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REVIEW OF THERAPEUTICS

Use of oral tetracyclines in the treatment of adult outpatients with skin and skin structure infections: Focus on doxycycline, minocycline, and omadacycline

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Abstract

Oral tetracyclines have been used in clinical practice for over 60 years. One of the most common indications for use of oral tetracyclines is for treatment of adult outpatients with skin and soft infections (SSTIs), including acute bacterial skin and skin structure infections (ABSSSIs). The 2014 Infectious Diseases Society of America (IDSA) skin and soft tissue guideline strongly recommends sulfamethoxazole/trimethoprim, clindamycin, and tetracyclines as oral treatment options for patients with purulent SSTIs, especially when methicillin-resistant *Staphylococcus aureus* is of clinical concern. Despite the long-standing use of tetracyclines, practice patterns indicate that they are often considered after other guideline-concordant oral options for the treatment of patients with SSTIs. Clinicians may therefore be less familiar with the clinical data associated with use of commercially available tetracycline agents for treatment of patients with SSTI. This review summarizes the literature on the use of oral tetracyclines (ie, doxycycline, minocycline, and omadacycline) for the treatment of adult patients with SSTIs. As part of this review, we describe their common mechanisms of resistance, susceptibility profiles against common SSTI pathogens, pharmacokinetics and pharmacodynamics, and comparative clinical data.

KEYWORDS
ABSSSI, doxycycline, minocycline, omadacycline, skin, soft tissue, tetracycline

1 | INTRODUCTION

Skin and soft tissue infections (SSTIs), or acute bacterial skin and skin structure infections (ABSSSIs), are among the most common indications for outpatient antibiotic prescriptions in the USA.[1,2] To guide treatment decisions, the Infectious Diseases Society of America (IDSA) skin and soft tissue guideline from 2014 recommends characterizing SSTIs as either non-purulent or purulent.[3] This approach is particularly important in outpatient settings where treatment is often empiric, and therefore, agents should be selected to target suspected pathogens. Cellulitis and erysipelas are the most common non-purulent SSTIs and are caused in most cases by streptococci. Guideline-concordant outpatient oral antibiotics for treating common non-purulent SSTIs include penicillin VK, cephalosporins, dicloxacillin, and clindamycin. In contrast, purulent infections are commonly caused by *Staphylococcus aureus*, and the presence of methicillin-resistant *S. aureus* (MRSA) is often of clinical concern. Oral agents with MRSA activity that are recommended by IDSA

guidelines include sulfamethoxazole/trimethoprim (SMX/TMP), clindamycin, linezolid, and oral tetracyclines (ie, doxycycline and minocycline). Though less common relative to Gram positives, Gram negatives may also be implicated in SSTIs in at-risk patients (eg, patients with long-standing diabetes, chronic kidney disease, and heart failure),[4] with guidelines recommending use of an agent expected to have activity against suspected pathogens (eg, *Escherichia coli*).

Oral antibiotics listed in the 2014 IDSA SSTI guideline are "strongly" recommended for use based on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system, indicating that these agents can be used for most patients in most circumstances.[3] However, there are some important effectiveness (largely due to microbiologic resistance) and safety considerations with many of the IDSA-recommended oral antibiotics.[3,5–13] Despite their infrequent use relative to other oral SSTI agents,[1,14] doxycycline and minocycline are attractive options given their high oral bioavailability, generally favorable safety profiles, and low potential for drug interactions. In addition to their high in vitro activity against *S. aureus*, including MRSA, they also have Gram-negative activity if broader coverage is clinically indicated, similar to SMX/TMP. Although not included in the 2014 IDSA guideline, omadacycline is another tetracycline derivative that was approved by the United States Food and Drug Administration (FDA) in 2018 for treatment of ABSSSIs and is available both intravenously and orally.[15] Given the need for alternatives to clindamycin, SMX/TMP, and oxazolidinones for certain outpatients with SSTIs, this review summarizes the microbiologic and clinical data on use of oral tetracyclines (doxycycline, minocycline, and omadacycline) for this indication. As part of this review, we describe common mechanisms of tetracycline agent resistance among SSTI pathogens (ie, staphylococci, streptococci, Enterobacterales), reported in vitro activity against SSTI pathogens across recent surveillance studies, data on pharmacokinetics and pharmacodynamics, and summaries of comparator clinical studies. Important considerations for use of oral tetracyclines for the treatment of adult outpatients with SSTIs are summarized. Safety profiles of these agents are not included in this review, as they are described in extensive detail elsewhere.[16]

2 | METHODS

A comprehensive search of PubMed was performed to identify relevant articles pertaining to use of FDA-approved tetracycline agents for treatment of SSTI. To ensure all appropriate articles were captured, the initial search terms included "tetracycline" and "skin." The initial search resulted in 3203 articles, and all were screened for inclusion based on the title and abstract. Specific interest was placed on titles that included specific tetracycline agents, studies that specifically mentioned tetracyclines for treatment of SSTIs (eg, clinical trials), or studies that compared resistance among SSTI treatments for the most common bacterial pathogens (eg, *S. aureus*, streptococci). All relevant articles identified in the initial literature search underwent cross-referencing to ensure that other relevant articles not captured in the initial search were reviewed and included as applicable. Clinical studies were included if patient outcomes were stratified by antibiotic treatment received. Case reports or studies on non-FDA-approved tetracycline agents were excluded. For in vitro microbiologic susceptibility surveillance studies, emphasis was placed on articles published after 2000 that were conducted in adult patients (hospitalized and community-dwelling) with SSTIs from North America and Europe. Minimum inhibitory concentration (MIC) data specific to clinical isolates associated with SSTI were included when available.

2.1 | Common resistance mechanisms

Tetracycline agents exert their activity by binding to the 30S subunit of the bacterial ribosome to inhibit protein synthesis.[17] The three major classifications of resistance to tetracycline class agents include efflux pumps, ribosomal protection proteins (RPPs), and enzymatic deactivation.[17–19] Notably, tetracycline is the least stable agent against common resistance mechanisms, and therefore, non-susceptibility to tetracycline does not necessarily predict non-susceptibility to doxycycline, minocycline, or omadacycline. However, susceptibility to doxycycline, minocycline, and omadacycline can be inferred in the setting of tetracycline susceptibility.[20]

