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Minocycline and Tigecycline: What Is Their Role in the Treatment of Carbapenem-Resistant Gram–Negative Organisms?

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Carbapenem-resistant organisms are increasingly common worldwide, particularly in India and are associated with high mortality rates especially in patients with severe infection such as bacteremia. Existing drugs such as carbapenems and polymyxins have a number of disadvantages, but remain the mainstay of treatment. The tetracycline class of antibiotics was first produced in the 1940s. Minocycline, tetracycline derivative, although licensed for treatment of wide range of infections, has not been considered for treatment of multidrug-resistant organisms until recently and needs further *in vivo* studies. Tigecycline, a derivative of minocycline, although with certain disadvantages, has been frequently used in the treatment of carbapenem-resistant organisms. In this article, we review the properties of minocycline and tigecycline, the common mechanisms of resistance, and assess their role in the management of carbapenem-resistant organisms.

Keywords: tetracycline, minocycline, tigecycline, carbapenem-resistant organisms, *Klebsiella pneumoniae*, *Acinetobacter* spp.

Background

Carbapenem-resistant organisms are increasingly common worldwide, particularly in India where resistance is predominantly mediated by NDM and OXA carbapenemases. They are associated with high mortality rates, especially in patients with severe infections such as bacteremia.[1] Existing drugs such as carbapenems and polymyxins have a number of disadvantages, but remain the mainstay of treatment.

The tetracycline class of antibiotics was first produced in the 1940s. In 2005, a minocycline derivative, tigecycline, was first approved, becoming the first in class of the glycylcycline antibiotics, structural derivatives of the tetracyclines. In this article, we review the properties of minocycline and tigecycline, the common mechanisms of resistance, and assess their role in the management of carbapenem resistant organisms.

Tetracyclines

Tetracyclines are broad spectrum antibiotics, which inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor site (A). Structurally, they consist of a linear fused tetracyclic nucleus to which a variety of functional groups can be assigned. Chlortetracycline, obtained from *Streptomyces aureofaciens*, was the first tetracycline and was described in 1948.[2] The second generation tetracyclines, doxycycline and minocycline, are synthetic tetracyclines and are more commonly used in clinical practice due to improved pharmacological properties.[2] More recently, the minocycline derivative, tigecycline, has become available for intravenous use.[3] Although it is the first in class of the glycylcyclines, it shares a number of common features with its parent drugs.[4]

Both the tetracyclines and tigecycline are broad spectrum antimicrobials with activity against Gram-positive, Gram-negative, and atypical organisms. There is some variation; tigecycline for instance is more active against *Enterobacteriaceae* than its ancestors. They share common dose-related gastrointestinal side effects, including abdominal pain, vomiting, and anorexia, together with photosensitivity. They can all interfere with bone formation and cause yellow-brown discoloration of the teeth; hence, should not be used in pregnancy or in children less than 8 years old.[3,5–7]

There are a number of common mechanisms that may result in resistance to one or more members of the tetracyclines or tigecycline. Resistance can be mediated through efflux pumps, enzymatic inactivation by *tetX* gene product, and production of ribosomal protection proteins.[2] The efflux pumps are membrane bound efflux proteins of around 46 kDa, coded by genes from the major facilitator superfamily. These are found in both Gram-positive and Gram-negative bacteria and most confer resistance to tetracycline, but not minocycline or tigecycline. The exception is the *tetB* gene, which has the widest host range among Gram-negative *tet* genes. *tetB* encodes an efflux protein conferring resistance to tetracycline and minocycline, but not tigecycline.

