REVIEW ARTICLE

Staphylococcus Infections and Emerging Drug Resistance: A Global Concern

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Abstract

Staphylococcus aureus (*S. aureus*) infections are a global health concern resulting in morbidity and mortality worldwide. Numerous antimicrobial agents (AMAs) have been developed over the years to treat *S. aureus* infections and then followed by the rapid emergence of resistance to them. Methicillin-resistant *S. aureus* (MRSA) is one of the modern pathogens which poses a formidable clinical threat. Despite the ongoing development of new antibiotics, active surveillance, and advances in infection prevention, MRSA remains an eminent pathogen persevering with high mortality. The clinical impact can be achieved with some promising newer antibiotics which can deal with different types of infections caused by *S. aureus*. In this review, we provide an overview of clinical research on the treatment of MRSA infections and summarize the expansive body of literature on the clinical trials done to explore new drugs to counteract *S. aureus* infections.

Keywords: Bacterial infection, Drug resistance, Gram-positive, Methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*.

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Background

Infections due to *S. aureus* are worldwide—a familiar cause of morbidity and mortality. Extended hospital stays, need for intensive care, and surgical intervention clubbed with an increased economic burden for patients/healthcare system can happen as a result of these infections. The mortality due to *S. aureus* infections may be due to the association of *S. aureus* with serious infections, along with the development of rapid antimicrobial resistance, which makes it difficult to treat.[1]

Staphylococcus aureus (S. aureus)

Microbiology

Staphylococcus aureus (*S. aureus*) is a gram-positive cluster forming cocci, nonmotile, nonsporing, catalase, and coagulase-positive facultative anaerobe. It is a normal human commensal found in the anterior nares, oropharynx, skin, vagina, axilla, and perineum. This normal colonization acts as a trigger for future infections, especially for those at risk. These include the elderly, diabetics, immunocompromized, and those with prosthetic devices. Mild to life-threatening infections are attributed to this bacteremia. These include dermatological infections and serious systemic infections of the blood, skeletal, pulmonary, and cardiovascular systems. A number of reported outbreaks of community-based infections in the last decade have been attributed to poor hygiene, contamination, close contact, and damaged skin.[1,2]

A meta-analysis study by Patil et al. from India revealed a cumulative 37% MRSA prevalence in India (2015–2020). The study depicted that the east zone has shown a 43% prevalence of MRSA in the states of West Bengal and Odisha. In fact, the states of Northern India had the second-highest (41%) MRSA prevalence. On the contrary, the northeast zone—Assam, Tripura, and Sikkim, had shown the third-highest prevalence of MRSA (40%).[3] The most common reasons attributable to antimicrobial resistance in literature are—lack of awareness and overuse of antimicrobials in humans/livestock. Inadequate/inappropriate sanitation and hygiene and lack of stringent rules and regulations for the use of antimicrobials are the other contributory factors.

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Pharmacology

Various antimicrobial agents (AMAs) have been developed over the years to treat *S. aureus* infections. The primary mechanism of action includes inhibition of cell wall synthesis or protein synthesis. The bacteria show a propensity to develop antimicrobial resistance (AMR) rapidly; hence, a continuous endeavor to look for newer options and agents.

Development of Resistance

The rapid development of resistance to antimicrobials is attributed to continuing genomic variations involving horizontal transfer, spontaneous mutations, and positive selection. Elaboration of enzymes by bacteria that inactivate the antibiotic (β-lactamases and aminoglycoside modification enzymes),

decreased affinity for AMAs following alteration of the bacterial target, trapping of the antibiotic, and efflux pumps expelling the antibiotic out of the bacterial cell are some of the mechanisms of resistance.[4,5]

The mortality due to bloodstream infections caused by *S. aureus* was above 80% before antibiotics came into existence. Soon following the discovery of penicillin, the mortality dramatically reduced due to *S. aureus* infections.[6] However, after the introduction of penicillin, bacteria-producing penicillinase came into existence in a short time, and these strains spread initially into hospitals and then into the community. To counteract this resistance due to the production of penicillinase by the bacteria, the first semisynthetic penicillinase-resistant penicillin, methicillin, was developed in 1959.[7,8] Subsequently, other penicillinase-resistant penicillins like oxacillin, flucloxacillin, dicloxacillin, and nafcillin were developed. Then very shortly (1960), *S. aureus* developed resistance to methicillin too. These bacteria came to be known as MRSA.[9,10]

