



# Tigecycline: a new antimicrobial agent against multiresistant bacteria

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Tigecycline (Tygacil®, Wyeth Pharmaceuticals) is a glycylcycline that is active against many aerobic and anaerobic Gram-positive and -negative microorganisms, atypical microorganisms and rapidly growing mycobacteria. It binds to the bacterial 30S ribosomal subunit and blocks entry of amino-acyl transfer RNA molecules into the A site. Tigecycline evades acquired efflux and target-mediated resistance to classic tetracyclines, but not chromosomal efflux in *Proteaeae* and *Pseudomonas aeruginosa*. It is administered intravenously as a 100 mg dose, followed by 50 mg every 12 h. The  $C_{max}$  is low but tissue penetration is good. Tigecycline is indicated for the treatment of skin and skin-structure infections and complicated intra-abdominal infections, and could be useful in infections due to multiresistant microorganisms such as methicillin-resistant *Staphylococcus aureus*, enterococci, extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae* and *Acinetobacter* spp.

The emergence and growth of bacterial resistance to existing antibiotics is a serious medical issue that has complicated the treatment of infectious diseases. As a result of the disproportionate use of antibiotics over the past 50 years, we are now losing the battle against many bacterial diseases [1]. In addition, when resistance increases, physicians switch from older to newer antibiotics as empirical therapy, healthcare workers implement the measures in order to prevent the transmission of infectious agents, infected patients become nonresponsive to older therapies, and all these components together increase healthcare costs [2].

In recent years we have faced not only the increase of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitalized patients, but also the emergence of severe infections caused by MRSA in patients who have had no exposure to hospitals or other medical care facilities, and moreover, the incursion of the more virulent community-associated MRSA strains into the hospital setting [3,4]. The excessive use of third-generation cephalosporins and glycopeptides has been implicated in the emergence of vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* as causes of serious intra-abdominal infections and endocarditis [5]. *S. aureus* isolates with intermediate resistance or heteroresistance to glycopeptides and, although currently rare, strains with high-level vancomycin resistance are a matter of grave concern [6–8]. The organisms causing respiratory tract infections are becoming increasingly resistant. Examples are the high rates

of resistance of *Streptococcus pneumoniae* to  $\beta$ -lactams and macrolides and the increasing resistance of *Streptococcus pyogenes* to the latter [9]. Pneumococci have also shown resistance to some fluoroquinolones, although at present the situation is not worrisome [10]. Among the Gram-negative organisms,  $\beta$ -lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* have been reported with increasing incidence from all countries. Multiresistant *Enterobacteriaceae* are widespread around the world. Many of these organisms produce extended-spectrum  $\beta$ -lactamases (ESBLs) that confer resistance to most  $\beta$ -lactams and are frequently associated to other genetic determinants that confer resistance to fluoroquinolones and aminoglycosides. The metalloenzymes, another group of  $\beta$ -lactamases, confer additional resistance to carbapenems, and are also increasingly being identified among *Enterobacteriaceae* and *Pseudomonas aeruginosa* [11]. The management of infections due to Gram-negative nonfermenters, such as *Acinetobacter baumannii*, can also be complicated due to the emergence of isolates with multidrug resistance (MDR), including resistance to carbapenems, and infections due to the MDR *Stenotrophomonas maltophilia* are becoming frequent mainly in intensive care units [12]. Finally, anaerobic bacteria are not exempt from developing resistance and examples of clindamycin-resistant and metronidazole-resistant *Bacteroides fragilis* are well known. Tigecycline (Tygacil®, Wyeth Pharmaceuticals) was developed to overcome mechanisms of microbial resistance, specifically against

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bacteria that are resistant to many other antibiotics. It is the first glycolcycline to be launched and exhibits potent activity against a broad spectrum of Gram-positive organisms such as *S. aureus* and coagulase-negative staphylococci, including methicillin-resistant isolates, and enterococci, including vancomycin-resistant strains. In addition, it has substantial anti-Gram-negative activity that includes most *Enterobacteriaceae*, including ESBL producers, and MDR *A. baumannii* and *S. maltophilia*. It is also active against most anaerobic bacteria, as well as most atypical microorganisms, including many rapidly growing nontuberculous mycobacteria [13].

### Overview of the market

During the past 10 years some pharmaceutical companies have reduced or eliminated their research in and development of antibacterial drugs. However, new antibacterial compounds have been developed for clinical use in recent years. Examples of antimicrobials recently introduced into the market include linezolid, daptomycin, ertapenem, quinupristin–dalbopristin and tigecycline [13–17]. In addition, some newer glycolipopeptides in development (oritavancin, dalbavancin, telavancin) active against Gram-positive microorganisms, and newer  $\beta$ -lactams (ceftobiprole) and carbapenems (faropenem, doripenem, tebipenem) are examples of attempts to meet the challenge of increasing antibiotic resistance [18–23]. Linezolid and quinupristin–dalbopristin were specifically designed to combat MDR Gram-positive organisms, but resistance to both agents has emerged, and quinupristin–dalbopristin intrinsically has no useful activity against *E. faecalis*. Daptomycin also overcomes the mechanisms of resistance of Gram-positive bacteria; however some cases of development of resistance have recently been reported during treatment. Ertapenem is a broad-spectrum carbapenem that is active against most common pathogens, except enterococci, nonfermenters and methicillin-resistant staphylococci. It remains active against most ESBL-producing *Enterobacteriaceae* species, although this activity is not quite as universal as it is for other carbapenems, and *in vivo* development of ertapenem resistance has been described in infections produced by ESBL-producing *Klebsiella pneumoniae*. Among the newer glycolipopeptides, although all are active against methicillin-resistant staphylococci, its activity against vancomycin-resistant enterococci is variable.

Oritavancin is active against vancomycin-resistant enterococci, telavancin retains certain activity against these microorganisms, and dalbavancin is not active against VanA enterococci. Cefetoprole is a new cephalosporin active against methicillin-resistant staphylococci, *Enterobacteriaceae* and *P. aeruginosa*, but it is not active against enterococci, Gram-negative anaerobes (with the exception of *Fusobacterium nucleatum*), and *S. maltophilia*, and has variable activity against other Gram-negative nonfermentative bacilli. Finally, the newer carbapenems do not represent any improvement over the old ones against methicillin-resistant staphylococci.

It is in this context that the new glycolcycline antibiotic, tigecycline, is introduced for parenteral use in the treatment of serious skin and skin-structure and intra-abdominal infections. This antimicrobial presents an acceptable tolerability profile, with nausea and vomiting being the most common drug-related adverse effects. Tigecycline acts at the ribosomal level inhibiting protein synthesis and is primarily bacteriostatic (although it has been reported to be both bacteriostatic and bactericidal against *S. pneumoniae* and *H. influenzae*). It is active against many aerobic and anaerobic Gram-positive cocci and Gram-negative bacilli, and evades the common mechanisms of resistance that affect the classical tetracyclines, namely acquired efflux and target-mediated resistance (ribosomal protection) [24,25].