With respect to *Staphylococcus* species, the two major described mechanisms of tetracycline resistance involve efflux pump expression and the presence of RPP. Both mechanisms are conferred by *tet* genes and appear to be inducible in *S. aureus* in vitro.[21] Efflux pump expression is most mediated by plasmid-acquired genes *tetK* and *tetL*, while RPP-mediated *tetM* or *tetO* can be transposon- or chromosomally mediated.[21] Most MRSA isolates that are tetracycline-resistant harbor *tetK* or *tetM*, and some isolates may express both genotypes.[21,22] The *tetL* gene has also been reported to be co-expressed with *tetM*.[21] *S. aureus* that exhibit the TetK efflux pump tend to be resistant to tetracycline and have higher but susceptible MIC values per the Clinical and Laboratory Standards Institute (CLSI)/Food and Drug Administration (FDA) susceptibility breakpoints to doxycycline.[23] However, exposure to subinhibitory concentrations of tetracycline and doxycycline has been shown to induce doxycycline resistance in the presence of the TetK pump, while minocycline and omadacycline retain activity.[21,22,24] Expression of the RPP TetM results in a broader resistance profile as it confers resistance to tetracycline, doxycycline, and minocycline.[21] The RPP TetO, although expected to confer a similar phenotype, is seemingly not as common as TetM in *S. aureus*.[21] Omadacycline in vitro activity is retained in the setting of TetM and TetO.[24,25] Although these appear to be the most common mechanisms for tetracycline agent resistance in *S. aureus*, other mechanisms have also been described.[17,26]

With respect to other common SSTI pathogens, *tetM* is the most commonly expressed resistance gene in *S. pyogenes*, and expression has been reported to be inducible.[18] In addition, *tetO*, *tetS*, and *tetT* have been described as mechanisms of antibiotic resistance associated with *S. pyogenes*.[23] Many viridans group streptococci harbor

tetK, *tetL*, *tetM*, or *tetO*.[18] Expression of these resistant genes in streptococci affects the susceptibility of doxycycline, minocycline, and omadacycline in a similar nature to that observed in *S. aureus* as described above. More specifically, doxycycline and minocycline would not necessarily be expected to be active against many tetracycline-resistant streptococci given common expression of TetM. Omadacycline activity, however, is not affected by RPPs.

Efflux pump expression is well described among *Enterobacterales*, conferring narrower (eg, TetA, TetB) to broad-spectrum and multidrug resistance (eg, AcrAB).[17] Notably, tetracycline, doxycycline, and minocycline are all substrates for TetB,[14] resulting in reduced susceptibility to all aforementioned agents. Resistance to all agents, including omadacycline, can be seen with AcrAB expression.[19,27,28] TetM[17] and TetO[19] have also been described in *Enterobacterales*, including *E. coli*, both of which confer resistance to "traditional" tetracyclines but not omadacycline. TetX, although uncommon, confers resistance to all tetracycline agents including omadacycline via hydroxylation of the tetracycline core structure.[17,19] Mutations in the ribosomal subunit, although infrequent, can also confer non-susceptibility to doxycycline, minocycline, and omadacycline.[19,29]

2.2 | Surveillance

Susceptibility breakpoints for clinical use of tetracyclines are established by CLSI, European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the FDA.[30–32] However, there are variations in both availability of and designated susceptibility breakpoint concentrations across organizations (Table 1). In general, organisms that are reported to be susceptible to tetracycline can be considered susceptible to doxycycline, minocycline, and omadacycline. However, as described earlier, activity of these agents in the setting of tetracycline resistance is variable based on the mechanism, and susceptibility should be confirmed whenever possible.

In vitro data (MIC_{50}, MIC_{90}) for tetracycline, doxycycline, minocycline, and omadacycline against SSTI-associated pathogens from mostly observational cohort and large surveillance studies are summarized in Table 2. Most studies indicated that isolates were from clinical sources, including but not necessarily limited to SSTI. The MIC values specific to SSTI-associated pathogens were included whenever specified. A focus was placed on recent (ie, from 2000 or later) data from North America or Europe. Non-susceptibility rates from these studies were included when available, though these values are subject to study methodology and susceptibility breakpoints at the time of the respective publication.

2.2.1 | *Staphylococcus aureus*

Despite well-described resistance mechanisms, studies suggest that resistance to tetracycline agents is generally low among *S. aureus* (<10%).[33–39] However, if data are stratified by methicillin susceptibility, higher rates of tetracycline agent non-susceptibility are observed for MRSA (as high as 18% for tetracycline)[34,36,38,40] relative to MSSA.[25,34,36,38,40] In one study of over 3000 isolates from the European SENTRY program, *tetM* expression was more common in MRSA, whereas *tetK* was prevalent in MSSA,[41] and *tetM and tetK* co-expressions were also more frequent in MRSA.[41] Doxycycline and minocycline data are not widely reported, though studies suggest that doxycycline non-susceptibility rates are generally low (≤6%). However, this trend may be reflective of tetracycline susceptibility at large, given that in one study of tetracycline-resistant *S. aureus* isolates ($n = 237$), 38% were also non-susceptible to doxycycline.[38] Omadacycline MICs are favorable against *S. aureus*, and activity is generally retained in the presence of tetracycline-resistant strains.[33,35,38]

Few studies have evaluated susceptibility trends among the various oral tetracycline agents against *S. aureus* in the setting of known resistance mechanisms. One study evaluated MIC data for tetracycline, doxycycline, and omadacycline in the presence of clinical *S. aureus* isolates harboring *tetK* ($n = 5$ isolates) and *tetM* ($n = 19$ isolates) genes.[25] Given that both *tetK* and *tetM* confer resistance

TABLE 1 Susceptibility breakpoints for tetracycline agents as reported by CLSI, EUCAST, and the FDA

	Susceptibility breakpoints (mcg/ml)											
	Tetracycline			Doxycycline			Minocycline			Omadacycline		
Pathogen	CLSI	EU	FDA	CLSI	EU	FDA	CLSI	EU	FDA	CLSI	EU	FDA
S. aureus	≤4	≤1	≤4	≤4	≤1	–	≤4	≤0.5	≤4	–	–	≤0.5
S. lugdunensis	≤4	≤1	≤4	≤4	≤1	–	≤4	≤0.5	≤4	–	–	≤0.12
Beta-hemolytic streptococci	≤2	≤1	≤2	–	≤1	–	–	≤0.5	–	–	–	≤0.12[a]
Viridans group streptococci	≤2	–	–	–	–	–	–	–	–	–	–	≤0.12[b]
Enterobacterales spp.	≤4	–	≤4	≤4	–	≤4	≤4	–	≤4	–	–	≤4

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration.

[a]*S. pyogenes only.*

[b]*S. anginosus only*; – indicates no breakpoint is established.