After methicillin, a number of drugs from different groups were developed and used against it, like vancomycin, fluoroquinolones, aminoglycosides (gentamicin), cotrimoxazole, linezolid, etc., but resistance developed rapidly against them too (Tables 1 and 2). The vancomycin intermediate-resistant *S. aureus* (VISA) came into existence in the year 1997, followed by vancomycin-resistant *S. aureus* (VRSA).[11,12] Over the years, it has evolved as a multidrug-resistant *S. aureus* (MDRSA). The emergence of resistance does not contribute to intrinsic virulence, but resistance does make treatment of MRSA infection challenging due to the limited therapeutic options.

MRSA is widespread worldwide, with the highest rates (>50%) of MRSA prevalence reported in North and South America, Asia, and Malta. Some European countries like Netherlands and Scandinavia have reported low prevalence rates.[13]

Some studies from India reported an increasing prevalence of MRSA, where isolation rates steadily went up from 9.83% (1992) to 45.44% (1998). These strains are more commonly found in South India than in West or North India.[14] Studies from Delhi reported a prevalence rate of 51.6% in 2001 and 38.44% in 2008.[15,16]

Treatment of *S. aureus* Infections

Penicillin

The discovery of penicillin in the 20th century is an outstanding contribution to medicine. It had been one of the landmark discoveries in marking the beginning of the AMA era. Previous agents had a limited spectrum of activity. The effectiveness of penicillin against *Staphylococci* and *Streptococci* was established. Within 2 decades of widespread use of penicillin G, 99% resistance was reported to most strains of *S. aureus*.[6,11,17,18]

Methicillin

Methicillin is semisynthetic penicillin which is also known as staphcillin, and acts by inhibiting bacterial cell wall synthesis. This penicillinase-resistant derivative of penicillin was developed in the 1950s because some *S. aureus* strains had acquired penicillinase-based resistance to penicillin.[9,17] The resistance to β-lactam antimicrobials (penicillin, oxacillin, dicloxacillin, and flucloxacillin) was attributed to penicillin-binding proteins (PBP) PBP2a or PBP2 of subclass B1, known as encoded by the *mecA* gene located on staphylococcal cassette chromosome mec.[18] Likewise, resistance to methicillin was determined by the presence of *mecA* gene encoding altered PBP showing low affinity to β-lactam antibiotics.[19]

Table 1: Mechanism of resistance in *S. aureus*[4]

Mechanism	*Genetic factor*	*Antimicrobial agent*
• Reduced affinity for PBP. • Elaboration of enzymes that hydrolyze β-lactam ring.	• (PBP2a)/Mec A gene • *blaZ*.	β-lactams (penicillin, oxacillin, and flucloxacillin) Methicillin
• Synthesis of dipeptide with reduced affinity for vancomycin. • Trapping of vancomycin in the cell wall.	• D-Ala-D-Lac on transposon Tn1546 (Van).[77] • Altered peptidoglycan.	Vancomycin
The reduced affinity of enzyme DNA complex for quinolones.	*parC* of topoisomerase IV, gyr A/B of gyrase	Quinolones (ciprofloxacin and moxifloxacin)
Modification of enzymes acetylating/ phosphorylating	*Aac, aph* gene for acetyltransferase, phosphotransferase	Aminoglycosides (gentamicin)
• P-aminobenzoic acid (PABA) overproduction. • Reduced affinity for dihydrofolate reductase (DHFR).	• Sulphonamide: sulA. • TMP: dfrB.	TMP-SMX
Interferes with ribosomal binding	Domain V of 23s rRNA gene: rRNA gene	Oxazolidinone (Linezolid)
• Reduced binding to 23s rRNA. • Enzymatic modification of dalfopristin.	• Ribosomal methylase Q: ermA/B/C. • Acetyltransferase D: vat, vat B.	Quinupristin-dalfopristin (Q-D)
Reduced surface binding	Multipeptide resistance factor gene and yycFGHI operon[78]	Daptomycin
Mutation in PBP2 and membrane protein	Transposon Tn1546	Teicoplanin

