Journal of Biomedical Insights

Open Access

Review Article

Comparative review of tetracycline antibiotics versus glycylcycline antibiotics in the management of complicated skin and soft tissue infections

Nurin Zarifah Binti Rosairie [1]*, Nur Ain Syazwani Binti Abdul Rahman [1], Nuranis Faatihah Binti Borhan [1], Yasmin Syamini Binti Zarin [1]

1 Faculty of Pharmacy, Universiti Sultan Zainal Abidin, Besut, Terengganu, Malaysia

***Corresponding author:** 072322@putra.unisza.edu.my

Citation:
Rosairie NZ, et al. (2026). Comparative review of tetracycline antibiotics versus glycylcycline antibiotics in the management of complicated skin and soft tissue infections. *Journal of Biomedical Insights, 1(2), 03-16*

Received: 25th February, 2026

Revised: 06th July, 2026

Accepted: 13th August, 2026

Published:30th September, 2026

Abstract:

Complicated skin and soft tissue infections (cSSTIs) comprise a variety of infections affecting the dermis, subcutaneous tissue, fascia, or muscle. These infections frequently require hospitalization and systemic antibiotic therapy. They often arise from a variety of bacteria, including both Gram-positive and Gram-negative strains. This includes multidrug-resistant organisms like methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacilli producing extended-spectrum beta-lactamase (ESBL). Due to increasing concern surrounding antimicrobial resistance, it is essential to choose the right antibiotic regimen. This review compares the efficacy, pharmacology, and clinical applicability of tetracyclines, specifically doxycycline and minocycline, with the glycylcycline tigecycline in managing cSSTIs. While tetracyclines remain valuable for mild-to-moderate infections due to their oral availability and effectiveness against MRSA, their utility is limited by rising resistance and narrower activity against Gram-negative organisms. Tigecycline, a synthetic derivative of minocycline, was developed to overcome common tetracycline resistance mechanisms and shows efficacy against an expanded spectrum of bacteria, including drug-resistant Gram-positive and Gram-negative strains. The review explores evidence from clinical trials, pharmacokinetics and safety concerns to support rational antibiotic selection. It highlights that although tigecycline is a potent option for severe, polymicrobial, or resistant infections, its use should be cautious due to mortality risks and IV-only formulation. Tetracyclines, meanwhile, remain a cost-effective and well-tolerated choice for less complex cases, underscoring the importance of individualized treatment strategies.

Keywords: Complicated skin and soft tissue infections (cSSTIs); tetracycline; glycylcycline; antibiotic resistance; clinical efficacy; individualized treatment

Introduction

Complicated skin and soft tissue infections (cSSTIs) represent a significant burden on healthcare systems worldwide, accounting for substantial morbidity, prolonged hospital stays, and increased healthcare costs [1]. Unlike uncomplicated infections, which are often limited to the superficial skin layers, cSSTIs involve deeper soft tissues, may be polymicrobial, and frequently occur in patients with comorbidities such as diabetes, peripheral vascular disease, or immunosuppression [1–3].

The clinical presentation varies from abscesses and cellulitis to necrotizing fasciitis and infected ulcers, necessitating prompt and effective antimicrobial therapy [2,3]. The evolving landscape of antimicrobial resistance has complicated the management of these infections. Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria are increasingly common pathogens, especially in health care-associated

Copyright: © 2026 The Author(s). Licensed under a Creative Commons Attribution (CC BY) 4.0 International License. Users are free to share and adapt the material by giving an appropriate credit to the original author(s).

infections, which tend to have worse outcomes and longer hospital stays than community-acquired infections [1,2]. MRSA prevalence in cSSTIs is high, with some studies reporting over 70% of S. aureus isolates as MRSA [1,4]. Among the available options, the tetracycline class, particularly doxycycline and minocycline, has regained clinical relevance due to its efficacy against community-acquired MRSA and availability in oral formulations, which facilitate outpatient therapy [3].

Tetracyclines exert their antibacterial effects by attaching to the 30S ribosomal subunit, thereby hindering protein synthesis in organisms that are susceptible [3]. While these agents remain useful for mild-to-moderate infections, their effectiveness is diminished due to the increasing incidence of resistance mechanisms, including efflux pumps and ribosomal protection proteins. In response, the glycylcycline class was developed, with tigecycline emerging as the first and only agent currently approved in this category. Derived from minocycline, tigecycline offers a broader spectrum of activity, including coverage against MRSA, VRE, ESBL-producing organisms, and anaerobes, making it a compelling option for severe or polymicrobial cSSTIs [2,3]. Clinical trials have demonstrated tigecycline's efficacy comparable to vancomycin plus aztreonam in hospitalized cSSTI patients, with cure rates around 87–89% [5].

Despite its advantages, tigecycline has limitations. It is available only in intravenous form and has been associated with increased mortality in some patient populations, leading to cautious guideline recommendations. Furthermore, its poor serum concentrations render it less effective in bloodstream infections [5]. Antimicrobial stewardship programs improve appropriate antibiotic use in SSTIs, reducing complications and promoting a timely transition from intravenous to oral therapy, which is critical for optimizing outcomes and minimizing resistance development [6].

This review aims to provide a comprehensive comparison between traditional tetracycline antibiotics and tigecycline in the context of cSSTI management. It evaluates their antimicrobial spectra, resistance patterns, pharmacokinetics, clinical efficacy, safety profiles, and guideline-supported use. The goal is to help clinicians in selecting the most appropriate antibiotic therapy based on infection severity, microbial etiology, and patient-specific factors, with an emphasis on antimicrobial stewardship and personalized care.