### Introduction to tigecycline

Tigecycline (9-*t*-butylglycylamido-minocycline; formerly GAR-936; Wyeth Pharmaceuticals) is a new, semisynthetic glycolcycline that was licensed by the US FDA in June 2005 and received approval from the European Agency for the Evaluation of Medicinal Products (EMA) in April 2006. It is the first glycolcycline to be launched and the first new tetracycline analogue since minocycline over 30 years ago. Tigecycline has demonstrated potent *in vitro* antibacterial activity against a wide range of clinically important Gram-positive and -negative aerobic bacteria and anaerobes including, among others, MRSA, vancomycin-resistant enterococci, most ESBL-producing *Enterobacteriaceae*, *A. baumannii* and rapidly growing mycobacteria. Tigecycline retains activity against tetracycline-, doxycycline- and minocycline-resistant strains, but remains susceptible to the chromosomally encoded multidrug efflux pumps of *Proteae* and *P. aeruginosa*, and to Tet (X), a tetracycline-degrading mono-oxygenase, rarely found in *Bacteroides* spp. [26].

### Chemistry

Glycylcyclines are tetracycline derivatives that possess the central four-ring carbocyclic skeleton that is essential for antibacterial activity. Substitution of an *N*-alkyl-glycylamido group at position 9 on the D ring confers to glycylcyclines a broader spectrum of activity and permits evasion of the resistance mechanisms that affect to tetracycline. Tigecycline has a 9-*t*-butyl-glycylamido side chain on the central skeleton of minocycline (Figure 1). The formula for tigecycline is  $C_{29}H_{39}N_5O_8$ ; the drug has a molecular mass of 585.65 [24].

### Mechanism of action

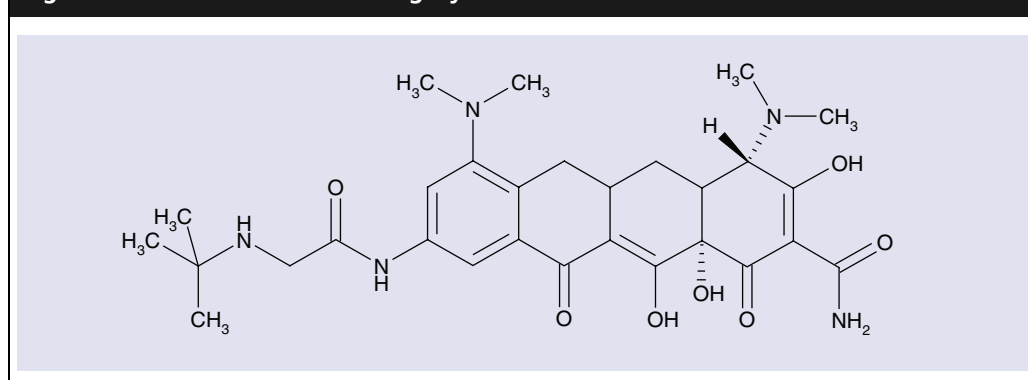
Tigecycline acts by binding to the bacterial 30S ribosomal subunit and by blocking entry of amino-acyl transfer RNA molecules into the A site of the ribosome. This binding has substantially higher affinity than that of the tetracyclines. Amino acid residues are prevented from becoming incorporated into elongating peptide chains, which leads to inhibition of protein synthesis. Although molecular modelling predicts that the tigecycline binding site overlaps with that of the tetracyclines, the glycylcyclines interact directly with another region of the A site in a manner never before seen for any A site-binding antibiotic [24]. Tigecycline is known to overcome the two major determinants of tetracycline resistance: active efflux of drug from inside the bacterial cell and protection of ribosomes. Tigecycline evades the Tet(A–E) efflux pumps [27,28], which account for most acquired resistance to tetracycline and minocycline in *Enterobacteriaceae* and *Acinetobacter* spp., and the Tet(K) pumps, which occur in staphylococci and confer resistance to tetracycline, though not minocycline or doxycycline [29]. In addition, it binds to bacterial ribosomes that have been modified by the Tet(M)

protein [27,28], a mechanism that compromises all available tetracyclines and which is frequent in Gram-positive cocci and *Neisseria* spp. [29]. Tigecycline appears to overcome these mechanisms as a result of steric hindrance produced by the large substituent at position 9 on the D-ring, as evidenced by dimethylsulfate modification of tigecycline binding sites, mutational analysis of 16S ribosomal RNA, and structural modeling of tigecycline at a binding site in the 30S ribosomal subunit [30].

### Pharmacodynamics

Tigecycline exhibits a time-dependent killing and has a prolonged postantibiotic effect. The time-dependent pattern of bactericidal activity has been demonstrated against *S. pneumoniae*, *H. influenzae* and *Neisseria gonorrhoeae*, and it has been reported to be both bacteriostatic and bactericidal against *S. pneumoniae* and *H. influenzae* [27]. This new antimicrobial is a bacteriostatic agent against *E. faecalis*, *Escherichia coli*, *S. aureus* and *K. pneumoniae*, as demonstrated in *in vitro* time-kill studies [31]. The pattern of killing of tigecycline against *S. aureus*, *E. coli* and *K. pneumoniae* in time-kill studies at four-times the minimal inhibitory concentration (MIC) over 24 h resulted in a  $-2.0 \pm 1.3 \log_{10}$  colony-forming units (CFU)/ml reduction for *S. aureus*,  $-0.7 \pm 0.7 \log_{10}$  CFU/ml reduction for *E. coli* and  $+0.4 \pm 1.5 \log_{10}$  CFU/ml growth for *K. pneumoniae*. At a concentration of 2 mg/l, 0.5–0.7  $\log_{10}$  CFU/ml reductions in *E. faecium* and 0.7–1.4  $\log_{10}$  CFU/ml reduction in glycopeptide intermediate *S. aureus* were observed over 24 h [32]. Minimal bactericidal concentrations (mg/l) of tigecycline are twofold higher than the MIC for *S. pneumoniae* and two- to four-times the MIC for *S. aureus* [33]. Tigecycline is bacteriostatic against enterococci, and this

Figure 1. Chemical structure of tigecycline.



effect is not enhanced by increasing concentrations to more than 1 mg/l [34]. Bacterial inoculum appears to have a modest effect on tigecycline MICs, which are one to two dilutions higher with ten- to 100-fold increases in inoculum [35]. The combination of tigecycline plus gentamicin has enhanced *in vitro* activity against vancomycin-resistant *E. faecalis* and *S. aureus* [32].

Tigecycline exhibits *in vitro* postantibiotic effect (PAE) durations of 4.1 h (tetracycline-susceptible *S. aureus*), greater than 3 h (tetracycline-resistant *S. aureus*), 2.9 h (tetracycline-susceptible *E. coli*), 1.8–2.6 h (tetracycline-resistant *E. coli*), and 1–4.5 h (*E. faecalis*) [36]. *In vivo* PAE durations of 4.9 h (*E. coli*) and 8.9 h (*S. pneumoniae*) have been reported [33].

A pharmacodynamic (PD) study of tigecycline using a murine model was conducted in order to identify and characterize the pharmacokinetic (PK)/PD indices required for optimal *in vivo* activity and the efficacy against several bacterial species. Data obtained from this study suggest that the drug exposures to clear different bacterial species with tigecycline may be different, with *S. pneumoniae* requiring the lowest exposures, *S. aureus* and *E. coli* higher, and *K. pneumoniae* even higher. In this murine model, the area under the concentration–time curve (AUC) from time of administration to infinity ( $AUC_{0-\infty}$ ) and the time above the MIC for the organisms could be related to antibacterial effect using nonlinear regression analysis. This study demonstrates that in order to achieve 80% maximum efficacy, the concentration of unbound drug in serum should be maintained above the MIC for at least 50% of the dosing interval for tigecycline [33].

