Emergence of third generation tetracyclines: New magic bullets to tackle antibiotic resistance in the post-antibiotic era

ABSTRACT

Tetracyclines are broad-spectrum antibiotics effective against a wide variety of microorganisms including bacteria, both Gram-positive and Gram-negative, mycoplasmas, rickettsiae, chlamydiae, and protozoan parasites. Owing to their broad spectrum antimicrobial activities and inexpensiveness, tetracyclines have been used extensively in both humans and animal infections and in animal feed as growth promoters. Owing to this, the global prevalence of antibiotic resistance, particularly of tetracyclines, for Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumonia* and Gram-negative extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* species is high. Indeed, the acquisition of tetracycline-specific resistance genes, mutations within the ribosomal binding site, and/or chromosomal mutations lead to both class-specific and intrinsic antimicrobial resistance (AMR) mechanisms. As drug resistance increases globally, rendering diseases difficult to manage and eventually to mortality, and antibiotics are becoming progressively less effective. Therefore, the discovery and development of novel antibiotics with appropriate indications is of the utmost importance. Among all antibiotics, the tetracyclines have acquired much attention due to optimization of their chemical structures that paved way to develop and introduce modern tetracyclines, referred to as third generation, namely tigecycline in the recent past, followed by omadacycline, eravacycline, and sarecycline very recently. Intriguingly, these novel tetracyclines are unique in two ways, first, these are highly effective against pathogens that acquired tetracycline-class resistance and second, these agents exhibit either narrow or broad spectrum of *in vitro* activity against Gram-positive, Gram-negative, anaerobic, and atypical pathogens, including many drug-resistant strains lead to approval for limited use and unique indications. These beneficial effects represent a new era in the rational use of newer tetracyclines, the new magic bullets to tackle AMR in the post-antibiotic era. The present review focuses on third generation tetracyclines emphasizing on their safety, efficacy, and therapeutic choices in various clinical conditions of in-patient and out-patient settings.

Keywords: Antimicrobial resistance, Eravacycline, Multidrug resistance, Omadacycline, Sarecycline, Tigecycline, Tetracyclines, Third generation

1. INTRODUCTION

Pre-antibiotic era is the period before the discovery and potential use of first antibiotic wherein the understanding and knowledge about microbes and infectious diseases were inadequate. During this period, epidemics, morbidity, and mortality due to infectious diseases were common due to lack of successful approaches for treatment and prevention of spread of contagious diseases [1,2]. Since Paul Ehrlich's discovery of salvarsan in 1909 for the treatment of syphilis has led to the basis of the concept of chemotherapy. This chemical, also known as compound 606 or arsphenamine, is widely termed as the first

magic bullet [2-4]. “Several chemicals with disinfectant and bacteriostatic potential have been developed and their uses in antimicrobial chemotherapy are the milestone in the history of modern medicine and these agents are life-saving weapons against numerous infectious diseases. An antibiotic was a substance produced by one microorganism that selectively inhibits the growth or kills another microorganism. Antibiotics were initially viewed as ‘Wonder Drugs’ primarily because these were introduced at a time when only surgical drainage or spontaneous cures were available to treat serious bacterial infections” [2,4-6]. The mid-20th century was named the “antibiotic era”, and infectious diseases were believed to be eradicated by the end of the last century [1,6]. Contrary to the original belief, over a period of 50 years since the first antibiotic approved for human use, many antibiotics lost efficacy due to safety concerns and development and spread of antimicrobial resistance (AMR). Many microorganisms are continuously evolving and developing resistance and such resistant pathogens, ‘superbugs’, are rendering previously active antibiotics into ineffective [1,5,6]. Much of the medical and pharmaceutical research and development has been focused on life style disorders and cancer and many antibiotics were not approved since 1980s entering the ‘post-antibiotic era’ wherein resources for discovery and development active and effective antibiotics are limited.

