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Re-establishing the utility of tetracycline-class antibiotics for current challenges with antibiotic resistance

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ABSTRACT

The progressive increase in antibiotic resistance in recent decades calls for urgent development of new antibiotics and antibiotic stewardship programs to help select appropriate treatments with the goal of minimising further emergence of resistance and to optimise clinical outcomes. Three new tetracycline-class antibiotics, eravacycline, omadacycline, and tigecycline, have been approved within the past 15 years, and represent a new era in the use of tetracyclines. These drugs overcome the two main mechanisms of acquired tetracycline-class resistance and exhibit a broad spectrum of *in vitro* activity against gram-positive, gram-negative, anaerobic, and atypical pathogens, including many drug-resistant strains. We provide an overview of the three generations of tetracycline-class drugs, focussing on the efficacy, safety, and clinical utility of these three new third-generation tetracycline-class drugs. We also consider various scenarios of unmet clinical needs where patients might benefit from re-engagement with tetracycline-class antibiotics including outpatient treatment options, patients with known β-lactam antibiotic allergy, reducing the risk of *Clostridioides difficile* infection, and their potential as monotherapy in polymicrobial infections while minimising the risk of any potential drug-drug interaction.

KEY MESSAGES

- The long-standing safety profile and broad spectrum of activity of tetracycline-class antibiotics made them a popular choice for treatment of various bacterial infections; unfortunately, antimicrobial resistance has limited the utility of the early-generation tetracycline agents.
- The latest generation of tetracycline-class antibiotics, including eravacycline, tigecycline, and omadacycline, overcomes the most common acquired tetracycline resistance mechanisms.
- Based on *in vitro* characteristics and clinical data, these newer tetracycline agents provide an effective antibiotic option in the treatment of approved indications in patients with unmet clinical needs – including patients with severe penicillin allergy, with renal or hepatic insufficiency, recent *Clostridioides difficile* infection, or polymicrobial infections, and those at risk of drug–drug interactions.

Introduction

Over the past decade, there has been a substantial increase in the number of infections caused by bacteria that are resistant to one or more antibiotics [1]. Annually, more than 2.8 million antibiotic-resistant infections occur in the United States with approximately 35,000 deaths attributed to antibiotic-resistant infections [1]. This increased morbidity and mortality caused by antibiotic-resistant infections is associated with a considerable economic burden: $4.6 billion is spent annually to treat infections caused by six multidrug-resistant bacteria alone [2]. The US Centres for Disease Control and Prevention (CDC) has identified major bacterial and fungal drug-resistance threats, of which carbapenem-resistant *Acinetobacter* and Enterobacterales, drug-resistant *Neisseria gonorrhoeae*, and *Clostridioides difficile* pose urgent threats [1]. Recognising the need for creative approaches to address the problem of a dwindling antimicrobial research and development pipeline, in 2010 the Infectious Diseases Society of America launched the 10 × '20 initiative to encourage the development of 10 new systemic antibacterial agents by 2020 [3]. In total, 14 new agents were approved between 2010 and 2020, with several others in late-stage clinical development [4]. Of these newly approved agents,

two were novel third-generation tetracycline-class antibiotics (eravacycline and omadacycline), with a third (tigecycline) approved by the US Food and Drug Administration (FDA) in 2005. This commentary focuses on the history of the three generations of tetracycline-class antibiotics, their mechanism of action, the emergence of resistance, and relevant data regarding the clinical utility of newer tetracycline agents.

History and clinical utility of tetracycline-class drugs

The first tetracycline-class drugs were discovered in the late 1940s, isolated from *Streptomyces* spp [5]. Aureomycin (also known as chlortetracycline) was approved for use in the United States in 1948; the other three commonly used first- and second-generation tetracycline-class drugs (tetracycline, doxycycline, and minocycline) were approved in 1954, 1967, and 1971, respectively. No new tetracycline-class drugs were then developed until the third generation in the 2000s [5].

Tetracycline-class drugs inhibit bacterial protein synthesis by binding to bacterial ribosomes and interacting with the highly conserved 16S ribosomal RNA (rRNA) in the 30S ribosomal subunit [6]. The drug class demonstrates a broad spectrum of activity against a wide range of gram-positive, gram-negative, and atypical pathogens, resulting in the extensive use of the tetracycline class in both humans and animals after the drugs were initially discovered [5]. Indications for treatment of bacterial infections include pneumonia; skin infections; bone and joint infections; sexually transmitted infections including chlamydia, syphilis, and gonorrhoea; intra-abdominal infections; biothreat pathogens, including *Yersinia pestis, Bacillus anthracis*, and *Francisella tularensis*; and other specific bacterial pathogens such as *Rickettsia* spp, *Borrelia* spp, and nontuberculous mycobacteria. Tetracycline-class agents are recommended as first-line treatment options for many of these indications [7–13].

Tetracycline resistance

While tetracycline-class drugs have a broad spectrum of antibacterial activity and many clinical applications, their utility has declined over time through the emergence of antibiotic resistance. In the early antibiotic era (up until the mid-1950s), most commensal and pathogenic bacteria remained susceptible to tetracyclines; however, within 2 years of the approval of aureomycin, resistance had emerged in *Staphylococcus aureus* [14]. In 1954, resistant strains of *Streptococcus pyogenes* were first noted in patients with burn injuries [15]. The first-generation tetracycline and second-generation minocycline and doxycycline demonstrated improved activity versus aureomycin against *S. aureus*, yet many *Streptococcus* species remained resistant. By 1968, approximately 23% of *Streptococcus pneumoniae* isolates were resistant to all three drugs, and at least half of these resistant infections were acquired outside of hospital settings [16]. The increasing rates of acquired resistance to tetracycline-class drugs during the 1960s and 1970s, and the growing availability of other antibiotic agents such as cephalosporins and fluoroquinolones [17], led to this class being used mainly as a second-line treatment option.

