Tigecycline: an overview and update

Tigecycline is the first novel broad-spectrum glycylcycline antimicrobial agent. This agent has been shown to have broad spectrum *in vitro* activity against Gram-positive and -negative bacteria, atypical pathogens, anaerobic bacteria and organisms that have become resistant to other antimicrobial agents. Specifically, tigecycline is active against: *Escherichia coli* – including extended spectrum β-lactamase producing strains; *Staphylococcus aureus* – including methicillin-resistant strains; *Enterococcus* – including vancomycin-resistant strains; and *Streptococcus pneumoniae* – including penicillin-resistant strains and tetracycline-resistant strains *in vitro*. Characteristics of the drug include: it is bacteriostatic, it is given via intravenous administration and twice-daily dosing, it has a post-antibiotic effect and good tissue penetration, and no dosage adjustment for renal or hepatic impairment is needed. Tigecycline has been shown to be efficacious for treatment of complicated skin and soft-tissue infections, for complicated intra-abdominal infections and, more recently, has been approved in Canada for the treatment of community-acquired pneumonia requiring hospitalization. Additionally, this drug has a safety profile comparable with other agents and classes of antimicrobial agents. The most common side effects reported from clinical trials with tigecycline include nausea (24.4%), vomiting (19.2%) and diarrhea (13.8%), and these values are similar or more frequent than that seen with comparator agents.

KEYWORDS: broad spectrum ■ multidrug resistant ■ overview ■ tigecycline ■ update

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Tigecycline is the first glycylcycline antimicrobial to be approved in the USA and Canada. It is derived from minocycline and has sufficient novel modification to be considered a new class of compound [1]. The drug is active *in vitro* and clinically against Gram-positive and -negative pathogens, and atypical, anaerobic and drug-resistant bacteria – including multidrug-resistant strains. It is currently approved for treatment of complicated skin and skin-structure infections, for complicated intra-abdominal infections, and most recently, for the treatment of community-acquired pneumonia (Canada) requiring hospitalization. The specific list of pathogens listed with approved indications will be reviewed in full throughout the manuscript. The approval of tigecycline for clinical use is significant given the relative scarcity of new antibacterial agents under clinical development. Livermore commented that tigecycline was one of few new antimicrobial agents with Gram-negative activity [2]. This comment was undoubtedly referring to other newer agents with activity restricted to Gram-positive pathogens (i.e., linezolid, daptomycin and dalbavancin) [3–5]. Additionally, some previously approved antibacterial agents were withdrawn from the market (i.e., gatifloxacin) [6] or restricted in indication and use due to toxicity concerns (i.e., telithromycin) [201], thereby diminishing the benefit:risk ratio.

Clinical structure & mechanism of action

Tigecycline is a semi-synthetic derivative of minocycline and was designed to be active against tetracycline-resistant organisms where resistance was the result of ribosomal protection and/or efflux [7–9]. It possesses a 9-t-butylglycylamido substitution [10] and binds fivefold more strongly to the ribosome than either minocycline or tetracycline, resulting in enhanced ribosomal protection against resistant organisms [11]. In Gram-negative bacteria, tigecycline is thought to enter the cell via the OmpF and OmpC outer membrane porins – probably as positively charged cation–tigecycline complexes. Ultimately, these complexes dissociate, yielding free tigecycline that can diffuse through the inner cytoplasmic membrane. For Gram-positive bacteria, it is assumed that unbound lipophilic tigecycline crosses the cytoplasmic membrane. Once in the cell, the drug is thought to chelate with magnesium, forming Mg^{2+}–tigecycline, and this complex subsequently binds to the ribosomal complex [12]. Functionally, it acts by

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binding to the 30S ribosomal subunit, thereby blocking the entry of aminoacyl transfer RNA into the acceptor site. Specifically, tigecycline reversibly binds to a helical region (H34) on the 30S subunit, blocking the entry of aminoacyl tRNA into the A binding site [13–15]. The reversible binding is likely contributory to the reported bacteriostatic action of the agent [14,16,17]. Protein synthesis and bacterial growth is blocked as the drug prevents the incorporation of amino acid residues into elongating peptide chains.

Tigecycline remains active against tetracycline-resistant organisms [12]. Tetracycline resistance occurs primarily following acquisition of mobile *tet* and *otr* genes, which confer resistance to tetracycline and oxytetracycline, respectively. Mobile genes are those present on transmissible genetic elements – that is, plasmids or transposons. Expression of these genes yields proteins that are associated with the major mechanisms of resistance: ribosomal protection through dissociation of tetracyclines from their ribosomal binding sites (*tet*[M], *tet*[O], *otr*[B]); and drug efflux through active transport of tetracyclines out of bacterial cells (*tet*[A], *tet*[B], *otr*[B]) – a bulky side chain likely also provides steric hindrance, thereby making it difficult to efflux tigecycline out of the cell [7,18].

Regarding the bacteriocidal versus bacteriostatic action of tigecycline, Blondeau and Borsos reported on kill experiments whereby 10^6 and 10^7 colony-forming units (CFU)/ml of *Escherichia coli* (two clinical isolates) were exposed to tigecycline minimum inhibitory concentration (MIC) and mutant prevention concentration (MPC) drug concentrations [19]. For the *E. coli* isolates, measured MIC values were 0.063 mg/l and MPC values were 1 µg/ml. The $\log_{10}$ reduction in viable cells was measured at 30 min, 1, 2, 3, 4, 6, 12 and 24 h. At 10^6 CFU/ml, a 1 $\log_{10}$ reduction or more was seen after 24 h of exposure to the tigecycline MIC drug concentration; however, this was not seen for the 10^7 CFU/ml inocula, where growth occurred over all time periods. Exposure of the 10^6 CFU/ml to the tigecycline MPC drug concentration resulted in a 0.38 $\log_{10}$ reduction (58% kill) by 6 h and a 1.86 $\log_{10}$ reduction (99% kill) by 24 h; 0.31 $\log_{10}$ reduction (51% kill) in viable cells by 4 h, 0.71 $\log_{10}$ reduction (81% kill) by 12 h and 1.14 $\log_{10}$ reduction (99% kill) following 24 h of drug exposure for the 10^7 CFU/ml. The authors concluded that killing of *E. coli* by tigecycline was slow and incomplete when 10^6 CFU/ml or 10^7 CFU/ml were exposed to MIC drug concentrations. This likely relates to the less susceptible cells being present in bacterial populations in excess of 10^5 CFU/ml. When *E. coli* (10^6 CFU/ml or 10^7 CFU/ml) was exposed to the measured tigecycline MPC drug concentration, killing was progressive and time dependent. Following 12–24 h of drug exposure, 93–99% and 81–99% of viable cells were killed, respectively. The clinical definition of bactericidal versus bacteriostatic based on testing of 10^5 CFU/ml inocula may not be relevant when higher bacterial burdens are tested.

Pharmacology

Various pharmacokinetic parameters of tigecycline following a single 100-mg dose (n = 224 patients) and after multiple 50 mg doses (n = 103 patients) in healthy volunteers is summarized in Table 1. The usual dosage of tigecycline is as a 100 mg loading dose, followed by 50 mg b.i.d. for the remainder of the treatment duration. The plasma protein-binding ranges from 71 to 89%, and the volume of distribution was 7–9 l/kg, suggesting tigecycline is extensively distributed beyond the plasma

Table 1. Mean (CV%) pharmacokinetic parameters of tigecycline.

	Single dose 100 mg (n = 224)	Multiple dose* 50 mg every 12 h (n = 103)
C_{max} (µg/ml)‡	1.45 (22%)	0.87 (27%)
C_{max} (µg/ml)§	0.90 (30%)	0.63 (15%)
AUC (µg•h/ml)	5.19 (36%)	–
$AUC_{0–24h}$ (µg•h/ml)	–	4.70 (36%)
C_{max} (µg/ml)	–	0.13 (59%)
$t_{1/2}$ (h)	27.1 (53%)	42.4 (83%)
CL (l/h)	21.8 (40%)	23.8 (33%)
CL_r (ml/min)	38.0 (82%)	51.0 (58%)
V_{ss} (LL)	568 (43%)	639 (48%)

**100 mg initially, followed by 50 mg every 12 h.*
‡30-min infusion.
§60-min infusion.

volume and into tissues. The C_{max} was reported to be 0.63 µg/ml and the C_{min} was 0.13 µg/ml. The $AUC_{0–24}$ was 4.70 µg h/ml and the elimination half-life ($t_{1/2}$) was 42.4 h [20]. Following a 100 mg dose (n = 224), the C_{max} was 1.45 µg/ml after a 30-min infusion and 0.90 µg/ml after a 60-min infusion; the AUC was 5.19 and the $t_{1/2}$ was 27.1 h (TABLE 1).