Methodology

Study Design

This article is a narrative comparative review of the published evidence on the tetracyclines doxycycline and minocycline and the glycylcycline tigecycline in the management of complicated skin and soft tissue infections (cSSTIs). The review compares the two classes in terms of historical development, mechanism of action, pharmacokinetics and pharmacodynamics, antimicrobial spectrum, resistance, clinical efficacy, safety and guideline-supported use.

Literature Search Strategy

Relevant literature was identified through PubMed/MEDLINE, ScienceDirect and Google Scholar. The search terms were combined with Boolean operators as follows: (“tetracycline” OR “doxycycline” OR “minocycline”) AND (“tigecycline” OR “glycylcycline”) AND (“complicated skin and soft tissue infection” OR “cSSTI” OR “skin and skin structure infection” OR “MRSA”). Additional terms covering pharmacokinetics, resistance mechanisms, tet(X), safety and mortality were used to retrieve evidence for specific sections. The reference lists of key reviews and trials were hand-searched for further studies. Regulatory and guideline documents were obtained from the US Food and Drug Administration, the Infectious Diseases Society of America (IDSA) and the Ministry of Health Malaysia National Antimicrobial Guideline. The search was last updated in May 2025.

Eligibility Criteria

Full-text articles published in English were eligible, mainly those published between 2001 and 2025. Randomised controlled trials, observational studies, systematic reviews and meta-analyses, pharmacovigilance analyses, pharmacological reviews and clinical practice guidelines were included when they reported on the mechanism, pharmacokinetics, antimicrobial activity, resistance, efficacy or safety of tetracyclines or glycylcyclines. Older landmark publications were retained for historical background. Where cSSTI-specific data were limited, evidence from related dermatological indications and from in vitro or animal studies on resistance was included and identified as such in the text. Conference abstracts without full text, non-English articles and duplicate reports were excluded.

Study Selection and Data Synthesis

Titles and abstracts were screened for relevance, and the full texts of potentially eligible articles were reviewed by the authors. Information was extracted on study design, population, antibiotic regimen, clinical cure or success, mortality, adverse events and resistance findings. Because the included studies differed widely in design, population and outcomes, no meta-analysis was performed. The evidence was synthesised narratively, first for each class separately (Sections 3 and 4) and then comparatively (Section 5), and the main differences are summarised in Table 2.

Tetracycline Antibiotics

Historical Development and Classification

Tetracyclines represent one of the earliest classes of broad-spectrum antibiotics developed in the 20th century, with their discovery significantly advancing antimicrobial therapy during the post-World War II era. The first compound, chlortetracycline (also known as Aureomycin), was isolated from *Streptomyces aureofaciens* in 1945. It was soon followed by oxytetracycline, derived from *Streptomyces rimosus* in 1948 [7]. These initial antibiotics were naturally occurring substances characterized by their four-fused hydrocarbon rings, known as the tetracyclic nucleus. Due to the limitations of the early tetracyclines, such as poor oral absorption and resistance development, semi-synthetic modifications led to the development of second-generation tetracyclines, including doxycycline and minocycline. These agents displayed improved pharmacokinetics, including increased oral bioavailability and better tissue penetration [8]. More recently, third-generation tetracyclines, classified as glycylcyclines, were developed to combat growing bacterial resistance. Tigecycline, the first drug in this subclass, was approved by the U.S. Food and Drug Administration (FDA) in 2005. Glycylcyclines are structurally derived from minocycline with a glycylamido group substitution at position 9 of the D ring, enhancing their activity against resistant organisms [9]. This evolution from first- to third-generation tetracyclines demonstrates ongoing efforts to address the increasing burden of antimicrobial resistance and improve clinical outcomes in infectious disease management.

Mechanism of Action

Tetracycline antibiotics primarily inhibit the synthesis of proteins by bacteria. According to Nguyen et al. [10], they work by binding to the 30S ribosomal subunit, which stops aminoacyl-tRNA from binding to the ribosome's A site and stops the elongation of peptide chains. However, it is still unclear exactly what causes this activity to be selective for bacterial ribosomes while being indifferent to eukaryotic ribosomes. Non-antibiotic characteristics of several tetracyclines, such as doxycycline and minocycline, include anti-inflammatory, matrix metalloproteinase-inhibiting, and anti-apoptotic activities [11].

Tetracyclines have also been shown to bind to synthetic double-stranded RNAs with random base sequences as a mechanism of action [12]. Tetracyclines are known to be widely efficient against a variety of bacteria; however, new resistance mechanisms have made their usage more difficult [7,10]. In order to combat resistant strains and improve their effectiveness in treating a variety of illnesses, including acne vulgaris and complex skin infections, newer tetracycline derivatives such as tigecycline and eravacycline have undergone chemical modification [11].

Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profiles vary significantly between individual tetracyclines, affecting their clinical applications. Second-generation agents such as doxycycline and minocycline exhibit improved oral bioavailability compared to their predecessors. Doxycycline, in particular, is well absorbed from the gastrointestinal tract and demonstrates a long half-life of approximately 18–22 hours, allowing for once or twice daily dosing. It is predominantly excreted via feces, making it suitable for patients with renal impairment [13]. Minocycline, on the other hand, possesses high lipophilicity, facilitating excellent penetration into tissues and the central nervous system (CNS). This property makes minocycline a favorable option in treating infections involving hard-to-reach sites such as the brain or bone. Tigecycline, the first glycylcycline, differs from earlier tetracyclines in both pharmacokinetics and pharmacodynamics. It maintains the class's mechanism of action but binds more strongly to the bacterial ribosome due to its structural modifications, allowing it to overcome traditional resistance mechanisms such as efflux pumps and ribosomal protection proteins [14]. Tigecycline has a large volume of distribution (7–10 L/kg), indicating extensive tissue penetration. However, its low serum concentrations may limit its effectiveness in bloodstream infections, necessitating cautious use depending on infection type [15].