Source: CLSI M100,[30] EUCAST,[31] and FDA.[32]

TABLE 2 Minimum inhibitory concentrations (mcg/ml) and non-susceptibility rates for oral tetracyclines against SSTI pathogens

Pathogen	Tetracycline MIC_{50}/MIC_{90}/%NS	Doxycycline MIC_{50}/MIC_{90}/%NS	Minocycline MIC_{50}/MIC_{90}/%NS	Omadacycline MIC_{50}/MIC_{90}/%NS	Reference (geographic location, years obtained)
S. aureus	0.125/64/– (*n* = 55)	≤0.06/8/– (*n* = 55)	0.125/8/– (*n* = 55)	0.125/0.5/– (*n* = 55)	Macone 2014 (USA)[25]
	≤0.5/≤0.5/5.9% (*n* = 4632)	≤0.06/0.25/1.9% (*n* = 4632)		0.12/0.25/1.0% (*n* = 4632)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
	≤0.5/≤0.5/7.3% (*n* = 2216)	≤0.06/0.12/1.7% (*n* = 2216)			Sader 2019 (Europe, Asia–Pacific, Latin America; 2014–2016)[34]
	≤0.5/≤0.5/4.6% (*n* = 21,056)				Sader 2017 (US; 2010–2016)[36]
			–/0.5/0.4%[a] (*n* = 5118)		Tarnberg 2016 (North America, Europe, Africa, Latin America, Middle East; 2010–2014)[37]
				0.12/0.25/1.3% (*n* = 2684)	Huband 2019 (USA and Europe; 2017)[33]
				0.12/0.25/1.9% (*n* = 18,577)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.12/0.25/1.4% (*n* = 4215)	Pfaller 2018 (USA and Europe; 2016)[35]
MSSA	≤0.06/0.125/– (*n* = 16)	≤0.06/≤0.6/– (*n* = 16)	≤0.06/0.125/– (*n* = 16)	0.125/0.125/– (*n* = 16)	Macone 2014 (USA)[34]
	≤0.5/≤0.5/3.8% (*n* = 3194)	≤0.06/0.12/2.5% (*n* = 3194)		0.12/0.25/0.1% (*n* = 3194)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
	≤0.5/≤0.5/4.8% (*n* = 1805)	≤0.06/0.12/0.7% (*n* = 1805)			Sader 2019 (Europe, Asia-Pacific, Latin America; 2014–2016)[34]
	≤0.25/0.5/5.8% (*n* = 4966)	0.12/0.12/0.8% (*n* = 4966)			Jones 2013 (North America, Europe, Latin America, Asia-Pacific; 2010)[40]
	≤0.5/≤0.5/3.9% (*n* = 11,377)				Sader 2017 (USA; 2010–2016)[36]
				0.12/0.25/0.2% (*n* = 1792)	Huband 2019 (USA and Europe; 2017)[33]
				0.12/0.25/0.3% (*n* = 10,836)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.12/0.25/0.1% (*n* = 2777)	Pfaller 2018 (USA and Europe; 2016)[35]

(Continues)

TABLE 2 (Continued)

Pathogen	Tetracycline MIC_{50}/MIC_{90}/%NS	Doxycycline MIC_{50}/MIC_{90}/%NS	Minocycline MIC_{50}/MIC_{90}/%NS	Omadacycline MIC_{50}/MIC_{90}/%NS	Reference (geographic location, years obtained)
MRSA	0.25/64/– (*n* = 39)	0.125/8/– (*n* = 39)	0.25/8/– (*n* = 39)	0.25/0.5/– (*n* = 39)	Macone 2014 (USA)[25]
	≤0.5/8/10.5% (*n* = 1438)	≤0.06/1/4.7% (*n* = 1438)		0.12/0.25/2.9% (*n* = 1438)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
	≤0.25/1/4.8% (*n* = 2708)	0.12/0.5/1.6% (*n* = 2708)		0.12/0.5/– (*n* = 2708)	Pfaller 2017 (North America; 2010–2014)
	≤0.5/>8/18.2% (*n* = 411)	≤0.06/2/6.1% (*n* = 411)			Sader 2019 (Europe, Asia-Pacific, Latin America; 2014–2016)[34]
	≤0.25/2/8.8% (*n* = 4046)	0.12/1/3.8% (*n* = 4046)			Jones 2013 (North America, Europe, Latin America, Asia-Pacific; 2010)[40]
	0.5/16/47%[a] (*n* = 38)		1/4/– (*n* = 38)		Borbone 2008 (Italy; 2004–2005)[42]
	≤0.5/1/5.4% (*n* = 9679)				Sader 2017 (USA; 2010–2016)[36]
			–/0.5/0.6%[a] (*n* = 1926)		Tarnberg 2016 (North America, Europe, Africa, Latin America, Middle East; 2010–2014)[37]
				0.12/0.25/3.5% (*n* = 892)	Huband 2019 (USA and Europe; 2017)[33]
				0.12/0.25/4.2% (*n* = 7741)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.12/0.25/3.9% (*n* = 1438)	Pfaller 2018 (USA and Europe; 2016)[35]
Community-acquired MRSA	≤0.25/0.5/4.5% (*n* = 1560)	0.12/0.25/1.2% (*n* = 1560)		0.12/0.25/– (*n* = 1560)	Pfaller 2017 (North America; 2010–2014)[71]
Hospital-acquired MRSA	≤0.25/2/5.7% (*n* = 598)	0.12/1/1.9% (*n* = 598)		0.06 to 4/– (*n* = 598)	Pfaller 2017 (North America; 2010–2014)[71]
Tetracycline-resistant *S. aureus*	>8/>8/100% (*n* = 237)	2/>8/37.6% (*n* = 237)		0.12/0.5/7.2% (*n* = 237)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.12/0.5/6.1% (*n* = 148)	Huband 2019 (USA and Europe; 2017)[33]
				0.12/0.5/4.5% (*n* = 221)	Pfaller 2018 (USA and Europe; 2016)[35]
S. lugdunensis	≤0.5/≤0.5/4.9% (*n* = 103)	≤0.06/≤0.06/0% (*n* = 103)		0.06/0.12/1.9% (*n* = 103)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.06/0.12/0% (*n* = 48)	Huband 2019 (USA and Europe; 2017)[33]

(Continues)

TABLE 2 (Continued)

Pathogen	Tetracycline MIC_{50}/MIC_{90}/%NS	Doxycycline MIC_{50}/MIC_{90}/%NS	Minocycline MIC_{50}/MIC_{90}/%NS	Omadacycline MIC_{50}/MIC_{90}/%NS	Reference (geographic location, years obtained)
Coagulase-negative staphylococci	2/2/– (*n* = 16)		0.06/0.25/– (*n* = 16)		Borbone 2008 (Italy; 2004–2005)[42]
	≤0.5/8/10.6% (*n* = 348)			0.12/0.5/– (*n* = 348)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.25/1/– (*n* = 2992)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.12/0.5/– (*n* = 723)	Pfaller 2018 (USA and Europe; 2016)[35]
Beta-hemolytic streptococci	0.5/>4/38.8% (*n* = 960)			0.06/0.12/– (*n* = 960)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
	≤0.5/>8/39.7% (*n* = 418)				Sader 2019 (Europe, Asia-Pacific, Latin America; 2014–2016)[34]
				0.06/0.12/– (*n* = 3196)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.06/0.12/– (*n* = 966)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.12/0.25/– (*n* = 651)	Huband 2019 (USA and Europe; 2017)[33]
Tetracycline-resistant beta-hemolytic strep				0.12/0.25/– (*n* = 421)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.12/0.25/– (*n* = 295)	Huband 2019 (USA and Europe; 2017)[33]
S. pyogenes	≤0.06/64/– (*n* = 30)	≤0.06/8/– (*n* = 30)	0.25/8/– (*n* = 30)	0.125/0.25/– (*n* = 30)	Macone 2014 (USA)[25]
	≤0.25/>8/19.7% (*n* = 793)	0.12/8/18.8% (*n* = 793)			Jones 2013 (North America, Europe, Latin America, Asia-Pacific; 2010)[40]
	16/32/80%[a] (*n* = 20)		2/2/– (*n* = 20)		Borbone 2008 (Italy;;2004–2005)[42]
	≤0.25/>4/17.9% (*n* = 544)			0.06/0.12/1.8% (*n* = 544)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.06/0.12/2.3% (*n* = 299)	Huband 2019 (USA and Europe; 2017)[33]
				0.06/0.06/0.9% (*n* = 1576)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.06/0.12/1.6% (*n* = 448)	Pfaller 2018 (US and Europe; 2016)[35]