Following administration of a 50 mg every 12 h dose (n = 103), the C_{max} was 0.87 µg/ml after a 30-min infusion and 0.63 µg/ml after a 60-min infusion, and the AUC was 4.70 (TABLE 1) [21]. For 32 healthy volunteers administered tigecycline 100 mg followed by 50 mg every 12h, the $AUC_{0–12}$ (134 µg·h/ml) in alveolar cells was approximately 78-fold higher than in serum [22]. Similarly, the $AUC_{0–12}$ (2.28 µg·h/ml) in epithelial lining fluid was approximately 32% higher than the $AUC_{0–12}$ in serum [22]. The $AUC_{0–12}$ (1.61 µg·h/ml) in blister fluid was approximately 26% lower than the $AUC_{0–12}$ in serum for ten healthy volunteers [23]. The major routes of elimination includes biliary (59% – mostly as unchanged drug) and renal (33%) as unchanged drug, glucuronides, epimers or *N*-acetylated metabolites. Approximately 22% of the total dose is excreted unchanged in urine [24]. Van Wort *et al.* reported on population pharmacokinetics of tigecycline in healthy volunteers using a structural population pharmacokinetics model based on full-profile sampling data from subjects enrolled in five Phase I studies where patients were administered either single or multiple doses intravenously [25]. This modeling supported Phase II/III population pharmacokinetics model development to further determine individual patient tigecycline exposures for safety and efficiency analysis.

MacGowan recently provided an update on tigecycline pharmacokinetics and pharmacodynamics data [26]. Median/mean $AUC_{0–24}$ (mg·h/l) for CSF, synovial fluid, bone, lung, colon, gallbladder and bile were 0.5, 1.7, 2, 9, 17, 120 and 2815, respectively. In a summary of data related to patients with complicated skin and skin-structure infections, AUC_{SS} in those receiving a 50-mg loading dose was 2.67 ± 0.99 mg·h/l (range: 1.49–4.98) and the AUC:MIC ratio was 13.3 ± 13.5 (range: 0.09–54.1). For the 100 mg loading dose regimen, the tested drug AUC_{SS} was 5.46 ± 1.62 mg·h/l (range: 2.81–9.36) and the AUC:MIC ratio was 33.4 ± 24.3 (range: 0.21–102). Data from patients treated for complicated intra-abdominal infections were also analyzed. All patients were treated with a l00 mg loading dose followed by 50 mg intravenously every 12 h. The mean observed tigecycline AUC_{24} was 6.08 ± 2.5 mg·h/l (range: 2.88–22.6) and the AUC:MIC ratio was 28.9 ± 75.1 (range: 0.97–802). From the skin and skin-structure infection modeling data, two AUC:MIC breakpoints were possible – 12.5 or 16.4 – and Monte Carlo simulation (12.5 breakpoint) suggested a target attainment rate of at least 99.99% for an MIC of 0.12 mg/l or less, 94.13% for an MIC of 0.25 mg/l, 22.6% for an MIC of 0.5 mg/l and 5% or less for an MIC of 1 mg/l or more. For the AUC/MIC breakpoint of 16.4, the target attainment rates would be greater than 99.99% for an MIC of 0.12 mg/l or less, 74.5% for an MIC of 0.25 mg/l, and 5% or less for an MIC greater than 0.5 mg/l. MacGowan indicated that these data support a clinical breakpoint of 0.25–0.5 mg/l for *Staphylococcus aureus*. The AUC:MIC breakpoints from the intra-abdominal infections data was suggested at 6.96 and 11.07. For the 6.96 breakpoint, the chance of cure was 94% above this value versus 60% below this value. For an AUC:MIC ratio between 20 and 25, there was a 90% chance of microbiological eradication. Monte Carlo simulation using the AUC:MIC ratio of 6.96 resulted in target attainment rates greater than 93.89% for a MIC of 0.5 mg/l, 27.2% for an MIC of 1 mg/l and less than 5% for an MIC of 2 mg/l or more. Using the AUC/MIC ratio of 11.07, target attainment rates were 100% for an MIC of 0.12 mg/l or less, 98.8% for an MIC of 0.25 mg/l, 54.2% for an MIC of 0.5 mg/l, 20.3% for an MIC of 1 mg/l and 5% or less for an MIC of 2 mg/l or more. MacGowan cautioned that use of these breakpoints is needed when surgery is an important part of treatment. Having said that, the data suggested a clinical breakpoint for *E. coli* in the range of 0.25–0.5 mg/l.

Dosage adjustments are not required in patients with mild-to-moderate hepatic impairment (Child Pugh A and Child Pugh B); however, in patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by 25 mg every 12h, and these patients should be treated with caution and monitored for treatment response.

Dosage adjustments are not required in patients with renal impairment, nor in those undergoing hemodialysis. Dosage adjustments are also not required in the elderly, and also not required based on gender or race [27]. The pharmacokinetics of tigecycline have not been established in patients less than 18 years of age.

Tigecycline can be co-administered with digoxin without dosage adjustments, and it did not significantly alter the effects of warfarin

on international normalized ratio (INR) [27,28]. Tigecycline does not alter the metabolism of drugs metabolized through the cytochrome P450 system [27].

In vitro activity

Tigecycline has been tested *in vitro* against a wide variety of Gram-positive, Gram-negative, anaerobic and atypical microorganisms. The *in vitro* susceptibility results are summarized in TABLE 2. From studies investigating over 6900 to more than 16,000 *S. aureus* isolates, MIC_{50} values ranged from 0.12 to 0.25 mg/l, and the MIC_{90} value was 0.5 µg/ml. The range of MIC values was 0.016–1 µg/ml or less. Similar values were obtained from *S. aureus* isolates that were resistant to methicillin or demonstrated intermediate resistance to glycopeptides. For testing against coagulase-negative Staphylococci, MIC_{50} and MIC_{90} values were 0.25 and 0.5 µg/ml, respectively. No strain had an MIC greater than 2 µg/ml. For *Enterococcus* strains tested against tigecycline, MIC_{50} values ranged from 0.12 to 0.25 mg/l or less, and MIC_{90} values ranged from 0.25 to 0.5 mg/l. No organism had an MIC in excess of 2 µg/ml, and these values were similar for strains that were either susceptible or resistant to vancomycin. For *Streptococcus* species (including *Streptococcus pneumoniae*) MIC_{90} values were 0.12 µg/ml or less. No strain had a MIC higher than 0.5 µg/ml to tigecycline. MIC_{90} values were not influenced by *S. pneumoniae* susceptibility or resistance to penicillin. MIC_{90} values for *Listeria monocytogenes* and *Corynebacterium jeikieum* were 0.5 and 2 µg/ml, respectively.

For *E. coli* (TABLE 2), the MIC_{50} and MIC_{90} values for over 1800 strains were 0.12 and 0.25 µg/ml, respectively. The MIC range was from 0.03 to 2 µg/ml. The MIC_{90} value for strains that were extended spectrum β-lactamase-positive was 1 µg/ml. MIC_{90} values were slightly higher against *Klebsiella pneumoniae* strains regardless of their extended-spectrum β-lactamase (ESBL) status. MIC_{50} values ranged from 0.5 to 1 µg/ml, and MIC_{90} values were at 2 µg/ml. The MIC range was 0.06–8 µg/ml. For *Pseudomonas aeruginosa*, the MIC_{50} value was at 8 µg/ml, and the MIC_{90} value was higher than 16 µg/ml; the MIC range values were from 0.25 to 32 µg/ml. In studies testing a large number of *Enterobacteriaece*, the MIC_{90} value was at 1 µg/ml. For organisms such as *Morganella morganii* and *Providencia stuartti*, the MIC_{90} value was at 8 µg/ml. Against *Moraxella catarrhalis* isolates and *Haemophilus influenzae* isolates, MIC_{90} values ranged from 0.25 to 1 mg/l. For *Stenotrophomonas multophilia* and *Acinetobacter baumannii* strains, MIC_{90} values were 2 µg/ml.

The MIC_{90} values for *Bacteroides* species ranged from 2 to 8 µg/ml (TABLE 2), being lowest for *Bacteroides uniformis*. Against *Clostridium perfringens* isolates, the MIC_{90} value was reported to be 1 µg/ml, and no strain had a MIC value in excess of 2 µg/ml. MIC_{90} values were low against *Fusobacterium nucleatum*, ranging from 0.06 to 0.12 µg/ml, and MIC_{90} values ranged from 0.06 to 0.5 µg/ml or less for *Peptostreptococcus micros, Porphyromas* species, *Prevotella* species, *Propionibacterium acnes* and *Veillonella* species.

Tigecycline has also been tested *in vitro* against isolates of *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* and MIC_{90} values ranged from 0.125 to 0.25 µg/ml. No strain had a MIC value greater than 0.25 µg/ml for either of these pathogens.