The AUC is the PD parameter of tigecycline that appears to best correlate with bacteriologic eradication. The relationship between tigecycline AUC, MIC and microbiological outcome has been evaluated using data from three trials in complicated skin and soft tissue infection [37,38]. Two different dose regimens were used: 100 mg load plus 50 mg every 12 h and 50 mg load plus 25 mg every 12 h. The serum  $AUC_{0-24}$  at steady state was 5.16 mg/l (median), range 2.81–9.36 mg/l (high dose) and median 2.33, range 1.49–4.98 mg/l (low dose). Among the pathogens isolated, the most useful for the analysis were all Gram-positive pathogens ( $n = 36$ ). If the AUC/MIC value was less than 25, five patients failed therapy and ten were cured, if the AUC/MIC was over 25, no patients failed and 20 were cured. An AUC/MIC of 12.3 was identified for both microbiological and clinical responses. Given an AUC/MIC

breakpoint of 12–18 for infection mainly caused by *S. aureus*, this PD breakpoint would be less than or equal to 0.25 mg/l [39].

A similar analysis was performed on patients in three trials of complicated intra-abdominal infection. Patients received tigecycline 100 mg followed by 50 mg twice daily, and the median AUC was 5.6 mg/h/l. An AUC/MIC of 6.96 was significant for both microbiological and clinical outcomes. An AUC/MIC of over 30 was associated with over 90% chance of success [40]. These data were used to try to develop a PD breakpoint for *E. coli*, which was found to be 0.5 mg/l [41].

## Pharmacokinetics & metabolism

### Absorption & distribution

The oral bioavailability of tigecycline is very limited. Tigecycline is only available as an injectable formulation. It is administered parenterally as a 1-h infusion twice daily. Overall, the PK in animals is characterized by a low total clearance ( $CL_T$ ), a large apparent volume of distribution at steady state ( $V_{ss}$ ), and a long elimination half-life ( $t_{1/2}$ ) [42]. Tigecycline exhibits linear PK, it is rapidly distributed and has a large volume of distribution. Initial values of  $V_{ss}$  are over 10 l/kg, indicating extensive distribution into the tissues. Total volumes of distribution are approximately 350 l in women and 500 l in men. After a 100 mg loading dose, followed by 50 mg every 12 h, the steady-state maximum concentration in serum after a 1-h infusion is approximately 0.6 mg/l, the 24-h steady-state AUC is approximately 5–6 mg.h/l, and the terminal elimination half-life is approximately 40 h [13,42]. The single- and multiple-dose PK of tigecycline in healthy volunteers have been evaluated after intravenous administration of 12.5, 25, 50, 75, 100, 200, and 300 mg during 1 h. For single-dose exposures, the  $V_{ss}$  were 2.8, 6.4, 6.5, 7.5, 6.8, 13 and 12 l/kg, respectively, indicating some dose-dependency. In the multidose studies, the  $V_{ss}$  for the 25, 50 and 100-mg doses were 8.6, 7.2 and 9.1 l/kg, respectively. The reasons for these differences are unclear, but given tigecycline's large volume of distribution there must be tissues into which it is concentrated [43].  $C_{max}$  and AUC were dose proportional, rising from a mean of 0.11 mg/l and 0.9 mg.h/l, respectively, after 12.5 mg, to 2.8 mg/l and 17.9 mg.h/l, respectively, after 300 mg. The  $t_{1/2}$  of tigecycline ranges from 37–67 h. Food improved tolerability, increasing the maximum tolerated dose from 100–200 mg. The duration of infusion does not affect tolerability. Neither administration with

food or the sex or age of the patient appreciably altered the PK profile of tigecycline. Total body clearance was independent of dose and ranged from 0.2–0.3 l/kg/h [24,43]. PK parameters are summarized in Table 1.

Similar findings were observed in a study conducted in healthy Japanese volunteers [44]. Four dose levels were evaluated (25, 50, 100 and 150 mg intravenously during 1 h after feeding). In contrast to the previous study, the maximum tolerated dose was 100 mg, being limited by dose-related nausea and vomiting. Dose proportionality was noted for  $C_{max}$  and AUC, rising from a mean of 0.20 mg/l and 0.8 mg.h/l, respectively, after 25 mg, to 1.52 mg/l and 8.6 mg.h/l, respectively, after 150 mg.  $V_{ss}$  and  $t_{1/2}$  increased with increasing dose (mean 4.4, 7.1, 9.1 and 10.8 l/kg and 8.2, 15.7, 24.3 and 35.5 h after 25, 50, 100 and 150 mg, respectively). The relative importance of serum versus tissue levels in predicting outcomes for tigecycline is still unclear, but this may be important given its large volume of distribution.

Studies in adult humans who received 100 mg intravenous tigecycline have indicated concentrations in lung tissue of 0.8 mg/l at 4 h postdose, 0.2 mg/l at 8 h, 0.4 mg/l at 12 h, and 0.4 mg/l at 24 h. Cerebrospinal fluid (CSF) concentrations in noninflamed meninges were low, with values of 5% 1 h postinfusion and 41% after 24 h. Bile concentrations were high, ranging from 0.16–4.37 mg/l [45]. In a single-dose rat study, excellent overall tissue penetration was noted, with the highest levels observed in bone and bone marrow, followed by salivary gland, thyroid, spleen and kidney. The tissue AUC/plasma AUC was more than 1 mg.h/l for most tissues over the 168 h of the experiments [46]. In a rabbit

model of meningitis, single doses of tigecycline of over 20 mg/kg yielded concentrations in CSF of more than 1 mg/l at 3 h that stayed at a steady level or increased at 6 h [47].

Tigecycline protein binding ranges from 73% at 0.1 mg/l to 79% at 1 mg/l – the reason for this atypical pattern is as yet unknown.

### Metabolism

Tigecycline is eliminated primarily by the liver via biliary excretion of unchanged drug and via glucuronidation, with less than 15% of the drug excreted unchanged in the urine. Renal clearance accounts for less than 20% of total clearance. An *N*-acetyl-9-aminomincycline metabolite is also formed to a less degree. At least five human metabolites have been described in urine, serum, feces and plasma [13,42,48].

The effects of severe renal impairment (defined as creatinine clearance < 30 ml/min) and hemodialysis on the PKs of tigecycline were evaluated after intravenous administration of a single 100-mg dose. In comparison with a control group of healthy volunteers, the mean  $C_{max}$  in the severe renal impairment group was similar (0.604 mg/l in both groups) whereas the AUC was 40% higher and urinary recovery was lower (5 vs 16% of the dose). Compared with the control group, the mean  $C_{max}$  in the hemodialysis group was 60% higher, whereas the AUC was 20% higher. Since hemodialysis had no significant effect on tigecycline PKs, and only 5% of unchanged drug is recovered in the dialysate, no dose adjustment is required in patients with renal dysfunction, and patients undergoing hemodialysis can receive tigecycline either before or after a dialysis session [49].