1.1 Irrational use of antibiotics

It is highly essential to use antibiotics prophylactically in hospitalized patients for various surgeries, therapeutically in primary care settings for various community acquired infections (CAIs), to prevent and treat infections in various invasive procedures and hospital acquitted infections (HAIs) adhere to international, national and hospital antibiotic use policies [7-10]. “Moreover, antibiotic use is compulsory in certain unavoidable clinical conditions, such as sepsis and in immunocompromised patients who are at risk of developing mixed infections” [9-12]. “Inarguably, when there are no clinical practice guidelines, there is need and necessary to use of antibiotics for prophylactic as well as therapeutic purposes in the recent unprecedented pandemic time due to coronavirus disease (COVID-19) and in multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2, the virus that causes COVID-19” [11,12]. However, inappropriate and irrational use, such as incorrect use, misuse, overuse, and often real abuse of antibiotics lead to the development of tolerance or antibiotic resistance from the time it is first employed [2,13]. Indeed, antibiotic consumption most prevalent in many developing and developed countries. It is reported that India is among the highest use in the world and antibiotics sales continue to peak rapidly despite the prevalence of infectious diseases remained stagnant [10,11,14]. It is a well known fact that bacteria survive antibiotics challenges by selection pressure, undergo mutations, evolve as resistant, and regrow lading to emergence and spread of new infectious diseases are one of the greatest life threats to human health. Consequently, the use of antibiotics is compromised and several microorganisms, including bacteria are developing and spreading antibiotic resistance [2,14-16]. Therefore, AMR is increasing worldwide due to increased prescription, dispensing, over the counter sales, and consumption of antibiotics and is now considered as a threat to global health and sustainable economic development.

1.2 Antimicrobial resistance

“AMR occurs when microbes, such as bacteria, viruses, fungi, and parasites undergo mutations and develop resistance that make several previously effective medications into ineffective and render such infections untreatable. The term antibiotic resistance is a subset of AMR, as it applies to bacteria that become resistant to antibiotics. Resistant microbes are more difficult to treat, it requires higher doses, alternative medications, and multidrug treatment which may prove more toxic and may also be more expensive. In 2019 alone, an estimated 4·95 million deaths associated with bacterial AMR that also implies the economic

burden of the country" [16-18]. "Among the antibiotic-resistant bacteria, 'ESKAPE' pathogens, including, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and, *Enterobacter* species, cause the majority of hospital infections with a higher rate of mortality" [19]. "In addition, other pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE), effectively escape the effects of many antibacterial drugs which may lead to a longer hospital stay and decreasing workforce productivity" [20]. Moreover, most of the microbes exposed to one class of antimicrobials for longer period develop AMR wherein cross-resistance becomingly troublesome. Microbes resistant to multiple antimicrobials (at least three different classes of antimicrobials) are called multidrug-resistant (MDR). Those bacteria that are considered extensively drug-resistant (XDR) or totally drug-resistant (TDR) are sometimes called 'superbugs' [8,9,21]. "There is a high risk of entering into a "post-antibiotic era", a period in which bacteria have become resistant to existing antibiotics and the antibiotics no longer work" [13,22].

1.3 WHO Global Action Plan to tackle antimicrobial resistance

"In order to tackle AMR, the World Health Organization (WHO) has developed Global Action Plan in 2015 keeping view of implementation in various nations across the world" [23]. "This plan is based on 5 objectives, includes first, to improve awareness and understanding of AMR, second, to strengthen knowledge and generate large amount of data, third, to reduce the incidence of infections through effective hygiene measures and good hygiene practice, fourth, to optimize the use of antimicrobial drugs in human and animal health by surveillance and stewardship programs, and fifth, to increase investment in new drugs, diagnostic tools, vaccines, and other interventions for discovery and development of new treatment modalities. In 2016, WHO listed the world's leading antibiotic-resistant bacteria and priority pathogens, for which there is an utmost need for new antibacterial agents for effective treatments against superbugs, MDR and XDR pathogens that are resistant to traditional antibiotics" [11,13,22,23]. "Since 2017, U.S. Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved several new antibiotics with predominant activity against Gram-negative bacteria, include plazomicin, eravacycline, cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam (combination of beta-lactam with beta-lactamase inhibitors), imipenem-cilastatin/relebactam, and temocillin, a beta-lactam antibiotic effective against Gram-negative bacteria" [1,6,24].

2. TETRACYCLINE ANTIBIOTICS

Tetracyclines have been one of the first antibiotics used to treat infections, they possess many properties considered ideal for antibiotic drugs, including a broad spectrum of activity against Gram-positive and Gram-negative pathogens, proven clinical safety, acceptable tolerability, low adverse effect profile, and availability of intravenous and oral formulations for most members of the class [25,26]. Tetracyclines are divided into three generations based on their spectrum of activity, and pharmacological properties such as half-life and binding to plasma protein (Table 1) [17,27].