Streptomycin

The aminoglycoside group of drugs is mainly used for aerobic gram-negative bacteria, especially in drug-resistant cases. However, in some cases of staphylococcal endocarditis, streptomycin is given in combination with penicillins or sulphonamides.[20] In fact, *S. aureus* resistant strains were reported in some studies in the 1970s when streptomycin was used alone for the treatment of *S. aureus* infections. Another study demonstrated *in vitro* antimicrobial synergism of combinations of β-lactam-aminoglycoside (cefadroxil–streptomycin) against clinical isolates of *S. aureus*.[21] Further studies may help in exploring in combination use of streptomycin in this direction.

Trimethoprim-sulfamethoxazole (TMP-SMX)

It is a synergistic combination of sulphonamides and trimethoprim. This combination was in use to treat both gram-negative as well as gram-positive infections, including *S. aureus*. Bacterial resistance to TMP-SMX is a rapidly increasing problem. Some studies in the past (1966–2003) have reported 8–100% worldwide resistance to TMP-SMX.[22,23]

Table 2: Pharmacokinetic/pharmacodynamics property of AMA for treatment of *S. aureus* infections[90]

Drug	*Mechanism of action*	*Pharmacokinetics*	*Adverse drug reactions*	*Precautions*
Penicillin	Acts by interfering with the synthesis of bacterial cell wall.	It is rapidly destroyed by gastric acidity. Only 1/3rd of the orally administered is absorbed. Both oral and parenteral preparations are available.	Hypersensitivity, anaphylactic shock, serum sickness, angioneurotic edema, seizures in patients with renal failure, and neutropenia.	Renal failure
Streptomycin (aminoglycoside)	Irreversibly inhibits protein synthesis and has bactericidal activity.	Absorption from the gastrointestinal (GI) tract is poor, but intramuscular injection is rapid. It is widely distributed in extracellular fluids. It can cross the placental barrier. It is excreted unchanged in the urine. Elimination half-life is 2–3 hours in normal renal function.	Nausea, vomiting, hypersensitivity, pain/ irritation at the injection site, ototoxicity, nephrotoxicity, and neuromuscular blockade.	Hypomagnesemia, cross allergenicity, superinfection, and pregnancy/lactation.
TMP-SMX	Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid (DHF) by competing with PABA. Trimethoprim blocks the production of THF from DHF by inhibiting dihydrofolate reductase.	Rapid oral absorption. Administered as 800/160 mg combination twice daily. Wide distribution and can cross the placenta. Metabolized primarily by N4-acetylation. Excretion by kidneys through glomerular filtration and tubular secretion.	Gastrointestinal disturbances, hypersensitivity, agranulocytosis, QT prolongation, hyperkalemia, and hyponatremia	Cross-sensitivity with oral hypoglycemics and diuretics
Tetracyclines	Reversibly bind to the 30s subunit of the ribosome, inhibiting protein synthesis, and are thus bacteriostatic.	Incompletely absorbed by GI tract. Can cross the placenta. Absorption is interfered with by divalent or trivalent ions, milk, and food. Concentrated in the bile by the liver. Excreted both in urine and feces.	Anorexia, diarrhea, dyspepsia, alopecia, hyperpigmentation, fixed drug eruption, anemia, hepatic toxicity, Steven–Johnson syndrome, and toxic epidermolysis,	Cross-resistance within the group. Hypersensitivity, renal and hepatic impairment, pregnancy, lactation, and photosensitivity.
Clindamycin	Binds to the 50s subunit of the bacterial ribosome and suppresses protein synthesis.	Rapid GI absorption. Widely distributed in the body tissues and fluids. Excreted in the bile.	Hypersensitivity, pseudomembranous colitis, and superinfections.	Children, elderly, renal/ hepatic impairment, pregnancy, and lactation.
Vancomycin	Tricyclic glycopeptide, bactericidal. Inhibits cell wall synthesis and alters cell membrane permeability and RNA synthesis.	Poor oral absorption. Eliminated by kidneys.	Abdominal pain, nausea, vomiting, diarrhea, hypersensitivity, nephrotoxicity, ototoxicity, and hypokalemia.	Renal impairment, elderly, children, anephric patient, pregnancy, and lactation.
Linezolid	It is an oxazolidinone and inhibits bacterial growth by inhibition of ribosomal protein synthesis and is bacteriostatic against *Staphylococci*.	Good oral absorption. Cmax reached within 1–2 hours after dosing. High-fat food interferes with its absorption. It is primarily metabolized by oxidation. Major excretion is nonrenal. It is available both in oral and injectable forms.	It is contraindicated in cases with known hypersensitivity to linezolid or its use with or within 14 days of monoamine oxidase inhibitors.	Thrombocytopenia, peripheral and optic neuropathy, serotonin syndrome with serotonergic agents, convulsions, lactic acidosis, and *Clostridium difficile*-associated diarrhea.

