

Methicillin-Resistant *Staphylococcus aureus* in Diabetic Foot Infection in India: A Growing Menace

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Abstract

Diabetic foot infection (DFI) is a serious and common complication of diabetes mellitus. These infections are potentially disastrous and rapidly progress to deeper spaces and tissues. If not treated promptly and appropriately, DFI can be incurable or even lead to septic gangrene, which may require foot amputation. Mostly, these infections are polymicrobial, where Gram-positive pathogens mainly *Staphylococcus aureus* play a dominant causative role. Methicillin-resistant *Staphylococcus aureus* (MRSA) is present in 10% to 32% of diabetic infections and is associated with a higher rate of treatment failure, morbidity, and hospitalization cost in patients with DFIs. The increasing resistance of bacteria and the adverse effects pertaining to the safety and tolerability towards currently available anti-MRSA agents have limited the available treatment options for patients with DFI. Infection control, antimicrobial stewardship, and rapid diagnostics based on the microbiological culture and the antimicrobial susceptibility testing results are important components in helping curb this disturbing trend. Emphasis to revisit a vigorous research effort in order to improve the therapeutic options for the increasingly resistant and highly adaptable MRSA is the need of hour. Through this review article, we have made an attempt to explore the ongoing therapeutic trends in the management of DFI and highlighted the challenges in treatment of DFI. We have also given a brief overview of a few novel drugs that are under development to treat MRSA infections.

Keywords

diabetic foot infection (DFI), methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant infection, antimicrobial resistance, newer anti-MRSA agents

Introduction

India has about 71.3 million people with diabetes, and diabetic foot infection (DFI) is one of its most challenging clinical complications. Per the population-based studies in India, more than two-thirds of the patients with diabetes were predisposed to DFIs, whereas 9% had prevalent ulcers of whom 20.2% required foot amputation. The prevalence of DFI was estimated to be 6% to 11%.¹ In another multicentric study conducted in India with 1985 patients with diabetes, the major cause of amputation in 90% of patients was found to be microbial infection.²

Staphylococcus aureus is the most common causative agent in DFIs, and among these 23.7% were reported as Methicillin-resistant *Staphylococcus aureus* (MRSA) in one study.³ DFIs are the infections of soft tissue or bone below the malleoli.⁴ They usually begin as a skin ulceration, where in ~25% of the cases, it spreads contiguously from the skin to deeper subcutaneous tissues and/or bone. Mostly, an infected foot ulcer precedes ~60% of amputations, which may be minor (ie, foot sparing) or major.⁵

Antimicrobial resistance is one of the major health care issues worldwide that hinders the effective treatment and prevention of fast-growing infections and outbreaks caused by microbes.⁶ MRSA has been implicated as the main cause of nosocomial infections worldwide since the 1970s. The rising emergence of antibiotic resistance, especially to methicillin and vancomycin,⁷ has made the treatment challenging for clinicians, despite the availability of antibiotics for nearly 70 years.

Antibiotic-resistant organisms, especially MRSA are frequently isolated from 10% to 32% of the patients with DFIs,

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eventually leading to a higher rate of treatment failure.⁸ Patients with DFIs usually require several episodes of hospitalization because of its chronic nature. However, prolonged hospital stay, indiscriminate use of antibiotics, lack of awareness, multiple lines of antibiotics before admission to the hospital, and so on are predisposing factors of MRSA emergence.⁹⁻¹¹ Hence, early detection of MRSA and effective antibiotic policy in referral hospitals are of paramount importance from the hospital epidemiological point of view.¹²

This article reviews the present state of DFIs in India and focuses on choice of treatment for MRSA, limitations of available treatments, and resistance to available antibiotics. It also discusses a brief overview of novel drugs that are under development to treat MRSA infections.