Fraise entitled a paper 'Tigecycline: the answer to β-lactam and fluoroquinolone resistance?' [29]. In this manuscript, the author provided an overview of tigecycline, including its *in vitro* activity against Gram-negative and Gram-positive pathogens that were resistant to other antimicrobial agents. A summary of the *in vitro* activity of tigecycline against selected resistant Gram-positive and Gram-negative pathogens is summarized in TABLE 2. As highlighted earlier, the MIC_{90} values for *S. aureus* isolates demonstrating resistance to oxacillin or with intermediate resistance or full resistance to vancomycin ranged from 0.12 to 0.5 mg/l. In addition, for *S. aureus* isolates that were tetracycline-resistant, the MIC_{90} value was 0.5 µg/ml. Similarly, for oxacillin- and tetracycline-resistant coagulase-negative *Staphylococci*, MIC_{90} values were 0.5 µg/ml. For vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium*, MIC_{90} values ranged from 0.12 to 0.25 µg/ml. In strains with either of *vanA* or *vanB* phenotypes, the MIC_{90} was 0.25 µg/ml. Regarding *Streptococcus pneumoniae*, MIC_{90} values ranged from 0.12 to 10.25 µg/ml and was not influenced by penicillin resistance. In reviewing the data for the *Enterobacteriaece*, tigecycline was active against strains demonstrating resistance to aminoglycosides, carbapenems, fluoroquinolones, ESBL-producing strains and strains producing *ampC* β-lactamase, with MIC_{90} values ranging from 1 to 4 µg/ml. For strains of *Enterobacteriaece* that were tetracycline resistant, MIC_{90} values ranged from 0.25 to 4 mg/l. Finally, for ampicillin-resistant *Haemophilus influenzae*, the MIC_{90} value for tigecycline was 2 µg/ml.

Table 2. *In vitro* activity of tigecycline against a variety of pathogens.

Organism	No.	MIC (μg/ml)			Ref.
		50%	*90%*	*Range*	
Gram-positive pathogens					
Staphylococcus aureus	16,151	0.12	0.5	<0.016–1	[90–94]
Coagulase-negative *Staphylococci*	5011	0.12–0.25	0.5	<0.016–2	[90–94]
Enterococcus spp.	5083	<0.12	0.25–0.5	<0.016–2	[90–94]
Streptococcus pneumoniae	3861	<0.12	<0.12	<0.12–0.5	[90,91,93]
β-hemolytic *Streptococci*	1243	<0.12	<0.12	<0.12–0.5	[90–94]
Viridans group *Streptococci*	412	<0.12	<0.12	<0.12–0.5	[91,92]
β-hemolytic *Streptococci*	681	≤0.12	≤0.12	0.015–0.25	[90,95,96]
Viridans group *Streptococci*	317	≤0.12	≤0.12	0.015–0.5	[95,96]
Penicillin-susceptible *Streptococcus pneumoniae*	1685	≤0.12	≤0.12	0.015–0.5	[96–98]
Penicillin intermediate *Streptococcus pneumoniae*	393	≤0.12	≤0.12	0.06–0.125	[96,97,99]
Penicillin-resistant *Streptococcus pneumoniae*	370	≤0.12	≤0.12	0.015–0.5	[96–99]
Listeria monocytogenes	20	0.25	0.5	0.25–0.5	[100]
Lactobacillus spp.	12	0.06	0.12	0.03–0.12	[100]
Mycoplasma pneumoniae	30	0.12	0.25	0.06–0.25	[101]
Chlamydia pneumoniae	10	0.125	0.125	0.125–0.25	[102]
Gram-negative pathogens					
Acinetobacter spp.	753	0.5–1	2–4	0.06–8	[90–94]
Enterobacter spp.	1484	0.5	1–2	0.06–8	[90–94]
Escherichia coli	4349	0.12–0.25	0.25–0.5	0.03–2	[90–94]
Haemophilus influenzae	4011	0.5	1	<0.016–2	[93]
Indole-positive *Proteeae*	281	1	4	1–16	[94]
Klebsiella spp.	2403	0.5	1	0.06–8	[90–94]
Moraxella catarrhalis	600	<0.12	0.25	<0.12–0.5	[93]
Proteus mirabilis	411	2–4	4	0.25–16	[91,92]
Pseudomonas aeruginosa	2720	8	16	0.12–32	[90–94]
Serratia spp.	543	1	2	0.12–16	[90,91,93]
Stenotrophomonas maltophilia	391	1	2–4	0.12–8	[90,91,93]
Serratia marcescens	664	1	1	0.12–8	[97–99,103]
Acinetobacter baumannii	1487	0.5	2	0.06–16	[90,97–99,104]
Neisseria meningitidis	17	≤0.12	≤0.12	≤0.12	[96]
Enterobacteriaece	5450	0.25	1	0.03–16	[92,96–98]
Enterobacter aerogenes	685	1	2	0.12–16	[97,98,103,104]
Enterobacter cloacae	1269	0.5	2	0.06–16	[97,98,103,104]
Morganella morganii	10	1	8	1–8	[103]
Providencia stuarti	10	4	8	1–8	[103]
Salmonella spp.	20	0.5	0.5	0.25–2	[103]
Shigella spp.	20	0.25	0.25	0.12–0.25	[103]
Moraxella catarrhalis	495	≤0.12	0.25	≤0.12–25	[93,96]
Citrobacter spp.	82	0.25	0.5	0.25–4	[99,103]
Anaerobic pathogens					
Bacteroides caccae	19	0.25	8	0.12–16	[105]
Bacteroides distasonis	98	4	8	0.5–8	[106]

[*]With heterogeneous susceptibilities
ESBL: Extended-spectrum β-lactamase; MIC: Minimum inhibitory concentration; NA: Not available; ORSA: Oxacillin-resistant Staphylococcus aureus.

Table 2. *In vitro* activity of tigecycline against a variety of pathogens.

Organism	No.	MIC (µg/ml)			Ref.
		50%	*90%*	*Range*	
Anaerobic pathogens (cont.)					
Bacteroides fragilis	289	2	8	0.25–32	[106]
Bacteroides ovatus	90	2	4	0.25–16	[106]
Bacteroides thetaiotaomicron	185	2	8	0.25–16	[106]
Bacteroides uniformis	26	1	2	0.25–8	[106]
Bacteroides vulgarus	86	1	4	0.5–8	[106]
Other *Bacteroides fragilis*	57	1	8	0.5–64	[106]
Clostridium immocuum	12	<0.06	<0.06	<0.06	[105]
Clostridium perfringens	51	0.12	1	<0.06–2	[105]
Eubacterium lentum	14	0.12	0.5	<0.06–1	[105]
Fusobacterium nucleatum	25	0.06–0.12	0.06–0.12	<0.016–0.25	[105,107]
Peptostreptococcus micros	39	<0.06	<0.06	<0.016–0.12	[105]
Porphyromonas spp.	19	0.06	0.06	<0.015–0.125	[107]
Prevotella spp.	28	0.06–0.12	0.25	0.06–0.25	[107]
Propionibacterium acnes	17	<0.06	0.12	<0.06–0.5	[105]
Veillonella spp.	12	0.25	0.5	0.12–1	[105]
Peptostreptococcus spp.	52	0.032	0.25	0.008–0.25	[108]
Clostridium difficile	30	≤0.06	0.125	≤0.016–2	[99,108]
Oxacillin-resistant *Staphylococcus aureus*	2679	<0.12	0.25	0.3–4	[90,109]
Vancomycin intermediate *Staphylococcus aureus*	25	0.25	0.5	NA	[110]
Vancomycin intermediate *Staphylococcus aureus*[*]	22	0.25	0.5	NA	[110]
Vancomycin-resistant *Staphylococcus aureus*	2	–	0.12	–	[111,112]
Community-acquired ORSA *Staphylococcus aureus*	652	0.25	0.5	<0.12–1	[113]
Tetracycline-resistant *Staphylococcus aureus*	329	0.25	0.5	<0.12–1	[90]
Oxacillin-resistant coagulase-negative *Staphylococci*	1004	0.25	0.5	<0.12–1	[90]
Tetracycline-resistant coagulase-negative *Staphylococci*	196	0.25	0.5	<0.12–1	[90]
Vancomycin-resistant *Enterococcus faecalis*	42	0.06	0.25	0.03–0.25	[114]
Vancomycin-resistant *Enterococcus faecium*	171	0.06	0.12	0.015–0.25	[114]
Van A phenotype	179	<0.12	0.25	<0.12–0.5	[90]
Van B phenotype	23	<0.12	0.25	<0.12–0.25	[90]
Penicillin intermediate *Streptococcus pneumoniae*	329	0.06–<0.12	<0.12–0.25	NA	[96,97]
Pencillin-resistant *Streptococcus pneumoniae*	286	0.06–<0.12	<0.12–0.25	NA	[96,97]
Aminoglycoside-resistant *Enterobacteriaece*	38	0.5	1	0.12–4	[115]
Carbapenem-resistant *Enterobacteriaece*	107	1	2	0.06–8	[115]
Fluoroquinolone-resistant *Enterobacteriaece*	1843	0.25	2	0.06–8	[115]
Tetracycline-resistant *Enterobacteriaece*	2053	<0.12–4	0.25–4	<0.03–16	[115]
ESBL producing *Enterobacteriaece*	354	0.5	2	0.06–8	[115]
AmpC β-lactamase producing *Enterobacteriaece*	303	1	4	0.06–8	[115]
Haemophilus influenzae, ampicillin resistant	83	1	2	0.06–2	[116]

[*] *With heterogeneous susceptibilities*
ESBL: Extended-spectrum β*-lactamase; MIC: Minimum inhibitory concentration; NA: Not available; ORSA: Oxacillin-resistant* Staphylococcus aureus.

