations in *E. coli* under tigecycline exposure may decrease the ability of mutants to trigger a successful infection [84]. The reduced fitness and virulence in clinical isolates when *acrA* and *tolC* were inactivated have already been described, implying that the AcrAB pump may also play a role in adaptation and host virulence [85]. However, more in vivo research is needed to determine how these different mutation types are involved in bacterial virulence.

Klebsiella pneumoniae

In *K. pneumoniae*, tigecycline resistance is related extensively to the overexpression of RamA [86, 87]. There is a positive association between the upregulation of *ramA* with an overexpression of AcrAB [75, 87–89]. Nevertheless, no association between the upregulation of *ramA* and AcrA expression has been described [90]. RarA is a new AraC-type global regulator that acts via the control of AcrAB and OqxAB efflux pump expression and is mediated by the MDR phenotype in *K. pneumoniae* [62, 88, 91]. However, He et al. have reported no marked correlation between OqxAB and tigecycline resistance [73]. Sheng et al. [92] have also proposed that RamA may be a positive regulator of the OqxAB pump since variants in *ramR* have been suggested as a mechanism of *acrAB* downregulation and tigecycline resistance [77, 92, 93]. *IS5* element integration in the new efflux pump operon kpgABC is correlated with a novel mechanism for the rapid in vivo development of tigecycline non-susceptibility [94]. Villa et al. [77] highlighted the role of the ribosomal S10 protein mutation (a mutation in the *rpsJ* gene that has already been reported to reduce tigecycline susceptibility in both Gram-negative and positive bacteria) in conferring tigecycline resistance. In addition, an alternative pathway involved in *K. pneumoniae* resistance to tigecycline is the overexpression of *marA* that is associated with AcrAB upregulation overexpression [62, 88]. The failure of tigecycline treatment in patients with carbapenem-resistant *K. pneumoniae* (CRKP) strains that harbor the *tetA* gene has been reported [95]. Additional tigecycline resistance mechanisms conferred by Tet proteins (mainly Tet(X)) have been published, [96]. In a recent study conducted in China [97], mutations in the *ramR* and *tet*(A) efflux genes were found to be the major tigecycline resistance mechanisms among the studied tigecycline- and carbapenem-resistant *K. pneumoniae* isolates.

Serratia marcescens

The upregulation of the SdeXY–HasF efflux pump (a part of the RND efflux pump family) has been associated with tigecycline resistance in *S. marcescens* [98]. The upregulation of the SdeXY–HasF efflux system that confers resistance to tigecycline is also active against ciprofloxacin and cefpirome. On the other hand, in an experimental mutant strain, the insertional independent inactivation of the *sdeY* and *hasF* genes also led to a reduced sensitivity to ciprofloxacin, cefpirome, and tetracycline [98].

Enterobacter spp.

In *Enterobacter* spp., the *ramA*-mediated mechanisms involving AcrAB efflux pump regulation are the primary mechanisms of tigecycline resistance [62, 99]. In *E. aerogenes* and *E. cloacae*, the nucleotide mutations include frameshifts, deletions, and amino acid variations in *ramR* (mainly in the ligand-binding domain) that lead to the overexpression of *ramA* and tigecycline resistance [62]. However, the other probable alternative mechanisms of tigecycline resistance that have been reported in *E. cloacae* include *ramA* overexpression without any ramR alterations; *rarA* overexpression and upregulation of the OqxAB pump; and upregulation of the AcrAB through SoxS, RobA, and RamA [62, 85]. Further in vivo and in vitro investigations are needed to characterize fully the probable other efflux pumps and/or regulators involved in tigecycline resistance mechanisms in *Enterobacteriaceae* [73, 75, 90, 100].

Salmonella spp.

In *S. enterica*, a positive correlation between the upregulation of *ramA* (*via* an inactivating mutation in *ramR*) and the consecutive overexpression of AcrAB with tigecycline resistance have been reported [101–103], although how *ramA* is controlled in bacteria other than *Salmonella* spp. is currently unknown. Similar to tigecycline resistance in carbapenem-resistant *K. pneumoniae* isolates, the combination of mutations in *ramR* and *tet(A)* genes was also reported in tigecycline-resistant *S. enterica* [61, 97, 104].