Review of the Literature

MRSA: History, Types, and Prevalence

Staphylococcus aureus is a Gram-positive bacterium and is a facultative anaerobe found on the skin and in the nasal passages of humans. It has been recognized as an important cause of human disease for more than 100 years.¹³ The organism is toxigenic, and one of the effects of the toxin is reducing the efficacy of antibiotics.⁷ Methicillin, the first synthetic penicillin was launched in 1960 for the treatment of *Staphylococcus aureus* infections. However, soon afterward, methicillin-resistant strains appeared in the hospital setup,¹⁴ and outbreaks of MRSA were reported that resulted in significant morbidity and mortality.¹⁵

There are 2 major categories of MRSA. One is called a nosocomial infection, an infection that is transmitted mostly in health care settings (hospital-acquired [HA]-MRSA). The other is community-acquired MRSA (CA-MRSA). People with diabetes are at risk of getting both CA- and HA-MRSA because of frequent sores and ulceration.¹⁶

MRSA produces an additional penicillin binding protein (PBP2a), which has low binding affinities for most of the penicillin as well as cephem antibiotics.¹⁷ Resistance to methicillin is a result of the presence of the staphylococcal cassette chromosome mec (SCCmec) element, which is a class of mobile genetic element that carries the methicillin-resistant determinant *mecA*.¹⁸ CA-MRSA strains possess small mobile SCCmec type IV or V genetic elements, whereas HA-MRSA strains carry larger SCCmec (Type I, II, III) elements and have multidrug resistant (MDR) gene.^{19,20}

Epidemiology of MRSA in India and Worldwide

The Centers for Disease Control categorizes MRSA as microorganisms with a serious threat level. The incidence and prevalence of MRSA vary geographically. In 2014, Europe was found to have a high percentage of MRSA cases; the percentage of invasive MRSA isolates ranged from 0.9% in the Netherlands to 56% in Romania, with a

population-weighted mean of 17.4%. However, the proportion of MRSA isolates in Europe decreased over time; 7 of the 29 European Union countries still report 25% or more of invasive *Staphylococcus aureus* isolates as MRSA.²¹ As per the 2005-2010 report by the US military health system, there was a reported decrease in hospital-onset MRSA bacteremia from 0.7 cases per 100 000 person-years to 0.4 cases per 100 000 person-years. Community-onset MRSA bacteremia decreased from 1.7 to 1.2 cases per 100 000 person-years during the same time period.²² In the United States alone, 80 461 people had severe MRSA infections, and at least 11 285 deaths directly related to MRSA were reported in 2011.²³ In 2015, invasive MRSA infections, including bacteremia, occurred at a rate of 18.8 per 100 000 people in the United States and accounted for 332 deaths.²⁴ One of the studies conducted in the United States for the epidemiology of MRSA in DFIs found that of 378 individuals recruited for the clinical trial in MRSA patients, 79 were identified with DFIs, and a total of 249 (65.9%) were molecularly classified as having CA-MRSA; 127 (33.6%) had a non-CA-MRSA infection, and 2 (0.5%) had a missing MRSA SCCmec.²⁵ Asia is also one of the regions with high prevalence rates of HA-MRSA and CA-MRSA in the world. Most hospitals in Asia are endemic for multidrug-resistant MRSA, with an estimated proportion of 28% (in Hong Kong and Indonesia) to >70% (in Korea) among all clinical *Staphylococcus aureus* isolates in the early 2010s.²⁶

One of the studies conducted in Saudi Arabia had reported that the most common pathogens identified in DFIs were *Pseudomonas aeruginosa* (15.6%), followed by *Klebsiella* (6.7%). The most common Gram-positive pathogen was *Staphylococcus aureus* (35%), followed by *Streptococcus* (8.9%).²⁷ Some of the previous such studies reporting the epidemiology of MRSA infections associated with DFIs are shown in Table 1.

In India, the significance of MRSA was recognized relatively late, and it emerged as a problem in the 1980s and 1990s. MRSA is now endemic in India, with the prevalence varying from 25% in the western part of India to 50% in South India.^{28,29} The Indian Network for Surveillance of Antimicrobial Resistance group, in a surveillance conducted across 15 tertiary care centers in India, reported the overall prevalence of MRSA as 42% in 2008 and 40% in 2009.⁷ According to a recent study, the frequency of 45% of *Staphylococcus aureus* clinical isolates being methicillin-resistant in India in the early 2010s is similar to what has been reported in the rest of the Asian countries (41.9% in Pakistan, 45.8% in China, 41% in Japan, 35.3% in Singapore, and 55.9% in Taiwan), except Hong Kong, Indonesia (28% each), and South Korea (>70%).²⁶ Another prospective study of 261 patients with DFIs performed during the period between January and June 2014 in India showed that the most frequently isolated bacteria were *Staphylococcus aureus* (26.9%), followed by *P aeruginosa*

Table 1. List of Studies Reported Previously for Diabetic Foot Infections Caused by MRSA.