Schafer *et al.* reported on tigecycline treatment for ventilator-associated pneumonia (VAP) and bacteremia caused by multidrug-resistant *Acinetobacter baumannii* [30]. A total of 25 patients received tigecycline: 19 with VAP, three with bacteremia and three with VAP plus bacteremia. Five patients were treated with tigecycline alone. Primary outcomes were resolution of clinical signs and symptoms of infections. Microbial eradication of *A. baumannii* by tigecycline was also determined. A total of 21/25 (84%) of patients had clinical resolution: 4/25 (16%) had clinical failure and one of these patients with VAP and bacteremia had an organism that developed resistance to tigecycline during therapy. Microbial eradication was seen in 12/15 (80%) patients. Three patients with VAP had a recurrence of infection (one patient had two recurrences; two patients had one recurrence each) – all four recurrences lead to clinical resolution. No patients discontinued tigecycline therapy due to adverse events. Schafer *et al.* concluded that tigecycline was effective in most of 25 VAP and/or bacteremia patients caused by multidrug-resistant *A. baumannii*. The authors concluded that emergence of a tigecycline-resistant strain during therapy was a concern.

Daly *et al.* reported on the use of tigecycline for the treatment of pneumonia and empyema caused by carbapenemase-producing *Klebsiella pneumoniae* [31]. The organism was resistant to gentamicin, intermediate to tobramycin and sensitive to amikacin; resistant to all β-lactams tested including ampicillin, first- to fourth-generation cephalosporins and carbapenems, trimethoprim/sulfamethoxazole and ciprofloxacin; susceptible to colistin, minocycline and tigecycline; and intermediate to chloramphenicol. The pneumonia was treated successfully; however, the empyema recurred. The MIC for tigecycline to the infecting strain of *K. pneumoniae* increased from 0.75 to 2 μg/ml. The authors concluded that clinicians need to be aware of the potential for MIC increases in a setting of sustained tigecycline therapy for multidrug-resistant pathogens.

Anthony *et al.* reported on clinical and microbiological outcomes of serious infections with multidrug-resistant Gram-negative pathogens treated with tigecycline [32]. Multidrug resistance was defined as resistance to three or more classes of antibiotics – that is, extended spectrum cephalosporins, carbapenems, β-lactams/β-lactamase inhibitor combinations and aminoglycosides. Patients needed to have received a full course (≥7 days) of tigecycline treatment (initial loading dose of 100 mg followed by 50 mg intravenously every 12 h) for inclusion in the study. Infecting organisms included *Acinetobacter baumannii* (n = 10), *Enterobacter cloacae* – ampC positive (n = 2), *Klebsiella pneumoniae* – ESBL, *Klebsiella pneumoniae* carbapenemase (KPC) (positive [n = 1]), *K. pneumoniae* – ESBL positive (n = 4 – one duplicate from the same patient), *E. coli* – KPC (inferred – n = 1) and *K. pneumoniae* – data unavailable (n = 1). Primary infection was as VAP (n = 3), VAP with empyema (n = 3), tracheobronchitis (n = 2), urinary tract infection (n = 2) and one each of mediastinitis/secondary bacteremia, cellulitis, diabetic ulcer/osteomyelitis, pelvic abscess, nosocomial pneumonia, aspiration pneumonia, endovasculitis and bacteremia. All patients had comorbidities.

Clinical responses at the end of therapy were defined as positive (partial or complete improvement of signs/symptoms of infection), negative (no improvement or clinical deterioration) or uncertain. Microbiological outcome was defined as positive (sterile culture results during or after antimicrobial therapy), negative (persistently positive cultures with same pathogens 3 days after initiation of antimicrobial therapy) or not documented. A total of 18 patients received a full course of tigecycline therapy: seven patients had a positive clinical outcome, eight were scored as negative (one patient had two courses of therapy) and four uncertain. Microbiological outcome was positive for four patients, negative for six patients (one patient had two courses of therapy) and not determined for eight patients.

Of the 18 patients treated with tigecycline, nine patients did not receive co-administered agents, two received inhaled tobramycin, one received inhaled colistin and one each received cefepime, vancomycin, amikacin/colistin, tobramycin, levofloxacin, gentamcin and meropenem/colistin.

Of the nine patients that received tigecycline therapy alone (one patient treated twice), five survived and three died for reasons unrelated to infection. The one patient treated twice with tigecycline was co-administered other antimicrobial agents during one course of therapy and subsequently died related to infection. Four patients treated with tigecycline, and co-administered antimicrobials, died related to infection.

In their discussion, the authors indicate that most patients were critically ill at the time of therapy with tigecycline and most infections were not indicated in the official US FDA labeling. For the *A. baumannii* isolates, tigecycline MICs ranged from 1 to 3 μg/ml, and for the *Enterobacteriaece* from 0.27 to 3 mg/l.

The authors also suggest that pretherapy tigecycline MICs may predict clinical outcome with *A. baumannii*. Of concern was that an *A. baumannii* strain from one patient treated with tigecycline acquired full resistance during therapy. Additional concerns were persistent *A. baumannii*, *E. coli* and *K. pneumoniae* bacteremia in tigecycline-treated patients.

In a review by Giamarellou and Poulakou, the issue of treatment options for multidrug-resistant Gram-negative infections was addressed [33]. An obvious concern is the relative scarcity of new antimicrobial agents in development; however, the authors acknowledged tigecycline and doripenem as newer agents approved for clinical use and potential agents for treatment of multidrug-resistant pathogens. Regarding tigecycline, it was acknowledged that it is active against multidrug-resistant *Enterobacteriaece*, including ESBL- and KPC-positive strains and against *A. baumannii* strains. For some isolates, MIC values for tigecycline are 2 mg/l and may compromise clinical outcome based on pharmacokinetic/pharmacodynamic parameters. The authors summarized that tigecycline appears to be an 'extremely useful' addition to the limited number of agents for treating multidrug-resistant organisms. Additionally, physicians should take a cautious approach to off-label use due to limited clinical evidence.

Finally, the issue of synergy has been questioned for tigecycline in combination with other antimicrobial compounds for multidrug-resistant pathogens. Time–kill studies conducted with tigecycline against *A. baumannii* strains showed indifference in: tigecycline plus any of carbapenem, polymyxin B, amikacin, ciprofloxacin and rifampicin; polymyxin and tigecycline; and colistin and tigecycline by checkerboard assay [34–36]. Clearly, additional studies are required to fully answer this question.