**Table 1. Mean pharmacokinetic parameters of tigecycline after various single and multidose intravenous doses.**

Pharmacokinetic parameter	25 mg	50 mg	100 mg	25 mg		50 mg		100 mg	
				Day 1	Day 10	Day 1	Day 10	Day 1	Day 10
$C_{max}$ (mg/l)	0.25	0.38	0.91	0.26	0.32	0.49	0.62	0.82	1.17
AUC (mg.h/l)	2.26	2.56	6.4	0.8	1.48	1.44	3.07	2.39	4.98
CL (l/h/kg)	0.20	0.28	0.2		0.2		0.2		0.24
$V_{ss}$ (l/kg)	6.4	6.4	8.6		8.26		7.2		9.1
$t_{1/2}$ (h)	32	18	38		49.3		36.9		66.5
$CL_R$ (l/h)			2.6						

AUC: Area under the concentration–time curve; CL: Clearance;  $CL_R$ : Renal clearance;  $C_{max}$ : Peak concentration;  $t_{1/2}$ : Half-life;  $V_{ss}$ : Volume of distribution at steady state.

Data taken from [24,42,43,48].



There are no published data as yet regarding the PK and safety of tigecycline in patients with hepatic impairment. Since most tigecycline is eliminated by the liver, clinicians treating patients with severe hepatic dysfunction must be cautious with the use of this agent.

### Drug–drug interactions

Coadministration of digoxin plus tigecycline or warfarin plus tigecycline in healthy male volunteers had no impact on the PK of either agent [50,51].

### In vitro activity

Tigecycline has demonstrated potent *in vitro* antibacterial activity against a wide range of clinically important Gram-positive and -negative aerobic bacteria in addition to anaerobes including *S. aureus*, *Enterococcus* spp., *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, *Neisseria meningitidis*, most *Enterobacteriaceae*, *A. baumannii* and *S. maltophilia* [52–54]. Its activity against anaerobes includes *Peptostreptococcus* spp., *Gemella* spp., *Propionibacterium* spp., *Clostridium* spp., *Prevotella* spp., *Fusobacterium* spp., and most *Bacteroides* spp. [55]. The agent is also active against *Mycoplasma hominis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, and several species of rapidly growing mycobacteria. Tigecycline is somewhat less active against *Legionella* spp. and *Ureaplasma urealyticum*, and is inactive against *P. aeruginosa*, *Burkholderia cepacia* and slowly growing mycobacteria [13,27,35,53,56–59]. Tigecycline has reduced activity against *Morganella morganii*, *Proteus* spp. and *Providencia* spp. [27,53]. Its activity is not affected by the presence of resistance to penicillin (for *S. pneumoniae* and viridans group streptococci), macrolides (for *S. pneumoniae*), vancomycin (for enterococci and staphylococci), or methicillin (for staphylococci). As tigecycline is structurally unrelated to the  $\beta$ -lactams, it is not affected by  $\beta$ -lactamase enzymes; indeed, it is active against  $\beta$ -lactamase-producing *H. influenzae* and *M. catarrhalis*, and against ESBL-producing *Enterobacteriaceae* [13,18,27,60]. It also exhibits substantial activity against the pathogens of animal and human bites such as *Eikenella corrodens*, *Ef-4b*, *Pasteurella* spp., *Corynebacterium* spp., and *Porphyromonas* spp., [61] and has shown good *in vitro* activity against *Nocardia* spp. [62].

Tigecycline is primarily bacteriostatic, although it has been reported to be both bacteriostatic and bactericidal against *S. pneumoniae* and *H. influenzae* [27].

### In vitro activity against Gram-positive microorganisms

Tigecycline MICs for staphylococci, enterococci and streptococci are mostly 0.06–0.5 mg/l with, in general, a unimodal distribution. The *in vitro* activity of tigecycline against Gram-positive microorganisms is shown in Table 2.

In a study of a worldwide collection of 10,127 staphylococci, streptococci, and enterococci, tigecycline inhibited all streptococci at a concentration of 2 mg/l or less. It was equally active against methicillin-susceptible and methicillin-resistant staphylococci with an MIC<sub>90</sub> of 0.5 mg/l. Against *S. pneumoniae*, viridans group streptococci, and  $\beta$ -hemolytic streptococci, the MIC<sub>90</sub> values of tigecycline were 0.12 mg/l or less [63].

Different studies have reported tigecycline MICs from 0.06–1 mg/l against methicillin-susceptible and -resistant *S. aureus*, MIC<sub>90</sub> values of 0.25 mg/l against methicillin-susceptible, and 0.5 mg/l against methicillin-resistant isolates. Tigecycline has excellent activity against *S. pneumoniae* (MICs  $\leq$  0.016–0.5 mg/l), and against *S. pyogenes* and *Streptococcus agalactiae*, including tetracycline- and macrolide-resistant isolates (MIC<sub>90</sub> 0.06 mg/l) [27,35,53,64].

Tigecycline is active *in vitro* against vancomycin-resistant enterococci (VanA, VanB and VanC) and staphylococci with diminished susceptibility to glycopeptides (*S. aureus* and coagulase-negative staphylococci). In a study that evaluated 157 strains, all were inhibited at concentrations from less than or equal to 0.03–1 mg/l, including those that were resistant to tetracycline, and 90% of isolates were inhibited with 0.5 mg/l of tigecycline. The MIC<sub>90</sub> of tigecycline against coagulase-negative staphylococci was 0.5 mg/l, and that against enterococci was 0.12 mg/l. All *S. aureus* isolates were inhibited by 1 mg/l tigecycline. Tigecycline did not exhibit bactericidal activity, with a minimal bactericidal concentration (MBC)<sub>90</sub> of over 32 mg/l [65].

There are few studies evaluating the activity of tigecycline against diphtheroids. In one study that included 20 isolates, the MIC<sub>90</sub> of tigecycline was 2.0 mg/l, and it was 4.0 mg/l against two isolates of *Corynebacterium jeikeium* [66].

### In vitro activity against Gram-negative microorganisms

Tigecycline MIC distributions for *Enterobacteriaceae* species are unimodal, with only a slight positive shift. Values range from approximately 0.12–0.25 mg/l for *E. coli*, and 0.5–1 mg/l for *Klebsiella* spp., *Enterobacter* spp., and *Citrobacter* spp., with fewer than 2% of isolates of these latter