Safety and Tolerability

It is well established that systemically applied oral and intravenous tetracyclines are not only safe but are among the most tolerable of antimicrobials [8]. Modern tetracyclines such as omadacycline have fewer drug–drug interactions (DDIs) and do not need dosage adjustment based on age, sex or organ dysfunction; hence, they are more suitable for broad categories of patients [16]. Doxycycline and minocycline are generally well tolerated and suitable for use in non-severe, uncomplicated cSSTIs, particularly in patients who have stable renal function, as tetracyclines are partially excreted through the kidneys.

Minocycline is more frequently associated with negative side effects in pediatric patients, such as skin responses, psychological symptoms including sadness and suicidal thoughts, and a substantial correlation with thyroid malfunction in teenagers [17]. It is also linked to severe hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS). Doxycycline, while generally safer, is associated with psychiatric effects, thyroid dysfunction, and potential tooth discoloration in children under eight, though the long-term impact of this discoloration is still unclear. In addition, patients with photosensitivity risk, pregnancy (Category D), or severe hepatic dysfunction may not be suitable candidates. They are also contraindicated in children <8 years due to risks of dental staining and bone growth suppression [18].

Clinical Trials in cSSTIs

Bhatia et al. [19] reported two phase 3 randomized clinical trials called MVOR-1 and MVOR-2, which evaluated the efficacy, safety, and tolerability of DFD-29, a low-dose oral formulation of minocycline hydrochloride to treat moderate to severe papulopustular rosacea (PPR). These were double-blind, placebo-controlled, multicenter randomized clinical trials conducted over 16 weeks that involved 653 adults aged 18 years and older with moderate to severe PPR. Participants were randomly assigned in a 3:3:2 ratio to receive either DFD-29 (minocycline hydrochloride) 40 mg once daily, doxycycline 40 mg once daily,

or placebo once daily.
In MVOR-1, 65.0% of participants in the DFD-29 group achieved Investigator's Global Assessment (IGA) treatment success, compared with 46.1% in the doxycycline group and 31.2% in the placebo group. Similarly, in MVOR-2, 60.1% of the DFD-29 group achieved IGA treatment success, compared with 31.4% in the doxycycline group and 26.8% in the placebo group. No serious adverse events were reported in either clinical trial. The incidence of treatment-emergent adverse events (TEAEs), including nasopharyngitis, was recorded across all groups. From this clinical trial, it can be concluded that DFD-29 (minocycline hydrochloride) 40 mg is significantly more effective than doxycycline 40 mg and placebo in reducing the inflammatory lesions in patients with moderate to severe PPR [19].
For the current research on minocycline and doxycycline, MVOR-1 and MVOR-2, the limitations involve a smaller percentage of participants who had darker skin, which may be because rosacea is less common in this demographic. In addition, participants were urged to limit their exposure to outside stimuli that could aggravate their rosacea symptoms, which might have helped to lower the number of flare-ups during the trial. Another limitation in this current research is the short study duration, which is only 16 weeks, which provides a short assessment of the efficacy and safety of minocycline hydrochloride (DFD-29). In addition, rosacea is a chronic condition that shows flushing and redness on the face for a long time. It can also cause enlargement of blood vessels and the development of pimples on the face. A longer study duration is recommended to provide accurate data on the effectiveness, safety, and treatment effects.

Glycylcycline Antibiotics

Historical Development and Classification

Tigecycline belongs to the tetracycline family of antibacterial agents, which were developed to treat multidrug-resistant (MDR) infections, including Gram-negative and Gram-positive bacteria. Tigecycline, also known as GAR-936 (Tygacil), is the first drug in the glycylcycline class of semisynthetic agents administered through the parenteral form [20]. Despite having structural similarities to minocycline, changes to the molecule lead to an increased range of activity and a reduced vulnerability to resistance development compared to other tetracycline antibiotics. Thus, the alterations in structure enable tigecycline to maintain activity against tetracycline-resistant organisms such as methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant Staphylococcus epidermidis (MRSE), vancomycin-resistant Enterococcus (VRE) species, and penicillin-resistant Streptococcus pneumoniae [21].
In 2005, it was approved by the Food and Drug Administration (FDA), while in 2010, the FDA warned that using tigecycline to treat sepsis and severe infections was significantly linked to a higher risk of death from all causes [15]. Other than that, tigecycline is widely used and approved as monotherapy to treat infections such as community-acquired bacterial pneumonia (CABP), complicated skin and skin structure infections (cSSSIs), except for diabetic foot infection, and complicated intra-abdominal infections (cIAIs) [22]. In addition, Kechagias et al. [23] reviewed evidence for a new indication of tigecycline, the treatment of severe *Clostridioides difficile* infection [23].

Mechanism of Action

Tigecycline is a bacteriostatic, broad-spectrum antibiotic that is a structural derivative of minocycline and a member of the glycylcycline class. By attaching itself to the 30S ribosomal subunit and preventing aminoacyl-tRNA from entering the ribosome's A-site during translation, tigecycline, like other antibiotics in the tetracycline family, prevents the synthesis of proteins by bacteria. In the end, this prevents protein synthesis and bacterial growth by blocking the addition of amino acids to the expanding peptide chain. However, due to its structural modifications, it is less susceptible to efflux pumps encoded by *tetA*,

tetB, or ribosomal protection proteins like *tetM* [24]. This allows tigecycline to retain activity against many MDR organisms that are resistant to conventional tetracyclines [25].