QT, interval on electrocardiogram; THF, tetrahydrofolate

However, a recent study in Israel by Paul et al., in four hospitals, compared TMP-SMX vs vancomycin for MRSA-related severe infections. It was found in this study that for the treatment of severe MRSA infections, a high-dose TMP-SMX monotherapy did not achieve noninferiority as compared to vancomycin.[24] Hence, further studies in this direction of TMP-SMX use in MRSA may provide evidence if it can be used alone or in combination as an alternative to present therapy.

Tetracyclines

Tetracyclines are broad-spectrum bacteriostatic antimicrobials that act against many gram-positive and gram-negative infections.[25]

According to retrospective cohort research, 95% of patients infected with MRSA strains were susceptible to tetracycline (minocycline, doxycycline) treatment. Long-acting tetracyclines (doxycycline and minocycline) may be an effective oral therapy

option for individuals with particular strains of MRSA, according to some research.[26]

Clindamycin

Clindamycin is derivative of lincomycin that acts by inhibiting protein synthesis, which has been in use for the treatment of skin and skin structure infections (SSSIs) caused by gram-positive cocci—*Streptococci* and *Staphylococci*.[27,28] A study in eastern India by Majhi et al. reported both clindamycin and erythromycin resistance in both MSSA and MRSA species causing SSSIs.[29,30]

Vancomycin

It is a glycopeptide antibiotic that is used to treat severe gram-positive infections that are resistant to other antibiotics, such as in patients who are allergic to penicillin, MRSA, and ampicillin-resistant *Enterococci*.[31]

It was the antibiotic of choice for MRSA infections for >40 years. Some reports have shown " minimum inhibitory concentration (MIC) creep," which is known as an increase in the MIC for vancomycin.[32,33] The first VISA isolates were identified in 1996 as a result of extensive vancomycin use. The first vancomycin-resistant strain of *S. aureus* was isolated in June 2002, and subsequently, increased reports of vancomycin failure started to appear in the literature.[30,34,35]

Teicoplanin

This is a glycopeptide used in the treatment of infections associated with MRSA and *Enterococcus faecalis*. Several studies have shown that teicoplanin is equally effective as vancomycin in the treatment of endocarditis, bacteremia, bone, and joint infections. It has a long half-life and has fewer adverse drug reactions, so better tolerated.[36,37]

Tigecycline

Tigecycline is a glycylcycline antibiotic that is bacteriostatic in action and acts against gram-positive bacteria. Tigecycline was approved by United States Food and Drug Administration (FDA) for indications of complicated SSSIs and complicated IAIs, which includes infections due to MRSA and extended-spectrum β-lactamase (ESBL) producing enterobacteriaeceae.[38–41]

The Tigecycline Evaluation and Surveillance Trial between 2004 and 2012 done in France showed that tigecycline exhibits good *in vitro* activity against many resistant pathogens, including ESBL producers.[41]

Linezolid

The FDA approved linezolid in the year 2000 for the treatment of community-acquired pneumonia (CAP) and nosocomial pneumonia, as well as SSSTIs caused by MRSA, based on a number of studies comparing linezolid to conventional antibiotic therapy. It has a high oral bioavailability, so it can be administered both orally and intravenously (IV).[42–44]