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Tet proteins are divided into 6 groups based on amino acid sequence identity; these groups are summarized in Table 1.[2]

Ribosomal protection proteins such as *tet*M, *tet*O, *tet*S, *tet*W, *tet*Q, *tet*T, *otr*A, and *tet*P (B) are present in the cell cytoplasm and can confer resistance to tetracycline, doxycycline, and minocycline. These proteins bind to the ribosome and cause conformational change, which inhibits tetracycline binding, but does not alter protein synthesis. Ribosomal protection proteins have high homology with elongation factors EF-G and EF-Tu. TetM and TetO have ribosome-dependant GTPase activity and compete with EF-G for binding to the ribosome. In their presence, binding to the ribosome decreases and tetracycline may be released through energy from GTP hydrolysis.

tetX codes for an oxidoreductase enzyme, which modifies and inactivates tetracycline, and is seen mostly in anaerobes such as *Bacteroides*. The enzyme requires oxygen for its activity and so has no role in the anaerobic host organism such as *Bacteroides.* There is no literature available explaining the relevance of *tetX* in *Bacteroides*. This enzyme has also been isolated from multidrug-resistant (MDR) *Enterobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonadaceae*, and *Comamonas testosteroni* from urinary specimens.[8]

The majority of *tet* genes in bacteria are associated with mobile plasmids, transposons, conjugative transposons, and integrons (gene cassettes)[9–15] except for *tetE*. These mobile units have enabled *tet* genes to move from species to species and into a wide range of genera by conjugation. In addition, some are associated with large conjugative transposons, which carry other resistance genes. For instance, *tet*M and *tet*Q are associated with conjugative transposons, which also carry the *ermF* gene, conferring additional resistance to erythromycin. The majority of Gram-negative isolates described in the literature carry a single type of *tet* gene, although it may occur on multiple plasmids. This was evident from the earliest studies of the distribution of *tet* genes, where it was found that only 3.5% of the lactose-fermenting coliforms carried two different *tet* genes.[16]

Minocycline

Minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline) is a second generation tetracycline introduced in 1967.[6] It inhibits protein synthesis by binding to the 30S ribosomal subunit, thus preventing its association with aminoacyl-tRNA to create magnesium–minocycline chelation complex.[6,17]

Minocycline is a broad spectrum antibiotic with antimicrobial activity against a wide range of Gram-positive, Gram-negative, and atypical bacteria.[17,18] Its principal clinical use is in the treatment of acne vulgaris, lyme disease, and perioral infections. Further indications include gastrointestinal infections (*Campylobacter* spp., *Vibrio cholera*), sexually transmitted diseases (*Chlamydia trachomatis, Ureaplasma urealyticum,* and *Klebsiella granulomatis*), skin and soft tissue infection (*Staph aureus, Actinomyces* spp.), Rickettsial infections (Rocky Mountain spotted fever and rickettsial pox), and zoonotic infections (*C. psittaci, Yersinia pestis, Francisella tularensis, Brucella* spp., and *Bartonella bacilliformis*).

However, in practice, it is rarely used for these infections due to the existence of alternative antibiotics, which are

Table 1. Major Efflux Proteins Coding for Tetracycline and Minocycline Resistance

Group	*Genes*	*Distribution*
Group 1	*tet*A, *tet*B, *tet*C, *tet*D, *tet*E, *tet*G, *tet*H, *tet*Z, *tet*I, *tet*J, and *tet*30	Predominantly found in Gram-negative bacteria, except *tet*Z, which is seen in Gram-positive bacteria. Two functional domains, α and β, which correspond to N and C terminal of the protein. Associated with large conjugative plasmids. Confer resistance to tetracycline, but not minocycline (except *tet*B, which confers resistance to tetracycline and minocycline, but not tigecycline).
Group 2	*tet*K and *tet*L	Primarily found in Gram-positive bacteria. Confer resistance to tetracycline and chlortetracycline, but not to minocycline or tigecycline. Found on small transmissible plasmids, which become integrated with chromosomes of organisms, including *Staphylococcus aureus* and *Bacillus*.
Group 3	*otr*B and *tcr*3	Found in *Streptomyces* spp. *otr*B confers resistance to oxytetracyclines and *tcr*3 confers resistance to tetracyclines
Group 4	*tet*A(P)	Found in *Clostridium* spp. and represents a different type of efflux protein unlike the other efflux proteins associated with tetracycline resistance unlike *tet*B(P), which confers low resistance to tetracycline and minocycline.
Group 5	*tet*V	Found in *Mycobacterium smegmatis* and *Mycobacterium fortuitum.* Confers resistance to tetracycline and not to derivatives such as minocycline.
Group 6	Not designated	Found in *Corynebacterium striatum.* Uses ATP than proton gradient as energy source.