2.1 Development of tetracycline antibiotics

Serendipitous discovery and extended use of earlier penicillins and streptomycin in the early 1940s has broadened the scope of identifying and developing newer antibiotics. With the advances of microbiology, biochemistry, and fermentation technology, several pharmaceutical scientists and academic researchers have focused on identifying several lesser known microbes from soil samples collected across the globe, started isolating and discovering new antibiotics produced by such microorganisms. Owing to these efforts,

aureomycin, the first tetracycline was discovered in 1945 lead to series of tetracyclines development during the last century. Chlortetracycline is the synthetic form of aureomycin, natural tetracycline antibiotic, which was discovered at Lederle Laboratories under the supervision of scientist Yellapragada Subbarow and Benjamin Minge Duggar [1,3,17]. Aureomycin was extracted from *Streptomyces aureofaciens* was approved by the FDA in 1948 for medical use in humans. In the following years, terramycin, the second tetracycline, obtained from *Streptomyces rimosus* and its synthetic form oxytetracycline were discovered and approved for human use in 1950 [3,17,25]. Molecular optimizations and structural changes in chlortetracycline lead to the discovery of tetracycline in 1953. Owing to favorable pharmacokinetic profile and enhanced water solubility, tetracycline is considered as widely successful first generation tetracyclines. The second generation tetracyclines include methacycline, doxycycline, and minocycline were approved due to reduced risk of toxicity, better pharmacokinetic profiles, extended antimicrobial spectrum were approved in the early 1970s (Table 1 and Table 2) [2,27,28].

Table 1. Classification of tetracycline based on generations (13, 27, 28)

Generation	Obtaining method	Agents
First	Biosynthesis	Chlortetracycline, oxytetracycline, tetracycline, demeclocycline
Second	Semi-synthesis	Doxycycline, minocycline, lymecycline, meclocycline, methacycline, rolitetracycline
Third	Semi-synthesis	Tigecycline, omadacycline, sarecycline
	Total synthesis	Eravacycline

2.2 The discovery of third generation tetracyclines

With the emergence of antibiotic resistance in recent times, there is an urgent need for microbial genomic research as well as discovery and development of new antibiotics. Indeed, antibiotic-resistant *Enterobacteriaceae* and *Acinetobacter baumannii* are problematic pathogens, with only few treatment options for multidrug-resistant (MDR) *A. baumannii* and few oral options for extended spectrum β-lactamase (ESBL)-producing and MDR-*Enterobacteriaceae* [19,20]. In particular, owing to extensive use of tetracyclines, these pathogens are becoming resistant to many older generation tetracyclines and further hampered by undesired classical side effects. These factors lead to the renewed interest in the development of new tetracyclines. Notably, molecular optimizations and structural changes with the addition of glycyl moiety led to the discovery of a novel class of aminotetracyclines, known as glycylcycline [24,27]. Novel tetracyclines include derivatives with more or less similar chemical structures include tigecycline and recently approved omadacycline, eravacycline, and sarecycline that are categorized as the third generation tetracyclines. These newer agents had high potency and increased efficacy with unique antimicrobial spectrum, even against bacteria resistant to older tetracyclines [24,28]. The antibacterial spectrum, pharmacokinetics, dosage regimen, safety, and indications of newer tetracyclines are summarized in Table 2.

2.3 Mechanism of action of tetracyclines

Tetracyclines inhibit protein synthesis by inhibiting the association of aminoacyl-tRNA with the bacterial ribosome and binding with high affinity to a 30s ribosomal subunit during translation. Then the penetration of aminoacyl-tRNA into the acceptor site (A) on the bacterial ribosome is blocked, which leads to the cessation in the incorporation of amino acid

residues in the process of elongation of the polypeptide chain (Figure 1). Thus, the bacteriostatic activity of antibiotics is achieved by stopping protein synthesis [28,29].