Mutant prevention concentration

The MPC was initially described by Dong *et al.* in 1999 as a novel measurement of *in vitro* susceptibility/resistance [37]. The initial description of MPC involved investigations with fluoroquinolones and *Staphylococcus* and *Mycobacterium* species. For MPC testing, bacterial inocula of at least 10^9 CFU (for *S. pneumoniae*, 10^{10} CFUs for *Staphylococci*, *Enterobacteriaceae* and *Pseudomonas* species) are exposed to the surface of agar plates containing predetermined drug concentrations. Following incubation, the drug concentration that blocks the growth of these high bacterial inocula is termed the MPC. By comparison, MIC testing involves exposing 10^5 CFU/ml to varying drug concentrations and, following incubation under ambient conditions, the lowest drug concentration preventing growth is the MIC. MIC testing may underestimate the true dynamics of bacterial populations if the bacterial burden associated with infection is substantially higher than that used for MIC testing. Several publications have reported on high bacterial burdens being present during infection and, as such, measurement of a drug's activity against these higher bacterial inocula seems to be relevant [38–42]. Since the initial description of MPC by Dong *et al.* [37], numerous other publications have appeared in the peer-reviewed literature reporting on MPC values against *Streptococcus pneumoniae* [43], *Staphylococcus aureus* [44], *Pseudomonas aeruginosa* [45], *E. coli* and other *Enterobacteriaece* [46] and *Haemophilus influenzae* [47]. Smith *et al.* suggested that MPC testing only applied to fluoroquinolone compounds and not to β-lactam, aminoglycoside and macrolide compounds. Indeed, Hesje *et al.* reviewed the literature available on MPC values for various Gram-positive and -negative organisms tested against a variety of antimicrobial compounds including those highlighted above [48]. More recently, Blondeau provided a further overview of MPC versus MIC testing and updated the MPC data published or presented in the peer-reviewed literature or international meetings, respectively [49]. **Table 3** shows MPC data for tigecycline tested against Gram-positive and Gram-negative pathogens. For 132 strains of *E. coli* tested by MPC to tigecycline, the MPC_{50} was 0.5 and the MPC_{90} 1 µg/ml [50]. For *Klebsiella* species, the MPC_{90} value was 8 µg/ml [51]. For isolates of *S. pneumoniae*, the MPC_{90} value was reported to be 0.063 µg/ml and no organism had an MPC value higher than 0.25 µg/ml [52]. Finally, for methicillin-susceptible and methicillin-resistant strains of *S. aureus*, MPC_{90} values were reported to be 2 and 4 µg/ml, respectively, and no organism had an MPC value in excess of 8 µg/ml [53,54]. More recently, tigecycline MPC data against contemporary clinical isolates of *Clostridium difficile* were reported to range between 0.016 and 0.125 µg/ml, as compared with 0.5–4 µg/ml for vancomycin [55]. To date, the clinical significance of MPC values remains to be determined.

Clinical trials

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

Table 3. Mutant prevention concentration values for tigecycline tested against various pathogens.

Organism	No.	MPC (µg/ml)			Ref.
		50%	90%	Range	
Escherichia coli	132	0.5	1	0.25–≥4	[50]
E. coli ATCC 25922	1			0.25	[50]
Streptococcus pneumoniae	100	0.063	0.063	0.031–0.25	[52]
S. *pneumoniae* ATCC 49619	1			0.06	[52]
E. coli	24	0.5	1	0.5–2	[72]
Klebsiella spp.	24	8	8	2–8	[72]
S. pneumoniae	125	0.063	0.063	0.063–0.5	[73]
Methicillin-susceptible *Staphylococcus aureus*	67	1	2	1–4	[53]
Methicillin-resistant *Staphylococcus aureus*	65	1	4	0.5–8	
C. difficile	32	0.063	0.063	0.016–0.125	[55]

MPC: Mutant prevention concentration.

infections and in Canada for community-acquired pneumonia (CAP) requiring hospitalization. The following represents a summary of the clinical trial data.

Complicated skin & skin-structure infections

Complicated skin and skin-structure infections, involving deep soft tissue, may occur in patients with underlying co-morbid conditions (diabetes mellitus, peripheral vascular disease or peripheral neuropathy) or pre-existing skin lesions [56–58]. They are often polymicrobial and, where multidrug-resistant bacteria are involved, therapy is further impacted by limited therapeutic choices. In many instances, patients with complicated skin and skin-structure infections require hospitalization, surgical intervention and intravenous antimicrobial therapy. Common organisms include *S. aureus*, *S. pyogenes* and *S. agalactiae*. A summary of clinical trial data for patients with skin and skin-structure infections and treated with tigecycline or comparator agents is summarized in Table 4.

Postier *et al.* reported on the results of a multicenter, randomized, open-label efficacy and safety study of two dosages of tigecycline for hospitalized patients with complicated skin and

Table 4. Summary of Phase II and III clinical trials of tigecycline.

Study	Design	No. patients (CE population)	Regimens	Cure rate at test-of-cure visit	Ref.
cSSSIs	Phase II, MC, R, OL	54	TGC 100 mg i.v. loading dose followed by 50 mg i.v. q12h	74% (95% CI: 60.3–85.0; p = NS)	[59]
		55	TGC 50 mg i.v. loading dose, followed by 25 mg i.v. q12h	67% (95% CI: 53.3–79.3; p = NS)	
	Phase III, MC, R, DB	199	TGC 100 mg i.v. loading dose, followed by 50 mg i.v. q12h	82.9% (95% CI: 77.0–87.9; p < 0.001 for noninferiority)	[60]
		198	Vancomycin 1 g + aztreonam 2 g i.v. q12h	82.3% (95% CI: 76.3–87.4)	
	Phase III, MC, R, DB	223	TGC 100 mg i.v. loading dose, followed by 50 mg i.v. q12h	89.7% (95% CI: 84.9–93.3; p < 0.001 for noninferiority)	[61]
		213	Vancomycin 1 g + aztreonam 2 g i.v. q12h	94.4% (95% CI: 90.4–97.1)	
cIAIs	Phase III, MC, R, DB	341	TGC 100 mg i.v. loading dose, followed by 50 mg i.v. q12h	82.7% (95% CI: 78.3–86.6; p < 0.001 for noninferiority)	[69]
		351	Imipenem/cilastatin 500 mg i.v. q6h (or adjusted based on CrCl)	84.0% (95% CI: 79.8–87.7)	
	Phase III, MC, R, DB	344	TGC 100 mg i.v. loading dose, followed by 50 mg IV q12h	90.7% (95% CI: NA; p < 0.001 for noninferiority)	[117]
		346	Imipenem/cilastatin 500 mg i.v. q6h (or adjusted based on CrCl)	90.2% (95% CI: NA)	

CI: Confidence interval; cIAI: Complicated intra-abdominal infections; CrCl: Creatinine clearance; cSSSI: Complicated skin and skin-structure infection; DB: Double-blind; i.v.: Intravenous; MC: Multicenter; NA: Not applicable; NS: Not significant; OL: Open label; q6h: Every 6 h; q12h: Every 12 h; R: Randomized; TGC: Tigecycline.
Data taken from [20].

skin-structure infections [59]. This was a Phase II study and was conducted between September 1999 and March 2001 and involved 14 investigative centers across the USA. Patients were randomized to receive tigecycline 25 or 50 mg intravenously every 12h for 7–14 days. In this study, the primary efficacy end point was the clinically observed cure rate among clinically evaluable (CE) patients at the test-of-cure visit. The secondary end points were clinical cure rate at the end of treatment and bacteriological response in the microbiological evaluable patients. This study also included *in vitro* susceptibility results for a number of selected pathogens that were known to be associated with skin infections, and included *S. aureus*, *S. pyogenes*, *E. coli* and *Enterococcus* species. There were 160 patients that received at least one dose of tigecycline, and of these, 109 patients were CE and 91 were microbiologically evaluable. The majority of patients (74%) were men and the average age was 49 years. At the test-of-cure visit, the clinical cure rate was 67% (95% CI: 53.3–79.3%) in the 25 mg treatment group and 74% (95% CI: 60.3–85.0%) in the 50 mg treatment group. In comparing bacterial eradication between groups, 56% of the patients in the 25 mg treatment group had pathogen eradication (95% CI: 40.0–70.4%) as compared with 69% (95% CI: 54.2–82.3%) in the 50 mg treatment group. MIC_{90} values for the isolates tested ranged from 0.06 to 0.5 µg/ml, being lowest for *Enterococcus faecium* and highest for methicillin-susceptible *S. aureus* isolates in the 25 mg treatment group. Similar values were seen for isolates recovered from patients in the 50 mg treatment group, with MIC_{90} values ranging from 0.12 to 0.5 µg/ml. The authors concluded that tigecycline appeared efficacious and showed a favorable pharmacokinetic and safety profile in the treatment of hospitalized patients with complicated skin and skin-structure infections.

The efficacy and safety of tigecycline monotherapy compared with that of vancomycin plus aztreonam in the treatment of patients with complicated skin and skin-structure infections was reported by Sacchidanand *et al.* [60]. This was a Phase III trial and was a randomized, double-blind design. This study was conducted in eight countries and enrolled adult patients with complicated skin and skin-structure infections that required intravenous antibiotic therapy for 5 days or more. Patients were randomized to receive either of tigecycline or vancomycin plus aztreonam in a 1:1 ratio. Duration of therapy was up to 14 days. The primary end point was clinical cure at the test-of-cure visit. Secondary end points included microbiological efficacy and *in vitro* susceptibility to tigecycline of the organisms associated with complicated skin and skin-structure infections. A total of 596 patients were screened for enrolment and of these, 573 were analyzed for safety, 137 were included in the clinical modified intent-to-treat (C-mITT) population, 396 were CE and 228 microbiologically evaluable. The results at test-of-cure indicated similar cure rates between tigecycline and vancomycin plus azteonam in the CE population – 82.9% versus 82.3%, respectively. Cure rates were also similar in the C-mITT population – 75.5% versus 76.9%, respectively. Bacterial eradication rates were also similar between the two treatment groups. Specifically, total eradication rates for *S. aureus* were 82.1% in tigecycline-treated patients versus 83.1% in the vancomycin/aztreonam group. A further breakdown of this data reveals eradication rates for methicillin-resistant *S. aureus* (MRSA) isolates of 76.2% versus 81.0%, respectively, and for methicillin-susceptible *S. aureus* (MSSA) isolates, 85.7% versus 84.2%, respectively. Tigecycline also eradicated *E. faecalis, E. coli, S.agalactiae* and *S. pyogenes* pathogens with eradication rates ranging from 66.7 to 100%; however, these values were not substantially different than those with vancomycin/aztreonam of 50% versus 77.8%, and the small number of isolates in each group makes any likely differences difficult to determine. The authors concluded that this study demonstrated the efficacy of tigecycline as monotherapy for the treatment of patients with complicated skin and skin-structure infections, and that it was statistically noninferior to the combination regimen of vancomycin plus aztreonam.