Multiple mechanisms confer acquired resistance to the tetracycline class, the most common being efflux pumps and ribosomal protection proteins (Figure 1). Efflux pumps are antiporters that exchange a monocationic magnesium–tetracycline complex for a proton, thus actively pumping antibiotics out of the bacterial cell. Efflux pumps are found in both gram-positive, e.g. Tet(K) and Tet(L), and gram-negative bacteria, e.g. Tet(A) and Tet(B), including *Staphylococcus*, *Streptococcus*, *Klebsiella*, and *Escherichia* species [5,18,19]. Ribosomal protection proteins such as Tet(O) and Tet(M), found in both gram-positive and gram-negative organisms, are cytoplasmic proteins that protect ribosomes from the inhibitory action of tetracycline-class drugs [19]. Although the exact mechanism of resistance is unclear, it is likely that the proteins cause a conformational change in the structure of the ribosome, either preventing tetracycline binding or resulting in dissociation [18]. Two other acquired tetracycline resistance mechanisms that are less common include target modification, where a mutation in the ribosomal RNA of the target binding site reduces antibiotic binding affinity; and drug degradation, where enzymatic action mediated by *tet*(X) genes degrades antibiotic products [5,18]. However, *tet*(X) could be an emerging threat to susceptibility to all tetracyclines particularly gram-negative pathogens [20]. In addition to these acquired resistance mechanisms, intrinsic resistance to tetracycline-class drugs has been noted in *Providencia* spp, *Proteus mirabilis*, and *Pseudomonas aeruginosa* among gram-negative organisms [21–23].

Since the 1990s, the prevalence of *S. aureus*, *S. pneumoniae*, and *S. pyogenes* resistance to β-lactams and non-β-lactams, such as macrolides and tetracycline-class antibiotics, has steadily increased. The
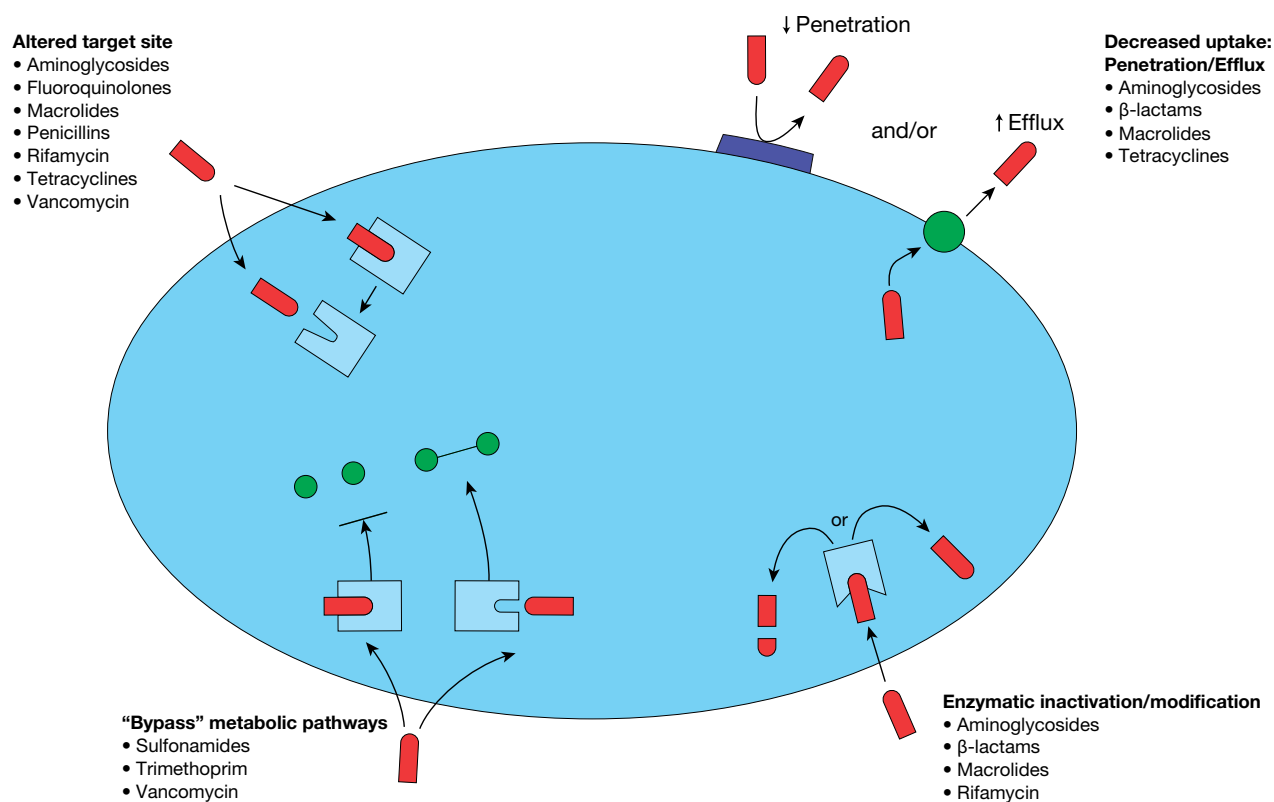
Figure 1. Overview of the four major mechanisms of antibiotic resistance, and antibiotic classes affected by each mechanism. Adapted with permission from Hawkey [106].

SENTRY Antimicrobial Surveillance Program reported that the global occurrence of methicillin-resistant *S. aureus* (MRSA) increased from 33% in 1997–2000 to 44% in 2005–2008, with the highest rates in North America [24]. A recent analysis of data from 329 US hospitals also showed that *S. pneumoniae* macrolide resistance was >25% in most regions and nearly 40% overall isolates tested [25]. In general, similar rates of resistance are seen in *Streptococcus* spp to the first-generation tetracycline and second-generation doxycycline, whereas *S. aureus* resistance rates decrease with later-generation tetracyclines [26–28]. As rates of antimicrobial resistance continue to increase, new antibiotics, including third-generation tetracycline-class drugs, offer an important therapeutic option for various bacterial infections.