There are a few older tetracycline drugs that are mostly used to treat specific microbes resistant to antibiotics. Similar to the classical tetracyclines, tigecycline, the first of the new generation tetracyclines, exhibits broad-spectrum antibacterial activity. Moreover, the three newer agents approved eravacycline, sarecycline, and omadacycline showed extended and unique antibacterial activity retaining the broad-spectrum activity of previous tetracyclines [17,27,28]. The antibacterial spectrum of newer agents comprises several resistant bacteria, including those resistant to older tetracyclines. Sarecycline is considered as a narrow-spectrum tetracycline due to highly selective antibacterial activity against *Cutinebacterium acnes* [30]. Exploratory research identified non-antibiotic properties of several tetracyclines, particularly anti-inflammatory and neuroprotective effects of minocycline and sarecycline, possibly attributed partly to their inhibition of microglial activation and in part by modulating oxidative stress [31-33]. However, the exact mechanisms are not well elucidated and understood. Recently, the novel tetracyclines-exploiting strategy for neuroprotection based on their antiamyloidogenic, anti-inflammatory, antiapoptotic and antioxidant activities has emerged for the treatment of Alzheimer's and Parkinson's diseases. Nevertheless, challenges of repurposing tetracyclines further hampered by safety issues, such as antibiotic-induced alteration of microbiota in gut and consequent dysbiosis and development and spread of AMR due to long-term antibiotic use.

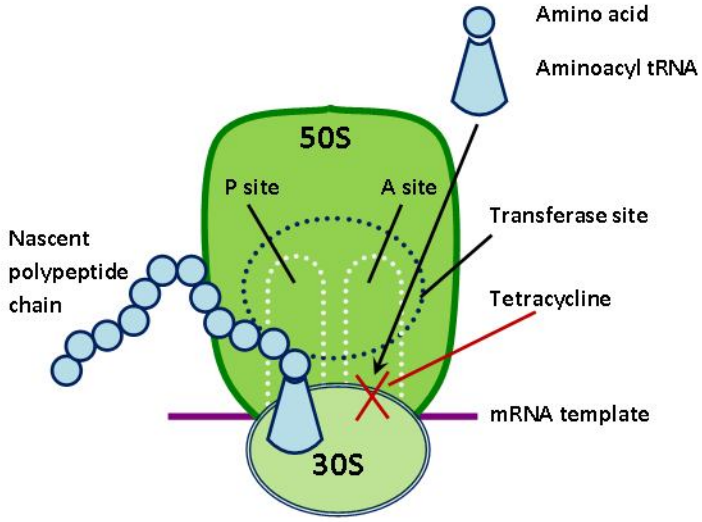

Figure 1. Mechanism of action of tetracyclines
(Figure created using Microsoft PowerPoint)

The tetracyclines reversibly bind to the 30S subunit of the bacterial ribosome thereby prevents binding of acyl-transfer RNA (tRNA) to the ribosome. Thus, tetracyclines by inhibiting protein synthesis that stops growth and replication of the bacterial organism leading to bacteriostatic effect.

3. THIRD GENERATION TETRACYCLINE ANTIBIOTICS

3.1 Tigecycline

Tigecycline is a unique glycylcycline antibiotic approved by the US FDA in 2005. It has susceptibility to clinically important MDR nosocomial and community-acquired bacterial pathogens and also against a broad range of Gram-negative and Gram-positive bacteria species. It inhibits the translation elongation step by binding to the ribosome 30S subunit (five times stronger than other tetracyclines) and also prevents aminoacylated tRNA accumulation in the ribosomal A site even in the presence of ribosomal protecting efflux pumps [28,34]. MDR Gram-negative pathogens, such as *A. baumannii* and ESBL producing *K. pneumoniae* and *E. coli* are highly susceptible to tigecycline. It is also active against VRE, MRSA, penicillin-resistant *Streptococcus pneumoniae*, anaerobes, and 'atypical' bacteria. However, it is not active against *P. aeruginosa* and *Proteus*, *Morganella*, and *Providencia* species [35]. Moreover, parenteral tigecycline was poorly tolerated and ineffective when tried as an agent in multidrug regimens for salvage therapy of *Mycobacterium abscessus* infection and alternative option of oral formulation is not available. Therefore, omadacycline and eravacycline may represent a new therapeutic option for treating *M. abscessus* complex infections [36,37]. Recent reports show that tigecycline remained active against Gram-positive and Gram-negative bacteria, at the same time resistant strains such as fluoroquinolone and broad spectrum β-lactam-resistant *Enterobacteriaceae*, vancomycin-resistant *E. faecium*, has increased during the same period [34,35]. Evidence exist that tigecycline is highly effective for the treatment of severe *Clostridioides difficile* infection in whom previous generation tetracyclines are ineffective. In addition, *Coxiella* spp., *Rickettsia* spp*.,* and MDR *Neisseria gonorrhea* strains showed *in vitro* susceptibility to tigecycline, indicating its possible use in the treatment of such infections [38].