	Study ^a	Objectives	Study Design	Findings
1.	Reveles et al 2016 ¹	Epidemiology of MRSA diabetic foot infections	Retrospective cohort study	<ul style="list-style-type: none"> • <i>Staphylococcus aureus</i> was present in 46% of culture-positive DFIs • A total of 273 patients received MRSA antibiotic coverage, resulting in 71% unnecessary use • Male gender and bone involvement were found to be independent risk factors for MRSA DFI • MRSA was the causative pathogen in a small number of DFIs; antibiotic coverage targeted against MRSA was unnecessarily high
2.	Puzniak et al, 2014 ²	MRSA infection epidemiology and clinical response from tigecycline soft-tissue infection trials	pooled analysis of data from 6 clinical trials	<ul style="list-style-type: none"> • A total of 378 patients with MRSA soft-tissue infections were identified, including 79 with DFIs • A total of 249 (65.9%) were molecularly classified as CA-MRSA • Clinical response rates for MRSA soft-tissue infection were similar between tigecycline and vancomycin
3.	Chhibber et al, 2013 ³	Evaluation of lytic bacteriophage and linezolid for effective treatment in eliminating MRSA from diabetic foot infections	—	<ul style="list-style-type: none"> • Use of combined agents (lytic bacteriophage and linezolid) decreases the frequency of emergence of resistant mutants • Lytic bacteriophage and linezolid effective in diabetic individuals who do not respond to conventional antibiotic therapy
4.	Ding et al, 2012 ⁴	Identification of risk factors for infections of MRSA in diabetic foot patients	Clinical trial	<ul style="list-style-type: none"> • Long course of ulcer, osteomyelitis, hypertension, and hypoproteinemia are identified as risk factors for the MRSA infection • Higher values of HbA1c is a risk factor for the MRSA infection
5.	Lipsky et al, 2011 ⁵	Determination of role of diabetes mellitus in the treatment of skin and skin structure infections caused by MRSA	Randomized clinical trial	<ul style="list-style-type: none"> • Nondiabetic patients had a shorter adjusted mean length of stay compared with diabetic patients (8.2 and 10.7 days, $P < .0001$). • Clinical success rates were lower in diabetic than nondiabetic patients with ABSSSIs caused by MRSA
6.	Lipsky, 2004 ⁶	Comparative study of linezolid versus ampicillin-sulbactam/ amoxicillin-clavulanate	Randomized, multicenter, open-label trial	<ul style="list-style-type: none"> • Among 371 patients, the clinical cure rates associated with linezolid and the comparators were statistically equivalent overall (81% vs 71%, respectively) but were significantly higher for linezolid-treated patients with infected foot ulcers (81% vs 68%; $P = .018$) and for patients without osteomyelitis (87% vs 72%; $P = .003$) • Drug-related adverse events were significantly more common in the linezolid group, but they were generally mild and reversible • Linezolid was at least as effective as aminopenicillin/β-lactamase inhibitors for treating foot infections in diabetic patients

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; CA-MRSA, community-acquired MRSA; DFI, diabetic foot infection; ABSSSI, acute bacterial skin and skin structure infection.

^aReference details for studies cited are given below.

1. Reveles KR, Duhon BM, Moore RJ, Hand EO, Howell CK. Epidemiology of methicillin-resistant *Staphylococcus aureus* diabetic foot infections in a large academic hospital: implications for antimicrobial stewardship. *PLoS One*. 2016;11:e0161658.

2. Puzniak LA, Quintana A, Wible M, Babinchak T, McGovern PC. Methicillin-resistant *Staphylococcus aureus* infection epidemiology and clinical response from tigecycline soft tissue infection trials. *Diagn Microbiol Infect Dis*. 2014;79:261-265.

3. Chhibber S, Kaur T, Kaur S. Co-therapy using lytic bacteriophage and linezolid: effective treatment in eliminating methicillin resistant *Staphylococcus aureus* (MRSA) from diabetic foot infections. *PLoS One*. 2013;8:e56022.

4. Ding Q, Li D, Wang P, Chu Y, Meng S, Sun Q. Risk factors for infections of methicillin-resistant staphylococci in diabetic foot patients [in Chinese]. *Zhonghua Yi Xue Za Zhi*. 2012;92:228-231.