Pseudomonas aeruginosa

Currently, several Resistance-Nodulation- Division (RND) efflux pumps including MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM have been suggested as mechanisms for drug resistance in *P. aeruginosa* [105–110]. Dean et al. suggested the overexpression of MexXY-OprM as a drug efflux-mediated tigecycline resistance mechanism [110, 111]. In addition, the overexpression of the SdeXY pump frequently underlies tigecycline intrinsic resistance in *P. aeruginosa* [110]. In addition, the expression of other efflux pumps in MDR *P. aeruginosa* isolates has also been reported [112, 113].

Gram-positive bacteria

Relatively few data on tigecycline resistance in gram-positive bacteria are available. Overexpression of the multi-antimicrobial extrusion protein (MATE) family efflux pump MepA has been suggested as mechanism of decreased susceptibility to tigecycline in *Staphylococcus aureus* but does not confer resistance [52, 114, 115]. More recently, Fiedler et al. confirmed that overexpression of two tetracycline-resistance determinants, a *tet*(L)-encoded Major facilitator superfamily (MFS) pump and a tet(M)-encoded ribosomal protection protein, confer tigecycline resistance in *Enterococci* spp. [116]. The mechanisms of resistance to tigecycline are shown in Fig. 1.

Effectiveness of tigecycline in clinical settings

In September 2010, the FDA Adverse Event Reporting System (FAERS) reported [117] an increased risk of mortality with tigecycline (4%; 150/3788) compared with other antibiotics (3%; 110/3646) used to treat similar infections. However, data from a prospective, multicenter, non-interventional study demonstrated the efficacy and safety of tigecycline in a population of severely ill patients with complicated infections [118]. In a retrospective observational study, Kwon et al. [119] evaluated the efficacy and safety profile of tigecycline in comparison with colistin in XDR *A. baumannii*-positive patients. No difference was observed between both antibiotic groups in terms of treatment success and mortality rates. Serum creatinine elevation and nephrotoxic prevalence cases were observed more commonly in the colistin group ($p = 0.028$). On the other hand, the excess mortality of 16.7% (60.7 vs. 44%, 95% confidence interval 0.9–32.4%, $p = 0.04$) was reported in 294 of subjects treated with tigecycline versus colistin for the treatment of pneumonia caused by the multidrug-resistant *A. baumannii* [120].

In September 2013, FAERS analyzed the data from 10 clinical trials conducted only for FDA-approved uses (cSSSI, cIAI, CABP) [121]. This analysis showed a higher risk of mortality among subjects treated with tigecycline compared with comparators: 2.5 (66/2640) vs. 1.8% (48/2628), respectively. In general, the deaths resulted from worsening infections, complications of infection, or other underlying medical conditions.

In a meta-analysis [122] of 5 trials, comparing tigecycline monotherapy versus combination therapy for the treatment of

patients with hospital-acquired pneumonia, no significant difference was observed in the development of the mortality rate from two prospective cohort studies (OR = 2.22, 95% CI 0.79–6.20 $p = 0.13$).

In a systematic review and meta-analysis [123], including 24 controlled studies, tigecycline-induced secondary bacteremia was found in 4.6% (91/1961) of patients with bloodstream infections. All-cause mortality and clinical cure rates for tigecycline were relatively similar to control antibiotic agents. Tigecycline, in combination with other antimicrobial agents, was suggested as a suitable choice for at-risk patients with BSI. However, tigecycline is not superior to comparator agents for the treatment of serious infections [2].

Due to the rise of multidrug-resistant infections, tigecycline has been used for non-approved indications. In a Spanish university hospital, one-third of tigecycline prescriptions were non-approved mainly as a rescue therapy and concomitantly with other antibiotics in patients with nosocomial pneumonia [124]; and in an Argentinean hospital, it was 79%, especially in ventilator-associated pneumonia due to MDR *Acinetobacter* spp. [125]. In a Taipei Veterans' General Hospital, tigecycline was used for non-Food and Drug Administration-approved indications, to treat healthcare-associated pneumonia (38, 57.6%), bacteremia (3, 4.5%), catheter-related infections (3, 4.5%), urinary tract infection (4, 6.1%), osteomyelitis (4, 6.1%), and others (2, 3%) [126]. In a Turkish university hospital, tigecycline was used in the intensive care unit for patients infected with carbapenem-resistant *Acinetobacter baumannii* [127]. A study carried out in a Lebanese tertiary-care hospital reported 81% of tigecycline non-approved indications in critically ill patients with non-inferior outcome to that of FDA-approved indications [128].