Tigecycline is indicated for the treatment of complicated skin and skin structure infections (SSSIs) caused by *E. coli*, *E. faecalis* (vancomycin-susceptible isolates), *Staph. aureus* (MSSA and MRSA isolates), *S. agalactiae*, *S. anginosus* group. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *S. pyogenes*, *E. cloacae*, *K. pneumoniae*, and *B. fragilis*. It is also indicated for the treatment of complicated intra-abdominal infections (cIAIs) caused by *Citrobacter freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *E. faecalis* (vancomycin-susceptible isolates), *Staph. aureus* (MSSA and MRSA isolates), *S. anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *Cl. perfringens*, and *Peptostreptococcus micros*. Further, it is also approved for the treatment of community-acquired bacterial pneumonia (CABP) caused by *S. pneumoniae* (penicillin susceptible isolates), including cases with concurrent bacteremia, *H. influenzae* (beta-lactamase negative isolates), and *L. pneumophila* [37,38]. It is administered as intravenous infusion for a duration of about 30–60 min every 12 h. The recommended initial dose of tigecycline is 100 mg followed by 50 mg every 12 h and duration of treatment with tigecycline for cSSTIs or cIAIs and CAP is 5–14 and 7–14 days, respectively (Table 2) [39,40]. As the tetracyclines tigecycline also exhibits the same adverse events such as gastrointestinal symptoms commonly nausea, vomiting, anorexia and other rare events including injection site irritation, pain and swelling [41,42]. It is to be noted that tigecycline has no approved indication for treatment of diabetic foot infection or for hospital-acquired or ventilator-associated pneumonia, in which high rate of mortality is reported [39]. The US FDA has already warned that there is an increased risk of death resulted from complications of infection, worsening infections, or other underlying medical conditions when intravenous tigecycline is used for approved and non-approved uses. Presently, tigecycline is a reserve antibiotic for use in situations when alternative antibiotic therapies are not appropriate [39,41,43]. Importantly, advice and concordance between health care professionals, patients, and their caregivers are highly essential for using tigecycline in such situations.

3.2 Omadacycline

Omadacycline, a novel aminomethyl tetracycline antibiotic, has been developed to combat the AMR resistance to earlier tetracyclines [43]. It possesses excellent activity against many bacterial species and reversibly binds to the 30S ribosomal subunit and inhibits protein synthesis. Due to its reversible binding to microbial ribosome, it acts as bacteriostatic. *In vitro* omadacycline has demonstrated bactericidal activity against *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* [44]. *Mycobacterium abscessus* complex (MABC)- non-tuberculous mycobacteria that include (*M. abscessus*, *M. bolletii*, and *M. massiliense*) which are the major cause of human pulmonary or skin and skin structure infections (SSSI) has acquired resistance to older tetracyclines but now sensitive to omadacycline [45-47]. The characteristics of omadacycline include broad-spectrum activity, and overcoming the two primary mechanisms of tetracycline resistance, efflux and ribosome protection. It has shown efficacy and is well-tolerated when used for acute bacterial SSTIs and CAP [17,27,48]. The other two pharmacological benefits for its effective oral administration include good oral bioavailability and lack of glycylcycline-induced dose-limiting nausea and vomiting [43]. Omadacycline has minimal known drug–drug interactions, and should be administered in a fasting state, avoiding dairy and cation-containing products for at least 4 h after dosing [48]. The chemical structure of omadacycline is similar to tigecycline, and it is the derivative of minocycline [26,27]. With increasing awareness and surveillance of antibiotic utilization, antimicrobial stewardship programs has continuously been considering utilization of omadacycline as potential therapeutic option in the treatment of infections caused by MSSA isolates as well as antibiotic-resistant and MDR Gram-positive bacteria, including MRSA, VRE, including vancomycin-resistant *E. faecium* and *E. faecalis*, penicillin and tetracycline-resistant *S. pneumoniae* and *S. viridans*, erythromycin-resistant *S. agalactiae*. Moreover, omadacycline is also equally effective against Gram-negative pathogens, such as *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, *H. influenzae*, *H. parainfluenzae Citrobacter* spp., and *P. mirabilis.* Further, its antibacterial spectrum is also extended to respective ESBL and carbapenem resistant *Enterobacteriaceae* (CRE) phenotypes as well as ceftazidime resistant strains [26,46]. It also exhibits potent *in vitro* activity against non-mycobacterial atypical organisms, including *Mycoplasma pneumoniae* and *M. hominis*, *Legionella pneumophilia*, and *Chlamydia pneumoniae*. Omadacycline could positively affect hospitalization-associated expenses for both bacterial CAP and acute bacterial SSTIs by providing another oral agent active against resistant Gram-positive pathogens [48].