Breedt *et al.* reported on the safety and efficacy of tigecycline in the treatment of skin and skin-structure infections [61]. This was a randomized, double-blind control trial comparing the efficacy of tigecycline to that of vancomycin plus aztreonam. A total of 546 patients with complicated skin and skin-structure infections received 100 mg/day of tigecycline (a 100 mg initial dose and then 50 mg intravenously twice a day [b.i.d.]) or they received a combination of vancomycin 2 g/day (1 g intravenously b.i.d.) and aztreonam 4 g (2 g intravenously b.i.d.) for up to 14 days. The primary end point in this study was clinical response in the C-mITT and CE populations at the test-of-cure visit 12–92 days after the last dose. The microbiological response at test-of-cure visit was also assessed (TABLE 5). A total of

Table 5. Clinical cure rates by infecting pathogen in microbiologically evaluable patients with complicated skin and skin-structure infections*.

Pathogen	Tigecycline n/N (%)	Vancomycin/aztreonam n/N (%)
Escherichia coli	27/32 (84.4)	26/30 (86.7)
Enterococcus faecalis (vancomycin-susceptible only)	13/17 (76.5)	24/29 (82.8)
Methicillin-susceptible *Staphylococcus aureus*	125/139 (89.9)	118/126 (93.7)
Methicillin-resistant *Staphylococcus aureus*	29/37 (78.4)	26/34 (76.5)
Streptococcus agalactiae	8/8 (100)	11/13 (84.6)
Streptococcus anginosus grp‡	16/20 (80.0)	9/10 (90.0)
Streptococcus pyogenes	31/33 (93.9)	24/27 (88.9)
Bacteroides fragilis	6/8 (75.0)	4/5 (80.0)

*Two complicated skin and skin-structure infection pivotal studies and one Phase III resistant pathogen study.
‡*Includes* Streptococcus anginosus, Streptococcus intermedius *and* Streptococcus constellatus.

520 patients were included in the C-mITT population (261 receiving tigecycline; 259 receiving vancomycin/aztreonam) and 436 patients were CE (223 receiving tigecycline and 213 receiving vancomycin/aztreonam). Clinical responses were similar between regimens in the C-mITT population (84.3% versus 86.9%) and in the CE population (89.7% versus 94.9%) – neither comparisons being statistically different. Regarding microbiological eradication (documented or presumed), 94.8% were tigecycline-treated patients versus 93.2% for those receiving vancomycin and aztreonam – a nonstatistically significant difference. The authors concluded that tigecycline is effective for the treatment of complicated skin and skin-structure infections.

Eillis-Grosse *et al.* summarized the efficacy data for tigecycline in the treatment of skin and skin-structure infections in two Phase III comparison studies with vancomycin and aztreonam [62]. As indicated in the above-summarized reports, tigecycline was found to be safe and efficacious when compared with vancomycin and aztreonam for the treatment of patients with complicated skin and skin-structure infections.

Complicated intra-abdominal infections

Intra-abdominal infections result from growth of bacteria in sterile regions, and are those that extend beyond the hollow viscus within the abdomen to produce peritonitis or abscess [63]. Such infections are said to be complicated when they require broad-spectrum antimicrobial therapy in combination with surgical intervention. Intra-abdominal infections are caused by multiple intestinal microorganisms and are usually polymicrobial. *Enterobacteriaceae* (i.e. *E. coli* and *K. pneumoniae*), enterococci and *Baceroides fragilis* are frequently causative [63–66]. Unfortunately, the emergence of extended spectrum β-lactamase-producing strains of *E. coli* and *Klebsiella pneumoniae* (and other *Enterobacteriaceae*) compromise the use of most β-lactam agents. New agents are necessary, as inappropriate therapy may delay clinical resolution, increase hospital stay and impact negatively on mortality [67,68].

Tigecycline was evaluated in a multicenter trial for efficacy in patients with complicated intra-abdominal infections compared with imipenem/cilastatin [69]. This was a prospective, double blind, multinational trial (Argentina, India, USA, Brazil and Chile) (Table 4). The patients were randomly assigned to receive tigecycline (100 mg initial dose, then 50 mg every 12 h) or intravenous imipenem/cilastatin (500/500 mg every 6 h or adjusted for renal dysfunction) for 5–14 days. The co-primary efficacy end points were clinical response at the test-of-cure visit, as well as microbiologically evaluable and microbiologically C-mITT populations. A total of 825 patients received at least one dose of the study drug. Primary diagnosis for the microbiologically evaluable group were complicated appendicitis (59%) and intestinal (8.8%) and gastric/duodenal perforations (4.6%). In the microbiologically evaluable group, clinical cure rates at test-of-cure were 80.6% (199/247) for tigecycline-treated patients, versus 82.4% (210/255) for the imipenem/cilastatin-treated group. This was a nonstatistically significant difference. The corresponding clinical cure rates within the modified intent to treat populations were 73.5% (227/309) for tigecycline versus 78.2% (244/312) for the imipenem/cilastatin treated group – a nonstatistically significant observation. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was similar between the tigecycline and imipenem/cilastatin treatment groups at 5.6 and 5.5, respectively. The mean duration of therapy (in days) was 8.1 versus 7.9, respectively. In both arms, the

Table 6. Clinical cure rates by infecting pathogen in microbiologically evaluable patients with complicated intra-abdominal infections*.

Pathogen	Tigecycline n/N (%)	Vancomycin/aztreonam n/N (%)
Citrobacter freundii	12/16 (75.0)	3/4 (75.0)
Enterobacter cloacae	14/16 (87.5)	16/17 (94.1)
Escherichia coli	281/329 (85.4)	298/343 (86.9)
Klebsiella oxytoca	19/20 (95.0)	18/20 (90.0)
Klebsiella pneumoniae	46/52 (88.5)	53/60 (88.3)
Enterococcus faecalis (vancomycin-susceptible only)	25/33 (75.8)	35/47 (74.5)
Methicillin-susceptible *Staphylococcus aureus*	26/29 (89.7)	22/24 (91.7)
Streptococcus anginosus grp‡	102/120 (85.0)	61/81 (75.3)
Bacteroides fragilis	67/87 (77.0)	60/74 (81.1)
Bacteroides thetaiotaomicron	36/41 (87.8)	31/36 (86.1)
Bacteroides uniformis	12/17 (70.6)	14/17 (82.4)
Bacteroides vulgatus	14/16 (87.5)	5/7 (71.4)
Clostridium difficile	19/20 (95.0)	20/22 (90.9)
Peptostreptococcus micros	14/18 (77.8)	9/12 (75.0)

*Two complicated intra-abdominal infection pivotal studies.
‡*Includes* Streptococcus anginosus, Streptococcus intermedius *and* Streptococcus constellatus.

majority of patients were male and the mean age ranged from 42.9 to 43.1 years. Clinical cure rates were also not different between groups from the microbiologically evaluable patient population based on monomicrobial versus polymicrobial infection – 89.9% and 75.3%, respectively, for tigecycline-treated patients versus 88.5% and 78.1%, respectively for imipenem/cilastatin-treated patients (Table 6). The authors concluded that tigecycline was effective for the treatment of patients with complicated intra-abdominal infections and had comparable efficacy to that of imipenem/cilastatin. The authors also indicated that tigecycline was a promising new monotherapeutic agent with good empiric coverage against Gram-positive and nonpseudomonal Gram-negative bacteria – including those strains that may be resistant to other classes of antibiotics.