In a pediatric population, tigecycline is not recommended in children and adolescents below 18 years of age. However, clinical studies reported the efficacy of a tigecycline therapy combined with other antimicrobial agents in the treatment of multidrug-resistant infection, i.e., nosocomial infections in newborn infants [129–131] and carbapenem-resistant gram-negative bacteria infections in liver transplant recipients [132]. Recently, tigecycline was used as a treatment in a case of ventriculoperitoneal shunt-related meningitis in a 5-month-old infant [133].

Adverse effects

Available evidence from 15 randomized controlled trials (RCTs), including a recent meta-analysis [134], assessed the available data with regard to the effectiveness and safety of tigecycline in comparison to other antimicrobials in the treatment of 7689 adult patients with infectious diseases. Adverse events and all-cause mortality were frequent in the tigecycline group. Twelve of the 15 RCTs (6292/7689) described various adverse events with tigecycline use. The adverse events rate was considerably higher in the tigecycline group compared with the comparator drug group (OR = 1.49, 95% CI = 1.23 to 1.80, $p < 0.0001$).

Based on the results from the preclinical animal safety studies, tigecycline was not thought to be teratogenic [27]; however, in rats and dogs a decrease of white and red blood cells, bone marrow hypocellularity, reductions in fetal weights, and an increased incidence of fetal loss and minor skeletal abnormalities were reported [27, 135]. Now, tigecycline is categorized as teratogenic effect class D and should be used with caution in specific populations, including nursing mothers, pregnant women, pediatrics, and patients with severe hepatic impairment [4, 13, 27, 135, 136]. In addition, the use of tigecycline may affect tooth development particularly if used during the last half of pregnancy and in children under the age of 8 as it can cause permanent tooth discoloration [137].

The human clinical trial studies and the FAERS [138] reported that the most common side effects following tigecycline administration, especially in adults aged between 18 and 50 years, and which were more likely in women, are gastrointestinal (GI) symptoms, i.e., nausea, vomiting, and diarrhea. Further reported side effects relevant to tigecycline administration were pancreatitis, acute generalized exanthematous pustulosis, local reaction at the *i.v.* site, increased hepatic function, thrombophlebitis, pruritus, fever, mitochondrial dysfunction-associated acute metabolic acidosis abdominal pain, headache, cholestatic, jaundice, and Steven-Johnson syndrome [2, 139–144].

Clinical studies showed a significant higher (~ > 4-fold) incidence of nausea and vomiting induced by tigecycline in patients treated for cSSSI compared with patients treated with vancomycin/aztreonam. However, in patients with cIAI, the incidence of nausea and vomiting occurred equally often in patients treated with imipenem/cilastatin as it did in patients treated with tigecycline (25%/20% for tigecycline and 21%/15% for imipenem/cilastatin group, respectively). In community-acquired bacterial pneumonia, the occurrence of GI symptoms was higher in the group of patients treated with tigecycline than the group treated with levofloxacin [138].

The mechanism of action of tigecycline-associated nausea and vomiting remains uncertain and their incidence is dose-related [145]. Whether it is preventable by the pre-emptive use of antiemetics as concomitant drugs (metoclopramide. ondasetron, prochlorperazine, sucralfate, and trimethobenzamide) is unclear [146, 147] . From 2514 patients, the total *discontinuation* rate was 7% during *tigecycline* treatment and discontinuation was most frequently associated with nausea (1%) and vomiting (1%) [138].

The phase III clinical trials evaluated tigecycline tolerability and efficacy in patients receiving tigecycline (i.e., 100-mg IV loading dose followed by 50 mg IV q12h) [2, 148–151]. The difference in the incidence of nausea and vomiting between tigecycline and the comparators (vancomycin+aztreonam or imipenem/cilastatin) was statistically significant ($p < 0.05$) in ≥ 2 of the 4 Phase III trials.