It is indicated for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) based on susceptible pattern against several microorganisms. Further, it is also indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by several resistant bacteria, including *Staph. lugdunensis*, *S. pyogenes*, and *S. anginosus* group. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*) [48,49]. It is indicated for CABP given once-daily oral and intravenous administration [48,49]. For injection, omadacycline is available as single-dose vials containing 100 mg of omadacycline as sterile lyophilized powder. It is recommended intravenous dose of 200 mg should be administered slowly as an infusion over 60 min duration whereas that of 100 mg dose is administered over 30 min (Table 2) [44,49,]. Besides, omadacycline is an ideal choice even in out-patient and ambulatory care settings wherein such treatment option enable health care facilities to discharge patients who cannot take other oral antibiotics and reduce the duration of hospital stay. Adding to this, such therapeutic option would be a preferable choice for treatment on outpatient basis that

Table 2. Antibacterial spectrum, pharmacokinetics, dosage regimen, safety, and indications of newer tetracyclines (17,26,35,53,68)

Drug name	Spectrum	Pharmacokinetics ($t_{1/2}$, T_{max}, C_{max}, MIC)	Dose and duration	Side effects	Indications
Tigecycline	Broad spectrum	$t_{1/2}$: 1.05-2.34 h C_{max}: 0.42-11.1 µg/mL T_{max}: 2.0-2.8 h MIC: ≤ 2 µg/mL	Initial dose of 100 mg followed by 50 mg every 12 h for 5–14 and 7–14 days	Nausea, vomiting, injection site irritation, pain, swelling, and anorexia	cSSTIs cIAIs (cholecystitis, gangrenous perforated diverticulitis, appendicitis, peritonitis) CAP
Omadacycline	Gram-positive and negative aerobic pathogens	$t_{1/2}$: 16-17 h T_{max}: 2.5 h C_{max}: 0.3-4.5 µg/mL MIC: 0.06 and 0.125 µg/mL	Intravenous dose of 200 mg infusion over 60 min, 100 mg dose is administered over 30 min	Nausea, vomiting, diarrhea, tooth discoloration, inhibition of bone growth, increased heart rate, increased hepatic enzymes	cSSTIs CAP UTIs
Eravacycline	Broad-spectrum against aerobic and anaerobic Gram-negative and positive bacteria, except *P. aeruginosa* and *Burkholderia cenocepacia*	$t_{1/2}$: 20 h C_{max}: 1 h T_{max}: 1.5-2 h MIC: 0.5-2 µg/mL	1 mg/kg every 12 h, i.v. infusion approximately over 60 min every 12 h for 4 to 14 days	ISRs, nausea, vomiting, diarrhea hypotension, and wound dehiscence	cIAIs (diverticulitis, appendicitis, intra-abdominal abscess, cholecystitis, gastric and duodenal perforation, intestinal perforation, and peritonitis)
Sarecycline	Narrow-spectrum activity against aerobic and anaerobic Gram-negative bacteria, limited activity against Gram-positive organisms	$t_{1/2}$: 21-22 h T_{max}: 1.5-2.0 h C_{max}: 1.5-2.0 h MIC: 0.5 µg/mL	0.75, 1.5, 3.0 mg/kg, OD, for 12 weeks 33 to 54 kg: 60 mg 55 to 84 kg: 100 mg 85 to 136 kg: 150 mg No dose adjustments for hepatic/renal impairment	Nausea, vomiting, abdominal pain and discomfort, nasopharyngitis, sunburn, vulvovaginal candidiasis, and vulvovaginal mycotic infection	Acne vulgaris (inflammatory skin lesions of non-nodular with moderate-to-severe acne vulgaris in patients who are 9 years old and above)

CAP: Community acquired pneumonia; cIAIs: Complicated intra-abdominal infections; cSSTIs: Complicated skin an soft tissue infections; MIC: Minimum inhibitory concentration; UTI: Urinary tract infection

could further reduce the cost and risk of hospitalization(s) [50]. Overall, omadacycline is well tolerated, although nausea and vomiting are frequently reported [49]. Notwithstanding to this favorable safety profile, omadacycline caused a moderate increase in heart rate during the treatment period and such effects possibly mediated through muscarinic m2 receptors [49,51]. On the other hand, omadacycline reported to cause an increase in hepatic enzymes, albeit relatively low. Indeed, it shares many of the undesirable side effects of tetracyclines, such as tooth discoloration, inhibition of bone growth, etc., [49].