**Table 2. *In vitro* activity of tigecycline against Gram-positive microorganisms.**

Organism	MIC range*	MIC <sub>50</sub> range*	MIC <sub>90</sub> range*
<i>Staphylococcus aureus</i>	≤0.02–2	0.06–0.5	0.125–1.0
Oxacillin susceptible	0.06–1	≤0.13–0.5	0.25–0.5
Oxacillin resistant	≤0.06–2	≤0.13–0.5	0.25–1.0
Vancomycin intermediate	0.06–2	0.25	0.5
Coagulase-negative staphylococci	≤0.03–2	0.06–1.0	0.25–1.0
Oxacillin susceptible	≤0.03–1	0.25–0.5	0.25–1.0
Oxacillin resistant	≤0.03–2	0.5–1.0	0.25–1.0
Enterococcus species	≤0.02–2	0.03–0.25	0.06–0.5
<i>Enterococcus faecalis</i>	≤0.02–2	0.13–0.25	0.13–0.5
Vancomycin resistant	≤0.03–0.5	0.13	0.13–0.5
<i>Enterococcus faecium</i>	≤0.03–0.5	0.06–0.25	0.13–0.25
Vancomycin resistant	≤0.03–0.5	0.06–0.13	0.13
<i>Enterococcus avium</i>	≤0.06–0.13	0.06	0.06
<i>Enterococcus casseliflavus</i>	0.03–0.5	0.13–0.25	0.13–0.25
<i>Enterococcus gallinarum</i>	0.06–2	0.13	0.13–0.25
<i>Enterococcus raffinosus</i>	0.06–0.5	0.06	0.13
<i>Streptococcus pneumoniae</i>	≤0.01–1	≤0.02–0.25	≤0.02–0.5
Penicillin susceptible	≤0.02–0.5	0.03–0.25	0.13–0.25
Penicillin intermediate	≤0.02–1	0.03–0.25	0.06–0.5
Penicillin resistant	≤0.02–1	0.06–0.25	0.13–0.25
Tetracycline susceptible	0.01–0.13	0.03	0.03
Tetracycline resistant	0.02–0.5	0.03	0.03
<i>Streptococcus pyogenes</i>	≤0.02–0.5	0.06–0.13	0.06–0.25
<i>Streptococcus agalactiae</i>	0.03–0.5	0.06–0.13	0.06–0.25
<i>Viridans streptococci</i>	0.01–2	≤0.02–0.06	0.03–0.5
Penicillin susceptible	0.03–0.25	0.06	0.25
Penicillin resistant	0.02–0.13	0.03	0.06
Tetracycline susceptible	0.02–0.06	0.03	0.06
Tetracycline resistant	0.01–0.5	0.06	0.13

\*MICs are expressed in mg/l. US FDA recommendations for MIC susceptibility breakpoints: *Staphylococcus*: ≤0.5 mg/l; *Streptococcus* spp. other than *S. pneumoniae*: ≤0.25 mg/l; *E. faecalis* (vancomycin-susceptible isolates only): ≤0.25 mg/l.

MIC: Minimal inhibitory concentration; MIC<sub>50</sub>: MIC required to inhibit the growth of 50% of organisms;

MIC<sub>90</sub>: MIC required to inhibit the growth of 90% of organisms.

Data taken from [17,27,35,52–54,63–66].

species having MICs over 2 mg/l. Values against ESBL-producing *Enterobacteriaceae* range from 0.5–1 mg/l, with approximately 6% of isolates having MICs over 1 mg/l [60]. *Acinetobacter* spp. and *S. maltophilia* are mostly susceptible at 0.5–2 mg/l, although MICs of tigecycline as high as 16 mg/l have been reported against *Acinetobacter* spp. MICs for Proteaceae (*Proteus* spp., *Morganella morganii* and *Providencia* spp.) are mostly 2–8 mg/l and those for *P. aeruginosa* are 8–32 mg/l. Tigecycline MICs against *H. influenzae* and *M. catarrhalis* range from less than or equal to 0.06 to over

8 mg/l [53,63,67]. *E. corrodens* is inhibited at concentrations from less than or equal to 0.06 to 4 mg/l (MIC<sub>90</sub> of 2 mg/l) [68].

In a worldwide study, the MIC<sub>90</sub> of tigecycline against *Enterobacteriaceae* was 1 mg/l and 96.1% of the isolates of *Acinetobacter* spp. were susceptible at 4 mg/l or less, including imipenem-resistant isolates [69]. In other studies, tigecycline inhibited over 95% of the isolates of *S. maltophilia* tested at a concentration of less than or equal to 4 mg/l [70]. The *in vitro* activity of tigecycline against Gram-negative microorganisms is shown in Table 3.

**Table 3. *In vitro* activity of tigecycline against Gram-negative microorganisms.**

Organism	MIC range*	MIC <sub>50</sub> range*	MIC <sub>90</sub> range*
<i>Escherichia coli</i>	0.06–2	0.13–0.5	0.25–1
Non-ESBL-producing	0.06–2	0.13–0.5	0.25–1
ESBL-producing	0.06–2	0.13–0.25	0.5–1
Ciprofloxacin susceptible	0.5–2	1	1
Ciprofloxacin resistant	0.5–2	1	1
<i>Klebsiella pneumoniae</i>	0.06–8	0.25–1	1–2
Non-ESBL-producing	0.06–4	0.25–1	1–2
ESBL-producing	0.06–8	0.25–1	1–2
<i>Klebsiella oxytoca</i>	0.5–2	0.5–1	1
<i>Morganella morganii</i>	1–8	2–4	4
<i>Proteus mirabilis</i>	1–8	4	8
<i>Proteus vulgaris</i>	0.13–16	4	4
<i>Providencia</i> species	4–8	4	8
<i>Shigella</i> species	0.13–0.5	0.25	0.5
<i>Salmonella</i> species	0.25–2	1	1
<i>Citrobacter</i> species	0.25–16	0.5–1	0.5–2
<i>Citrobacter freundii</i>	0.25–16	0.5–1	2
<i>Enterobacter</i> species	0.25–8	1	1–2
<i>Enterobacter cloacae</i>	0.25–4	1	2
<i>Enterobacter aerogenes</i>	0.25–8	1	1
<i>Serratia marcescens</i>	0.5–8	2–4	2–4
<i>Stenotrophomonas maltophilia</i>	0.25–8	0.5–2	2–4
<i>Pseudomonas aeruginosa</i>	0.5–32	8–>16	16–32
<i>Acinetobacter</i> species	≤0.03–16	0.25–2	0.5–8
<i>Acinetobacter baumannii</i>	0.03–16	0.5–2	2–8
<i>Burkholderia cepacia</i>	0.5–64	2–4	4–32
<i>Haemophilus influenzae</i>	≤0.13–4	0.25–1	0.5–2
<i>Moraxella</i> spp.	≤0.03–0.25	0.06–0.13	0.13–0.25
<i>Moraxella catarrhalis</i>	≤0.03–2	0.06–0.13	0.13–0.5
<i>Neisseria gonorrhoeae</i>	≤0.02–1	0.06–0.5	0.13–1
Tetracycline-susceptible	≤0.02–0.25	0.06	0.13
Tetracycline-intermediate	0.06–0.25	0.13	0.25
Tetracycline-resistant	0.06–1	0.25	0.5
<i>Eikenella corrodens</i>	≤0.06–4	0.5	2

\*MICs are expressed in mg/l. US FDA recommendations for MIC breakpoints for Enterobacteriaceae are: susceptibility: ≤2 mg/l; intermediate: 4 mg/l; resistant: ≥8 mg/l.

ESBL: Extended-spectrum  $\beta$ -lactamase; MIC: Minimal inhibitory concentration; MIC<sub>50</sub>: MIC required to inhibit the growth of 50% of organisms; MIC<sub>90</sub>: MIC required to inhibit the growth of 90% of organisms.

Data taken from [27,52–54,60,61,67,68,70].

### ***In vitro* activity against anaerobic bacteria**

Preclinical and clinical studies demonstrated that the MIC distribution curves of tigecycline are not unimodal against anaerobes, and present a shoulder of isolates with higher MICs. Tigecycline inhibits *Bacteroides* spp. at concentrations from 0.02–8 mg/l [27,53,55,71].