Table 2 The prevalence of tigecycline resistance by continents and pathogens.

Asian Countries	Pathogen	Area	No. (%) of Resistant rate	Type of study	First author, year
	Klebsiella pneumoniae	Saudi Arabia	1	Case report	Al-Qadheeb et al., 2010 [160]
	Acinetobacter spp.	India	224/32 (14.2)	Original research	Taneja et al., 2011 [161]
	Acinetobacter spp.	Kuwait	250/34 (13.6)	Original research	Al-Sweih et al., 2011 [162]
	E. coli	India	166/0 (0)	Original research	Manoharan et al., 2010 [163]
	Acinetobacter spp.		50/6 (12)		
	Pseudomonas aeruginosa		50/47 (94)		
	S. aureus		125/0 (0)		
	S. pneumoniae		102/0 (0)		
	Enterococcus spp.		100/0 (0)		
	Enterobacteriaceae	Taiwan	412/10 (2.4)	Original research	Hsu et al., 2011 [164]
	Stenotrophomonas maltophilia	Taiwan	377/66 (17.5)	Original research	Wu et al., 2012 [165]
	Stenotrophomonas maltophilia	China	442/71 (16.1)	Original research	Zhang et al., 2012 [166]
	Enterobacteriaceae (MBL-producing)	Taiwan	95/36 (37.9) (resistant or intermediately susceptible)	Original research	Liao et al., 2011 [167]
	Enterobacteriaceae (NDM-1-producing)	Pakistan	64/7 (11)	Original research	Perry et al., 2011 [168]
	E. coli	Lebanon	150/0 (0)	Original research	Araj and Ibrahim, 2008 [169]
	K. pneumoniae		100/3 (3)		
	Acinetobacter spp.		64/0 (0)		
	Acinetobacter baumannii	Taiwan	393/27 (6.9) (resistant or intermediately susceptible)	Original research	Liu et al., 2008 [170].
	Acinetobacter baumannii (MDR)	India	26/15 (57.7)	Original research	Behera et al., 2009 [171]
	Acinetobacter baumannii (imipenem-non-susceptible)	Taiwan	114/21 (18)	Original research	Lee et al., 2009 [172]
	Acinetobacter baumannii (MDR)	Thailand	148/4 (2.7) (resistant or intermediately susceptible)	Original research	Tiengrim et al., 2006 [173]
	Acinetobacter baumannii (MDR)	Israel	82/54 (66)	Original research	Navon-Venezia et al., 2007 [174]
	Acinetobacter baumannii (MDR)	Taiwan	134/61 (45.5)	Original research	Chang et al., 2012 [175]
	Colistin-resistant Acinetobacter spp.	South Korea	145/14 (9.7) (non-susceptible)	Original research	Park et al., 2009 [176]
	OXA carbapenemase-producing Acinetobacter baumannii	South Korea	47/11 (23.4)	Original research	Kim et al., 2010 [177]
	Acinetobacter baumannii (MDR)	Turkey	82/21 (25.8)	Original research	Dizbay et al., 2008 [178]
	S. aureus	India	127/68 (53.5)	Original research	Swati Sharma.,2017 [179]
	Acinetobacter baumannii	Taiwan	393/27 (6.9)	Original research	Liao CH.,2008[180]
	Stenotrophomonas maltophilia	China	450/61 (13.56)	Original research	Jin Zhao.,2018[181]
	Carbapenemase-producing Klebsiella pneumoniae	Saudi Arabia	1 case	Case report	Nada S. Al-Qadheeb.,2010[160]
	Carbapenem-resistant Klebsiella pneumoniae	Taiwan	16/16 (100)	Original research	Sheng-Kang Chiu., 2017[182]
	Enterobacter spp.	Asia	516/4 (0.8)	Original research	Harald Seifert., 2018[183]
	Serratia marcescens		204/1 (0.5)		
	E. coli		314/1 (0.3)		
	K. pneumoniae		541/7 (1.3)		
	Bacteroides fragilis	Europe	824/14 (1.7)		Nagy et al., 2011 [184]

Table 2 (continued)