3.3 Eravacycline

Eravacycline is a novel broad-spectrum tetracycline that has been developed to overcome tetracycline resistance. It is indicated for the treatment of intra-abdominal infections caused by susceptible microorganisms and has a broad antibacterial spectrum that includes all common clinical pathogens except *P. aeruginosa*, including Gram-negative and Gram-positive aerobic and anaerobic strains [52]. It is a totally synthetic fluorocycline specifically designed to overcome tetracycline-acquired resistance associated with ribosomal protection mechanisms and efflux pumps [53]. It also shows good antibacterial activity against MDR bacteria, including *Enterobacteriaceae* and *A. baumannii*, expressing extended-spectrum. It is more effective than omadacycline against Gram-negative and broad-spectrum beta-lactamase-producing bacteria [53]. It is particularly active against all rapidly growing *Mycobacterium* species which includes *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, *M. chelonae*, *M. immunogenum*, *M. fortuitum*, and *M. mucogenicum* groups [54]. It shares the same mechanism of action as other tetracyclines and the main effects are bacteriostatic and reversible, with some bactericidal activity against certain bacterial species. It was previously believed that eravacycline could be utilized in complicated urinary tract infections (cUTI), but failed to show efficacy in comparison to carbapenems. Despite this, it is characterized by a broad-spectrum antimicrobial spectrum with coverage of several resistant strains, such as MRSA, VRE, CRE, tetracycline-resistant bacteria, as well as *A. baumannii* [55]. It has extended spectrum of antimicrobial activity against *E. coli*, *K. pneumoniae*, *Citrobacter freundii, E. cloacae*, *Streptococcus anginosus* group, *Cl. perfringens*, *Bacteroides* species, and *Parabacteroides* distasonis, *Klebsiella oxytoca*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staph. aureus*. However, it is not indicated for the treatment of cUTI.

It is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by *E. coli*, *K. pneumoniae*, *Citrobacter freundii*, *E. cloacae*, *K. oxytoca*, *E. faecalis*, *E. faecium*, *Staph. aureus*, *S. anginosus* group, *Cl. perfringens*, *Bacteroides* species, and *Parabacteroides distasonis* in patients 18 years or older [56]. In practice, it should be used only to treat or prevent infections that are suspected to be caused by susceptible bacteria. It has advantage over other new tetracyclines as both oral and intravenous formulations are available. The recommended dosage regimen is 1 mg/kg every 12 h for slow intravenous infusion over 60 min every 12 h. The commonly reported adverse effects are infusion site reactions, nausea, vomiting, diarrhea, hypotension, and wound dehiscence. Though well studied for antibacterial activity against infections in adults, its safety and effectiveness in paediatrics have not been established. Moreover, dosage adjustment is warranted in patients with severe hepatic and/or renal impairment (Table 2) [57,58]. To some extent, resistance in some bacteria to eravacycline is associated with up-regulated, non-specific intrinsic MDR efflux, and target-site modifications, such as 16s rRNA or certain 30S ribosomal proteins [53]. It approved only for the treatment of CAP and acute SSTIs, such as appendicitis, cholecystitis, diverticulitis, gastric and duodenal perforation, intra-abdominal abscess, intestinal perforation, and peritonitis. Recent clinical trials also demonstrated its use in pyelonephritis and cystitis. Though it has very less drug-drug interactions, it should be

avoided with dairy and divalent cation containing products for at least 4 h of duration after the dosing [52,56,58].