better tolerated and more readily available such as doxycycline and erythromycin. The immunomodulatory and antioxidant effects of minocycline are increasingly recognized for inflammatory diseases, including rheumatoid arthritis,[19] rosacea,[20] and sarcoid,[21] and as a neuroprotective/neuroregenerative agent in spinal cord injury,[22] and even depression.[23]

The pharmacokinetic and dynamic properties of minocycline are outlined and compared to those of tigecycline in Table 2. Minocycline is available in oral and intravenous preparations. The oral form has a bioavailability of 95%, considerably higher than first generation tetracyclines,[24] and rapidly achieves good serum concentration.[25] Although minocycline is bacteriostatic, *in vitro* data suggest a synergistic bactericidal effect when it is used in combination with meropenem or colistin.[26] It is lipophilic with good tissue penetration, particularly into lung parenchyma where concentration is reported to be 378% of that in serum.[27] Minocycline does not require dose reductions in either hepatic or renal dysfunction. It is usually well tolerated, and gastrointestinal and central nervous system side effects are related to high dose and long-term usage.[6,7,24]

In recent years, there has been growing interest in minocycline as an agent for multidrug-resistant Gram–negative infections. Most investigations have focused on *Acinetobacter baumannii* where it has been shown to have good *in vitro* activity.[28,29] The TEST study reports a global minocycline susceptibility rate of 84.5% when using CLSI interpretative criteria, the highest levels of *in vitro* susceptibility of *A. baumannii* to any antibiotic tested.[30] EUCAST and BSAC do not set breakpoints for *A. baumannii* for minocycline due to a lack of available data. *In vivo* data are limited. There are no randomized controlled trials, but small descriptive case series show consistently favorable results in oral and intravenous use of minocycline.

A recent systematic review of 10 retrospective studies found that combination treatment, including a tetracycline, was successful in 76.9% of patients with *A. baumannii* infection.[31] Chan *et al.*, highlighted its role in the treatment of carbapenem-resistant *A. baumannii* ventilator–associated pneumonia. They found that 80.6% ($n=29$) of patients responded clinically to minocycline or doxycycline.[28] This was similar to a 90% clinical response rate in 10 patients treated with tigecycline and 77.8% in 36 patients treated with aminoglycosides, but compared favorably to 66.7% in nine patients treated with polymyxins and 60% in five patients treated with ampicillin/sulbactam.[28] Griffith *et al.*, emphasize the role of oral minocycline in the treatment of wound infections. Seven of eight patients with MDR *A. baumannii* soft tissue infections were clinically cured after 4–6 weeks of minocycline alone or in combination with another antibiotic.[32] Further clinical studies are summarized in Table 3.

There are limited data on the use of minocycline in *Enterobacteriaceae*. EUCAST does not set breakpoints for *Enterobacteriaceae* as it considers them a poor target for minocycline therapy. However, the rationale document was produced in 2011 in an era where there were far fewer carbapenem-resistant *Enterobacteriaceae* (CRE). The TEST study reports that 71.4% of *K. pneumoniae* isolates globally are susceptible to minocycline ($n=28928$, minimum inhibitory concentration [MIC] 90 = 16 mg/L), but this falls to 52.2% in isolates, which are resistant to carbapenems ($n=1330$, MIC 90 ≥ 32 mg/L).[30] Interestingly, the same data set also shows a gradual decline in the susceptibility of *K. pneumoniae* to minocycline between 2004 and 2011, but then a 22.9% increase in minocycline susceptibility between 2011 and 2013.