Generations of tetracycline-class drugs: similarities and differences

All tetracycline-class drugs share a core chemical structure, with variations in the side groups (Figure 2). The generations of tetracycline-class drugs are defined by the methodology used to develop the drug: the first generation is obtained from

biosynthesis, the second generation is semi-synthetic products, and the third generation is entirely synthetic and can therefore have more elaborate side chains than earlier generations; this enhances their antibacterial activity (Figure 2). In all tetracycline-class drugs, the amino group present in the C4 position of the A ring is vital for antibiotic activity [29]. While the second-generation drugs have increased oral bioavailability compared with the first generation, they largely did not overcome the acquired resistance mechanisms through efflux pumps and ribosomal protection proteins, with the exception of *S. aureus* efflux pumps for minocycline [30]. Additionally, inducible resistance against doxycycline has been observed in previously susceptible community-associated MRSA isolates [31]. In the third-generation tetracycline-class drugs, the addition of a lipophilic side group at the C9 position on the D ring enhances the antibiotic activity further, and all three are designed to overcome the two main tetracycline resistance mechanisms [27]. While only tetracycline is still in routine use from the first generation of tetracycline-class drugs (developed between 1948 and 1963), two second-generation drugs (developed between 1965 and 1972), doxycycline and minocycline, are also still
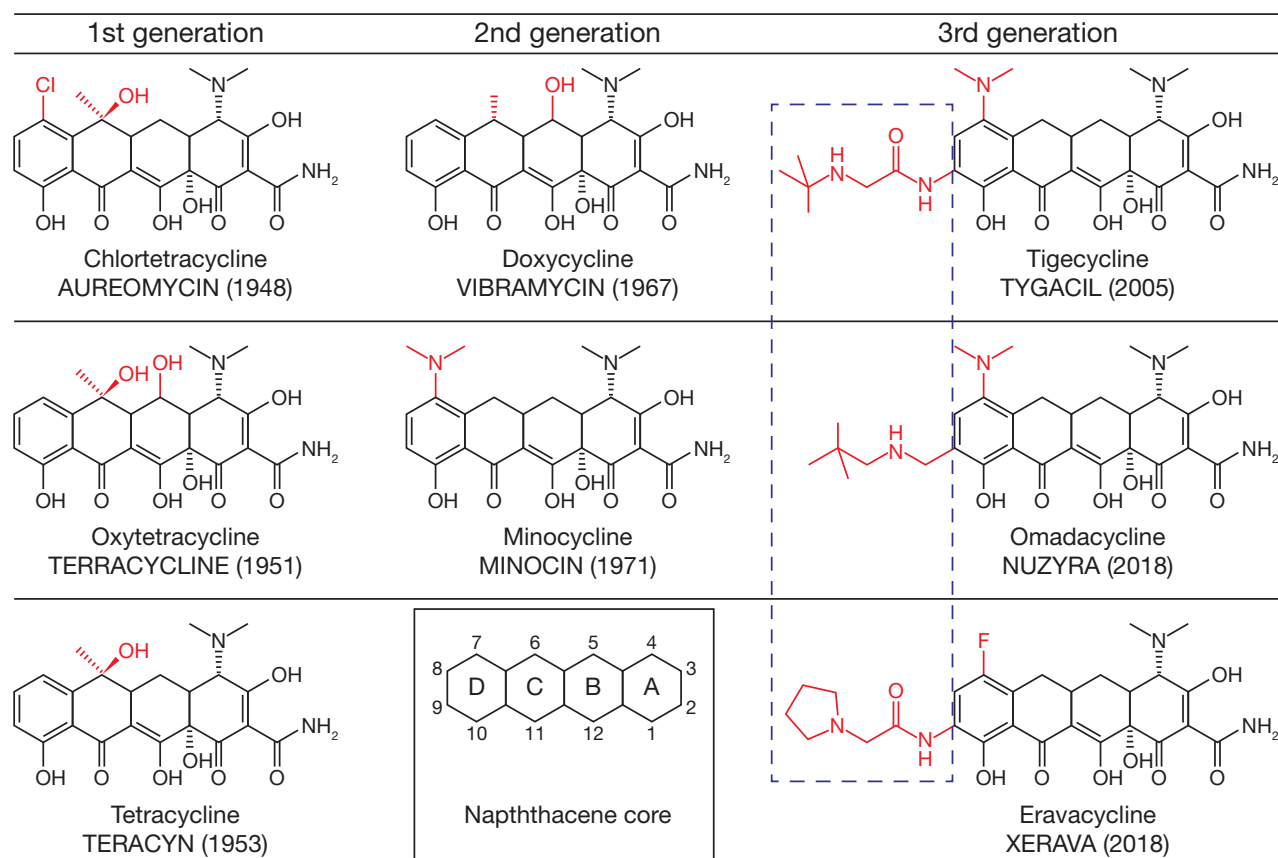
Figure 2. Chemical structures of tetracyclines. Chemical structures of (A–C) rst generation tetracyclines. (A) chlortetracycline (aureomycin), (B) oxytetracycline (terracycline) and (C) tetracycline (teracyn), (D–E) second generation tetracyclines; (D) doxycycline (vibramycin) and (E) minocycline (minocin), and (F–G) third generation tetracyclines; (F) the glycylcycline tigecycline (tygacil), (G) the aminomethylcyclineomadacycline (PTK 0796) and (H) the uorocycline eravacycline (TP–434). The numbers in parentheses indicates the year the antibiotic was discovered/reported. The inset of the DCBA naphthacene core provides the carbon atom assignments for rings A–D.

routinely used in humans. Tetracycline is currently only available in an oral formulation, whereas second-generation drugs are available in both oral and intravenous (IV) formulations. Of the third-generation drugs, eravacycline and tigecycline are available only in IV formulation, whereas omadacycline is available in both oral and IV formulations.

In vitro activity of tetracycline-class antibiotics

Tetracycline-class drugs show a broad range of *in vitro* activity against gram-positive, gram-negative, anaerobic and atypical pathogens [5]. While the clinical relevance of *in vitro* activity is unknown, third-generation tetracycline-class drugs have improved activity against many common community-acquired bacterial pneumonia (CABP) and skin and skin structure infection pathogens when compared with first-generation tetracycline (Table 1) [32].

Minimum inhibitory concentrations (MICs) obtained from *in vitro* studies provide the key context for antibiotic selection against those pathogens. Lower MICs indicate that less drug is required for inhibition of organism growth, thus providing greater antimicrobial activity than a drug with a higher MIC value, assuming pharmacodynamic (PD) exposure is the same [33]. Susceptibility testing varies and is based on breakpoint criteria developed by two organisations, the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [27,28]. In general, CLSI breakpoints have been approximately fourfold higher than EUCAST, but CLSI breakpoints for *S. pneumoniae* were revised in 2013 to more accurately reflect the presence or absence of *tet* resistance genes [27]. There remains an unmet need for harmonisation of tetracycline breakpoints against other pathogens, as variations between the two criteria show large ranges in susceptibility rates against other pathogens, such as MRSA (Table 2).