Murray *et al.* reported the clinical response to tigecycline in the treatment of complicated intra-abdominal infections in hospitalized patients from a Phase II clinical trial [70]. This was a multicenter Phase II, open-label study in hospitalized patients with clinical evidence of complicated intra-abdominal infection who required surgical extirpation of the source of infection plus antibiotic therapy. In the study, all the patients received a loading dose of 100 mg of tigecycline intravenously followed by 50 mg b.i.d. for at least 5 days and not more than 14 days. Clinical response was determined by the investigator as cure, failure or undetermined. A total of 111 patients were enrolled (69% male) and ranged in age from 18 to 80 years. Patients with perforated and gangrenous appendicitis, complicated cholecystitis, perforated diverticulitis and peritonitis were included in the study. A total of 66 patients met all inclusion criteria and were evaluable for efficacy. Cure rates at test-of-cure and end of treatment visits were 67 and 76%, respectively. In the intent-to-treat analysis, the cure rate and test-of-cure was 55%, and the end of treatment was 72%. The authors concluded that this study demonstrated tigecycline to be efficacious in the treatment of hospitalized patients with complicated intra-abdominal infections.

Babinchuk *et al.* provided an analysis of the pooled clinical trial data on the efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections [71]. The pooled analysis included data from the two Phase III double-blind trials where tigecycline was compared with imipenem/cilastatin. From those studies, a total of 1642 adults with complicated intra-abdominal infections were randomized to receive either of tigecycline (initial dose of 100 mg followed by 50 mg b.i.d. dosing intravenously) or imipenem/cilastatin (500/500 mg intravenously every 6 h) for 5–14 days. In these trials, the primary end point was clinical response and test-of-cure (12–42 days after therapy), and the co-primary end point was microbiologically evaluable and microbiologically C-mITT populations. For the patients in the microbiologically evaluable group, clinical cure rates were 86.1% (441/512) for tigecycline versus 86.2% (442/513) for imipenem/cilastatin,

and statistical evaluation showed this to be a noninferiority difference. For the microbiological C-mITT population, clinical cure rates were 80.2% (506/631) for tigecycline-treated patients versus 81.5% (514/631) for imipenem/cilastatin, and once again this was a nonstatistically significant difference. No differences were noted between either treatment arms or microbiologically evaluable patients that had either monomicrobial or polymicrobial infections. Differences were also not seen in the microbiologically C-mITT population based on either monomicrobial or polymicrobial infections for either of the treatment arms. Included in clinical diagnosis was complicated appendicitis, complicated cholelcystitis, intra-abdominal abscess, perforation of the intestines, complicated diverticulitis, gastritis and abdominal perforations, and peritonitis. In all instances, clinical cure rates were similar between tigecycline and imipenen/cilastatin treatment groups. In addition, for patients with concomitant bacteremia, clinical cure rates were 82.5% for tigecycline- versus 80.0% for imipenem/cilastatin-treated patients.

Community-acquired pneumonia

Community-acquired pneumonia (CAP) is a well-defined clinical entity and the etiology is well established [72–74]. For outpatients, *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae* and respiratory viruses (influenza A, B, adenovirus, respiratory syncytial virus, parainfluenza virus) are the most common etiologies. For inpatients that are not in the intensive care unit (ICU), *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae*, *H. influenzae*, *Legionella* spp., organisms associated with aspiration and respiratory viruses are common etiologies. For the patient in the ICU, *S. pneumoniae*, *S. aureus*, *Legionella* species, Gram-negative bacilli and *H. influenzae* are common etiologies. Indeed, expert working groups have developed and advanced antimicrobial therapy recommendations for the empiric therapy of patients with CAP based on disease severity and where the patient is to be treated – that is, outpatient versus inpatient treated on the general ward or the intensive care unit [74,75]. **Box 1** summarizes the current recommended empiric therapy for adult patients with CAP.

Tanaseanu *et al.* reported on the integrated results of two Phase III studies comparing tigecycline and levofloxacin in CAP [76]. These two Phase III trials were multicenter, randomized, double-blinded studies and were conducted to compare the efficacy and safety of tigecycline versus levofloxacin in adult patients hospitalized with CAP. The first study was conducted between June 2003 and July 2005 at 54 centers in eight countries (North America, South America, Mexico/Central America), and the second study was conducted from January 2004 to January 2005 at 62 centers in 20 countries (Europe, Africa and Asia Pacific region). Patients were randomly assigned to receive either intravenous tigecycline (100 mg initially followed by 50 mg b.i.d.) or intravenous levofloxacin (500 mg every 24 h in one study or 500 mg b.i.d. for every 24 h, at the investigators discretion, based upon local practice, in the other trial). The co-primary efficacy end points were as follows: clinical response in the CE and C-mITT populations at test-of-cure. The secondary end points were as follows: microbiological efficacy and susceptibility to tigecycline for CAP-associated bacteria. Safety evaluations were also included. A total of 891 patients were screened. Of 846 patients in the mITT group, 424 were randomized to receive tigecycline as compared with 422 for levofloxacin. Of 574 patients in the CE groups, 282 received tigecycline and 292 received levofloxacin. Most patients had fine pneumonia severity index scores of II to IV: 80.7% in the tigecycline arm, as compared with 74.4% in the levofloxacin arm in the mITT groupings. At the test-of-cure in the CE population, cure rates were 89.7% (253/282) in tigecycline-treated patients versus 86.3% (252/292) in those receiving levofloxacin. This was a nonstatistically significant difference. In the C-mITT analysis, tigecycline cure rate was 81% (319/394) versus 79.7% (321/403) for levofloxacin-treated patients, and this was also a nonstatistically significant difference. For drug-related adverse events, nausea was seen in 20.8% of tigecycline-treated patients versus 6.6% of those receiving levofloxacin, and vomiting was seen in 13.2% versus 3.3%, respectively, and were significantly higher in those patients receiving tigecycline. Elevated liver enzymes were significantly higher in those patients receiving levofloxacin. When comparing discontinuation rates between treatment arms, 26 patients (6.1%) receiving tigecycline discontinued therapy, as compared with 34 (8.1%) of those receiving levofloxacin. The authors concluded that tigecycline appeared to be safe and achieved a cure rate similar to levofloxacin hospitalized patients with CAP. Regarding microbiological responses in patients treated with tigecycline versus levofloxacin, there were no significant differences between treatment groups and pathogens identified in the

Box 1. Recommended empirical antibiotics for community-acquired pneumonia.

Outpatient treatment

- Previously healthy, no use of antimicrobials within the previous 3 months.
  - A macrolide (strong recommendation; level I evidence)
  - Doxycycline (weak recommendation; level III evidence)
- Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
  - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin or levofloxacin [750 mg]) (strong recommendation; level I evidence)
  - A β-lactam plus a macrolide (strong recommendation; level I evidence)
- In regions with a high rate (>25%) of infection with high-level (MIC ≥ 16 μg/ml) macrolide-resistant *Streptococcus pneumoniae*, consider use of alternative agents listed above for patients without comorbidities (moderate recommendation; level III evidence)

Inpatients, non-ICU treatment

- A respiratory fluoroquinolone (strong recommendation; level I evidence)
- A β-lactam plus a macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment

- A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin (level II evidence) or a respiratory fluoroquinolone (level I evidence; strong recommendation; for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Special concerns

- If *Pseudomonas* is a consideration
  - An antipneumococcal, antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg), or
  - The above β-lactam plus an aminoglycoside and azithromycin, or
  - The above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above β-lactam; moderate recommendation; level III evidence)
- If CA-MRSA is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)

CA-MRSA: Community-acquired methicillin-resistant Staphylococcus aureus*; ICU: Intensive care unit; MIC: Minimum inhibitory concentration.*
Data taken from [75,119].
Reproduced with permission from [75].

microbiologically evaluable population, including *C. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *L. pneumophila, M. catarrhalis, M. pneumoniae* and *S. pneumoniae*. The MIC_{90} value for penicillin-susceptible and nonsusceptible *S. pneumoniae* isolates was 0.06 μg/ml, and for *H. influenzae* and *H. parainfluenzae* strains was 0.5 μg/ml.