At our own center, a large teaching hospital in South India where NDM and OXA 48 are the predominant

Table 2. Pharmacokinetic and Pharmacodynamic Differences Between Minocycline and Tigecycline

	Minocycline	*Tigecycline*
Class	Tetracycline	Glycylcycline (minocycline derivative)
License	Wide range of infections caused by several Gram-negative bacteria[6]	Skin and soft tissue infections, complicated intra-abdominal infections[36]
Preparation	Oral, intravenous	Intravenous
Usual dose	200 mg PO/IV loading dose, then 100 mg PO BD[6]	100 mg IV loading dose, then 50 mg IV BD[4]
Renal adjustment	No[18]	No[36]
Liver adjustment	No	Child Pugh category 3, reduce dose to 25 mg BD[36]
Adverse effects	Vestibular symptoms, nausea, vomiting, increased pigmentation with long-term use, reversible hypersensitivity pneumonitis[6]	Nausea and vomiting, other side effects rare[36]
PK/PD index	24 hr AUC/MIC	24 hr AUC/MIC
Cmax (mg/l)	2.0–3.5 (200 mg oral dose), 4.2 (200 mg IV dose)[6]	0.82 (100 mg dose), 0.49 (50 mg dose)[81]
Protein binding (%)	76[81]	71–87[82]
Serum half-life (hours)	12–16 hr[6]	36 hr[37]
T max (hour)	2–4[81]	—
Volume of distribution (Vd)	80–115 L[81]	350–500 L[81]
AUC 24 mg/[hr·L]	45 mg/[hr·L][81]	2.2 ± 0.3 mg/[hr·L][81]
Contraindications	Pregnancy, <8 years[6]	Pregnancy, <8 years[5]

AUC, area under the concentration-time curve; MIC, minimum inhibitory concentration.

Table 3. *In Vivo* Data for the Use of Minocycline in Drug-Resistant Infections

Treatment	*Other antibiotics*	*Infection/cause*	*Outcome*	*Reference*
Monotherapy	—	Wound infection due to Acb	88% clinical cure ($n=8$)	Griffith *et al.*[32]
Monotherapy	—	VAP due to Acb	100% clinical cure ($n=4$)	Wood *et al.*[29]
Monotherapy and combination therapy	Colistin, tobramycin, and ampicillin/sulbactam	BSI and pneumonia due to Acb and CRKp	67% clinical cure ($n=9$)	Pogue JM *et al.*[33]
Monotherapy and combination therapy	Aminoglycoside/tigecycline+ aminoglycoside, polymyxin+ aminoglycoside	VAP due to CRAcb	81% clinical cure ($N=36$)	Chan *et al.*[28]

BSI, blood stream infection; CRKp, carbapenem-resistant *Klebsiella pneumoniae*; VAP, ventilator-associated pneumonia.

mechanisms of carbapenem resistance, we found that 65% of carbapenem-resistant *K. pneumoniae* (CRKp) isolates taken from blood cultures in 2014 and 2015 were susceptible to minocycline while 90% were susceptible to tigecycline ($n=98$). In comparison, among carbapenem susceptible isolates, 98% were susceptible to tigecycline, while 88% were susceptible to minocycline ($n=104$) (unpublished data). By contrast, in 59 isolates from Detroit, an area where KPCs predominate, only 12% of CRKp were susceptible to minocycline with an MIC90 of 32.[33] These data highlight significant geographical variation in minocycline susceptibility. There is very limited *in vivo* data on the use of minocycline in carbapenem-resistant *K. pneumoniae* infection. In the aforementioned study, two of three patients with *K. pneumoniae* blood stream infection were cured when minocycline was used in combination therapy.[33]

A final advantage in the use of minocycline for CR organisms is its price. In India, oral minocycline costs just Rs100 ($1.51) per single dose, 30 times less than IV tigecycline.

To summarize, the pharmacokinetic and pharmacodynamics of minocycline, together with the fact that it often retains activity against CR *A. baumannii* and sometimes against CRE, suggest that it may have a role in the treatment of these organisms.[28,29,32,33] Clinical data, however, are very limited and further trials are needed.