European Countries				Original research	
	Acinetobacter baumannii	Spain	142/17 (12)	Original research	Insa et al., 2007 [185]
	S. maltophilia		120/2 (2)		
	E. coli	Spain	220/0 (0)	Original research	Tubau et al., 2010 [186]
	K. pneumoniae		28/0 (0)		
	K. oxytoca		14/0 (0)		
	Enterococcus faecalis		53/1 (1.9)		
	Enterococcus faecium		39/0 (0)		
	Enterobacter cloacae		23/1 (4.3)		
	M. morganii		14/0 (0)		
	P. mirabilis		12/4 (33.3)		
	P. vulgaris		7/1 (14.3)		
	Citrobacter spp.		9/0 (0)		
	S. aureus		18/0 (0)		
	viridans group streptococcus		23/1 (4.3)		
	E. coli (ESBL-producing)	Italy	430/7 (1.6)	Original research	Grandesso et al., 2010 [187]
	Klebsiella spp.	Poland	108/7 (7.5)	Original research	Sekowska and Gospodarek, 2010 [188]
	KPC-producing Klebsiella pneumoniae	Spain	215/24 (11.2)	Original research	Vázquez et al., 2008 [73]
	ESBL producing E. coli	Belgium	Nonsusceptibility rates 26/9 (35)	Original research	Naesens et al., 2009 [189]
	ESBL-producing Klebsiella spp.		10/10 (100)		
	Enterobacter spp.		27/26 (96)		
	Enterobacteriaceae	France	1070/52 (4.9)	Original research	Froment Gomis P et al., [190]
	Acinetobacter baumannii		47/25 (53)		
	Bacteroides fragilis		645/102 (15.8)		
	MDR-producing *Enterobacteriaceae*	Greece	152/12 (7.9) (Intermediate)	Original research	Falagas ME et al., [191]
	Enterobacteriaceae spp. (carbapenem-resistant)	Europe	280/32 (11.4)	Original research	Sader HS et al., [192]
	Enterobacteriaceae (imipenem resistant)	Greece	110/1 (1)	Original research	Papaparaskevas J et al., [193]
	Enterococcus spp. (vancomycin resistant)		151/0 (0)		
	Methicillin-resistant S. aureus		338/3 (<1)		
	ESBL-positive E. coli	Eastern Europe	337/5 (1.5)	Original research	Balode A et al., [194]
	Vancomycin-resistant *Enterococci*	France	18/0 (0)	Original research	Cattoir V et al., [195]
	Methicillin-resistant *S. aureus*		631/0 (0)		
	ESBL-positive E. coli		275/3 (1.1)		
	ESBL-positive K. pneumoniae		274/60 (21.9)		
	Enterobacter hormaechei	France	1 case	Case report	Daurel et al., 2009 [196]
	Enterococcus faecalis	Germany	1 case	Case report	Werner et al., 2008 [197]
African Countries	*carbapenem resistant A. baumannii* complex	South Africa	232/17 (7.6)	Original research	Nahid H Ahmed et al., 2012 [198]
	Acinetobacter baumannii	South Africa	(Non-susceptible) 705/53 (7.5)	Original research	Olga Perovic et al., 2015 to 2016 [199, 200]
	E. coli	Africa	199/0 (0)	Original research	Harald Seifert et al., 2018[183]
	Klebsiella pneumoniae		185/0 (0)		
	Enterobacter spp.		188/2 (1.1)		
	Serratia marcescens		79/1 (1.3)		
	carbapenem resistant A. baumannii complex	South Africa	232/17 (7.6)	Original research	Ahmed et al., 2010 [198]

Table 2 (continued)