3.4 Sarecycline

Sarecycline is a novel, narrow-spectrum, once-daily, and oral tetracycline class antibiotic approved in October 2018. It has potent activity against Gram-positive bacteria, including activity against multiple strains of *Cutibacterium acnes*, an anaerobic Gram-positive bacterium that causes acne lesions and possesses anti-inflammatory properties similar to other tetracyclines. Most of the older tetracyclines have broad-spectrum antibacterial activity, contrary to that sarecycline is less potent due to its activity against enteric aerobic Gram-negative bacteria and anaerobic bacteria is minimal [30,59-61]. Owing to its narrow-spectrum antibacterial activity, sarecycline is associated lower risk of potential adverse effects, thus making it a potential therapeutic choice for definitive treatment among antibiotics, including tetracyclines. In addition to this, sarecycline had shown low susceptibility to resistance over other tetracyclines. Importantly, it is active against erythromycin- and clindamycin-resistant C. acnes strains as well as tetracycline-resistant *Staph. aureus* [59,64]. It is well known that acne vulgaris affects almost everyone, particularly during teenage and young adult years, though over 40% of individuals still suffer from acne in adulthood as well. Keeping in view of this, sustained efforts have been made to identify the most safe, well-tolerated, and effective treatments. [62,63,65]. Despite many studies being conducted to determine the antimicrobial spectrum of sarecycline compared to other tetracyclines, it is still a narrow spectrum antibiotic with a purpose to reduce and tackle AMR [30,64]. It exerts its antimicrobial effect mainly as a ribosomal protein synthesis inhibitor. Intriguingly, it has a unique mechanism of action due to it has the longest and largest chemical moiety attached at the carbon-7 (C7) position of ring D of the four-ring core thus exerting antibiotic effect by binding to the decoding centre of the 30S subunit of the bacterial ribosome, thereby inhibiting mRNA to protein translation [29,30,66]. It is active against both methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) strains of *S. aureus* as well as *S. epidermidis*, but less active than doxycycline and minocycline by twofold. Indeed, it is more active than tetracycline and doxycycline against *S. pyogenes*, *S. agalactiae*, *E. faecalis*, and *E. faecium* (both vancomycin susceptible and resistant).

It is used as a narrow-spectrum antibiotic specifically indicated for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne in patients 9 years old and above [62,63,67]. The treatment regimen for acne includes one sarecycline tablet per day (equivalent to 1.5mg/kg/day) administered orally as 60 mg, 100 mg, or 150 mg with or without food for duration up to 40 weeks (Table 2) [60,67,68]. Patient education and medication adherence is highly essential while taking sarecycline. It is recommended that patients should ingest the tablet at the same time each day at least one hour before or two hours after eating for beneficial and desirable therapeutic outcome. It is recommended not to use this drug beyond 12 month since its safety beyond 12 months has not been established yet [67]. The common adverse effects of sarecycline include nausea, bloody stools, stomach irritation, phototoxic adverse effects, light-headedness, vertigo, dizziness, and abnormal pressure in the brain. Apart from threat of developing AMR, use of some of the oral antibiotics is often limited by their vestibular side effects, such as dizziness and vertigo. It is reported that sarecycline poorly crosses blood-brain barrier due to its weak lipophilicity when compared with other tetracyclines that may explain relatively lower rates of vestibular-related side effects observed in clinical trials [69]. In animal toxicity studies, it has shown skeletal defects in offspring, decreased fertility, and decreased spermatogenesis. Therefore, it is contraindicated in pregnant and breastfeeding women due to the risk of teratogenic effects [67].

4. CONCLUSIONS

Emergence and tackling of antimicrobial resistance is a crisis for the health and wealth of the nations across the world. Irrational and inappropriate use of antibiotics is one the main cause of development and spread of AMR. Owing to this, most of the microorganisms are evolving due to selection pressure, developing resistance, and rendering antibiotics ineffective in treating many infectious diseases. The discovery and emergence of newer tetracyclines has shown remarkable effect against bacteria that are resistant to previous antibiotics including older tetracyclines. Recently approved tetracyclines, omadacycline, eravacycline, and sarecycline as well as tigecycline, have the advantage of a superior potency against both Gram-positive and Gram-negative aerobic as well as anaerobic MDR bacteria. These drugs also have a broad spectrum of activity which is very advantageous in treating many infectious diseases. These newer tetracyclines act like magic bullets, particularly against antibiotic-resistant pathogens and 'superbugs' and had shown promising results in treating infections caused antibiotic-resistant, MDR, and XDR bacteria. Through these new antibiotics are categorized as the third generation tetracyclines, their discovery, development, and subsequent approval with specified indications are important milestone in medicine, particularly, to rationalize appropriate use and to minimize development and spread of AMR. Essentially, these agents serve as leading molecules and maneuver for discovery and development of newer antibiotics in the post-antibiotic era. Inarguably, continuous surveillance on antibiotic utilization and implementation of antibiotic stewardship programs are warranted to help select appropriate treatment, to optimize therapeutic outcomes, to minimize AMR, and to sustain therapeutic efficacy for future.

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