For the tetracycline-class agents, MICs for a particular pathogen are generally substantially lower for the

Table 1. *In vitro* activity of tetracycline and third-generation tetracycline-class drugs against select gram-positive, gram-negative, and anaerobic pathogens [35,103,104].

Organism (n)	Tetracycline		Tigecycline		Omadacycline		Eravacycline	
	MIC90 (mg/L)	%S*	MIC90 (mg/L)	%S*	MIC90 (mg/L)	%S*	MIC90 (mg/L)	%S*
Bacteroides fragilis	_a	_a	4	_a	_a	_a	1	_a
Enterococcus faecalis	>16	24.8	0.12	99.1	0.25	98.2	0.06	94.5
Vancomycin resistant	>16	17.0	0.12	100	0.12	_a	0.12	89.8
Escherichia coli	>16	69.3	0.25	100	2	_a	0.25	99.2
ESBL phenotype	>8	88.1	0.25	100	2	_a	_a	_a
Haemophilus influenzae	1	99.7	0.25	90.5	1	99.7	0.25	_a
Klebsiella pneumoniae	>16	77.0	1	96.8	4	91.0	1	85.7
ESBL phenotype	>16	39.8	2	92.0	16	73.9	_a	_a
Staphylococcus aureus	0.25	98.3	0.12	100	0.25	97.8	0.12	84.5
Methicillin resistant	0.12	99.7	0.25	95.2	0.5	97.2	0.12	80.8
Streptococcus pneumoniae	>4a	79.7a	0.12	86.9	0.12	97.6	0.015	a
Penicillin resistant, oral	>4a	48.5a	0.12	84.8	0.12	93.9	0.016	_a
Macrolide resistant	>4a	61.0a	0.12	84.9	0.12	95.1	0.016	_a
Tetracycline resistant	>4a	0	0.12	82.4	0.12	91.2	0.016	_a
Streptococcus pyogenes	>4	73.9	0.12	98.6	0.12	_a	0.03	100

*Susceptibility data are derived from FDA identified breakpoints. Criteria as published by CLSI.
CLSI: Clinical and Laboratory Standards Institute; ESBL: extended-spectrum β-lactamase; FDA: Food and Drug Administration: MIC: minimum inhibitory concentration.
[a]Breakpoints unavailable.

Table 2. Susceptibility rates for first- and second-generation tetracycline-class drugs against common gram-positive pathogens [27,28].

Organism	Antibiotic[a]	MIC (µg/mL)		% Susceptible / % Resistant	
		50%	90%	CLSI	EUCAST
Streptococcus pneumoniae	Tetracycline	0.5	>8	73.2 / 26.7	73.2 / 26.7
	Doxycycline	0.25	8	71.3 / 26.8	73.9 / 24.7
	Minocycline	NR	NR	71.7 / 27.3[b]	72.7 / 26.4
Streptococcus pyogenes	Tetracycline	≤0.25	>8	80.3 / 19.7	79.6 / 19.7
	Doxycycline	0.12	8	81.2 / 16.0	80.2 / 18.8
	Minocycline	NR	NR	78.0 / 20.7	78.0 / 22.0
Methicillin-resistant *Staphylococcus aureus*	Tetracycline	≤0.25	2	91.2 / 8.0	88.1 / 9.0
	Doxycycline	0.12	1	96.2 / 0.6	93.5 / 5.5
	Minocycline	NR	NR	97.2 / <0.1	88.3 / 11.3

CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing; MIC: minimum inhibitory concentration; NR: not recorded.
[a]Tetracycline is considered a first-generation tetracycline-class drug. Doxycycline and minocycline are second-generation tetracycline-class drugs.
[b]Using CSLI 2013 susceptibility breakpoint for doxycycline of ≤0.25 µg/mL applied to the minocycline.

Table 3. *In vitro* activity of tetracycline-class drugs in the presence and absence of acquired tetracycline resistance genes [34,98,102,103].

Strain	Tet[R] determinant	Mechanism type	MIC range (µg/mL)				
			Firstgeneration	Secondgeneration	Third-generation		
			Tetracycline[a]	Doxycycline[a]	Omadacycline[a]	Eravacycline[b]	Tigecycline[b]
Staphylococcus aureus	None	–	≤0.06–0.25	≤0.06–0.125	≤0.06–0.5	0.015–0.12	0.03–0.25
	tet(M)	RPPs	32 to >64	2–16	0.125–1	NR	NR
	tet(K)	Efflux pump	16–32	1–4	0.125–0.25	0.063	0.13
Streptococcus pneumoniae	None	–	≤0.06–0.25	≤0.06–0.25	≤0.06–0.25	0.004–0.03	0.015–0.12
	tet(M)	RPPs	4–64	2–4	≤0.06	0.016	≤0.016
β-hemolytic streptococci[c]	None	–	≤0.06–0.125	≤0.06	≤0.06–0.50	0.004–0.25	≤0.008–0.25
	tet(M)	RPPs	4–64	2–16	≤0.06–0.50	NR	NR
	tet(O)	RPPs	32–64	8	≤0.06–0.25	NR	NR

MIC: minimum inhibitory concentration; NR: not recorded; RPP: ribosomal protection protein.
[a]Data for first- and second-generation tetracycline-class drugs and omadacycline adapted from [34].
[b]Data for eravacycline and tigecycline adapted from [98,104,105].
[c]S. pyogenes and S. agalactiae.

third-generation drugs relative to values for tetracycline and doxycycline [34]. Third-generation tetracycline-class drugs also maintain their activity against pathogens that are resistant to first- and second-generation drugs, and overall, show more potent antibacterial activity than older generations (Table 3) [32,34–37]. A full list of susceptible pathogens is provided in Table 4.

Table 4. Indications and susceptible pathogens for third-generation tetracycline-class drugs [9,10,12].