Pharmacokinetics and Pharmacodynamics

Tigecycline is administered intravenously (IV), bypassing gastrointestinal absorption, and therefore has 100% bioavailability; it is not available orally because of its poor gastrointestinal absorption. It is infused over 30–60 minutes every 12 hours [26]. Tigecycline has a systemic clearance from 0.2 to 0.3 L/h/kg and exhibits extensive tissue penetration, with a large volume of distribution (Vd 7–10 L/kg), allowing intracellular accumulation [27]. Its tissue distribution includes the lungs, liver, and gallbladder. Since the unbound portion of tigecycline dropped as the total concentration of tigecycline increased, the in vitro plasma protein binding of tigecycline at 0.1, 1, and 15 µg/mL was reported to be 71%, 89%, and 96%, respectively [28]. This demonstrated nonlinear plasma-protein-binding behavior. Tigecycline is eliminated mainly unchanged in the bile and has a long elimination half-life (approximately 36 hours); it is given twice daily.

According to data from many pharmacokinetic and pharmacodynamic studies, analyses, and clinical trials, the ratio of the area under the concentration-time curve to the minimal inhibitory concentration (AUC/MIC) for serum tigecycline concentrations is a predictor of therapeutic response [29]. It has been demonstrated that tigecycline is a bacteriostatic agent against Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, and Escherichia coli. There have been reports of both bacteriostatic and bactericidal action against Streptococcus pneumoniae [30].

Safety and Tolerability

While tigecycline offers a broader antimicrobial spectrum, its safety profile has been a point of concern. When a meta-analysis showed that patients on tigecycline had a higher risk of all-cause death than those receiving other antibiotics, especially in cases of severe infections such as hospital-acquired pneumonia or those needing surgery, the FDA issued a drug safety communication in 2010 and added a boxed warning in 2013 [26].

Adverse events such as nausea and vomiting are commonly reported, affecting up to 30% of patients in some studies, and may limit adherence in prolonged treatment courses [21]. Hepatic dysfunction, pancreatitis, and coagulation abnormalities have also been documented, especially with extended use [21]. Despite these issues, tigecycline remains a viable option in settings where resistance limits the use of other agents.

Since the drug is primarily excreted in the bile and feces, renal dose adjustments are not necessary, which is beneficial in patients with kidney dysfunction. However, the drug's metabolism in the liver warrants caution in hepatic dysfunction, where dose adjustments may be necessary [15].

Clinical Trials in cSSTIs

Tigecycline is effective against a wide range of pathogens such as Gram-negative, Gram-positive, and anaerobic bacteria, even multidrug-resistant strains, such as MRSA and ESBL-producing Enterobacteriaceae [31]. Observational data and randomized controlled studies show that tigecycline monotherapy is equally effective as combination therapies like vancomycin and aztreonam, with cure rates between 73% and 83% along with a similar safety profile [32,33]. Moreover, Bassetti et al. [33] demonstrated its effectiveness under real-world circumstances across Europe, particularly in critically ill patients. Ibrahim et al. [34] showed that a high dose tigecycline regimen can increase the survival of obese and critically ill patients by significantly reducing both the death rate and the duration of the ICU stay while not increasing the adverse effects.

Nevertheless, compared to other substitute medicines, tigecycline is associated with an increased incidence of gastrointestinal adverse events, such as nausea or vomiting, but lacked other significant adverse events in the study by Curcio [31]. Tigecycline does not

require dose adjustment in renal dysfunction and has minimal medication interactions, which means it may be useful for a variety of patients. However, a systematic review and meta-analysis by Yahav et al. [35] suggested a slight, statistically non-significant increase in mortality, including in infections such as cSSTI. In terms of microbiology, tigecycline covers the main cSSTI pathogens, MRSA, S. aureus, E. coli and Enterococcus spp. [5], though there might be less efficacy for Acinetobacter spp. if the MICs are too high [5]. To conclude, tigecycline is not the first-line alternative, but its extensive coverage and success with multidrug-resistant and critically ill patients make it an effective and viable substitute for cSSTIs.

Tetracyclines are limited mainly by widespread bacterial resistance, while glycylcyclines were developed to overcome this but have their own constraints, such as limited clinical data and formulation issues. Additionally, much of the current evidence is derived from observational studies, which may introduce selection bias and limit generalizability. Tigecycline also demonstrates limited efficacy against certain pathogens, such as Acinetobacter spp. with elevated MICs, and is frequently associated with gastrointestinal side effects that could affect treatment adherence. Finally, the lack of direct comparative trials against other agents like linezolid or doxycycline limits the ability to establish its relative clinical and economic value in routine practice.

Discussion

A recent network meta-analysis by Liu et al. [36], involving 38 trials, revealed that the combination of minocycline and rifampin had a significantly higher clinical cure rate for MRSA-induced cSSTIs than vancomycin, suggesting a promising alternative to traditional glycopeptides in resistant infections. The same analysis indicated that clinical success rate of vancomycin in treating MRSA-associated cSSTIs was inferior to that of linezolid and minocycline-based combinations, underscoring concerns about vancomycin overuse and the growing need for effective alternatives. Interestingly, while tigecycline is often considered a key agent in resistant infections, minocycline and rifampin combinations outperformed vancomycin in cSSTI treatment, suggesting that certain tetracycline-based regimens remain clinically valuable even in the era of glycylcyclines. Although linezolid had superior efficacy, it was associated with higher adverse reaction rates than teicoplanin, highlighting the need to balance efficacy with tolerability, especially when considering long-term treatment.

Other research highlights that tetracyclines have long been used for treating a broad range of bacterial infections; however, their clinical utility has diminished due to rising resistance. Glycylcyclines, a newer subclass derived from tetracyclines, were developed to overcome common resistance mechanisms, including efflux and ribosomal protection. Both classes act on the 30S ribosomal subunit, but structural modifications of tigecycline confer enhanced activity against multidrug-resistant pathogens.