(Continues)

TABLE 2 (Continued)

Pathogen	Tetracycline MIC_{50}/MIC_{90}/%NS	Doxycycline MIC_{50}/MIC_{90}/%NS	Minocycline MIC_{50}/MIC_{90}/%NS	Omadacycline MIC_{50}/MIC_{90}/%NS	Reference (geographic location, years obtained)
Tetracycline-resistant *S. pyogenes*				0.12/0.12/6.4% (*n* = 78)	Pfaller 2018 (USA and Europe; 2016)[39]
				0.12/0.25/11.3% (*n* = 53)	Huband 2019 (USA and Europe; 2017)[33]
S. agalactiae	32/64/– (*n* = 18)	8/8/– (*n* = 18)	16/16/– (*n* = 18)	0.125/0.125/– (*n* = 18)	Macone 2014 (USA)[25]
	>8/>8/85.4% (*n* = 1058)	8/8/84.3% (*n* = 1058)			Jones 2013 (North America, Europe, Latin America, Asia-Pacific; 2010)[40]
	32/64/69%[a] (*n* = 13)		4/32/62%[a] (*n* = 13)		Borbone 2008 (Italy; 2004–2005)[42]
				0.12/0.25/– (*n* = 776)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.06/0.12/– (*n* = 1570)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.12/0.25/– (*n* = 358)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.12/0.25/– (*n* = 261)	Huband 2019 (USA and Europe; 2017)[33]
Tetracycline-resistant *S. agalactiae*				0.12/0.25/– (*n* = 294)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.12/0.25/– (*n* = 211)	Huband 2019 (USA and Europe; 2017)[33]
Viridans group streptococci	0.5/>4/37.5% (*n* = 97)			0.06/0.12/– (*n* = 97)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.06/0.12/– (*n* = 1538)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				0.06/0.12/– (*n* = 327)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.06/0.12/– (*n* = 132)	Huband 2019 (USA and Europe; 2017)[33]
Tetracycline-resistant viridans group streptococci				0.12/0.25/– (*n* = 112)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.12/0.25/– (*n* = 38)	Huband 2019 (USA and Europe; 2017)[33]

(Continues)

TABLE 2 (Continued)

Pathogen	Tetracycline MIC_{50}/MIC_{90}/%NS	Doxycycline MIC_{50}/MIC_{90}/%NS	Minocycline MIC_{50}/MIC_{90}/%NS	Omadacycline MIC_{50}/MIC_{90}/%NS	Reference (geographic location, years obtained)
S. anginosus	0.5/>4/24.8% ($n = 67$)			0.06/0.12/0% ($n = 67$)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				0.06/0.12/0% ($n = 107$)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.06/0.06/0% ($n = 50$)	Huband 2019 (USA and Europe; 2017)[33]
Tetracycline-resistant *S. anginosus*				0.06/0.12/0% ($n = 34$)	Pfaller 2018 (USA and Europe; 2016)[35]
				0.06/0.12/0% ($n = 14$)	Huband 2019 (USA and Europe; 2017)[33]
Enterobacterales				1/8/12.5% ($n = 20,028$)	Pfaller 2020 (USA and Europe; 2016–2018)[38]
				2/8/13.7% ($n = 20,305$)	Pfaller 2017 (North America, Europe, Asia-Pacific, Latin America; 2010–2011)[39]
				1/8/13.1% ($n = 5993$)	Huband 2019 (US and Europe; 2017)[33]
ESBL phenotype *Enterobacterales*				2/8/15.1% ($n = 1002$)	Huband 2019 (USA and Europe; 2017)[33]
Tetracycline-resistant *Enterobacterales*				4/16/33.0% ($n = 2136$)	Huband 2019 (USA and Europe; 2017)[33]

[a]% resistant; –, not available; ESBL, extended spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NS, non-susceptible.

to tetracycline, MIC ranges for tetracycline were expectedly high (16–32 mcg/ml and 32 to >64 mcg/ml, respectively). Respective elevations in MIC ranges were less extreme with doxycycline, particularly in the presence of *tetK* relative to *tetM* (1–4 mcg/ml and 2–16 mcg/ml) and were lowest for omadacycline (0.125–0.25 mcg/ml and 0.125–1 mcg/ml). This supports the notion that doxycycline MICs are more likely to be in the susceptible range based on current breakpoints in the presence of *tetK* compared with *tetM*, and omadacycline is generally expected to be active in the presence of either determinant.[25]

Though minocycline was not included in the aforementioned study, a similar analysis of 66 clinical MRSA isolates described both doxycycline and minocycline MIC trends in the presence of confirmed *tetK* and *tetM*.[21] The doxycycline MIC_{90} was 4 mcg/ml among isolates harboring *tetK* alone, whereas MIC_{90} increased to 8 mcg/ml in isolates with *tetM*.[21] The MIC_{90} for minocycline in *tetK* and *tetM* isolates were ≤0.25 and 4 mcg/ml, respectively. Notably, when *tetK*-containing isolates were pre-incubated with a subinhibitory concentration of tetracycline, MICs increased for doxycycline (MIC_{90} 16 mcg/ml) but not minocycline (MIC_{90} 0.25 mcg/ml), suggesting potential for inducible doxycycline resistance in the presence of *tetK*. MIC_{90} increases for both doxycycline and minocycline (16 mcg/ml) were observed for pre-incubated *tetM* isolates. Ultimately, investigators concluded that concern for inducible doxycycline resistance be considered in the setting of all tetracycline-resistant MRSA isolates, with consideration also given to the possibility of minocycline resistance. Though minocycline appears to be less impacted by inducible resistance than doxycycline, these findings highlight the apparent clinical importance of confirming individual agent susceptibility if tetracycline resistance in *S. aureus* is known or suspected. However, it is worth noting that these findings from the aforementioned studies,[21,25] which was also echoed by others,[20,40] suggest that the current CLSI and FDA susceptibility breakpoint for doxycycline (≤4 mcg/ml) does not appear to appreciably differentiate between wild-type and resistance determinant-containing strains.[20,21,25,40] Therefore, potential for development of resistance may not be readily identifiable.