Tigecycline

Tigecycline is the first in class of the glycylcycline antibiotics. It inhibits protein synthesis by binding to the 30 S ribosomal subunit with five times the affinity of tetracycline thus preventing aminoacyl-tRNA binding to the ribosome.[4,34,35] Structurally, it is a derivative of minocycline with a 9-tert-butyl-glycylamido side chain added to the D ring at the ninth position of minocycline. This side chain aids in overcoming the ribosomal protection proteins and efflux pumps, which confer resistance to other tetracyclines.[2,34]

Tigecycline is a broad spectrum antibiotic with activity against Gram-positive, Gram-negative, anaerobic, atypical, and multidrug-resistant organisms.[4,35] In particular, it is active against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, *Acinetobacter*, and carbapenem-resistant *Enterobacteriaceae*. It has reduced activity against *Pseudomonas* spp., *Proteus* spp., *Providencia* spp. and *Morganella* spp.[36,37] Hence, its primary role for multidrug-resistant Gram–negative infections is for *Acinetobacter* spp., *Klebsiella* spp., and *E. coli*.

Table 2 summarizes the pharmacological properties of tigecycline and compares these to minocycline. Tigecycline is administered intravenously over 30–60 min and is not orally absorbed. It has low steady-state serum concentration raising concerns about its effectiveness in bloodstream infections. However, it is widely distributed, achieving good concentrations in the lung, skin, liver, heart, and bone.[36,38] It is excreted predominantly through the biliary systems and, thus, requires dose adjustment in severe liver failure. It does not need dose adjustment in renal failure as only 10–15% is renally excreted. The commonest side effects are class-related gastrointestinal side effects, which may occur in up to 35.9% of patients, but only result in 1% patients discontinuing therapy.[39]

Like the tetracyclines, it may cause photosensitivity and abnormal liver function tests and is contraindicated in children and pregnancy.[5] Tigecycline has little potential for drug interactions.[40,41]

Tigecycline can overcome the effect of ribosomal protection proteins and efflux pumps, which confer resistance to tetracycline. However, there has been increasing incidence of tigecycline resistance in Gram-negative bacteria worldwide,[42] which is mostly mediated by overexpression of efflux pumps. In *Enterobacteriaceae*, the main efflux pump is AdeABC. RamR inactivation and mutations leading to upregulation of *ramA* result in increased activity of the AcrAB efflux pump leading to tigecycline resistance. In *A. baumannii*, AdeABC efflux-mediated resistance predominates. In 2015, in our own hospital, 15% of *A. baumannii*, but only 3% of *K. pneumoniae*, were resistant to tigecycline.

There are a number of issues with *in vitro* susceptibility testing for tigecycline. The gold standard is microbroth dilution. Disk diffusion is unreliable and gives inconsistent results, attributed to changes in cations within the media. When disk diffusion was compared to broth microdilution using U.S. Food and Drug Administration (FDA) criteria, error rates were 38.4% for ESBL producing *K. pneumoniae* and 33.8% for *A. baumannii*. EUCAST and BSAC advise that disk diffusion should be avoided in all *Enterobacteriaceae* except *E. coli*. Furthermore, E-tests and automated systems such as VITEK2 may significantly overestimate tigecycline MIC resulting in overcalling of the resistant phenotype.[43]

Second, due to lack of sufficient data, CLSI has no established breakpoints for *Acinetobacter* spp. or *Enterobacteriaceae*. There are EUCAST, BSAC, and FDA approved breakpoints available for *Enterobacteriaceae*,