Tetracyclines cover Gram-positive pathogens, including *Staphylococcus aureus* (including MRSA) and *Streptococcus pneumoniae* [18], and Gram-negative pathogens such as *Haemophilus influenzae*, *Neisseria gonorrhoeae*, some *Enterobacteriaceae* [18], as well as atypical organisms such as *Chlamydia spp.*, *Mycoplasma pneumoniae*, and *Rickettsia spp.* [18]. Notably, both doxycycline and minocycline retain substantial activity against community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), which has made them valuable in managing cSSTIs in outpatient settings [37]. In a study of 24 adult patients with CA-MRSA infections, 54% (13/24) received doxycycline, whereas 46% (11/24) received minocycline. Minocycline had a 73% success rate, whereas doxycycline had a 92% success rate [38].

Tigecycline also has significantly expanded the antimicrobial spectrum of tetracyclines. Tigecycline demonstrates a robust activity against a broad range of Gram-positive and Gram-negative bacteria, including multidrug-resistant strains that pose substantial challenges in clinical practice. It is particularly effective against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* [9]. These features make

tigecycline a valuable therapeutic option in complicated infections where empirical treatment often fails due to resistance. The key to tigecycline's efficacy lies in its structural modification, which enables it to avoid two major tetracycline resistance mechanisms: active efflux and ribosomal protection. By attaching a bulky glycylamido side chain at the D ring, tigecycline gains steric hindrance properties that reduce its susceptibility to efflux and enhance its binding to the ribosome, even in the presence of resistance proteins [14]. However, tigecycline's spectrum has some notable limitations. It lacks reliable activity against *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Providencia* species, which are clinically significant pathogens in hospital-acquired infections [15]. Additionally, its low plasma concentrations can hinder its efficacy in bloodstream infections, raising concerns regarding optimal indications for use.

In vitro studies show that glycylcyclines possess broader and more potent antibacterial activity than tetracyclines, particularly against MRSA, VRE, and ESBL-producing Enterobacteriaceae, with MICs often 16- to 100-fold lower [11]. Clinically, tigecycline has demonstrated noninferiority to standard comparators in cSSTIs, with cure rates typically above 80%. These findings support its utility in managing infections where traditional tetracyclines are less effective, particularly in cases involving resistant organisms [39].

Resistance to tetracyclines and glycylcyclines is becoming a serious problem, especially when treating complicated skin and soft tissue infections (cSSTIs). Several studies have reported that bacteria can fight these antibiotics by producing more efflux pumps (e.g., Tet(A), Tet(B)) and ribosomal protection proteins (e.g., Tet(M), Tet(O)) [7,8]. These resistance factors either push the drug out of the bacterial cell or change the ribosome so the drug cannot attach properly, making tetracyclines less effective. While glycylcyclines such as tigecycline were developed to avoid these problems by staying in the cell and still binding to the ribosome, newer reports show that some bacteria are now resistant to tigecycline as well. Notably, the production of tet(X) enzymes has been linked to the breakdown of tigecycline, especially in Enterobacteriaceae and Acinetobacter spp. [40]. This reduces the usefulness of tigecycline in treatment and raises concern about future options. The clinical impact is serious. Infections caused by multidrug-resistant (MDR) bacteria with these resistance methods often need last-resort antibiotics, which are more expensive and can cause more side effects.

Cross-resistance between tetracyclines and glycylcyclines remains a complex issue. Structurally, glycylcyclines are man-made versions of minocycline with a special change at the D-9 position that helps them bind better to the ribosome and avoid being pushed out by common Tet efflux pumps. However, plasmid-mediated tet(X) genes, which were first linked to resistance against tetracyclines, have now also been found to break down tigecycline, showing a risk for cross-resistance [41]. Clinically, this means that using older tetracyclines may lead bacteria to develop resistance that also weakens the effect of glycylcyclines. For example, a study by Feng et al. [42] found E. coli in farm animals with this gene, showing that these resistant bacteria can spread from animals to humans. This means that infections like cSSTIs could become harder to treat, even outside of hospitals. Thus, while glycylcyclines were once thought to be safe from common tetracycline resistance, new findings challenge that idea. The possibility of cross-resistance means that we need to be careful with how tetracyclines are used in both people and animals to protect the usefulness of glycylcyclines.

Based on the 2014 Infectious Diseases Society of America (IDSA) guidelines for skin and soft tissue infections (SSTIs), doxycycline and minocycline are recommended to be used as oral treatment options for purulent SSTIs, especially when involving methicillin-resistant *Staphylococcus aureus* (MRSA) [43]. Their efficacy, safety profiles, and high oral bioavailability make doxycycline and minocycline suitable for outpatients with mild to moderate infections. The dosing regimen of minocycline and doxycycline that was suggested for adult patients with SSTIs or acute bacterial skin and skin structure infections (ABSSSIs) is shown in Table 1. In addition, these agents do not require dose adjustment in renal or hepatic impairment, or for weight, sex, race, or age. They also do not significantly interact with the drugs that are metabolized by cytochrome P450 enzymes, which can minimize the potential for drug-drug interactions [44].

Table 1. Dosing regimens of minocycline and doxycycline for adult patients

Antibiotic	Administration route: loading dose	Administration route: maintenance dose
Minocycline	200 mg orally on day 1	100 mg orally every 12 h or 50 mg orally 4 times a day
Doxycycline	200 mg orally on day 1	100 mg orally every 12 h

Furthermore, tigecycline is also indicated for complicated skin and skin structure infections (cSSSIs), complicated intra-abdominal infections (cIAIs), and community-acquired bacterial pneumonia (CABP). For cSSSIs, tigecycline is commonly prescribed for severe infections involving *methicillin-resistant Staphylococcus aureus* (MRSA) and polymicrobial infections. The standard dosing regimen is a 100 mg loading dose followed by 50 mg every 12 hours [33]. It is reported that tigecycline induced nausea and vomiting more often in patients with cSSSIs than vancomycin–aztreonam treatment did [45]. However, among patients with cIAI, the incidence of nausea and vomiting was the same for those treated with imipenem/cilastatin as it was for those treated with tigecycline (21%/15% for the imipenem/cilastatin group and 25%/20% for the tigecycline group, respectively). In individuals treated with tigecycline for community-acquired bacterial pneumonia, GI symptoms were more common than in those treated with levofloxacin. In 2010, the FDA also reported an increased risk of mortality in severe infections and sepsis [46].