American Countries	*Acinetobacter baumannii*	USA	1	Case series	Anthony et al., 2008 [148]
	Bacteroides fragilis	USA	1	Case report	Sherwood et al., 2011 [201]
	E. coli *Klebsiella pneumoniae* *E. aerogenes* *E. cloacae* *S. marcescens*	USA	131/0 (0) 174/16 (9.2) 24/5 (20.8) 126/32 (25.4) 20/4 20	Original research	DiPersio and Dowzicky, 2007 [202]
	Bacteroides fragilis	USA	1	Case report	Sherwood et al., 2011 [201]
	E. faecium *Enterobacter spp.* *K. pneumoniae* *E. coli* *S. marcescens*	Latin America	106/0 (0) 766/2 (0.3) 763/10 (1.3) 932/0 (0) 328/2 (0.6)	Original research	Rossi F et al., [203]
	E. coli *K. pneumoniae* *Klebsiella oxytoca* *Serratia marcescens* *Enterobacter spp.*	USA	6643/0 (0) 4951/208 (4.2) 1170/13 (1.1) 2421/99 (4.1) 6065/285 (4.7)	Original research	Denys GA et al., [204]
	ESBL-E. coli *ESBL-K. pneumoniae* *K. oxytoca* *Enterobacter spp.* *S. marcescens*	Latin America	870/0 (0) 1045/15 (1.4) 311/0 (0) 2804/14 (0.5) 1126/9 (0.8)	Original research	Fernández-Canigia L et al., [205]
	ESBL-producing K. pneumoniae *K. oxytoca* *E. coli* *E. aerogenes* *E. cloacae* *S. marcescens*	USA	337/7 (2) 801/2 (0.2) 4861/0 (0) 1095/11 (0.01) 2866/56 (0.02) 1698/11 (<0.01)	Original research	Dowzicky MJ et al., [206]
	S. aureus *Klebsiella pneumoniae* *E. coli* *A. baumannii* *Enterobacter cloacae* *Serratia*	Mexico	250/23 (9) 150/5 (3) 150/6 (4) 550/6 (1) 100/7 (7) 100/0 (0)	Original research	Garza-González et al., 2010 [207]
	E. coli	Canada	3789/4 (0.1)	Original research	Lagacé-Wiens et al., 2011 [208]
	CTX-M-producing *Enterobacteriaceae*	USA	67/0 (0)	Original research	Castanheira et al., 2010 [209]

ESBL, extended-spectrum b-lactamase; MDR, multidrug-resistant. MBL, Metallo-β-lactamase. NDM; New Delhi Metallo-beta lactamase.

Clinical and pharmacokinetic literature outcomes stated that co-administration of tigecycline with food led to an improvement in the gastrointestinal adverse events; however it did not change the drug's pharmacokinetics [152].

In pancreatitis, the data from all phase 3 and 4 clinical trials found no significant difference in the incidence of pancreatitis between patients treated with tigecycline and patients treated with comparators [153]. On the other hand, a significantly higher rate of pancreatitis of 20% (cases = 10) was observed in a French study [154]. The exact mechanism of tigecycline-induced pancreatitis is unclear; however, some suggested mechanisms are hypertriglyceridemia and toxic metabolite formation that might be involved in the development of tigecycline-induced pancreatitis [153–155].

Several studies also reported tigecycline-induced coagulopathy [156, 157]. The impact of a recommended dose of tigecycline, 50 mg q12h and/or a higher dose of 100 mg q12h, on coagulation parameters in 50 patients with severe infection was evaluated in a Chinese retrospective analysis [158]. A considerable decrease in the levels of plasma fibrinogen ($p < 0.001$) and a significant increase in the mean values of prothrombin time (PT) and activated partial thromboplastin time (aPTT) ($p \leq 0.002$) were observed. In another study, non-anion gap acute metabolic acidosis (NAGAMA), developed through mitochondrial toxicity, was observed after an unusually high dose

Table 3 Worldwide reports of tigecycline resistance in gram negative and positive-bacteria.