Bergallo *et al.* reported on the safety and efficacy of intravenous tigecycline in comparison with levofloxacin for the treatment of patients with CAP [77]. This was a Phase III multicenter double-blind study that was conducted between June 2003 and July 2005 at 54 medical centers in eight countries (North America, South America and Mexico/Central America). Patients were randomly assigned to receive either intravenous tigecylcine or levofloxacin for a minimum of 3 days. Patients were stratified at randomization based on the fine pneumonia severity index and geographic location. Patients that were randomly assigned to receive tigecycline were treated with an initial dose of 100 mg, followed by 50 mg every 12 h thereafter. Patients randomly assigned to receive levofloxacin (creatinine clearance rates of at least 50 ml/min) were to receive 500 mg once daily. Dosage modification was allowed for patients with renal insufficiency. The study was restricted to adult patients (≥18 years old) requiring hospitalization and with clinical signs and symptoms suggestive of CAP. Patients could be switched to oral levofloxacin after receiving six or more doses of intravenous study medication. Therapy duration was for 7–14 days. The co-primary efficacy end points were clinical responses in the CE population and the C-mITT arms at test-of-cure. Safety was assessed in the C-mITT. In the CE population, 138 patients received tigecycline as compared with 156 for levofloxacin: in the C-mITT arms, 191 patients received tigecycline as compared with 203 receiving levofloxacin. For the safety analysis, 208 patients receiving tigecycline and 210 receiving levofloxacin were included in this analysis. The cure rates in the tigecycline and levofloxacin treatment groups were comparable with the CE population at 90.6% versus 87.2%, respectively; those values were 78% versus 77.8%, respectively in the C-mITT populations at test-of-cure. For microbiological assessment, baseline bacterial cultures were taken from the primary site of infection, as were two sets of blood cultures obtained within 24 h before patients received the first intravenous dose of test medication. In both the microbiological evaluable treatment groups, there were no statistical

differences in eradication rates between tigecycline- or levofloxacin-treated patients, regardless of whether the infections were considered to be mono-microbial, polymicrobial, persistence or super infection. Eradication rates at test-of-cure for common CAP pathogens were not significantly different between tigecycline and levofloxacin in the microbiological evaluable groups. Organisms recovered from CAP patients during the study included *C. pneumoniae*, *H. influenzae*, *L. pneumophila*, *M. catarrhalis*, *M. pneumoniae* and *S. pneumoniae*. The tigecycline MIC_{90} value for the *H. influenzae* strains was 1 mg/l, as compared with 0.06 mg/l for *S. pneumoniae* strains, regardless of their susceptibility or non-susceptibility to penicillin. Nausea and vomiting occurred commonly in tigecycline-treated patients and those receiving levofloxacin, and this was statistically significant. Elevated liver enzymes were significantly seen more often in levofloxacin-treated patients. The authors concluded that tigecycline was safe, effective and noninferior to levofloxacin in the treatment of hospitalized patients with CAP [74].

Clostridium difficile

Clostridium difficile is a Gram-positive anaerobic spore forming bacilli that is often associated with hospital-acquired diarrhea. Many variables have been published summarizing the risks associated with *C. difficile*-associated infection in hospitalized patients [78]. Of these variables, broad-spectrum antibiotics are often associated with *C. difficile* infection. Other factors associated with hospital-acquired *C. difficile*-associated colitis [79–83] include: advanced age (>65 years), laxative use, proton pump inhibitors, antineoplastic chemotherapeutic use, renal insufficiency, gastrointestinal surgery/procedures, severity of underlying disease, nasogastric intubation, gastric acid suppressants, duration of hospital stay, duration of antibiotic course, multiple antibiotics and prolonged hospital stay [49].

Wilcox reviewed literature suggesting that there was evidence indicating a low risk of *Clostridium difficile* infection associated with tigecycline use [84]. Wilcox indicated that despite the marked broad-spectrum activity of tigecycline, it does not appear to result in an increased risk for *C. difficile*-associated diarrhea. In his summary, Wilcox indicated that broad-spectrum agents such as cephalosporins are often implicated as increased risks for *C. difficile*-associated disease, and not all broad-spectrum agents are equally implicated – such as piperacillin/tazobactam [85,86]. Blondeau *et al.* reported on the *in vitro* activity of tigecycline against contemporary clinical isolates of *C. difficile* [55]. Tigecycline MIC and MPC values against three strains (collected September 2008 to December 2008) ranged from 0.016 to 0.125 mg/l.

Limited clinical information is available on the use of tigecycline for treatment of *C. difficile* infections. Herpers *et al.* reported on the treatment of four patients with severe refractory *C. difficile* infection [87]. One patient was simultaneously being treated with vancomycin; however, the patient had previously failed to respond to either vancomycin or metronidazole, and previous standard therapy had failed in two other patients. All patients had at least four of the following severity markers: leukocytosis, elevated creatinine level, elevated lactate level, hypoalbuminemia, fever, and signs of severe colitis. Patients were administered standard dosing of tigecycline (intravenous); 100-mg loading dose and 50 mg b.i.d. Patients treated with tigecycline had symptom resolution within 1 week, and no relapses were observed during the follow-up period.

Nord *et al.* reported the fecal concentrations of tigecycline on day 8 ranged from 3.0 to 14.1 mg/kg (mean: 6.0 mg/kg; median: 5.6 mg/kg) [88]. As such, tigecycline drug concentrations would be 48-times higher than the MIC/MPC drug concentration (based on median value). Clearly, further research and clinical experience is needed.

Safety

The safety of tigecycline has been evaluated in over 1400 patients from the Phase III clinical studies. The number of patients receiving comparator agents and evaluated for safety was 1382. Nausea, vomiting and diarrhea were the most frequently reported side effects associated with tigecycline therapy, occurring in 29.5, 19.7 and 12.7% of patients, respectively. The incidence of these same side effects in patients receiving comparator regimens was 15.8, 10.8 and 10.8%, respectively. Babinchak *et al.* summarized the number of patients in the mITT population that withdrew because of any adverse event [71]. Withdrawal due to any adverse event occurred in 2.6% of 817 patients treated with tigecycline as compared with 1.5% of 825 patients treated with imipenem/cilastatin. This was a nonstatistically significant difference. As such, discontinuation rates were not higher in patients receiving tigecycline than in those receiving imipenem/cilastatin. Similarly, in patients treated with tigecycline (n = 566) as compared with those treated with vancomycin/astreonam (n = 550), the number

of patients in the mITT population who discontinued treatment because of any adverse event was 3.5% for tigecycline-treated patients, versus 5.3% for those receiving vancomycin/aztreonam – a nonstatistically significant difference. Patients received these regimens for the treatment of skin and skin-structure infections.

In a review by Townsend, the author also indicated that the most commonly reported adverse effects with tigecycline in both Phase II and III studies were nausea and vomiting, and that it occurred most often during the first 2 days of therapy [89]. Nausea and vomiting as reported in the studies was characterized as being mild-to-moderate in severity in most patients.

Comments

Tigecycline is one of few new broader spectrum antimicrobial compounds approved for clinical use within the past 5 years – clearly a welcome addition given the scarcity of new drug development. As summarized in this review, tigecycline is active *in vitro* and clinically against Gram-positive and -negative pathogens, including those with multidrug-resistant phenotypes. Tigecycline is also active against tetracycline-resistant strains. Mutant prevention concentration measurements against MSSA, MRSA, *S. pneumoniae* (including penicillin-resistant strains) and *Enterobacteriaceae* reported values within clinically achievable and sustainable drug concentrations, thereby suggesting tigecycline has a low propensity to select for antimicrobial nonsusceptible or resistant subpopulations. *In vitro* kill studies against higher density populations (10^6–10^7 CFU/ml) of *E. coli* indicate bactericidal activity as substantial $\log_{10}$ reductions in viable cells were observed. The clinical impact of MPC and the high-density bacterial population kill studies remains to be determined.

Against contemporary *C. difficile* clinical isolates, tigecycline had low MIC and MPC values that may contribute to the reduced likelihood for selection of this pathogen during therapy.

Clinically, tigecycline was shown to be noninferior to vancomycin/aztreonam for skin and skin-structure infections; noninferior to imipenem/cilastatin for complicated intra-abdominal sepsis and, most recently, noninferior to levofloxacin for the treatment of CAP requiring hospitalization.

Tigecycline has a safety profile equivalent to the comparator regimens used in clinical trials, and withdrawal rates were not higher with this drug.

Livermore asked what is tigecycline and where should it be used [2]. He suggested that it might be particularly useful for treatment of surgical wound infections where both gut microorganisms and MRSA may be causative. He also suggested a potential role in the treatment of infections due to multiresistant pathogens including *Acinetobacter* spp., ESBLs, MRSA and enterococci. In his overview, Livermore acknowledged that tigecycline was one of few new antimicrobial agents with Gram-negative activity.

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Executive summary

- Tigecycline has broad-spectrum activity against Gram-positve, Gram-negative and atypical pathogens.
- Tigecycline remains active *in vitro* against multidrug resistant pathogens: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum β-lactamase-producing Gram-negative bacilli, penicillin-resistant *Streptococcus pneumoniae* and tetracycline-resistant pathogens.
- Tigecycline was efficacious for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections and community-acquired pneumonia requiring hospitalization.
- Tigecycline was shown to be safe with the most frequent side effects being nausea, vomiting and diarrhea.
- Tigecycline mutant prevention drug concentrations were within clinically achievable drug concentrations with approved dosing for most organisms investigated.
- Tigcycline may have a role for therapy for *Clostridium difficile*; however, additional clincial evidence is required.
- The role of tigecycline for therapy of organisms such as *Acinetobacter baumannii* and carbapenemase-producing *Klebsiella pneumonia* requires further investigation specifically to address the concerns for resistance selection during therapy.
- The potential for synergy between tigecycline and other antimicrobials has been investigated, but further investigation is required to resolve this issue.

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