The adverse effect profiles of tetracyclines and glycylcyclines are important determinants of clinical utility. As previously stated, tigecycline is associated with gastrointestinal side effects (nausea and vomiting in 30–40% of patients) and increased mortality in certain infections, leading to an FDA black box warning [21,26]. In contrast, doxycycline, a widely used tetracycline, is generally well-tolerated, with photosensitivity reactions and esophagitis being among the most reported adverse effects. The photosensitivity risk is dose-dependent and more common in fair-skinned individuals but is usually reversible and preventable with sun avoidance. From a risk-benefit perspective, doxycycline offers a favorable safety profile for long-term use (e.g., in acne or malaria prophylaxis), whereas tigecycline use is often restricted to severe, resistant infections due to its toxicity profile.

Tolerability directly influences patient adherence and ultimately, treatment outcomes. The gastrointestinal adverse events linked to tigecycline frequently lead to early discontinuation, which can compromise the treatment of serious infections. Its intravenous-only administration and broad tissue distribution with low serum concentrations further complicate therapy in bloodstream infections. On the other hand, doxycycline's oral bioavailability, convenient dosing, and relatively benign side effect profile enhance compliance, particularly in outpatient or resource-limited settings. Patient-centered factors such as ease of administration and fewer side effects contribute to better adherence, reduced risk of resistance development, and improved clinical outcomes.

These studies suggest glycylcyclines like tigecycline are newer, injectable, and more effective against resistant bacteria than older, often oral tetracyclines, but no information on drug pricing differences is provided [11,47]. The accessibility of tetracyclines versus glycylcyclines is a crucial factor influencing antibiotic selection, especially in resource-limited settings. Tetracyclines, such as doxycycline and minocycline, are widely available in oral formulations and have a long-established safety profile, making them convenient and cost-effective options for outpatient management of cSSTIs. In contrast, glycylcyclines like tigecycline are restricted to hospital use due to their intravenous-only formulation, which not only limits their accessibility but also increases treatment costs and logistical complexity [48]. Although glycylcyclines demonstrate superior activity against multidrug-resistant organisms, their limited availability and route of administration make them less practical for routine use, especially outside tertiary care centers. These factors collectively suggest that while glycylcyclines play a valuable role in severe or resistant infections, tetracyclines remain a more accessible option for broader clinical application. The key differences between the two classes are summarized in Table 2.

Table 2. Summary comparison of tetracyclines and glycylcyclines in the management of cSSTIs

	Tetracyclines (doxycycline and minocycline)	Glycylcyclines (tigecycline)	Remarks
Mechanism of Action	Inhibits 30S ribosomal subunit	Same, with enhanced binding to evade resistance	Tigecycline is a minocycline derivative with broader activity
Spectrum of Activity	Broad but limited by resistance	Broad, including MDR pathogens, MRSA, VRE and ESBL producers	Glycylcyclines more effective against resistant strains
Efficacy in cSSTIs	Moderate but limited in severe or resistant cases	Effective especially in critically ill patients	Tigecycline is non-inferior to vancomycin + aztreonam in trials
Administration	Oral and IV	IV only	Tetracyclines are more accessible for outpatients
Safety Profile	Generally well tolerated	Higher rate of GI side effects	Tigecycline tolerability can affect adherence
Adverse Events	Low to moderate photosensitivity	Moderate, mainly GI	Tigecycline may cause hepatic dysfunction and pancreatitis
Mortality Risk	Low	Slightly higher in non-cSSTI infections	Meta-analyses show higher mortality in some tigecycline-treated infections
Pharmacokinetics	Good oral bioavailability	Poor oral bioavailability, long half-life	Tigecycline does not need dose adjustment in renal failure
Cost	Low	High	Tigecycline is significantly more expensive
Guideline Recommendation in cSSTIs [49]	First-line for mild-moderate infections	Reserved for MDR or severe infections	Guidelines do not recommend tigecycline for mild cases

Conclusion and Future Perspectives

In conclusion, because of their broad-spectrum action, high oral bioavailability, and safety, tetracycline-class antibiotics, in particular doxycycline and minocycline, remain viable first-line treatments for mild to moderate cSSTIs, particularly those driven by community-acquired MRSA. In contrast, tigecycline offers broader coverage, including multidrug-resistant pathogens, making it suitable for severe or hospital-acquired infections, though its use is limited by safety concerns and IV-only administration.

This comparison highlights the importance of personalized antibiotic selection guided by infection severity, resistance patterns, and patient factors. Future research should prioritize safer oral broad-spectrum alternatives like oral glycylcyclines and support head-to-head trials comparing tigecycline with newer agents. Optimizing rapid diagnostics and antimicrobial stewardship will be crucial in preserving treatment efficacy and reducing resistance.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors received no any financial support for this publication.