Table 4. Interpretative Criteria for Minocycline and Tigecycline

Drug	Interpretative criteria		Disc diffusion: zone of inhibition (mm)			MIC (μg/ml)		
			S	I	R	S	I	R
Minocycline	CLSI	*Enterobacteriaceae*	≥16	13–15	≤12	≤4	8	≥16
		Acinetobacter spp.						
	EUCAST	*Enterobacteriaceae*	NA	NA	NA	NA	NA	NA
		Acinetobacter spp.	NA	NA	NA	NA	NA	NA
	BSAC	*Enterobacteriaceae*	NA	NA	NA	NA	NA	NA
		Acinetobacter spp.	NA	NA	NA	NA	NA	NA
Tigecycline	Pfizer and FDA	*Enterobacteriaceae*	≥19	15–18	≤14	≤2	4	>8
		Acinetobacter spp.	NA	NA	NA	NA	NA	NA
	CLSI	*Enterobacteriaceae*	NA	NA	NA	NA	NA	NA
		Acinetobacter spp.	NA	NA	NA	NA	NA	NA
	EUCAST	*Enterobacteriaceae*	≥18[a]	—	≤15[a]	≤1	—	>2
		Acinetobacter spp.	NA	NA	NA	NA	NA	NA
	BSAC	*Enterobacteriaceae*	≥24[a]	20–23[a]	≤19[a]	≤1	2	>2
		Acinetobacter spp.	NA	NA	NA	NA	NA	NA

[a]Zone diameter applicable only to *Escherichia coli*. For other *Enterobacteriaceae*, MIC should be performed.
BSAC, British Society for Antimicrobial Chemotherapy; CLSI, Clinical & Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, U.S. Food and Drug Administration; S, susceptible; I, intermediate; R, resistant; NA, interpretative criteria not available.

but not *Acinetobacter* spp. Lack of validated breakpoints may discourage clinicians from using tigecycline in clinical practice. The interpretative criteria for minocycline and tigecycline are summarized in Table 4.

Tigecycline is licensed for use in complicated skin and skin structure infections and complicated intra-abdominal infections based upon equivalence to comparator agents in randomized controlled trials.[44,45] Although licensed for community acquired pneumonia, it is inferior to imipenem for ventilator-associated pneumonia at standard doses.[46] Its broad spectrum action against multidrug-resistant organisms has led to its off-label use in a number of other settings with variable success. Tigecycline achieves low concentration in bone and, although a small retrospective study suggests good cure rates in culture-negative pyogenic vertebral osteomyelitis,[47] it is inferior to ertapenem with vancomycin in diabetic foot infections with osteomyelitis.[48]

Low urinary excretion of active drug has raised concerns about its efficacy in urinary tract infection (UTI).[49] Some authors have reported its successful use in MDR UTI,[50–52] but it appears to be less effective than comparator agents. van Duin *et al.*, recently reported worse clinical outcomes associated with tigecycline use in CR KP UTI.[53] Furthermore, they reported rapid development of resistance in patients treated for UTI with the drug, attributable to low urinary concentrations.[54] Finally, tigecycline minimally penetrates the blood–brain barrier achieving low concentrations in the cerebrospinal fluid.[55] A small number of case reports describe its uses in meningitis where no alternative drugs exist with varying results.[56–58]

The role of tigecycline in the treatment of *Clostridium difficile* infection (CDI) is slowly emerging and has recently been reviewed by Di Bella *et al.*[59] In brief, tigecycline is effective *in vitro* against *C. difficile* and inhibits both sporulation and toxin production. Although it does disrupt gut flora, this is probably counteracted by inhibition of sporulation and toxin production as it does not appear to predispose to CDI.[59] A number of case reports have documented successful use of tigecycline in refractory CDI,[60,61] while a small retrospective case–control study suggested no difference in outcome between patients who received tigecycline and those who did not.[62] Further research is needed before tigecycline can be recommended for use in CDI.

We believe that tigecycline should be used exclusively for the treatment of multidrug-resistant organisms. A number of meta-analyses have investigated the effect of tigecycline for the treatment of susceptible organisms against comparator agents with varying conclusions. One meta-analysis suggests no difference in mortality,[63] another suggests no difference in mortality, but a significant increase in adverse events in patients treated with tigecycline,[64] and three show increased mortality in patients treated with tigecycline.[65,67] Although questions have been raised about the methodology and statistical validity of these meta-analyses,[68] there is no suggestion that tigecycline is better than comparator agents for susceptible organisms. The black box warning issued by the U.S. FDA against tigecycline reflects this. Although concerning, it should be recognized that this warning and these meta-analyses examined studies in which tigecycline was used for the management of infections susceptible to other antimicrobials.