Antibiotic	Indication	Susceptible microorganisms
Tigecycline	Complicated skin and skin structure infection	*Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* group (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae,* and *Bacteroides fragilis*
	Community-acquired bacterial pneumonia	*Streptococcus pneumoniae* (penicillin-susceptible isolates), *Haemophilus influenzae* (β-lactamase negative isolates), and *Legionella pneumophila*
	Complicated intra-abdominal infection	*Citrobacter freundii, E. cloacae, E. coli, Klebsiella oxytoca, K. pneumoniae, E. faecalis* (vancomycin-susceptible isolates), *S. aureus* (methicillin-susceptible and -resistant isolates), *S. anginosus* group, *B. fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros*
Eravacycline	Complicated intra-abdominal infection	*E. coli, K. pneumoniae, C. freundii, E. cloacae, K. oxytoca, E. faecalis, Enterococcus faecium, S. aureus, S. anginosus* group, *C. perfringens, Bacteroides* spp, and *Parabacteroides distasonis*
Omadacycline	Acute bacterial skin and skin structure infection (ABSSSI)	*S. aureus* (methicillin-susceptible and -resistant isolates), *Staphylococcus lugdunensis, S. pyogenes, S. anginosus* group, *E. faecalis, E. cloacae,* and *K. pneumoniae*
	Community-acquired bacterial pneumonia	*S. pneumoniae, S. aureus* (methicillin-susceptible isolates), *H. influenzae, Haemophilus parainfluenzae, K. pneumoniae, L. pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*

Table 5. Pharmacokinetic parameters of tetracycline-class drugs [8–13,47].

Antibiotic	Maintenance dose	Dosing frequency	Food effect (C_{max} decrease)	Protein binding	Half-life	Metabolism	Excretion
Tetracycline	Oral: 250/500 mg	Oral: BID to QID	50%	55–64%	6–11 h	Yes	Fecal: 20–60% Renal: 30%
Doxycycline	IV: 100 mg Oral: 100 mg	Oral: QD or BID IV: BID	20%		12–25 h	Yes	Renal: 40%
Minocycline	IV: 100 mg Oral: 50/75/100 mg	Oral: BID	–	76%	11–24 h	Yes	Fecal: 20–35% Renal: 5–12%
Omadacycline	IV: 100 mg Oral: 300 mg	Oral: QD IV: QD	40–59%	20%	16 h	Yes	Fecal (oral): 81% Renal (IV/oral): 27%/14%
Tigecycline	IV: 50 mg	IV: BID	NA	71–89%	42 h	None	Biliary/Fecal: 59% Renal: 33%
Eravacycline	IV: 1 mg/kg	IV: BID	NA	79–90%	20 h	CYP3A4- and FMO-mediated oxidation	Biliary/Fecal: 47% Renal: 34%

BID: twice daily; IV: intravenous; NA: not applicable; QD: daily; QID: four times daily.

Third-generation tetracycline-class agents evade the two most common mechanisms of tetracycline resistance, but the emergence of resistance to these newer drugs remains a concern. Current resistance mechanisms to tigecycline mostly involve overexpression of efflux pumps and enzymatic inactivation, including by *tet*(X), a gene encoding a flavin-dependent monooxygenase [38–40]. Resistance to all tetracycline-class antibiotics has now been noted in carbapenem- and colistin-resistant multidrug-resistant pathogens that carry the *tet*(X) gene or homologs [41,42]. A global survey of the *in vitro* activity of tigecycline and comparators assessing trends in susceptibility from 2004 to 2013 indicated that susceptibility remained high, although decreases in susceptibility over time had been noted, for example against *Enterobacter* spp in Latin America [43].

Pharmacokinetics/pharmacodynamics of tetracycline-class drugs

Pharmacokinetic (PK)/PD characteristics, and thus drug dosage and dosing frequency, and available formulations of the tetracycline-class agents, vary: overall, tetracycline-class drugs have a longer half-life than older drugs, which supports once- or twice-daily administration (Table 5). Eravacycline and tigecycline, despite their prolonged half-lives, are dosed twice daily to improve tolerability related to concentration-dependent gastrointestinal adverse events (AEs) [44–46]. Dose adjustment is not required for the newer generation of tetracycline agents in patients with renal impairment. Doses need to be adjusted only for eravacycline and tigecycline in patients with severe hepatic impairment [8,10,12].

Pharmacokinetics

Absorption of tetracycline-class drugs is variable and ranges from approximately 25–60% for first-generation drugs to (near) complete absorption for later generations [47]. The absorption of all tetracycline-class drugs is impaired by antacids containing aluminium, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations [47]. Data on first- and

second-generation drugs are limited (owing to their development and approval before current regulatory standards were in place), but third-generation tetracycline-class antibiotics are known to have a high volume of tissue distribution including in pulmonary tissues [47,48]. Omadacycline, eravacycline, and tigecycline concentrations in unbound plasma, alveolar macrophages, and epithelial lining fluid are high, with a greater magnitude of omadacycline concentrations than those for the other two drugs (Figure 3). Tetracycline-class antibiotics are all metabolised, with the exception of tigecycline (Table 5) [47]. Excretion varies across the tetracycline class, but most of the drugs have a combination of majority biliary/fecal and some renal excretion [47].

Pharmacodynamics

The bacterial killing effect of second- and third-generation tetracycline agents has been evaluated in various *in vitro* and *in vivo* studies. Doxycycline demonstrates time-dependent killing at 2–4 times the MIC (i.e. low serum concentrations) but dose-dependent killing at higher concentrations (8–16 times the MIC) [49]. Post-antibiotic effect (PAE), the period after removal of the antibiotic after which no further bacterial growth occurs, is similar to doxycycline against both gram-negative and gram-positive organisms and is concentration dependent [49]. PAE for omadacycline varies with the pathogen tested, with similar PAE for tigecycline and eravacycline against *S. aureus*, *S. pneumoniae*, and *E. coli* [50,51].

As tetracycline-class drugs have substantial post-antibiotic effects, the area under the free concentration-time curve (*f*AUC) to MIC ratio is an important predictor of *in vivo* activity [46,47]. *In vitro* and *in vivo* studies of doxycycline showed *f*AUC/MICs of 24 and 25 to be associated with net stasis against *S. pneumoniae* and *S. aureus*, respectively [46,52]. For eravacycline, *f*AUC/MICs of 28.0 and 32.6 have been associated with net stasis and 1_{log}-kill endpoints, respectively, against *E. coli* in murine thigh infection models [46]. In PD studies of omadacycline, mean *f*AUC/MICs of 25.7 and 23.0 were required for stasis against *S. pneumoniae* and *E. coli*, respectively [53]. Data from neutropenic murine thigh and lung studies indicate the median *f*AUC/MICs required to achieve stasis for *S. aureus* and 1-$\log_{10}$ reduction for *S. pneumoniae* are 21.9 and 17.4, respectively [54,55]. For tigecycline, the mean effective exposure index at 80% for *f*AUC/MIC was 5.4 μg/mL (range, 2.8–13 μg/mL) against *S. aureus* in a murine thigh model [56].