Some studies have reported resistance to linezolid and also some outbreaks of linezolid-resistant *S. aureus* in intensive care units.[45–47] *S. aureus* resistant strains were developed *via* mutations in the 23S ribosomal ribonucleic acid (rRNA) gene's domain V region.[48,49] Linezolid is associated with potentially serious adverse events. According to studies, it is well tolerated; however, reversible myelosuppression (thrombocytopenia) is documented on prolonged usage. Other adverse drug reactions seen are lactic acidosis, ocular and peripheral neuropathy, and serotonin-like syndrome.[50–52] The majority of adverse events are partially or completely on discontinuation of treatment, but peripheral neuropathy may persist.[53]

Daptomycin

It is a cyclic lipopeptide in structure having bactericidal activity against *S. aureus*. It has a similar spectrum of actions to vancomycin. A study found the noninferiority of daptomycin over the established standard therapy in the treatment of subacute bacteremia with or without infective endocarditis.[52,54] It is also associated with the elevation of creatine kinase, rhabdomyolysis, nephropathy, peripheral neuropathy, and hepatotoxicity. However, daptomycin is safe and well-tolerated AMA. It has the extra advantage of only once-daily dosing and hence, better compliance for outpatients.[55,56] The important concern with it is emerging resistance, as depicted in some studies involving clinical *S. aureus* isolates.[56–58]

Telavancin

This is a semisynthetic lipoglycopeptide derived from vancomycin with a dual mechanism of action. It is also given once daily and is effective against MRSA, VISA, and VRSA strains. Telavancin is quite similar to vancomycin with respect to the treatment of MSSA and MRSA pneumonia.[52,59] It acts by inhibiting cell wall synthesis similar to vancomycin by binding to the D-Ala-D-Ala terminus of peptidoglycan in the growing cell wall. The researchers discovered that telavancin was just as effective as vancomycin for treating complex SSSIs caused by MRSA in a randomized, double-blind research, with clinical cure rates of 90.6 and 84.4%, respectively.[59]

The FDA authorized (2009) telavancin for the treatment of SSSIs due to MRSA. The most common adverse effects seen are nausea, vomiting, metallic taste, headache, dizziness, rash, thrombocytopenia, and prolonged heart rate corrected QT interval on electrocardiogram intervals were also reported. Furthermore, animal studies raised concern about potential teratogenicity, therefore, to be avoided in pregnant women.[52,59–61] Telavancin Observational Use Registry provided insights into clinicians' use of telavancin to treat gram-positive associated bone and joint infections. This registry depicted good clinical response rates and proved it to be an effective therapy in bone and joint infections when other AMAs are ineffective.[61]

Ceftaroline Fosamil

This is a fifth-generation cephalosporin with broad-spectrum β-lactam activity against MRSA as well as resistant *Streptococcus pneumoniae* (*S. pneumoniae)*. Basis two phase III studies in community acquired bacterial pneumonia (CABP) and in ABSSSIs, ceftaroline was granted approval from the FDA in the year 2010 for treating the CABP and complicated SSSIs due to *S. pneumoniae*.[62,63] The margin of safety and tolerability is comparable to other cephalosporins. The adverse effects seen in clinical trials were mild, and a few cases of swelling or tenderness at the infusion site were reported.[64]

CANVAS-1 and 2 trials compared the efficacy of ceftaroline with vancomycin plus aztreonam in a sample size of 1378 adults having complicated SSSIs. The results demonstrated that ceftaroline was noninferior to vancomycin plus aztreonam, with a clinical response of 91.6% CANVAS-1 vs 92.7% in the CANVAS-2.[63,65] The FOCUS trials were phase III multicenter, randomized, and double-blind trials comparing ceftaroline to ceftriaxone in CBAP. In these trials, too, it was found that ceftaroline (84.3% achieving clinical cure) was noninferior to ceftriaxone (77.7% clinical cure).[64–66]