In a world of increasing multidrug-resistant organisms, where we have very few antibiotic options, tigecycline may still be one of the best drugs available. Indeed, surveillance studies show that the MIC90 of global *A. baumannii* isolates is 2 mg/L; this is unchanged when only MDR *A. baumannii* isolates are examined. Similarly, the MIC 90 of *K. pneumoniae* remains stable at 2 mg/L when examining carbapenem susceptible and resistant isolates although the percentage susceptibility drops from 95.3% to 92% between the two groups.[30]

Table 5 summarizes clinical studies, in which tigecycline has been used for the treatment of infections with

Table 5. Clinical Studies in Which Tigecycline Has Been Used for the Treatment of CRO

Treatment (n)	*Other antibiotics*	*Infection*	*Outcome*	*Reference*
K. pneumoniae				
Monotherapy (7)	—	Urosepsis, tracheobronchitis, pneumonia, empyema, BSI	2/7 treatment failure	Weisenberg *et al.*[83] and Daly *et al.*[84]
Monotherapy (8)	—	BSI	Failure: breakthrough bacteremia	Nguyen *et al.*[85]
Monotherapy (11)	—	VAP, BSI, surgical infection	82% clinical cure	Poulakou *et al.*[86]
Combination therapy (19)	Polymyxin (7) Aminoglycoside (3) Carbapenem (2)	BSI	Treatment failure in combination with carbapenems	Goldfarb *et al.*[87]
Combination therapy (51)	Colistin	BSI	75% clinical cure	Neuner *et al.*[88]
Combination therapy (27)	Colistin Colistin+meropenem	BSI	70% clinical cure 50%	Tumbarello *et al.*[89]
Monotherapy (2) Combination therapy (14)	Colistin, meropenem, imipenem, pip/taz, ciprofloxacin	Pneumonia, UTI, peritonitis, CRB	100% clinical cure 63% clinical cure	Moreno *et al.*[90]
Acinetobacter spp.				
Monotherapy (5)	—	BSI, VAP	100% clinical cure	Schafer *et al.*[91]
Monotherapy (15)	—	Pneumonia, BSI, SI	80% clinical cure	Poulakou *et al.*[92]
Combination therapy (20)	Imipenem imipenem+ colistimethate colistimethate	BSI, VAP	100% clinical cure 75% clinical cure 57% clinical cure	Schafer *et al.*[91]
Monotherapy (155) Combination therapy (30)	Aminoglycoside, carbapenem, sulbactam	Pneumonia	83.3% clinical cure	Chuang *et al.*[93]
Monotherapy (17) Combination therapy (7)	Meropenem, cefoperazone, ciprofloxacin	BSI, respiratory infection	63% clinical cure	Shin *et al.*[94]

CRO, carbapenem-resistant organisms; SSTI, skin and soft structure infection; UTI, urinary tract infection.

carbapenem-resistant organisms (CRO). A very recently published meta-analysis by Ni *et al.*, has investigated the use of tigecycline in CRE. Although there are no randomized controlled trials, review of cohort studies and controlled trials found no statistical difference in mortality, clinical, or microbiological response rate between tigecycline and control groups. Tigecycline combination therapy was more effective than monotherapy in CRE or tigecycline given in high dose. They concluded that tigecycline was as effective as comparator antibiotics in treating CRE.[69]

We are concerned that standard dose tigecycline is too low in severe infections. The most accurate PK/PD parameter for tigecycline is the ratio of area under the concentration-time curve to MIC (AUC/MIC). By increasing the dose, the AUC increases thus optimizing this ratio.[70–72] The few *in vivo* studies that have been performed with high-dose tigecycline suggest favorable outcomes with a similar rate of severe adverse events. A randomized phase two study compared high dose and standard dose tigecycline with imipenem–cilastatin and found numerically higher clinical response in the group treated with high-dose tigecycline. Unfortunately, this trial was terminated early due to poor recruitment.[73]