Clinical data on third-generation tetracycline-class antibiotics

Third-generation tetracycline-class agents are approved for multiple therapeutic indications,
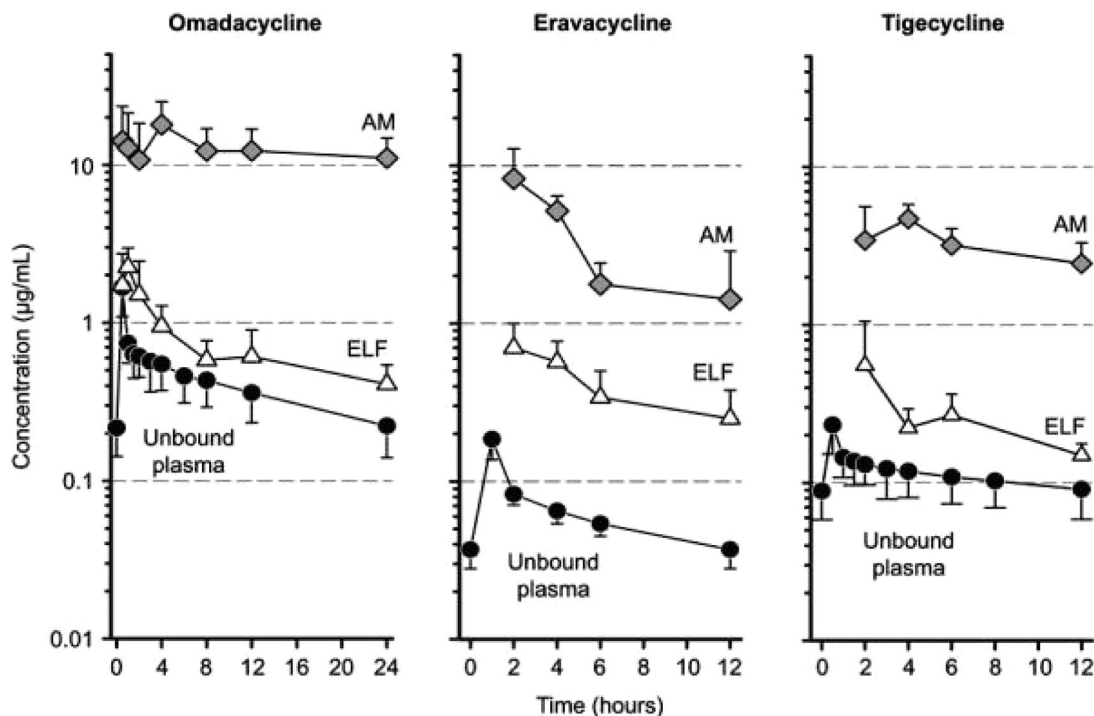

Figure 3. Mean (standard deviation) unbound plasma, alveolar macrophages (AM), and epithelial lining fluid (ELF) concentration–time curves after multiple intravenous doses in healthy patients. Taken from [48]. Originally published by and used with permission from Dove Medical Press Ltd.

including skin and skin structure infections, CABP, and complicated intra-abdominal infection (cIAI) (Table 4). Approval for these indications was based on efficacy and safety data from phase 3 studies using standard-of-care oxazolidinones or glycopeptides, fluoroquinolones, or carbapenems as respective comparators [10,12,57]. These studies were all designed to align with then-current FDA guidance, which leads to some of the differences in endpoints as reported below.

Efficacy data

Community-acquired bacterial pneumonia

Omadacycline and tigecycline are approved for the treatment of adults with CABP. In the phase 3 OPTIC study, omadacycline was non-inferior to moxifloxacin in the treatment of hospitalised adults with CABP, based on the primary outcome of early clinical response (ECR), defined as survival with the improvement of at least two of four symptoms (cough, sputum production, pleuritic chest pain, and dyspnea) and no worsening of symptoms at 72–120 h, without receipt of rescue antibacterial therapy [58]. Similar findings were observed at post-treatment evaluation (PTE; 5–10 days after last dose of the study drug). Tigecycline also demonstrated non-inferiority to levofloxacin in adults hospitalised for CABP based on clinical cure (all signs and symptoms of pneumonia improved or resolved, with no worsening of symptoms or new signs, and no requirement for further antibiotic therapy) at 10–21 days post therapy [59–62].

Skin and skin structure infections

Omadacycline and tigecycline are also indicated for the treatment of skin and skin structure infections; omadacycline is FDA approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs), whereas tigecycline is approved for the treatment of complicated skin and skin structure infections (cSSSIs). ABSSSI is considered a more specific categorisation and is defined as a bacterial infection of the skin with a lesion size area of ≥ 75 cm^2, whereas cSSSIs involve abnormal skin, wounds, or infections in immunocompromised individuals or infections requiring surgery [62]. In the phase 3 OASIS-1 and OASIS-2 studies in adult patients with ABSSSIs, IV-to-oral or oral-only omadacycline was non-inferior to linezolid at ECR (48–72 h after the first dose), based on a $> 20\%$ reduction in lesion size, with similar rates of clinical success observed at PTE [63,64]. Tigecycline achieved non-inferiority to vancomycin and aztreonam at the test-of-cure visit (12–92 days after the last dose of the study drug) based on the resolution of signs and symptoms such that no further antibiotic therapy was required [65,66].

Complicated intra-abdominal infections

Tigecycline and eravacycline are approved by the FDA for the treatment of complicated IAIs. In the phase 3 IGNITE1 and IGNITE4 studies, eravacycline demonstrated non-inferiority to ertapenem and meropenem, respectively, in patients with cIAI based on clinical efficacy 25–31 days after the first dose of the study drug [67,68]. Clinical efficacy was defined as complete resolution or significant improvement of signs or symptoms of the index infection such that no additional antibacterial therapy, surgical, or radiological intervention was required. Similarly, tigecycline demonstrated non-inferiority to imipenem–cilastatin for the treatment of cIAI, based on clinical cure 12–42 days after the first dose of the study drug [69,70]. In these studies, the cure was defined as resolution of the IAI process following the course of study drug and initial intervention.