2.2.2 | *Streptococcus* spp.

Surveillance data for streptococci suggest that non-susceptibility rates for tetracycline are high (18%–85%).[38,40] Resistance to doxycycline and minocycline against streptococci also appears to be commonplace (>20%), but data are limited.[25,40,42] In contrast, surveillance studies indicate that omadacycline resistance is exceedingly rare among streptococci (near 100% susceptibility).[35,38,39] Of note, there are reports of streptococcus isolates with elevated but susceptible omadacycline MICs against some tetracycline-resistant strains, but the clinical significance of this is unknown.[33,35] Very few studies have evaluated the activity of tetracycline agents in streptococcus strains with known resistance mechanisms. One large surveillance study of 1454 group A streptococci observed a 15% non-susceptibility rate to tetracycline, which was most commonly mediated by *tetM*, and less commonly by *tetO*.[43] In a small study evaluating isolates of *S. pyogenes* (19/20) and *S. agalactiae* (10/13) that exhibited either *tetM* or *tetO*,[42] minocycline MICs ranged from 2 to 8 mcg/ml.[9] Data for doxycycline were not reported, but favorable MIC ranges would not be expected in the setting of RPP expression.

2.2.3 | Enterobacterales

Among Enterobacterales, contemporary MIC data for tetracycline agents are not well described and data are only available for omadacycline. Surveillance studies suggest that omadacycline is active against many Enterobacterales, though susceptibility rates are not quite as high as those observed for common Gram-positive SSTI pathogens.[34] In one study of more than 20,000 Enterobacterales isolates, omadacycline inhibited 87.5% of isolates with MICs ≤4 mcg/ml. Omadacycline was reported to be most active against *E. coli* (MIC_{50}/MIC_{90}: 0.5/2), *Klebsiella oxytoca* (MIC_{50}/MIC_{90}: 1/2), and *Citrobacter* spp. (MIC_{50}/MIC_{90}: 1/4). The MIC values against non-extended spectrum beta-lactamase phenotype *K. pneumoniae* were comparable (MIC_{50}/MIC_{90}: 1/4). As with other tetracycline agents, omadacycline was noted to have limited activity against *P. mirabilis* (MIC_{50}/MIC_{90}: 16/>32).[38] Omadacycline is also expected to have limited to no activity against *Morganella* and *Providencia* species.

2.3 | Pharmacokinetics and Pharmacodynamics

Data on the pharmacokinetics (PK) of oral tetracyclines are described in extensive detail elsewhere.[16] Recommended dosing regimens of doxycycline, minocycline, and omadacycline for adult outpatients with SSTIs/ABSSSIs are shown in Table 3. Loading doses are included in the product labeling for omadacycline and encouraged for doxycycline and minocycline when used for adult patients with more serious SSTIs due to their long elimination half-lives.[44,45] With regard to dosing in specialized populations, all three agents do not require dose adjustment for patients with renal or hepatic impairment and dosing regimens do not need to be adjusted for weight, age, gender, or race. These agents also do not significantly interact with drugs metabolized by cytochrome P450 enzymes, minimizing the potential for clinically relevant drug-drug interactions.[46,47]

Although these three agents have similar PK properties, there are differences between agents with regard to their bioavailability. Both doxycycline and minocycline exhibit 90%–100% oral bioavailability,[48] and there are only modest reductions in absorption when they are given with food except when they are co-administrated with divalent and trivalent cations or bismuth subsalicylate.[44,47,49,50] In contrast, the bioavailability of omadacycline is reported to be approximately 35%,[51–54] and absorption is decreased in the setting of food.[53] The oral maintenance dose of omadacycline (ie, 300 mg) is three times the 100 mg IV dose to account for the lower bioavailability. To minimize the effect of food on absorption, patients are

Antibiotic	Administration route: loading dose	Administration route: maintenance dose
Doxycycline[47]	200 mg orally on day 1	100 mg orally every 12 h
Minocycline[50]	200 mg orally on day 1	100 mg orally every 12 h or 50 mg orally 4 times a day
Omadacycline[54]	450 mg orally on days 1–2	300 mg orally once daily

TABLE 3 Oral doxycycline, minocycline, and omadacycline dosing recommendations for adult outpatients with skin and skin structure infections/acute bacterial skin and skin structure infections

recommended to fast for at least 4 h prior to taking oral omadacycline and 2 h after administration. Dairy products, antacids, or multivitamins should also be avoided for 4 h after oral omadacycline administration.[54]

There are also distinct differences in protein binding and plasma exposure profiles between agents. Doxycycline and minocycline exhibit 75%–90% protein binding[55,56] in serum, whereas protein binding for omadacycline is only 20%.[51] For doxycycline and minocycline, the average areas under the curve (AUCs) for 200 mg/day oral doses range from 85 to 108 mg·h/L and 68.6 to 71.3 mg·h/L, respectively, whereas the daily AUC for omadacycline for 300 mg oral or 100 mg IV dose is ~8–10 mg·h/L. However, the observed free plasma AUC is largely similar between agents due to the differences in protein binding.[51,55,56] Furthermore, all three agents concentrate well in the skin and surrounding soft tissues.[44,45]

Limited in vitro and in vivo pharmacokinetic/pharmacodynamic (PK/PD) data are available for doxycycline and minocycline.[44] In a hollow fiber infection model of MRSA simulating free drug serum concentrations of oral minocycline 200 mg/day, a −1.8 −0.2 log reduction in count by 24 h was observed.[57] More PK/PD data exist for omadacycline, and the free 24-h AUC/MIC ratio (fAUC0–24/MIC) was found to best correlate with bacterial killing.[58–60] In a neutropenic mouse thigh infection model of *S. aureus*, median AUC_{0-24}/MIC ratio associated with net stasis and 1-log10 kill were 21.9 in MSSA and 57.7 in MRSA (range, 32.2–302.5).[59] It should be noted that only total drug concentrations were assessed in these studies and the protein binding of omadacycline is similar (20%) in humans and mice. Using the median AUC0-24/MIC ratio targets identified in this study and the population-predicted AUCs in patients at near steady-state conditions,[45] standard oral dosing of omadacycline is expected to result in exposures associated with net stasis-1-log10 killing against most *S. aureus* strains with MIC values ≤0.5 mg/L (current FDA breakpoint).