Pascale *et al.* retrospectively compared standard dose tigecycline to high-dose tigecycline (100 mg every 12 hr) in intensive care patients with microbiologically confirmed infection. Most patients had ventilator-associated pneumonias with KPC *K. pneumoniae* and CR *A. baumannii* (OXA 58 and OXA 23) as the predominant causative organisms.[74] Although most patients were treated with two or more antibiotics, the only independent predictor of clinical cure was the use of higher dose tigecycline. This was in spite of the fact that patients who received high-dose tigecycline had more resistant organisms with higher tigecycline MIC.[75] Although promising, clearly more robust PK/PD, clinical and safety data are needed to establish high-dose tigecycline as standard practice.[76] When high-dose tigecycline is used, clinical response and adverse effects should be carefully monitored.

The primary drugs used for carbapenem-resistant organisms are carbapenems and colistin. Tigecycline has a number of advantages over colistin. First, colistin is a heterologous mixture of fermentation products, with significant brand to brand and batch to batch variation. This results in a large variation in serum concentrations between patients and presumably variable clinical effects *in vivo*.[77] Because of this, and the drug's narrow therapeutic index, therapeutic drug monitoring should be performed for all patients on colistin. However, therapeutic drug monitoring for colistin is poorly standardized and not available in many places. Second, colistin promotes heteroresistance, which under pressure from further colistin may result in frank drug resistance.[78] Unfortunately, there are currently no randomized controlled trials that

directly compare tigecycline to colistin for the management of CROs.

There is increasing evidence for combination therapy in treatment of carbapenem-resistant organisms. In particular, a number of retrospective studies have found reduced mortality in patients treated with a carbapenem where the isolate has a meropenem MIC ≤8 mg/L.[79,80] Randomized controlled trials are underway and due to report in 2016/2017. All current trials compare meropenem monotherapy with meropenem and colistin combination therapy. If the superiority of combination therapy is established, it is essential that trials are performed to compare combination tigecycline–meropenem to tigecycline–polymyxin and polymyxin–meropenem.

To summarize, based on current evidence, we reserve tigecycline for use in multidrug-resistant infections. For CROs, it should be used in combination with either colistin or meropenem, at high dose, with careful monitoring for emergence of resistance and adverse effects. This aims to both maximize clinical effect and reduce the emergence of tigecycline resistance. Current evidence suggests using meropenem in combination with either tigecycline or colistin in organisms with MIC ≤8 mg/L although it is unclear whether tigecycline or colistin is a better agent. Isolates with MIC >8 mg/L are unlikely to respond to meropenem, suggesting that tigecycline and colistin in combination may be a better option.

The need of the hour is to monitor the change in MIC trend of tigecycline. An increase indicates emergence of resistance and its limited usefulness. However, in the past, few studies have not documented the MIC trend over years. The TEST study report by Hoban *et al.* 2015[30] has noted the MIC range of susceptible *E. coli* to be ≤0.008 to ≥32 μg/ml, while that for carbapenem-resistant *E. coli* to be ≤0.008–16 μg/ml. The upper limit of MIC for susceptible isolates is higher compared with the carbapenem-resistant strains. A similar difference in MIC range has been noted for susceptible and carbapenem-resistant *K. pneumoniae*, the ranges of which are ≤0.008 to ≥32 μg/ml and 0.03–16, respectively. However, this difference cannot be explained without a changing trend of MIC change over the years.

Conclusion

In conclusion, we believe that tigecycline should be reserved for multidrug-resistant infections where it should be used in combination with meropenem or colistin, at high dose and with careful monitoring. Minocycline can be considered on a patient by patient basis if the isolate is susceptible, and no other agents are available. Further PK/PD and clinical trial data are needed to establish optimal treatment regimens for these drugs in CRO.

Disclosure Statement

No competing financial interests exist.

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