Safety, tolerability, and drug interactions

Tetracycline class effects

All tetracycline-class drugs, including the third-generation agents, come with warnings and precautions including tooth discolouration and enamel hypoplasia during tooth development (last half of pregnancy up until 8 years of age), and inhibition of bone growth (second trimester of pregnancy until 8 years of age). Tigecycline also has a boxed warning for increased mortality risk and should be reserved for situations when alternative treatments are not suitable [10]. Other tetracycline-class AEs include photosensitivity, pseudotumor cerebri, and anti-anabolic action. As seen with other drug classes, while these AEs are attributed to the tetracycline class as a whole, the magnitude of the effect varies between specific drugs within the class (e.g. photosensitivity [71]). Tetracycline-class drugs have been shown to depress plasma prothrombin activity; patients taking anticoagulants may therefore need to be monitored or have their oral anticoagulant dosage adjusted while taking tetracycline-class drugs [9,10,12]. There is impaired absorption of oral tetracycline-class drugs by antacids containing aluminium, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations [9].

C. difficile infection

The potential for *C. difficile*-associated diarrhoea and the associated label warning is common to all

antibiotics, although there is evidence of lower rates of *C. difficile* infection (CDI) with the tetracycline class than with other classes of antibiotics, such as fluoro-quinolones and third-generation cephalosporins [72–75]. Tigecycline has been used in select cases, usually for severe disease, as a successful adjunctive treatment for CDI [76]. Across the phase 3 studies of omadacycline, no cases of CDI were observed in the omadacycline treatment groups [77]. A retrospective study of 50 patients receiving eravacycline as an inpatient or outpatient parenteral antibiotic therapy reported only one case of post-treatment CDI, where 40% of these patients had experienced CDI in the 12 months before receiving eravacycline [78]. While the mechanism of decreased risk of CDI with tetracyc-line-class drugs remains unclear, high drug concentrations in the bowel, less disruption to the gut microbiota than observed with other antibiotics, and *in vitro* and *in vivo* activity against *C. difficile* may all play a role [75,79,80].

Tigecycline

Pooled data across various studies show that nausea and vomiting were the most frequently reported AEs (Table 6). These gastrointestinal AEs are C_{max} related and thus dose-limiting; in general, the maximum single dose is 100 mg IV [44]. However, higher doses have been used in an attempt to maximise efficacy, which resulted in increased AEs and discontinuation [81], leading to attempts at reduced dosing of 25 mg once or twice daily in some long-term utilisation studies to minimise gastrointestinal side effects (e.g. [82]). Across clinical trials, 7% of 2514 patients discontinued tigecycline due to AEs, compared with 6% of those taking the comparator drugs [10].

A meta-analysis of phase 3 and 4 clinical trials demonstrated an increase in all-cause mortality in tigecyc-line-treated patients compared with controls, with a risk difference of 0.6% (95% CI 0.1, 1.2). The cause of this increase has not been established, and the increase was also seen when limited to approved indications. The greatest differences in mortality versus controls were observed in patients with ventilator-assisted pneumonia [10], which is not an FDA-approved indication for tigecycline.

Eravacycline

Nausea and vomiting are also frequently reported AEs for eravacycline (Table 6), with a trend towards increasing incidence of nausea and vomiting with increasing eravacycline C_{max} [46]. Rates of nausea were higher with twice- versus once-daily administration (11% vs 2%),

but rates of vomiting were lower (2% vs 6%) [83]. Local infusion-site reactions, most of which were mild, were also more frequent with eravacycline than the comparator drug in phase 3 studies [67,68]. Across clinical trials, 2% of 520 patients receiving eravacycline discontinued due to AEs, compared with 2% of patients who received the comparator [12]. Mortality rates were similar to those observed for the comparator drugs [67,68].

Omadacycline

Nausea and vomiting were the most frequently observed AEs in the omadacycline group (15% and 8%, respectively) (Table 6). This was largely driven by higher rates of nausea and vomiting reported during the high dose oral-only (450 mg) loading period in the first 2 days of the OASIS-2 study [63,77], with rates similar to the comparators in the IV-to-oral OPTIC (omadacycline, 2.4% and 2.6%; moxifloxacin, 5.4% and 1.5% for nausea and vomiting, respectively) and OASIS-1 trials (omadacycline, 12.4% and 5.3%; linezolid, 9.9% and 5.0% for nausea and vomiting, respectively) [58]. Discontinuation rates were 5.5% of 382 patients with CABP (7.0% for comparator) and 1.7% of 691 patients with ABSSSI (1.5% for comparator) [58,64]. An imbalance of mortality was observed for omadacycline (2%) versus moxifloxacin (1%) in the CABP OPTIC study, although the cause of this imbalance has not been established.

Special patient populations

Use of tetracycline-class drugs in pregnancy and for children under 8 years of age should be avoided, unless the benefit outweighs the risk, due to the risk of permanent tooth discolouration, enamel hypoplasia, and inhibition of bone growth. No dosage adjustments are needed for any of the third-generation tetracyclines in patients with renal impairment or mild-to-moderate hepatic impairment. However, dosage adjustments are required for eravacycline and tigecycline in patients with severe hepatic impairment (Child–Pugh Class C). Patient weight can impact PK and outcomes for some antibiotics, which may therefore require patient-specific dosing. Studies in most third-generation tetracycline-class antibiotics indicate that no adjustments are needed based on body weight [84], although dosing of eravacycline is based on 1 mg/kg body weight [12]. Efficacy of omadacycline and eravacycline is consistent across body mass index (BMI) groupings [57,85,86], and the PK of tigecycline is similar in patients with class III obesity (BMI $\geq$40 kg/m^2) or healthy weight [87]. Additionally, safety data

Table 6. Most frequently (≥2%) occurring adverse events from pooled phase 3 clinical studies of third-generation tetracycline-class drugs [10,12,77].