In a Spanish multicenter study, tigecycline inhibited 86.7% of all anaerobes tested, at a concentration of 4 mg/l, and its activity included *B. fragilis*, other members of the *B. fragilis* group, and toxigenic *Clostridium difficile* [53].

Another study evaluated the *in vitro* activity of tigecycline against *Bacteroides*, *Prevotella*, *Porphyromonas*, *Fusobacterium*, *Propionibacterium*,



*Peptostreptococcus*, and *Actinomyces* spp. Tigecycline was very active against all anaerobic species, with an MIC<sub>90</sub> of 0.25 mg/l or less [61].

The *in vitro* activity of tigecycline against anaerobic microorganisms is shown in Table 4.

#### **In vitro activity against atypical microorganisms & mycobacteria**

Tigecycline is active against *M. pneumoniae* and *M. hominis*. The reported MIC<sub>90</sub> values of tigecycline against *M. pneumoniae* and *M. hominis* are 0.25 and 0.5 mg/l, respectively. *U. urealyticum* is less susceptible to tigecycline (MIC<sub>90</sub> 8 mg/l) [56].

Tigecycline has been reported as active against rapidly growing mycobacteria, including *Mycobacterium fortuitum* group, *Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium immunogenum*, and the *Mycobacterium smegmatis* group. These species are highly susceptible to tigecycline, with an MIC<sub>90</sub> of 0.25 mg/l for *M. abscessus* and less than 0.12 mg/l for *M. chelonae* and the *M. fortuitum* group [58]. Tigecycline MICs are the same regardless of resistance or susceptibility to tetracycline. None of the slowly growing nontuberculous mycobacteria, including *Mycobacterium avium* complex, *Mycobacterium lentiflavum*, *Mycobacterium kansasii*, *Mycobacterium marinum*, *Mycobacterium xenopi*, and *Mycobacterium simiae* are susceptible to tigecycline [58]. Against *M. marinum*, tigecycline has been noted to have an MIC<sub>90</sub> of 3 mg/l, having a similar potency to that of the parent minocycline compound (MIC<sub>90</sub> of 2 mg/l) but the range of tigecycline MIC values extended to 24 mg/l [72].

In one study, tigecycline demonstrated to be active against different *Nocardia* species including *N. ciriacegeorgica*, *N. farcinica*, *N. otitidiscaviarum*, *N. abscessus*, *N. beijingensis*, *N. nova*, *N. veterana*, *N. transvalensis*, *N. carnea*, and *N. brasiliensis*. The MIC<sub>90</sub> and range were 4 and from less than or equal to 0.06 to 8.00 mg/l, respectively [62].

In a guinea pig model of Legionnaires disease, tigecycline was as effective as erythromycin against intracellular *Legionella pneumophila* although it was associated with persistence of *L. pneumophila* in the lungs at the end of therapy [59].

The *in vitro* activity of tigecycline against atypical microorganisms is presented in Table 5.

#### **Resistance**

Tigecycline is vulnerable to the chromosomally-encoded multidrug efflux pumps of Proteaceae (AcrAB multidrug efflux pump) and *P. aeruginosa* (MexAB-OprM and MexCD-OprJ), and to Tet(X), a tetracycline-degrading mono-oxygenase found in *Bacteroides* spp. [13,26,29].

*In vitro*-selected mutations of *tet(A)*, enabled the efflux of tigecycline. Emerging resistance during the Phase III trials has also been reported with *K. pneumoniae*, *Enterobacter cloacae*, *Morganella morganii* and *A. baumannii*, all apparently associated with upregulation of chromosomally-mediated efflux pumps [26]. Other studies from several laboratories have reported the existence of tigecycline nonsusceptible *A. baumannii* isolates [26,73,74].

**Table 4. *In vitro* activity of tigecycline against anaerobic microorganisms.**

Organism	MIC range*	MIC <sub>50</sub> range*	MIC <sub>90</sub> range*
<i>Bacteroides fragilis</i>	0.5–8.0	2	2
<i>Bacteroides fragilis</i> group	0.02–2.0	0.13–0.5	0.13–2.0
<i>Clostridium perfringens</i>	0.03–4.0	0.03–0.5	0.25–1.0
<i>Clostridium difficile</i>	≤0.02–0.25	0.03–0.13	0.03–0.13
<i>Propionibacterium acnes</i>	0.03–0.13	0.03	0.06
<i>Peptostreptococcus</i> species	≤0.02–0.5	0.03–0.06	0.03–0.25
<i>Fusobacterium</i> species	≤0.02–0.25	0.02–0.06	0.06
<i>Prevotella</i> species	0.02–1.0	0.03–0.5	0.06–1.0
<i>Porphyromonas</i> species	≤0.02–0.13	0.03–0.06	0.06

\*MICs are expressed in mg/l. US FDA recommendations for MIC breakpoints for anaerobes are: susceptibility: ≤4 mg/l; intermediate: 8 mg/l; resistant: ≥16 mg/l.

MIC: Minimal inhibitory concentration; MIC<sub>50</sub>: MIC required to inhibit the growth of 50% of organisms; MIC<sub>90</sub>: MIC required to inhibit the growth of 90% of organisms.

Data taken from [27,55,61].

**Table 5. *In vitro* activity of tigecycline against atypical microorganisms.**

Organism	MIC range*	MIC <sub>50</sub> range*	MIC <sub>90</sub> range*
<i>Mycobacterium abscessus</i>			
Tetracycline susceptible	≤0.06–1	≤0.13	0.25
Tetracycline resistant	≤0.06–1	≤0.13	0.25
<i>Mycobacterium chelonae</i>			
Tetracycline susceptible	≤0.25	≤0.06	≤0.13
Tetracycline resistant	≤0.25	≤0.06	≤0.13
<i>Mycobacterium fortuitum</i> group			
Tetracycline susceptible	≤0.25	≤0.06	≤0.13
Tetracycline resistant	≤0.25	≤0.06	≤0.13
<i>Mycobacterium avium</i> complex	≥32	>32	>32
<i>Mycobacterium lentiflavum</i>	≥32	>32	>32
<i>Mycobacterium marinum</i>	0.19–24	2–16	3–16
<i>Mycobacterium kansasii</i>	8–32	16	32
<i>Chlamydophila pneumoniae</i>	0.13–0.25	0.13	0.13
<i>Mycoplasma hominis</i>			
Tetracycline susceptible	0.13–0.5	0.25	0.5
Tetracycline resistant	0.13–0.5	0.25	0.5
<i>Mycoplasma pneumoniae</i>	0.06–0.25	0.13	0.25
<i>Ureaplasma urealyticum</i>	1–16	4	8
<i>Nocardia</i> spp.	≤0.06–8	1	4

\*MICs are expressed in mg/l.

MIC: Minimal inhibitory concentration; MIC<sub>50</sub>: MIC required to inhibit the growth of 50% of organisms; MIC<sub>90</sub>: MIC required to inhibit the growth of 90% of organisms.

Data taken from [56–58,62,72].

### Clinical efficacy

Tigecycline is currently approved for the treatment of patients with complicated skin and skin-structure infections and complicated intra-abdominal infections.