Oritavancin

It is a bactericidal lipoglycopeptide AMA with activity against gram-positive microorganisms, including MRSA.[52,59] SOLO I was a phase III, multicenter, randomized, double-blind, parallel, comparative efficacy, and safety study of single-dose IV oritavancin vs vancomycin twice daily was done for ABSSSIs. The trial revealed that oritavancin was noninferior to vancomycin in the treatment of ABSSSIs caused by gram-positive organisms. The adverse effects profile reported was almost similar for both the drugs except for nausea which was more common with oritavancin.[67]

Dalbavancin

Dalbavancin is a semisynthetic lipoglycopeptide which is a derivative of teicoplanin with a similar mechanism of action as vancomycin and teicoplanin. It differs from both of them, with better activity against gram-positive bacteria, including MRSA and VISA. DISCOVER 1 and DISCOVER 2 were similar in design noninferiority trials of dalbavancin for the treatment of ABSSSIs.[67,68] These trials were noninferior to each other, where Dalbavancin was administered once daily as compared with vancomycin–linezolid administered twice daily in seriously ill patients for the treatment of ABSSSIs.[68]

Ceftobiprole

This is another fifth-generation cephalosporin with bactericidal activity against gram-positive pathogens like MRSA. Ceftobiprole is licensed in numerous European and other countries for the treatment of CABP and HAP.[69,70] It was tested in phase III studies which evaluated the efficacy of ceftobiprole in the treatment of CABP and hospital-acquired pneumonia (HAP) due to *S. aureus*, respectively.[52,70] In two other randomized, multicenter, and double-blind phase III trials (STRAUSS 1 and STRAUSS 2), ceftobiprole's clinical effectiveness in hospitalized patients with complex SSSIs were investigated against ceftazidime and vancomycin. These trials showed the noninferiority of ceftobiprole—twice daily as compared with ceftazidime/vancomycin—twice daily administration for the treatment of ABSSSIs in seriously ill patients.[71] Ceftobiprole was also tested in phase III studies evaluating the efficacy of ceftobiprole in the treatment of CABP and HAP due to *S. aureus*, respectively. Ceftobiprole was shown to be noninferior to ceftazidime/linezolid in the preliminary findings of a phase III study in patients with CABP and HAP.[52,71]

Tedizolid

Tedizolid phosphate is an oxazolidinone prodrug that is converted to the active form of tedizolid, which inhibits bacterial protein synthesis. It has been FDA-approved (June 2014) for the treatment of gram-positive ABSSSIs, including MRSA.[67] It differs from other oxazolidinones due to the presence of a modified side chain which confers activity against certain linezolid-resistant pathogens and, thus, improves its potency.[72–74]

Arbekacin

Arbekacin sulfate is an aminoglycoside with broad antimicrobial activity. It has been used in Japan since 1990 to treat pneumonia and sepsis due to MRSA. It causes membrane damage and inhibits translation by binding to the ribosomal 50s and the 30s ribosomal subunits.[75,76] Some studies have reported that arbekacin was noninferior to vancomycin for treating MRSA infections.[77] However, more studies for the same would be required to confirm this finding.

Levonadifloxacin

Levonadifloxacin belongs to the subclass of quinolones—benzoquinolizine. Levonadifloxacin and its ester oral prodrug of alalevonadifloxacin have activity against MDR gram-positives, including MRSA, VISA, and VRSA.[78] It was approved by the FDA (2014), which gave it the status of a qualified infectious disease product for the treatment of ABSSSIs with concurrent bacteremia, diabetic foot, and respiratory tract infections. These infections are attributed to *S. pneumoniae*, *Haemophilus influenzae* (*H. influenza*), *Moraxella catarrhalis*, quinolone-susceptible gram-negative, and atypical bacteria.

It acts by inhibiting deoxyribonucleic acid (DNA) replication by introducing double-stranded breaks in the bacterial chromosome. The quinolones were otherwise seen to exhibit bactericidal activity by increasing the concentration of enzyme–DNA cleavage complexes.[79] Some studies revealed that levonadifloxacin therapy (IV and oral) was safe and well tolerated in the treatment of ABSSSIs. It was found to be noninferior to IV and oral linezolid therapy in the treatment of gram-positive ABSSSIs.[78,79]