5. Lipsky BA, Itani KM, Weigelt JA, et al. The role of diabetes mellitus in the treatment of skin and skin structure infections caused by methicillin-resistant *Staphylococcus aureus*: results from three randomized controlled trials. *Int J Infect Dis*. 2011;15:e140-e146.

6. Lipsky BA. Medical treatment of diabetic foot infections. *Clin Infect Dis*. 2004;39(suppl 2):S104-S114.

(20.9%). Among the staphylococci, 23.7% were found to be MRSA. Of these CA-MRSA were predominant.³

Pathophysiology of DFIs and Role of *Staphylococcus aureus*

DFI is a multifactorial process, and its pathogenesis is complex. The factors that lead to foot ulceration and tissue damage are neuropathy, trauma, deformity, high plantar pressures, peripheral arterial disease, and susceptibility to infection.³⁰ Most of the DFIs seem to be superficial when presented clinically. However, bacteria can spread to subcutaneous tissues, including tendons, joints, fascia, muscle, and bone. Depending on the severity, DFIs are classified as mild, moderate, and severe.³¹ DFIs generally begin when a break in the protective skin barrier allows pathogens to multiply in the soft tissues. Diabetic foot osteomyelitis usually occurs by the contiguous spread of infection from overlying soft tissue. The disease severity progresses from ulceration and infection, to gangrene that results in hospitalization, which often precedes lower-extremity amputation.³² DFIs are usually polymicrobial, caused by aerobic Gram-positive cocci like *Staphylococcus aureus*, Gram-negative bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, *P aeruginosa*), and anaerobes.^{33,34}

The numerous virulence factors and toxins secreted by *Staphylococcus aureus* during infection that evade host immune defenses are well characterized. This includes α -hemolysin (or α -toxin), phenol-soluble modulins and Panton-Valentine leukocidin. Other toxins include the pore-forming toxins, the exfoliatins, the super antigen exotoxins, and the EDIN (epidermal cell differentiation inhibitors) toxins. These cytolytic toxins can damage membranes of host cells, leading to cell lysis.³³ When *Staphylococcus aureus* enters the injured skin, neutrophils and macrophages migrate to the site of infection. *Staphylococcus aureus* evades this response using different mechanisms, such as blocking, sequestering host antibodies, chemotaxis of leukocytes, hiding from detection via capsule or biofilm formation, and resisting destruction after ingestion by phagocytes. Biofilm formation is an important virulence factor and results in treatment failure. It not only causes a delay in healing, but also potentially increases the risk of infection. The menace of biofilm is increasingly seen in surgical practice in addition to the standard protocols of treatment; the surgeon has to scoop out the biofilm till a judiciously bleeding area is exposed.^{35,36}

The first event at the beginning of DFI is the adhesion to surface components (fibrinogen, fibronectin, and epidermal keratinocytes). These surface proteins mediate adherence to microbial surface components recognizing adhesive matrix molecules and components of bone matrix and collagen.³⁷ *Staphylococcus aureus* also invades osteoblasts, fibroblasts, and endothelial cells and forms small-colony

variants. Because small-colony variants possess important metabolic and phenotypic differences from ordinary *Staphylococcus aureus* isolates, these are relatively resistant to antibiotics and, hence, difficult to eradicate with antibiotic therapy.³⁸⁻⁴⁰

In addition, *Staphylococcus aureus* possesses factors that activate T lymphocytes: the super antigens (SE: enterotoxins; SEI: enterotoxin-like protein; TSST: toxic shock-syndrome toxin). On the other side, exfoliative toxins (Ets) facilitate bacterial skin invasion. The synthesis and secretion of glycocalyx play a vital role in the virulence of *Staphylococcus aureus*. The polysaccharide production begins immediately after the adhesion and covers the bacteria, representing an essential component for the development of a biofilm, which is an important virulence factor and results in treatment failure.^{41,42}

Diagnosis of DFI and Treatment Approach

It is important to diagnose DFI clinically rather than bacteriologically because all skin ulcers harbor micro-organisms. The clinical diagnosis of foot infection is based on the presence of purulent discharge from an ulcer or the classic signs of inflammation (i.e, erythema, pain, tenderness, warmth, or induration). Foul odor, the presence of necrosis, and failure of wound healing despite optimal management are the other key indicators of DFI.⁴³ However, symptoms may vary depending on the etiology of the disease. All patients do not have a similar pattern of clinical symptoms. In some patients, local inflammatory changes may be less prominent or absent. Pain and tenderness may be reduced or absent in patients who have neuropathy, whereas erythema may be absent in those with vascular disease. Most patients with DFI do not have systemic features such as fever or chills. The presence of systemic signs or symptoms indicates a severe deep infection.⁴³