References

1. Zervos MJ, Freeman K, Vo L, Haque N, Pokharna H, Raut M, et al. Epidemiology and outcomes of complicated skin and soft tissue infections in hospitalized patients. J Clin Microbiol. 2012;50(2):238-45. https://doi.org/10.1128/JCM.05817-11
2. Merlino JI, Malangoni MA. Complicated skin and soft-tissue infections: diagnostic approach and empiric treatment options. Cleve Clin J Med. 2007;74 Suppl 4:S21-8.
3. Leong HN, Kurup A, Tan MY, Kwa AL, Liau KH, Wilcox MH. Management of complicated skin and soft tissue infections with a special focus on the role of newer antibiotics. Infect Drug Resist. 2018;11:1959-74. https://doi.org/10.2147/IDR.S172366
4. Harch SA, MacMorran E, Tong SY, Holt DC, Wilson J, Athan E, et al. High burden of complicated skin and soft tissue infections in the Indigenous population of Central Australia due to dominant Panton Valentine leucocidin clones ST93-MRSA and CC121-MSSA. BMC Infect Dis. 2017;17. https://doi.org/10.1186/s12879-017-2460-3
5. Sacchidanand S, Penn RL, Embil JM, Campos ME, Curcio D, Ellis-Grosse E, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: results from a phase 3, randomized, double-blind trial. Int J Infect Dis. 2005;9(5):251-61. https://doi.org/10.1016/j.ijid.2005.05.003
6. Gibbons JA, Smith HL, et al. Antimicrobial stewardship in the treatment of skin and soft tissue infections. Am J Infect Control. 2017;45(11):1203-7. https://doi.org/10.1016/j.ajic.2017.05.013
7. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev. 2001;65(2):232-60. https://doi.org/10.1128/MMBR.65.2.232-260.2001
8. Grossman TH. Tetracycline antibiotics and resistance. Cold Spring Harb Perspect Med. 2016;6(4):a025387. https://doi.org/10.1101/cshperspect.a025387
9. Curcio D. Off-label use of antibiotics in hospitalized patients: focus on tigecycline. J Antimicrob Chemother. 2009;64(6):1344-6. https://doi.org/10.1093/jac/dkp342
10. Nguyen F, Starosta AL, Arenz S, Sohmen D, Dönhöfer A, Wilson DN. Tetracycline antibiotics and resistance mechanisms. Biol Chem. 2014;395(5):559-75.
11. Rusu A, Buta EL. The development of third-generation tetracycline antibiotics and new perspectives. Pharmaceutics. 2021;13(12):2085. https://doi.org/10.3390/pharmaceutics13122085
12. Chukwudi CU. rRNA binding sites and the molecular mechanism of action of the tetracyclines. Antimicrob Agents Chemother. 2016;60(8):4433-41.
13. Streit JM, Jones RN, Sader HS, Fritsche TR. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY Antimicrobial Surveillance Program (North America, 2001). Int J Antimicrob Agents. 2004;24(2):111-8. https://doi.org/10.1016/j.ijantimicag.2003.12.019
14. Chopra I. Glycylcyclines: third-generation tetracycline antibiotics. Curr Opin Pharmacol. 2001;1(5):464-9.
15. Stein GE, Babinchak T. Tigecycline: an update. Diagn Microbiol Infect Dis. 2013;75(4):331-6. https://doi.org/10.1016/j.diagmicrobio.2012.12.004
16. Gallagher JC. Omadacycline: a modernized tetracycline. Clin Infect Dis. 2019;69(Suppl 1):S1-5.
17. Qiao Y, Chen Y, Wang Q, Liu J, Guo X, Gu Q, et al. Safety profiles of doxycycline, minocycline, and tigecycline in pediatric patients: a real-world pharmacovigilance analysis based on the FAERS database. Front Pharmacol. 2024;15:1413944. https://doi.org/10.3389/fphar.2024.1413944
18. Shutter MC, Akhondi H. Tetracycline. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [updated 2023 Jun 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549905/

19. Bhatia N, Del Rosso J, Stein Gold L, Lain E, Draelos ZD, Sidgiddi S. Efficacy, safety, and tolerability of oral DFD-29, a low-dose formulation of minocycline, in rosacea: two phase 3 randomized clinical trials. JAMA Dermatol. 2025;161(5):499-507. https://doi.org/10.1001/jamadermatol.2024.6542
20. Guay DR. Oritavancin and tigecycline: investigational antimicrobials for multidrug-resistant bacteria. Pharmacotherapy. 2004;24(1):58-68. https://doi.org/10.1592/phco.24.1.58.34808
21. Greer ND. Tigecycline (Tygacil): the first in the glycylcycline class of antibiotics. Proc (Bayl Univ Med Cent). 2006;19(2):155-61. https://doi.org/10.1080/08998280.2006.11928154
22. Lauf L, Ozsvár Z, Mitha I, et al. Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. Diagn Microbiol Infect Dis. 2014;78(4):469-80.
23. Kechagias KS, Chorepsima S, Triarides NA, Falagas ME. Tigecycline for the treatment of patients with Clostridium difficile infection: an update of the clinical evidence. Eur J Clin Microbiol Infect Dis. 2020;39(6):1053-8. https://doi.org/10.1007/s10096-019-03756-z
24. Li W, Atkinson GC, Thakor NS, Allas U, Lu CC, Chan KY, et al. Mechanism of tetracycline resistance by ribosomal protection protein Tet(O). Nat Commun. 2013;4:1477. https://doi.org/10.1038/ncomms2470
25. Korczak L, Majewski P, Iwaniuk D, Sacha P, Matulewicz M, Wieczorek P, et al. Molecular mechanisms of tigecycline-resistance among Enterobacterales. Front Cell Infect Microbiol. 2024;14:1289396. https://doi.org/10.3389/fcimb.2024.1289396
26. US Food and Drug Administration. FDA drug safety communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new boxed warning [Internet]. Silver Spring (MD): FDA; 2013 Sep 27 [cited 2025 May 13]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-increased-risk-death-iv-antibacterial-tygacil-tigecycline
27. Finch RG, Greenwood D, Norrby SR, Whitley RJ. Antibiotic and chemotherapy. 9th ed. Edinburgh: Saunders Elsevier; 2010.
28. Mukker JK, Singh RP, Derendorf H. Determination of atypical nonlinear plasma-protein-binding behavior of tigecycline using an in vitro microdialysis technique. J Pharm Sci. 2014;103(3):1013-9. https://doi.org/10.1002/jps.23872
29. Passarell JA, Meagher AK, Liolios K, Cirincione BB, Van Wart SA, Babinchak T, et al. Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. Antimicrob Agents Chemother. 2008;52(1):204-10. https://doi.org/10.1128/AAC.00813-07
30. Nathwani D. Tigecycline: clinical evidence and formulary positioning. Int J Antimicrob Agents. 2005;25(3):185-92. https://doi.org/10.1016/j.ijantimicag.2004.11.006
31. Curcio D. Skin and soft tissue infections due to methicillin-resistant Staphylococcus aureus: role of tigecycline. Clin Infect Dis. 2011;52(12):1468-9. https://doi.org/10.1093/cid/cir192
32. Hosgor-Limoncu M. Is tigecycline drug of choice for cIAI and cSSTI? Int J Clin Pract. 2013;67(6):492-3. https://doi.org/10.1111/ijcp.12169
33. Bassetti M, Eckmann C, Bodmann KF, Dupont H, Heizmann WR, Montravers P, et al. Prescription behaviours for tigecycline in real-life clinical practice from five European observational studies. J Antimicrob Chemother. 2013;68 Suppl 2:ii5-14. https://doi.org/10.1093/jac/dkt140
34. Ibrahim MM, Abuelmatty AM, Mohamed GH, Nasr MA, Hussein AK, Ebaed MED, et al. Best tigecycline dosing for treatment of infections caused by multidrug-resistant pathogens in critically ill patients with different body weights. Drug Des Devel Ther. 2018;12:4171-9. https://doi.org/10.2147/DDDT.S181834
35. Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother. 2011;66(9):1963-71. https://doi.org/10.1093/jac/dkr242