Omadacycline

This is a novel FDA-approved aminomethylcycline antibiotic for its action against ABSSSIs and CABP. A study depicted that omadacycline has *in vitro* activity against MSSA, MRSA, *S. pneumoniae*, hemolytic *Streptococci*, VRE, and *Legionella pneumophila*.[80,81] OASIS-1 (ABSSSIs), OASIS-2 (ABSSSIs), and OPTIC (CABP) were phase III trials that established noninferiority of omadacycline to linezolid (OASIS-1 and OASIS-2) and moxifloxacin (OPTIC), respectively.[81,82]

Delafloxacin

This is also a new anionic fluoroquinolone that may be administered orally or with IV, which was authorized by the FDA in the year 2017 for the treatment of ABSSSIs. It is currently being investigated for CABP and complicated urinary tract infection (cUTI). It is found to have action against *Neisseria gonorrhea*, *Legionella* species, *Chlamydia pneumoniae (C. pneumoniae)*, and *Mycoplasma pneumoniae (M. pneumoniae)*.[83] Delafloxacin indicated noninferiority to existing antibiotic alternatives in the treatment of ABSSSIs caused by MDR–MRSA, *P. aeruginosa* based on a few phase III studies.[84] It was also found to be noninferior to vancomycin/aztreonam in a phase III study (large, multicentre, double-blind, and randomized) for the treatment of ABSSSIs. Delafloxacin monotherapy is effective against various gram-positive and negative infections and is supposed to exhibit similar efficacy when compared to vancomycin in the treatment of MRSA.[85] The most commonly reported adverse drug reactions were nausea, vomiting, diarrhea, headache, and elevated serum transaminases. Tendinitis and tendon rupture were not among the common adverse effects observed in clinical studies as compared to other fluoroquinolones.[84]

Lefamulin

Lefamulin is another novel FDA-approved (2019) oral and IV antibiotic of class pleuromutilin for the treatment of CABP. Pleuromutilin's ability to attach to the 50S ribosomal subunit in the peptidyl transferase center inhibits bacterial protein production. This interaction inhibits tRNA from properly positioning in the A and P (acceptor and donor) sites, preventing the formation of peptide bonds. It has antibacterial action against respiratory infections, which includes MRSP, MRSA, *H. influenza*, *M. pneumoniae*, *C. pneumoniae*, and *Legionella pneumophila*.[86]

The phase III clinical trials of lefamulin in CBAP (LEAP 1–IV to oral lefamulin; LEAP 2–oral alone) have shown the efficacy and safety of oral and IV lefamulin for the treatment of CABP, noninferior to moxifloxacin. This prompted FDA, European Medical Agency, and Health Canada to approve lefamulin for CABP therapy in adults.[86,87] Prince et al. conducted a phase II clinical trial to see if lefamulin can be used to treat gram-positive ABSSSIs. It was found that clinical success rates with both IV and oral preparations of lefamulin in the clinically evaluable and modified intent to treat groups were high and equivalent to vancomycin. The most common adverse drug reactions seen were headache, nausea, diarrhea, hypokalemia, insomnia, and pain at the infusion site.[86]

Eravacycline

Eravacycline is a novel, fully synthetic fluorocycline derivative of tetracycline approved by the FDA (August 2018) with a wide spectrum against pathogens that cause cUTIs and complicated intra-abdominal infections. It does not need any dose adjustment in patients with renal disorder, and this makes it a good treatment option for patients suffering from renal impairment. Two trials (IGNITE-2 and IGNITE3) compared eravacycline to levofloxacin in the treatment of cUTIs; the results indicated that eravacycline was not as effective as levofloxacin.[88–90]

Conclusion

Staphylococcus aureus (*S. aureus*) is responsible for several difficult-to-treat infections in humans, and resistance is seen with most of the available treatment options. The continuous nature of genotypic variations in *S. aureus* thus poses serious clinical implications. Of concern are the few treatment options available and the rapidly emerging resistance resulting in treatment failure.

Some new AMAs are currently available for the treatment of serious MRSA infections. The current scenario of rapid antimicrobial resistance minimizes the availability of promising therapeutics against such infections and, thus, a growing global threat to human life. This review elaborates on the journey of AMAs used in the treatment of susceptible and resistant *S. aureus* infections, along with the resistance patterns.

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