Indication	Adverse event	Tetracycline-class agent	Comparator
Omadacycline			
ABSSSI, CABP		$N = 1073$	$N = 1077$[a]
	Nausea	15%	8%
	Vomiting	8%	3%
	ALT increased	4%	4%
	AST increased	3%	4%
	Headache	3%	2%
	Infusion-site extravasation	3%	2%
	Wound infection	3%	2%
	Cellulitis	3%	2%
	Diarrhoea	2%	5%
	Subcutaneous abscess	2%	3%
	Hypertension	2%	1%
Tigecycline			
CABP, cSSSI, cIAI		$N = 2514$	$N = 2307$[b]
	Nausea	26%	13%
	Vomiting	18%	9%
	Diarrhoea	12%	11%
	Infection	7%	5%
	Abdominal pain	6%	4%
	Headache	6%	7%
	SGPT increased	5%	5%
	Anemia	5%	6%
	Hypoproteinemia	5%	3%
	SGOT increased	4%	5%
	Phlebitis	3%	4%
	Rash	3%	4%
	Alkaline phosphatase increased	3%	3%
	Dizziness	3%	3%
	Asthenia	3%	2%
	Amylase increased	3%	2%
	Abnormal healing	3%	2%
	BUN increased	3%	1%
	Abscess	2%	2%
	Dyspepsia	2%	2%
	Pneumonia	2%	2%
	Bilirubinemia	2%	1%
	Hyponatremia	2%	1%
Eravacycline			
cIAI		$N = 520$	$N = 517$[c]
	Infusion-site reactions	8%	2%
	Nausea	7%	0.6%
	Vomiting	4%	3%
	Diarrhoea	2%	2%

[a]Comparators: linezolid, moxifloxacin.
[b]Comparators: vancomycin–aztreonam, imipenem–cilastatin, levofloxacin, linezolid.
[c]Comparators: ertapenem, meropenem.
ABSSSI: acute bacterial skin and skin structure infection; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CABP: community-acquired bacterial pneumonia; cIAI: complicated intra-abdominal infection; cSSSI: complication skin and skin structure infection; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

indicate tolerance of higher-dose eravacycline in patients with increased BMI [85].

Drug-drug interactions (DDIs) leading to adverse drug events are a common cause of emergency department visit and/or hospitalisation [88,89]. Patients, particularly at risk of these DDIs, are older patients who are on many long-standing medications, immunocompromised patients, and others with multiple medical problems [90]. Based on their PK/PD characteristics and ability to be used as monotherapy, newer tetracycline-class agents can be used to minimise the risk of severe drug-drug interactions in these high-risk patients.

Patients with labeled drug-drug penicillin allergy in the past have had multiple negative outcomes associated with the use of alternative antimicrobial agents including the risk of antimicrobial treatment failure, antimicrobial resistance, adverse drug reactions from the use of a broader-spectrum or alternative antibiotic, increased risk of CDI, and increased healthcare costs [91,92]. In these patients, a newer generation of tetracycline-class agents could provide a therapeutic option that is not only efficacious but also mitigates the risk of various negative sequelae.

The risk of recurrent CDI is higher in patients aged ≥65 years, or who have compromised immunity, prior

severe CDI, or ribotype 027/078/244 infections [93]. If these patients require ongoing or repeat antibiotic therapy immediately after the initial episode of CDI, then antibiotics with known increased risk of CDI (clindamycin, fluoroquinolones, β-lactam agents) could be avoided.

Re-engaging with tetracycline-class drugs – where could patients benefit?

Antimicrobial stewardship involves using the right antibiotic agent, at the right time, for the right patient. While the clinical utility of first- and second-generation tetracycline-class drugs has been decreasing, third-generation drugs overcome the most common acquired tetracycline resistance mechanisms and therefore may play an important role in antimicrobial stewardship and in reducing "collateral damage" of antibiotic therapies. The increases in extended-spectrum β-lactamase (ESBL)-producing bacteria have limited the use of β-lactams in both hospital and outpatient settings [94,95]. The broad-spectrum activity of the third-generation tetracycline-class agents, combined with their activity being unaffected by common resistance genes, including β-lactamases, makes them suitable for treating a wide range of infections including those caused by drug-resistant strains, such as MRSA, vancomycin-resistant enterococci, tetracycline-resistant *S. pneumoniae*, and anaerobic pathogens [35,96–101]. Additionally, these drugs can be used as a monotherapy to treat polymicrobial infections, such as IAIs and skin structure infections, thereby minimising the impact on global antimicrobial resistance. The emerging threat of the *tet*(X) which causes resistance to all tetracyclines but not to other antibiotic classes, warrants continued monitoring of tetracycline resistance, further restriction of tetracyclines (and other antibiotics) in farm animals, and robust antimicrobial stewardship to promote their optimal use including considerations to reduce selective pressure potential by deprioritizing the use of tetracyclines for pathogens that may harbour *tet*(X). In addition to the currently approved indications for the third-generation tetracycline-class drugs, clinical trials are ongoing in diabetes-related infections (NCT04144374), cystic fibrosis (NCT04460586), pulmonary *Mycobacterium abscessus* complex (NCT04922554) and multidrug-resistant blood-stream infections (NCT04489459, NCT04876430).

The reduced risk of CDI compared with other antibiotic classes such as β-lactams and fluoroquinolones suggest that third-generation tetracycline-class drugs may present alternative antibiotic treatment options for patients with an increased risk of primary or recurrent CDI.

As third-generation tetracycline-class drugs do not require dose adjustments for end-stage renal impairment or mild-to-moderate hepatic impairment and have a limited number of DDIs, they provide a suitable therapy option for patients who otherwise could experience reduced efficacy with other antimicrobial agents, and for older adults who are often taking multiple chronic medications.

Finally, the mode of delivery and frequency of administration may provide benefits to patients over previous therapies. For example, the availability of doxycycline, minocycline, and omadacycline as IV-to-oral therapies could potentially reduce inpatient treatment times, and oral-only options allow outpatient treatment of patients with appropriate indications who may otherwise have required IV therapy. Similarly, oral medications including antibiotics that require infrequent dosing can also improve treatment adherence and patient compliance [102].

In summary, in an era of multidrug antibiotic resistance, additional treatment options are needed to address infections in complex patient populations. The latest generation of tetracycline-class antibiotics overcome the most common mechanisms of tetracycline resistance that limit the use of prior tetracyclines and are well suited to treat various infectious syndromes including skin-soft tissue infections, community acquired pneumonia and intra-abdominal infections. While all antibiotics are subject to the development of resistance, judicious use of tetracyclines not only provides another class of antibiotic activity but also helps by not promoting resistance to other commonly used antibiotic classes (e.g. beta-lactams, fluoroquinolones). Therefore, the third-generation tetracycline class has the potential to play a key role in the treatment of a broad range of bacterial infections to provide a safe and effective treatment option for patients and to support antibiotic stewardship initiatives.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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