DFIs pose a crucial challenge in clinical practice in terms of management. Selection of appropriate antibiotics for the patients is most challenging. The emergence of antibiotic-resistant pathogens in recent years has made it increasingly difficult to prescribe empirical antibiotics for the treatment of DFI. The risk factors for MDR microorganisms in DFIs were reported to be prior antibiotic use and duration of antibiotics, duration of hospitalization, and presence of osteomyelitis.⁴⁴⁻⁴⁷

Infection/colonization with MRSA may result in prolonged hospital stay and excessive direct economic costs.⁴⁸ Therefore, appropriate management of these infections is needed with the right selection of antibiotics.³ The appendix shows the recommendations of the Infectious Diseases Society of America (IDSA) for the use of antibiotic treatment in DFIs, and Table 2 represents the choice of antibiotics and duration of treatment prescribed in different cases of DFIs per IDSA recommendations.⁴⁹

Table 2. Choice of Antibiotics in Diabetic Foot Infection.

Type of Infection	Antibiotics
Mild infection	Oral antibiotics: cephalexin, dicloxacillin, amoxicillin-clavulanate, or clindamycin are effective
Mild with MRSA	Clindamycin, trimethoprim-sulfamethoxazole, minocycline, or linezolid may be used
Moderate infection	Levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, etrapenem, tigecycline
Moderate with MRSA	Linezolid, daptomycin, vancomycin
Gram-negative aerobes and/or anaerobes infection	Dual-drug treatment with trimethoprim-sulfamethoxazole plus amoxicillin-clavulanate or clindamycin plus a fluoroquinolone, such as levofloxacin or moxifloxacin may be used
For moderate-to-severe infections	Parenteral antibiotic therapy is recommended. Empirical choices should cover streptococci, MRSA, aerobic Gram-negative bacilli, and anaerobes
For Gram-negative aerobic organisms and anaerobes	Ampicillin-sulbactam, piperacillin-tazobactam, meropenem, or ertapenem
For aerobic Gram-negative and anaerobic organisms	Ceftriaxone, cefepime, levofloxacin, moxifloxacin, or aztreonam plus metronidazole
Other New Antibiotics	
Gram-positive and Gram-negative pathogens and atypical pathogens	Tigecycline (Tygacil) is an injectable tetracycline antibiotic that was approved by the FDA in 2005. The drug carries a black box warning and is reserved for use in situations when alternative treatments are not suitable The recent IDSA guideline for the treatment of MRSA did not include tigecycline because of the FDA's September 2010 safety statement
Dry gangrene	Expectant care
Wet gangrene	Surgical debridement and/or antimicrobial therapy
Chronic osteomyelitis	Antimicrobial therapy with adequate surgical debridement
Duration of Antibiotic Treatment in Diabetic Foot	
Outpatient settings with oral antibiotics	1-2 Weeks for mild and 2-3 weeks for moderate infections
Inpatient, then outpatient settings (initial parenteral, switch to oral when possible)	2-4 Weeks for severe infection
Diabetic foot osteomyelitis	4-6 weeks (if residual infected, but viable bone) 3 months or more (if not surgically treated or residual infected dead bone after surgery)

Abbreviations: FDA, Food and Drug Administration; MRSA, methicillin-resistant *Staphylococcus aureus*.

Treatment Challenges in DFIs

Selecting an Effective Antibiotic Therapy. DFIs are polymicrobial in nature (more than 1 type of bacterium), with the most common culprits being *Staphylococcus* and *Streptococcus*. In recent years, *Staphylococcus aureus* strains have evolved to be more resistant to many types of antibiotics, including the first-line antibiotics such as penicillin or oxacillin. Although vancomycin has been the main therapeutic agent for MRSA infections over the past 50 years, there has been increasing concern with its efficacy in the face of increasing minimum inhibitory concentrations (MICs).^{50,51} There are some antibiotics and topical antibiotic treatments that are successful in treating MRSA, but a relapse can still be a major problem in many patients. Empirical antibiotic therapy should be modified on the basis of the clinical response and culture or susceptibility