First author, year	Type of study	Area	Pathogen	Resistant rate (%)
Anna Giammanco et al., 2014[210]	Original research	Worldwide	*E. coli*	0.2
			Klebsiella spp.	6
			Enterobacter aerogenes	12
			Klebsiella oxytoca	5.9
			K. pneumoniae	5.7
Sue C. Kehl et al., 2004 - 2012[211]	Original research	Worldwide	*E. coli*	< 0.1
			K. pneumoniae	3.5
			Klebsiella oxytoca	0.6
			Enterobacter spp.	2.6
			Serratia marcescens	3.8
Mendes et al et al., 2010 [212]	Original research	Worldwide	*Acinetobacter spp.*	3
Garrison MW et al., 2009 [213]	Original research	Worldwide	*E. cloacae*	1.5
			E. coli	0.01
			K. oxytoca	0.2
			K. pneumoniae	1.1
			S. marcescens	0.6
Hoban DJ et al., 2015 [214]	Original research	Worldwide	*Enterobacter spp*	1.1
			E. coli	< 0.1
			Klebsiella oxytoca	0.2
			Klebsiella pneumoniae	0.8
			Serratia marcescens	0.7
Sader HS et al., 2013 [215]	Original research	Worldwide	*S. aureus*	0
			Enterococcus spp.	0.2
			Streptococcus pneumoniae	0.2
			E. coli	0
			Klebsiella spp.	1.4
Bertrand X et al., 2012 [216]	Original research	Worldwide	*Klebsiella pneumoniae*	5.1
			Enterobacter cloacae	4.3
			E. coli	< 0.1
			Serratia marcescens	4.5
Harald Seifert et al., 2018 [183]	Original research	Worldwide	*E. coli*	< 0.1
			Klebsiella pneumoniae	0.6
			Enterobacter spp.	0.8
			Serratia marcescens	0.4

of 100 mg, twice daily following a single 200 mg loading dose of tigecycline administration; however, the mechanism of NAGAMA is unclear [34]. The routine monitoring of pancreatitis, NAGAMA, and coagulation parameters may be a necessity when administering tigecycline to critically ill patients.

Interaction

The coadministration of tigecycline and warfarin (25 mg single dose) to healthy volunteers resulted in a 40 and 23% decrease in the clearance of R-warfarin and S-warfarin and their AUC, from time zero extrapolated to infinity, was increased by 68 and 29%, respectively [159]. The prothrombin time, or any other suitable anticoagulation test, should be used if tigecycline is administered with warfarin.

The prevalence of tigecycline resistance by continent

A summary of tigecycline resistance studies according to the individual countries worldwide are shown in Table 2 and Table 3.

Asia

In Asia, the occurrence of tigecycline resistance was reported in different bacterial species ranging from 0.% to 66% with a different distribution within the individual Asian countries (Table 2). The most frequently reported species, regarding tigecycline resistance, was *A. baumannii* [174] with a high resistance rate of 66% revealed in Israel [150].

In *Enterobacteriaceae*, a tigecycline resistance of 11% was reported for NDM-1-positive isolates from Pakistan and, a resistance of 37.9% was reported for tigecycline non-susceptible Metallobeta-lactamases producing isolates from Taiwan [167]; the prevalence of tigecycline-resistant *K. pneumoniae* was found to be 1.3% [183]. The reports of tigecycline-resistant *K. pneumoniae* came from Saudi Arabia [160, 169, 173], Taiwan[144], and Lebanon[169]; further tigecycline resistance was reported for *Escherichia coli*, *Enterobacter cloacae*, and *S. marcescens* [194, 217].

In other gram-negatives, tigecycline resistance was reported in *S. maltophilia* from Taiwan and China [165, 166, 181] and in 90% of *Pseudomonas aeruginosa* isolates from India [163].

For gram-positive pathogens, a tigecycline resistance rate of 3% in MRSA isolates [49, 218] was reported from India by Veeraraghavan *et al*. and in the study of Sharma *et al*.; 53.5% ($n = 68$) of *S. aureus* isolates showed non-susceptibility to tigecycline [179]. In recent years, the trend of increasing minimal inhibitory concentrations to tigecycline and linezolid was observed in Taiwan; however, strains with resistance to these agents were rare [219]. Interestingly, a 2% tigecycline resistance rate was reported in *S. pneumoniae* isolates gathered between 2004 and 2010 from the Asia-Pacific region, while in 2015, all *S. pneumoniae* isolates investigated were susceptible to tigecycline [220].

Europe

Tigecycline resistance is frequently studied in *Enterobacteriaceae* in Europe (Table 2). In ESBL producing *Enterobacteriaceae*, tigecycline resistance was reported in Italy, Belgium, Turkey, and France [187, 194, 195, 207]. Sader et al. reported that 11.4% of European carbapenem-resistant *Enterobacteriaceae* are not susceptible to tigecycline [192]. In France, cephalosporin-resistant *Enterobacteriaceae* were shown to be not susceptible to tigecycline in 23.8% of isolates [190].