The clinical and microbiological efficacy, PK, and tolerability of tigecycline were evaluated in a Phase II, randomized, open-label, dose-comparison study performed in hospitalised patients with complicated skin and skin-structure infections. Patients were randomized to receive either tigecycline 25 mg intravenously twice daily after a 50-mg intravenous loading dose, or 50 mg intravenously twice daily after a 100-mg intravenous loading dose every 12 h for 7–14 days. Of 164 enrollees, 160 were evaluable for safety, 112 were clinically evaluable, and 91 were bacteriologically evaluable. Clinical cure rates of the clinically evaluable patients at the test-of-cure visit were lower in the 25-mg group (67%) than in the 50-mg group (74%). Similar findings were noted for the bacteriologic eradication (56% in the 25-mg group compared with 69% in the 50-mg group). Nausea and vomiting were noted

to be the most frequent adverse events. The authors concluded that tigecycline is efficacious, with a favorable PK profile, for treatment of hospitalized patients with complicated skin and skin-structure infections [75].

Tigecycline monotherapy was evaluated in another multicenter, Phase II, open-label study of hospitalized patients with complicated intra-abdominal infections requiring surgery. Diagnoses included perforated and gangrenous appendicitis, complicated cholecystitis, perforated diverticulitis, and peritonitis. All patients received tigecycline 100 mg administered intravenously as a loading dose, followed by 50 mg every 12 h for 5–14 days. Of 111 enrollees, aged 18–80 years, 66 were evaluated for efficacy. Clinical cure rates at the test-of-cure at the end-of-treatment visits were 67 and 76%, respectively. In the intent-to-treat analyses, corresponding clinical cure rates were 55 and 72%. Nausea and vomiting were the most common adverse events. The authors concluded that tigecycline was safe and efficacious for treatment of hospitalized patients with complicated intra-abdominal infections [76].

Microorganisms resistant to tigecycline have been noted in clinical trials including isolates of *K. pneumoniae*, *E. cloacae*, *M. morganii*, and *A. baumannii* [26].

Phase III studies have demonstrated equivalence in safety and efficacy of tigecycline monotherapy in comparison to vancomycin plus aztreonam in skin and skin-structure infections, and to imipenem in intra-abdominal infections.

Two Phase III, double-blind studies in hospitalized adults with complicated skin and skin-structure infections determined the safety and efficacy of tigecycline versus that of vancomycin–aztreonam. Patients received tigecycline (100 mg, followed by 50 mg intravenously twice daily) or vancomycin (1 g intravenously twice daily) plus aztreonam (2 g intravenously twice daily) for up to 14 days. The clinically evaluable population included 833 patients (422 treated with tigecycline and 411 treated with vancomycin–aztreonam) and 540 of these patients (279 treated with tigecycline and 261 with the comparators) had an isolate recovered prior to therapy. Most patients had extensive cellulitis or a soft-tissue infection requiring surgical intervention. Clinical responses to tigecycline and vancomycin–aztreonam at test-of-cure were similar: clinical modified intent-to-treat population, 79.7 versus 81.9%; and clinically evaluable, 86.5 versus 88.6% [77]. Microbiological success rates were also comparable in the two treatment groups (86 vs 88%). Similar eradication rates were observed in the two treatment groups in patients with monomicrobial and polymicrobial infections, as well as those patients who were bacteremic. No isolates developed a decreased susceptibility to tigecycline in this study.

Two Phase III, double-blind trials evaluated the safety and efficacy of tigecycline, versus that of imipenem–cilastatin, in adults with complicated intra-abdominal infections [78]. Patients were randomized to receive either tigecycline (initial dose of 100 mg, followed by 50 mg intravenously every 12 h) or imipenem–cilastatin (500/500 mg intravenously every 6 h) for 5–14 days. The clinically evaluable population contained 1382 patients (585 received tigecycline, and 607 received imipenem–cilastatin), of whom 1262 had a pretherapy isolate recovered from their infection site. Complicated appendicitis (50%) was the most common infection diagnosis, followed by complicated cholecystitis (14%). For the microbiologically evaluable group, clinical cure rates were 86.1% for tigecycline versus 86.2% for imipenem–cilastatin.

Clinical cure rates in the microbiological modified intent-to-treat population were 80.2% for tigecycline versus 81.5% for imipenem–cilastatin. A total of 12 (80%) of 15 patients with ESBL-producing *E. coli* or *K. pneumoniae* achieved bacterial eradication after receiving tigecycline. Two patients with isolates (*K. pneumoniae* and *M. morganii*) that were initially susceptible to tigecycline but that were subsequently found to be resistant (MIC values of 8 mg/l) following therapy had a clinical failure. Eradication rates for anaerobic bacteria were similar to those for aerobic organisms. A total of 40 patients who received tigecycline had concomitant bacteremia, and 33 (82%) of these patients experienced a clinical cure. Treatment failures with tigecycline were not associated with resistant isolates, and only one patient with *E. coli* bacteremia had a positive blood culture result after initiation of therapy.

In summary, monotherapy with tigecycline has exhibited noninferiority to other standard treatments for complicated skin and skin-structure and intra-abdominal infections. However, most patients had community-acquired infections and few patients had serious comorbid conditions, and received surgical drainage or debridement when necessary.

Nausea and vomiting were the most frequent adverse events in the tigecycline group in all Phase III studies. Trials in urinary tract infections were abandoned since excretion is largely biliary with limited urinary recovery of the active drug.

### Safety & tolerability

Tigecycline is generally well tolerated, with the digestive system being the most affected by adverse effects. In Phase I studies of tigecycline in healthy subjects, the most common adverse effects reported were dose-related nausea, vomiting and headache. Gastrointestinal (GI) side effects were dose limiting at 300 mg. Prolonging the duration of infusion did not improve the nausea in subjects receiving 200 mg of the drug but GI effects were diminished after food. Dosing schedules of 25 or 50 mg every 12 h were well tolerated in fed subjects without clinically relevant changes in laboratory parameters, blood pressure, or intervals on electrocardiography [43].

In a Phase II clinical trial of patients with skin and soft-tissue infections, nausea was the most common adverse event, occurring in 22 and 35% of patients treated with 25- and 50-mg dose, respectively. Other common

adverse effects included vomiting (13 and 19% of patients, respectively), diarrhea (11 and 9%), headache (8 and 5%), and pain (6 and 6%). In the 50-mg group, five patients (6%) discontinued therapy due to an adverse event (nausea and vomiting, diarrhea, paresthesia, allergic reaction). Abnormal laboratory test results were observed in nine patients (elevated serum transaminase, alkaline phosphatase, blood urea nitrogen levels, and anemia). Of the four deaths that occurred during this study, none were considered related to treatment with tigecycline [75]. In a Phase II clinical trial of patients with complicated intra-abdominal infections, nausea (42%) and vomiting (27%) were again the most commonly reported adverse effects. Although no patients withdrew from the study because of an adverse event, one patient developed moderately severe colitis due to infection with *C. difficile* [76].

In several Phase III clinical trials GI complaints were reported most often in patients who received tigecycline. The most frequent GI adverse events were nausea (18–34%), vomiting (13–20%) and diarrhea (6–8%). Headache was reported in 9% of patients. Abnormal laboratory values were reported infrequently, and approximately 5% of patients discontinued therapy as a result of an adverse reaction [77,78].