36. Liu Q, He D, Wang L, Wu Y, Liu X, Yang Y, et al. Efficacy and safety of antibiotics in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections: a systematic review and network meta-analysis. Antibiotics (Basel). 2024;13(9):866. https://doi.org/10.3390/antibiotics13090866
37. NeVille-Swensen M, Clayton M. Outpatient management of community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infection. J Pediatr Health Care. 2011;25(5):308-15. https://doi.org/10.1016/j.pedhc.2010.05.005
38. Bhambri S, Kim G. Use of oral doxycycline for community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) infections. J Clin Aesthet Dermatol. 2009;2(4):45-50.
39. Wallace RJ Jr, Brown-Elliott BA, Crist CJ, Mann L, Wilson RW. Comparison of the in vitro activity of the glycylcycline tigecycline (formerly GAR-936) with those of tetracycline, minocycline, and doxycycline against isolates of nontuberculous mycobacteria. Antimicrob Agents Chemother. 2002;46(10):3164-7. https://doi.org/10.1128/AAC.46.10.3164-3167.2002
40. Sun J, Chen C, Cui CY, Zhang Y, Liu X, Cui ZH, et al. Plasmid-encoded tet(X) genes that confer high-level tigecycline resistance in Escherichia coli. Nat Microbiol. 2019;4(9):1457-64. https://doi.org/10.1038/s41564-019-0496-4
41. He T, Wang R, Liu D, Walsh TR, Zhang R, Lv Y, et al. Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans. Nat Microbiol. 2019;4(9):1450-6. https://doi.org/10.1038/s41564-019-0445-2
42. Feng J, Su M, Li K, Ma J, Li R, Bai L, et al. Extensive spread of tet(X4) in multidrug-resistant Escherichia coli of animal origin in western China. Vet Microbiol. 2022;269:109420. https://doi.org/10.1016/j.vetmic.2022.109420
43. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10-52. https://doi.org/10.1093/cid/ciu296
44. Bidell MR, Lodise TP. Use of oral tetracyclines in the treatment of adult outpatients with skin and skin structure infections: focus on doxycycline, minocycline, and omadacycline. Pharmacotherapy. 2021;41(11):915-31. https://doi.org/10.1002/phar.2625
45. Chuang YC, Chang CM, Aradhya S, Nagari B, Pai V, Dartois N, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. J Microbiol Immunol Infect. 2011;44(2):116-24. https://doi.org/10.1016/j.jmii.2010.04.002
46. Yaghoubi S, Zekiy AO, Krutova M, et al. Tigecycline antibacterial activity, clinical effectiveness, and mechanisms and epidemiology of resistance: narrative review. Eur J Clin Microbiol Infect Dis. 2022;41(7):1003-22. https://doi.org/10.1007/s10096-020-04121-1

47. Chopra I. New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors. Drug Resist Updat. 2002;5(3-4):119-25. https://doi.org/10.1016/S1368-7646(02)00051-1
48. Burgos RM, Rodvold KA. Omadacycline: a novel aminomethylcycline. Infect Drug Resist. 2019;12:1895-915. https://doi.org/10.2147/IDR.S171352
49. Ministry of Health Malaysia. National antimicrobial guideline (NAG). 4th ed. [Internet]. Putrajaya: Ministry of Health Malaysia; 2024 [cited 2025 May 13]. Available from: https://sites.google.com/moh.gov.my/nag/home

Publisher's Note: *The views, data, claims, and opinions expressed in this article are solely those of the authors and do not necessarily reflect the official policy or position or endorsement of the publisher, editors, reviewers, or their affiliated organizations. No legal liability is assumed by the publisher, editors, or reviewers for the accuracy or practical use of the data disclosed. The publication of this material does not make the publisher, editorial team, or reviewers responsible for any damages incurred due to the information described in this article.*