2.4 | Clinical data

Available comparative clinical data for use of doxycycline, minocycline, and omadacycline for treatment of SSTI are summarized in Table 4. Although several descriptive case series involving doxycycline and minocycline for treatment of patients with SSTIs are available,[61,62] few comparative data exist. The largest study in adult patients with SSTIs who received doxycycline or minocycline was published in 2007.[63] This was a retrospective study of patients with MRSA SSTI who presented to either the emergency department or outpatient clinic at two tertiary care centers (n = 276 patients, 282 episodes). Most patients presented with cutaneous abscesses (75%) that underwent incision and drainage (80%). Patients initially received intravenous therapy and were transitioned to complete treatment with either an oral tetracycline (doxycycline or minocycline 100 mg twice daily) or a beta-lactam. The primary outcome was treatment failure, defined as need for an additional incision and drainage and/or SSTI-related hospital admission within at least 2 days of the initial incision and drainage or positive wound culture. Approximately one third of patients (32%) received doxycycline or minocycline (97% received doxycycline), while the remaining patients received beta-lactam therapy (68% received oral cephalexin and 25% received amoxicillin-clavulanate). A total of 28 failures (10%) were described after a median of 3 days. Failures were most prominent among patients who had received beta-lactam (13% in beta-lactam group vs. 4% in tetracycline group). Most clinical failures (23 of 28) consisted of patients who required a repeat incision and drainage, with or without a concomitant hospital admission. No patients who received tetracyclines required hospital admission, whereas 16 (8.3%) in the beta-lactam group were admitted. In the multivariate analysis, treatment with a beta-lactam was the only characteristic associated with treatment failure (adjusted odds ratio [OR] 3.94, 95% confidence interval [CI] 1.28–12.5, p = 0.02). Patients who received tetracyclines were more likely to experience a successful outcome compared with patients who received a beta-lactam (96% vs. 88%, p = 0.035). Though these findings support use of tetracyclines for MRSA SSTI, their apparent clinical superiority over beta-lactams in this setting is perhaps not unexpected as beta-lactams do not have activity against MRSA.

The findings of high clinical success rates with tetracyclines in the aforementioned study[63] were consistent with a small-scale prospective, open-label randomized study that evaluated empiric therapy with oral SMX/TMP or doxycycline for treatment of outpatients with SSTIs in an area with a high prevalence of MRSA.[64] The primary endpoint of this study was clinical failure, defined as a subsequent hospital admission, the administration of intravenous antibiotics, or a change in oral antibiotics over a period of 10–14 days after the initial emergency department presentation. Thirty-four patients were included in the study, and 14 received SMX/TMP (8 with MRSA) and 20 received doxycycline (15 with MRSA) for 7 days. The overall clinical failure rate was 9% (3 failures), with all failures occurring in the SMX/TMP group. However, there was no significant difference in clinical failure between empirical SMX/TMP or doxycycline therapy. All three SMX/TMP clinical failures were hospitalized due to worsening of the initial SSTI, which subsequently improved with no other

TABLE 4 Clinical data for use of oral tetracycline agents for treatment of SSTI

References	Study design and population	Key baseline characteristics	Comparators	Key primary clinical outcomes	Major findings	Other findings and comments
Keeney 1979[66]	Randomized double-blind clinical trial involving patients with SSTIs due to *S. aureus* or *S. pyogenes*	The most common diagnosis was superficial epidermis (61%) Minocycline group • 71.3% were male • Mean age was 26.9 years • Baseline culture: 67% had *S. aureus* only, 11% had *S. pyogenes* only, and 22% had both pathogens Penicillin-V group • 57.8% were male • Mean age was 27.7 years • Baseline culture: 76% had *S. aureus* only, 8% had *S. pyogenes* only, and 16% had both pathogens	Oral minocycline ($n = 115$) or oral penicillin-V ($n = 128$)	Clinical response (cure, improved, same, or worse) at the end in treatment	Cure at end of treatment was higher among those who received minocycline versus penicillin-V (76% vs. 55%) Clinical cure/improvement was 98% in the oral minocycline group versus 92% in the penicillin-V group At second clinical observation (time not specified), lesions healed or improved in 98% of patients in the minocycline group versus 89% in patients in the penicillin-V group	Higher proportion of baseline *S. aureus* isolates were susceptible to minocycline relative to oral penicillin-V (96% vs. 20%, respectively) Nearly all baseline *S. pyogenes* isolates were susceptible to minocycline (91%) and penicillin-V (100%)
Barnes 2006[65]	Retrospective observational study ($n = 30$) of adult outpatients with non-serious community-onset MRSA SSTIs (ie, abscess or cellulitis)	Community-onset purulent *S. aureus* SSTI Age: 48 (18–85) years	3 received minocycline, 1 received doxycycline, 6 received TMP/SMX, 8 received clindamycin, 5 received a β-lactam plus drainage, 3 received a fluoroquinolone, and 4 received drainage only	Improvement or resolution of infection 5 and 14 days after initiation of treatment with orally administered antibiotics and rates of recurrence within 30 days after completion of treatment	All patients exhibited improvement, without initial worsening, and no patients experienced a recurrence within 30 days after therapy completion	1 patient treated with drainage only, and 1 patient treated with β-lactam + drainage experience recurrence after 30 days
Ruhe 2007[63]	Retrospective cohort study of patients with MRSA SSTI who presented to emergency department or outpatient clinic at two tertiary centers ($n = 276$ patients, 282 episodes) October 2002–February 2007; USA	Abscess (75%), furuncles or carbuncles (13%), cellulitis (12%) 225 patients (80%) underwent I&D Median patient age was 48 years 69% of patients had community-acquired MRSA	Doxycycline or minocycline 100 mg twice daily or IV/oral beta-lactam	Treatment failure (need for second I&D) and/or admission to hospital within ≥2 days after time zero (first I&D or positive wound culture)	Doxycycline or minocycline given in 90 episodes (32%); 192 episodes treated with beta-lactam; median treatment duration 10 days Treatment failure: 28 episodes (10%) at median of 3 days after time zero Beta-lactam antibiotic was the only characteristic associated with treatment failure on logistic regression (aOR 3.94; 95% CI 1.28–12.5; $p = 0.02$)	95% susceptibility rate to tetracycline 86 (96%) had successful outcome with a tetracycline compared to 168 (88%) with beta-lactam ($p = 0.035$) No patients on tetracyclines required subsequent hospital admission compared with 16 beta-lactam patients

(Continues)

TABLE 4 (Continued)