At present, there are few clinical data concerning the safety of long-term use of tigecycline. In compassionate use experience, patients have tolerated treatment with tigecycline for atypical mycobacteria infections for several months without experiencing major organ toxicity [79].

Tigecycline may cause fetal harm when administered during pregnancy, and its use during dental development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth [24,43,48,80].

### Postmarketing surveillance

The activity of tigecycline is affected by the amount of dissolved oxygen in the media. The approved testing methodology for broth dilution tests with tigecycline requires the use of fresh Mueller–Hinton broth (media prepared and used within 12 h) or supplementation with Oxrase® for aerobic organisms, to minimize the oxidative degradation of tigecycline and standardize testing conditions. Organisms tested using aged Mueller–Hinton broth may have MICs that are one-to-two dilutions

higher than those obtained with fresh media. The use of automated microbiology systems must take into account this issue.

Since tigecycline has such a broad spectrum of activity and will be used empirically, there is a potential for the development of antimicrobial resistance. Of particular concern is the emergence of resistance among *A. baumannii*, *Klebsiella* spp., *Enterobacter* spp., and microorganisms producing ESBLs. New Phase III studies are underway in order to evaluate the clinical efficacy of tigecycline for the treatment of lower respiratory tract infections and for the treatment of selected serious infections in pediatric subjects aged 8–18 years. In addition, there are ongoing trials against infections caused by specific multiresistant pathogens, along with an extensive compassionate-use programs.

The true incidence of adverse effects will be observed in the postmarketing surveillance. Specific safety issues that will require further evaluation are nausea and vomiting, diarrhea, hypersensitivity, prothrombin time/partial thromboplastin time prolongation, hyperbilirubinemia and increased blood urea nitrogen elevation.

### Regulatory affairs

Tigecycline for injection was approved in June 2005 by the FDA for the treatment of skin and skin-structure infections and for the treatment of complicated intra-abdominal infections in adult patients. The FDA has established MIC susceptibility breakpoints for tigecycline for *S. aureus* (including methicillin-resistant isolates) less than or equal to 0.5 mg/l; *Streptococcus* spp. other than *S. pneumoniae* 0.25 mg/l or less; and *E. faecalis* (vancomycin-susceptible isolates only) 0.25 mg/l or less. The established breakpoints for *Enterobacteriaceae* are susceptibility 2 mg/l or less, intermediate 4 mg/l, and resistant at least 8 mg/l. For anaerobes, the breakpoints are susceptibility less than or equal to 4 mg/l, intermediate 8 mg/l, and resistant greater than or equal to 16 mg/l. The Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards) has been known to establish breakpoints in the USA in consultation with the FDA.

The EMEA approved the use of tigecycline in April 2006 for the same indications as the FDA in all the European Community countries. The European Committee on Antimicrobial Susceptibility Testing has established

tigecycline MIC breakpoints for *Staphylococcus* spp.: susceptible 0.5 mg/l or less; and resistant more than 0.5 mg/l; *Streptococcus* A, B, C, and G and *Enterococcus* spp.: susceptible 0.25 mg/l or less; and resistant over 0.5 mg/l; and *Enterobacteriaceae*: susceptible 1 mg/l or less; and resistant over 2 mg/l. For anaerobic bacteria no breakpoint for susceptibility testing is given.

### Conclusion

The new glycylcycline, tigecycline, is one of the new antimicrobials with activity against Gram-positive and -negative bacteria including isolates that are resistant to other antibiotic classes, such as  $\beta$ -lactams, glycopeptides, and fluoroquinolones. It is also active against most anaerobic bacteria, as well as most atypical microorganisms, including many rapidly growing nontuberculous mycobacteria. Tigecycline is not affected by most of the known mechanisms of resistance to tetracyclines encountered in bacteria but it is vulnerable to the chromosomally-encoded multidrug efflux pumps of *Proteae* and *P. aeruginosa*. The  $C_{\max}$  is low but it has good tissue penetration and its use as monotherapy has shown equivalence to imipenem in intra-abdominal infections and to vancomycin plus aztreonam in skin and skin-structure infections. Tigecycline is relatively safe and well-tolerated (nausea and vomiting are the most frequent adverse events), has the convenience of twice-daily dosing, and has the potential to treat infections caused by bacteria that are resistant to many other antibiotics.

### Expert commentary

Ideally, a single antimicrobial agent that confers broad-spectrum coverage with activity against drug-resistant pathogens is an important addition to our therapeutic armamentarium. In addition to the approved indications of tigecycline, it could be useful for the treatment of surgical wound infections, mainly after abdominal surgery, where the likely pathogens include MRSA, *Enterobacteriaceae*, streptococci and anaerobes. No other single agent covers this wide spectrum. In addition, tigecycline should find a role in the treatment of infections due to multiresistant pathogens, like pan-resistant *Acinetobacter* spp., *S. maltophilia*, ESBL-producing *Enterobacteriaceae*, MRSA, and vancomycin-resistant enterococci. However, the potential risks for the emergence or selection of resistant organisms will need to be monitored closely and will be the major factor determining the lifespan of use of tigecycline. Bacteria resistant to tigecycline have been noted in clinical trials and have included isolates of *K. pneumoniae*, *E. cloacae*, *M. morgani*, and *A. baumannii*. On the other hand, the low  $C_{\max}$  must be of some concern if bacteremia is present since there is no experience in the treatment of these patients.

### Future perspective

In 5 years, the use of tigecycline will be extended to the treatment of lower respiratory tract infections, and usage and dosing guidelines will have been drawn up for pediatric

### Executive summary

- Tigecycline is indicated for the treatment of skin and skin-structure infections and for the treatment of complicated intra-abdominal infections in adult patients.
- Tigecycline acts by binding to the bacterial 30S ribosomal subunit and by blocking entry of amino-acyl transfer RNA molecules into the A site of the ribosome. It is not affected by most of the known mechanisms of resistance to tetracyclines.
- Tigecycline has activity against Gram-positive and Gram-negative bacteria, including isolates that are resistant to other antibiotic classes. It is also active against most anaerobic bacteria and most atypical microorganisms, including many rapidly growing nontuberculous mycobacteria.
- Tigecycline is administered intravenously at an initial dose of 100 mg, followed by 50 mg every 12 h for 5–14 days. No dose adjustment is necessary in patients with renal impairment or in those undergoing hemodialysis.
- Peak plasma concentration of tigecycline is low, 0.911 mg/l after a single 100 mg dose.
- The volume of distribution is large ( $>10$  l/kg) and the half-life ranges from 37–67 h.
- The most common adverse events of tigecycline are nausea and vomiting.



populations. Tigecycline will be used as directed therapy of infections due to multiresistant Gram-positive pathogens. Although at present the clinical success rates reported are good and noninferior to those of the comparator agents, there is no accumulated experience in the treatment of neutropenic or immunocompromised patients, in patients with bacterial endocarditis or bacteremia, and in patients

with infections due to rapidly growing mycobacteria. In 5 years there will be accumulated experience in the treatment of these infections and studies of tolerance for long duration treatments. It is also possible that we will attend to the emergence and selection of resistant organisms such as *Klebsiella* spp., *Enterobacter* spp., *A. baumannii*, and group JK corynebacteria.

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