For other gram-negative pathogens, resistance to tigecycline was reported in *Acinetobacter baumannii* [185, 221–224], as well as *S. marcescens* [211] and *H. influenzae* [211]. In gram-positive pathogens, tigecycline resistance was reported in two and three MRSA isolates from the Netherlands [225]. In Spain, tigecycline resistance was identified in *E. faecium*, *E. faecalis* and *viridans streptococci* [186] and in Germany, in *E. faecalis* [197]. In anaerobes, tigecycline resistance was investigated in the *B. fragilis* group in a Europe-wide study involving 13 countries, and a resistance rate of 1.7% was detected [226].

America

In the USA, high resistance rates to tigecycline were reported in *K. pneumoniae* (9.2%), *E. aerogenes* (20.8%), *K. oxytoca* (38.5%), *E. cloacae* (25.4%), and *S. marcescens* (20.0%) [202]. Sporadic cases were detected in *A. baumannii* [148, 150, 227–229] and *B. fragilis* [201]. ESBL-producing *Enterobacteriaceae* were shown to be tigecycline-resistant in the USA and Latin America [206]. In gram-positive pathogens, tigecycline resistance was reported in 9% of *S. aureus* in Mexico [207].

Africa

The tigecycline resistance rates in isolates collected between 2004–2016 in Africa were 5.8% (37/642) lower than in Europe (37.4%; 240/642) and North America (36.8%; 236/642) [49]. In the study of Seifert et al., 1.1% of *Enterobacter* spp. and 1.3% of *S. marcescens* isolates were tigecycline-resistant [183]. In the South of the continent, resistance to tigecycline was reported in *A. baumannii*, *K. pneumoniae*, *Enterobacter* spp., *C. freundii*, *P. aeruginosa*, and *S. marcescens* [198, 230–234].

Conclusion

Tigecycline is a unique glycylcycline class of semisynthetic agents designed to overcome the main tetracycline resistance mechanisms. Although tigecycline was approved for cSSTI, cIAI, and CAP in adults, its therapeutic potential is undoubtedly wider. Its antimicrobial activity against anaerobes and its greater penetration into tissues is advantageous for the treatment of inflammatory lesions and granulomas. Recently available clinical data support the use of tigecycline in severe *C. difficile* infections. In *vitro* antimicrobial susceptibility testing showed the susceptibility of a number of pathogens to tigecycline including those MDR pathogens associated with healthcare infections. However, the bacteriostatic activity of tigecycline is probably associated with a higher mortality risk in patients with sepsis or severe infection.

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Compliance with ethical standards

Conflict of interest Authors declare that they have no competing interests.

Ethical approval Not applicable in this section.

Informed consent Not applicable in this section.

Abbreviations *MDR,* Multidrug-Resistant; *XDR,* Extensively Drug-Resistant; *FDA,* Food and Drugs Administration; *cSSTI,* Complicated Skin and Skin Structures Infections; *cIAI,* Complicated Intra-Abdominal Infections; *CAP,* Community-Acquired Bacterial Pneumonia; *PK/PD,* Pharmacokinetic-Pharmacodynamic; *AUC: MIC,* Concentration-Time Curve and Minimal Inhibitory Concentration; *PAE,* Post-Antibiotic Effect; *CLSI,* Clinical and Laboratory Standards Institute; *EUCAST,* European Committee on Antimicrobial Susceptibility Testing; *BSAC,* British Society for Antimicrobial Chemotherapy; *MRSA,* Methicillin-Resistant *Staphylococcus aureus*; *VRE,* Vancomycin-Resistant *enterococci*; *ESBL,* Extended-Spectrum β-lactamase; *CDI, Clostridium difficile* infection; *RND,* Resistance-Nodulation Division; *SAM,* S-adenosyl-L-methionine; *CRKP,* Carbapenem-Resistant *K. pneumoniae*; *MATE,* Multi-Antimicrobial Extrusion Protein; *MFS,* Major Facilitator Superfamily; *FAERS,* FDA Adverse Event Reporting System; *RCTs,* Randomized Controlled Trials; *GI,* Gastrointestinal; *aPTT,* Activated Partial Thromboplastin Time; *NAGAMA,* Non-Anion Gap Acute Metabolic Acidosis

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