References	Study design and population	Key baseline characteristics	Comparators	Key primary clinical outcomes	Major findings	Other findings and comments
Cenizal 2007[64]	Randomized, prospective, open-label investigation in the emergency department in adults with SSTI ($n = 34$) October 2005–May 2006; USA	Patients were included if SSTI abscesses required wound packing after I&D but not hospitalization Mean patient age was 38 years (range 18–72) 68% were MRSA	SMX/TMP 800 mg/160 mg ($n = 14$) twice daily or doxycycline ($n = 20$) 100 mg twice daily for 7 days	Clinical failure: hospital admission, need for IV antibiotics, or change in oral agent 10–14 days after initial presentation	No statistically significant difference in failure rates between treatments on intention-to-treat analysis ($p = 0.283$) All failures ($n = 3$) occurred in SMX/TMP group (2 MRSA, 1 *Streptococcus*)	All MRSA isolates susceptible to study agents Outcomes after enrollment: Days 2–5: 3 patients in each group required repeat I&D Days 10–14: all patietns had a favorable response Days 28–35: 3 patients in each group had recurrent SSTI
O'Riordan 2019 (OASIS-1)[68]	Phase 3, double-blind, randomized, non-inferiority trial of adults with qualifying skin infection ($n = 627$) June 2015-May 2016; multinational	Cellulitis (38%), wound (33%), major abscess (29%) Median patient age was 48 (OMC) and 46 (linezolid) years 30% of OMC-treated patients and 22% of linezolid-treated patients had MRSA in the microbiologic modified intention-to-treat group	OMC 100 mg IV q12h for 2 doses, then 100 mg IV daily, possible transition to 300 mg oral daily ($n = 316$) or linezolid 600 mg IV q12h, possible transition to 600 mg BID orally ($n = 311$), for 7–14 days	Early clinical response (survival with reduction in lesion size of ≥20% without rescue antibiotic therapy) at 48–72 h	Early clinical response (modified intention to treat): OMC 84.8% vs. 85.5% linezolid, (95% CI −6.3 to 4.9)	Adverse events: Gastrointestinal events were most common (18% OMC vs. 16% linezolid)
O'Riordan 2019 (OASIS-2)[67]	Phase 3, double-blind, double-dummy, randomized, non-inferiority trial of adults with ABSSSI ($n = 735$) August 2016-June 2017; USA	Wound (58%), cellulitis/erysipelas (23%), major abscess (17%) in patients with systemic signs of infection (eg, leukocytosis, fever)	OMC 450 mg oral daily for 48 h, then 300 mg oral daily ($n = 368$) or linezolid 600 mg oral BID ($n = 367$) for 7–14 days	Early clinical response (48–72 h post-first dose in the modified intention-to-treat group) and investigator-assessed clinical response at post-treatment evaluation (7–14 days after last dose)	Early clinical response in modified intention-to-treat population: OMC 88% (315/360) vs. LZD 83% (297/360) (95% CI −0.2 to 10.3) Investigator-assessed response: OMC 84% (303/360) vs. LZD 81% (291/360) (95% CI: −2.2 to 9.0)	Adverse events: mild-to-moderate nausea (30% OMC vs. 8% LZD) and vomiting (17% OMC vs. 3% LZD) were two of the most common AEs

Abbreviations: ABSSSI, acute bacterial skin and skin infection; BID, twice daily; I&D, incision and drainage; IV, intravenous; LZD, linezolid; MRSA, methicillin-resistant S. aureus; OMC, omadacycline; SMX/TMP, sulfamethoxazole/trimethoprim; SSTI, skin and soft tissue infection

complications. Telephone follow-up at 28–35 days after initial presentation with 31 of 34 patients found that 3 of 14 (21.4%) patients in the SMX/TMP group and 3 of 17 (17.6%) patients in the doxycycline group had recurrent SSTI; however, all recurrent SSTIs were at new sites compared with the index infection.

Two additional comparative studies have examined the effectiveness of oral doxycycline/minocycline relative to other oral treatments for outpatients with SSTIs.[65,66] In a retrospective observational study,[65] the efficacy of several oral antibiotics for the treatment of adult outpatients with non-serious community-onset MRSA SSTIs (ie, abscess or cellulitis) was evaluated. The primary outcomes were improvement or resolution of infection 5 and 14 days after initiation of treatment with orally administered antibiotics and rates of recurrence within 30 days after completion of treatment. The study included 30 patients; 3 received minocycline, 1 received doxycycline, 6 received TMP/SMX, 8 received clindamycin, 5 received a β-lactam plus drainage, 3 received a fluoroquinolone, and 4 received drainage only without concurrent antibiotics. All patients exhibited improvement, without initial worsening, and no patients experienced a recurrence within 30 days after therapy completion. A randomized double-blind clinical trial compared the effectiveness of oral minocycline ($n = 115$) relative to oral penicillin-V ($n = 128$) for patients with SSTIs due to *S. aureus* or *S. pyogenes*.[66] The primary outcome was clinical response (cure, improved, same, or worse) at the end of treatment. Not surprisingly, a higher proportion of baseline *S. aureus* isolates were susceptible to minocycline relative to oral penicillin-V (96% vs. 20%, respectively), whereas nearly all baseline *S. pyogenes* isolates were susceptible to minocycline and penicillin-V. Cure at end of treatment was significantly higher among those who received minocycline versus penicillin-V (76% vs. 55%), and overall cure rates were consistent with those with *S. aureus*, *S. pyogenes*, or both *S. aureus* and *S. pyogenes* in baseline culture. Although differences in cure rates at end of treatment were observed between treatment arms, most patients in both groups demonstrated clinical cure/improvement (98% in the oral minocycline group versus 92% in the penicillin-V group).

Omadacycline is the only tetracycline with an oral formulation to be evaluated in contemporary randomized, double-blind, multicenter, multinational phase 3 trials for the treatment of adult patients with ABSSSIs (OASIS-1 and OASIS-2).[67,68] In OASIS-1,[68] omadacycline (100 mg given intravenously every 12 h for two doses, then 100 mg given intravenously every 24 h, with the option to transition to 300 mg given orally every 24 h after ≥3 days, for total treatment of 7–14 days) was compared with linezolid (600 mg given intravenously every 12 h, with the option to transition to 600 mg given orally every 12 h after ≥3 days, for total treatment of 7–14 days) in adults with ABSSSIs (wound infection, cellulitis, erysipelas, major abscess requiring clear evidence of erythema, edema, or induration with a surface area of ≥75 cm^2). Notable exclusion criteria included the presence of chronic infection, recent antibiotic use, presence of immunocompromising conditions, and presence of clinically significant hepatic or renal impairment. The primary endpoint was early clinical response in the modified intention-to-treat population (mITT), which was comprised of all randomized patients who did not have a sole Gram-negative pathogen at baseline (given that linezolid does not have appreciable Gram-negative activity). Early response was defined as survival with reduction in lesion size of ≥20% without rescue antibiotic therapy at 48–72 h. Clinical response with resolution of signs and symptoms of infection 7–14 days after the last antibiotic dose in the mITT and clinical per protocol population was also evaluated.

A total of 655 patients were included in the study (627 mITT population). At least one Gram-positive pathogen was isolated in 69.5% of the ITT population. *S. aureus* was the most isolated pathogen in both groups (about 150 patients, the majority of which was MSSA). A low percentage of patients had concurrent bacteremia (omadacycline 3.5% vs. linezolid 2.9%) in the mITT group. The mean duration of intravenous and oral therapy in both groups was 4.4 and 5.5 days, respectively. Groups were well balanced with a similar distribution of patients with cellulitis, wounds, or major abscesses. Omadacycline was found to be non-inferior to linezolid with respect to early clinical response (omadacycline 84.8% vs. linezolid 85.5%, −0.7 percentage points, 95% CI −6.3 to 4.9). Non-inferiority was also demonstrated in the clinical per protocol group (omadacycline 92.6% vs. linezolid 94.6%, difference −1.9, 95% CI −6.1 to 2.1). Similar clinical responses to treatment were observed in other subgroup analyses. Nearly half of the patients in each group (omadacycline 48.3%, linezolid 45.7%) experienced an adverse event, the most common of which was gastrointestinal in nature (eg, nausea). However, only one patient in each group discontinued therapy prematurely due to a gastrointestinal adverse events. There were no reported occurrences of *Clostridioides difficile* infection in either treatment arm.

In OASIS-2,[67] adult outpatients with ABSSSI were randomly assigned (1:1) to receive omadacycline (450 mg orally every 24 h over the first 48 h, then 300 mg orally every 24 h) or linezolid (600 mg orally every 12 h) for 7–14 days. The primary endpoints were early clinical response among patients without solely Gram-negative ABSSSI pathogens at baseline and investigator-assessed clinical response at post-treatment evaluation, 7–14 days after the last dose, in the mITT population and clinically evaluable population. Overall, 368 were randomized to receive omadacycline and 367 were randomized to receive linezolid. For early clinical response in the mITT population (360 patients in the omadacycline group and 360 patients in the linezolid group), omadacycline was non-inferior to linezolid (88% vs. 83%, respectively, percentage-point difference 5.0, 95% CI: −0.2 to 10.3). For investigator-assessed clinical response at post-treatment evaluation, omadacycline was also found to be non-inferior to linezolid in the mITT (84% vs. 81%, respectively, percentage-point difference 3.3, 95% CI: −2.2 to 9.0) and clinically evaluable (98% vs. 96%, respectively, percentage-point difference of 2.3, 95% CI: −0.5 to 5.8) populations. Similar findings were observed in the pathogen, infection type, and patient subgroup analyses. Comparable response rates were observed in patients with mixed Gram-positive and Gram-negative infections (omadacycline 78% vs. linezolid 82%). Mild-to-moderate nausea and vomiting were two of the most frequent treatment-emergent adverse events in

omadacycline (30% and 17%, respectively) and linezolid (8% and 3%, respectively) groups. Effects appeared to be self-limiting, given that only one patient in the omadacycline group discontinued treatment due to moderate nausea and vomiting.

3 | DISCUSSION

The collective findings from this review suggest that doxycycline, minocycline, and omadacycline are viable options for the treatment of adult outpatients with purulent SSTIs when known or highly suspected to be caused by *S. aureus*, including MRSA, when given for guideline-recommended durations (eg, 5–10 days). Although comparative clinical data are scant for doxycycline and minocycline and largely limited to treatment of *S. aureus*,[63–66] findings largely support their use for treatment of purulent SSTIs. Use of omadacycline is also supported, given that it has been evaluated in two randomized phase 3 trials[67,68] and is approved by the FDA for the treatment of adult patients with ABSSSI caused by *S. aureus* (MSSA and MRSA).[15] Despite promising clinical trial results, real-world effectiveness and safety data with omadacycline for the treatment of purulent SSTIs are scant and, as with any new outpatient antibiotic, there is the potential for issues with drug access, prescription coverage, and out-of-pocket patient expenses. It is important to note that high clinical success rates for all three tetracycline agents in the aforementioned studies are reported in the context of concomitant incision and drainage of purulent sites including abscesses, in accordance with best practice. Furthermore, these studies were generally conducted in patients with acute infections, and therefore may not be sufficiently representative of patients who may require longer durations of treatment in the setting of complicated or chronic infectious processes.

Despite the favorable microbiologic and clinical data with oral tetracyclines, use of doxycycline and minocycline for treatment of purulent SSTIs should be guided by the results of culture and susceptibility reports when available. In particular, a certain degree of caution should be exercised when considering use of doxycycline for purulent SSTIs caused by *S. aureus* isolates that are suspected or reported to be tetracycline-resistant.[38] This concern stems from limited in vitro data suggesting potential for inducible doxycycline resistance on treatment, depending on the underlying mechanism for tetracycline resistance.[21] Some data also suggest that current CLSI and FDA susceptibility breakpoints for doxycycline may not sufficiently differentiate between wild-type strains and those expressing select resistance determinants.[20,21,25] Though the clinical significance of this observation is not well described, there are published reports of increased clinical failures with use of doxycycline relative to minocycline for treatment of *S. aureus* based on anecdotal experience.[69] Inducible resistance appears to be of less concern for minocycline and of seemingly no concern for omadacycline, but more data are needed.

The findings from this review also indicate that doxycycline and minocycline should not be routinely used for the empiric treatment of patients with non-purulent SSTIs, especially when there is documented or high suspicion of streptococci. Although limited, data from surveillance programs indicate that resistance to doxycycline and minocycline among streptococci exceeds 20%.[25,40,42] Doxycycline or minocycline should only be considered as targeted treatment agents against SSTIs caused by *Streptococcus spp.* if the culture and sensitivity report confirms susceptibility. If cultures are not possible in the setting of a suspected streptococcal SSTI, consideration should be given to use of either a non-tetracycline agent with reliable streptococcal activity (eg, beta-lactam, linezolid) or omadacycline.[70] If a polymicrobial infection (eg, both Gram positives and Gram negatives) is suspected, best available data support use of omadacycline over other oral tetracyclines.[70] Though anecdotal experience suggests that doxycycline or minocycline may retain activity in the setting of Gram-negative pathogens such as Enterobacterales, susceptibility should be confirmed in the absence of contemporary Gram-negative bacteria surveillance data from patients with SSTIs.

4 | CONCLUSION

The IDSA SSTI guidelines recommend several oral agents for the empiric treatment of non-purulent and purulent SSTIs.[3] Despite the "strong" GRADE recommendations for the oral agents listed in the guidelines, there are important microbiologic resistance, effectiveness, and safety concerns with many of them. In vitro surveillance and clinical data suggest that doxycycline, minocycline, and omadacycline are effective and safe oral treatment options for SSTIs known or suspected to be caused by *S. aureus*, including MRSA. If there is a need to use an oral tetracycline for a suspected or documented streptococcal SSTI, available surveillance and clinical studies support use of omadacycline and avoidance of doxycycline and minocycline unless susceptibility to these latter two agents can be confirmed. Though polymicrobial and Gram-negative SSTIs (eg, caused by Enterobacterales) are less common in outpatient settings, the best available study data suggest that omadacycline may be preferable to doxycycline or minocycline in the absence of culture data if there is a clinical need to use a tetracycline agent.

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CONFLICT OF INTEREST

TPL has served as a consultant, received grants, and is a speaker for Paratek. MRB has no conflicts to declare.

AUTHOR CONTRIBUTIONS

TPL conceptualized the study and contributed to funding acquisition. TPL and MRB contributed to methodology, wrote and prepared the original draft, and wrote, reviewed, and edited the manuscript.

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