testing. Parenteral antibiotics are indicated for patients who are systemically ill, have severe infection, are unable to tolerate oral agents, or have infection caused by pathogens that are not susceptible to oral agents. Using oral antibiotics for mild to moderate infection and switching early from parenteral to oral antibiotics, with appropriate spectrum coverage and good bioavailability and tolerability, are strongly encouraged. Besides antibiotic resistance, super infection, undiagnosed deep abscess or osteomyelitis, biofilm formation, and severe tissue ischemia also create hinderances in making an effective treatment choice.⁵² Furthermore, the antibiotic pipeline has dramatically declined for several key reasons: difficulties in discovering new agents with novel mechanism(s) of action, substantial changes and challenges in regulatory guidance and decision making, and lower financial return on corporate investment compared with other therapeutic classes in medicine. Inappropriate treatment

is given to 20% to 25% of patients, and outdated recommendations to the patients may affect the therapy.⁵³⁻⁵⁶

Safety of Antibiotics: Limitations of Current Anti-MRSA Agents. Vancomycin approved in the year 1958 has long been the gold-standard agent for the empirical management of serious MRSA infections in hospitalized patients. However, it has well-recognized limitations, including increasing prevalence of heterogeneous strains, variations between and within patients in tissue distribution, and nephrotoxicity. Although vancomycin remains active against MRSA, rising MICs within the susceptible range (MIC creep or leap) is a concern. MRSA strains with a vancomycin MIC of 2 mg/L have been associated in some prospective multivariate analyses with an increased risk of treatment failure and even an increased mortality rate in bacteremia patients compared with strains with a lower MIC.⁵⁷ There are insufficient data to support a recommendation on continuous vancomycin usage.⁵⁸

Daptomycin is an alternative for DFI patients with chronic kidney disease. If the creatinine clearance is less than 30 mL/min, an alternate-day therapy can be instituted. This is useful especially in outpatient antibiotic therapy.⁵⁹ However, cross-resistance has been seen between daptomycin and vancomycin in heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA) and VISA. The drug has potential for decreased susceptibility with increased vancomycin MIC and hVISA.^{60,61}

Linezolid is the first available oxazolidinone antimicrobial agent and has reversible monoamine oxidase (MAO) inhibitor action. Originally, it was discovered as a psychotropic agent with antidepressant effects through inhibition of MAO; however, it was also found to have antibiotic efficacy against drug-resistant Gram-positive cocci. The concomitant administration of a MAO inhibitor and a serotonin reuptake inhibitor is a well-documented cause of serotonin syndrome (life-threatening toxicity).⁶² Therefore, the risk of serotonin toxicity is well anticipated with linezolid. Its other side effects include lactic acidosis, and peripheral and optic neuropathy. It has generally been avoided as a front-line treatment for MRSA and endocarditis because of its bacteriostatic nature.⁶³⁻⁶⁵

Furthermore, tigecycline is a semisynthetic derivative of minocycline and the first licensed drug in the year 2005 from the glycylcycline class of antimicrobial agents. It has a broad-spectrum activity that includes aerobic and anaerobic Gram-positive and Gram-negative pathogens as well as atypical pathogens. The recent IDSA guideline for the treatment of MRSA did not include tigecycline because of the FDA's September 2010 safety statement.^{65,66} The drug carries a black box warning and is reserved for use in situations when alternative treatments are not suitable.⁶⁷

Telavancin is a once-daily parenteral lipoglycopeptide approved by the FDA in the year 2009 for the treatment of

adult patients with complicated SSTIs, including MSSA and MRSA. The limitations with telavancin are renal dysfunction associated with its use, propensity to cause QT prolongation, and alteration of laboratory values of prothrombin time (PT) and activated partial thromboplastin time (aPTT) and international normalized ratio.⁶⁸ In addition, the black box warning associated with telavancin further reduces its current role. Ceftaroline fosamil is the first FDA-approved cephalosporin with activity against MRSA. Diarrhea was the most commonly reported adverse event (AE) with the ceftaroline fosamil. Potential limitations of the drug include the lack of an oral formulation and the requirement for twice-daily administration.⁶⁹

Teicoplanin is a glycopeptide antibiotic that shares a similar structure and antimicrobial spectrum. It has several advantages over vancomycin in the treatment of serious infections: long half-life, lower nephrotoxicity, and lack of requirement for serum assays. Teicoplanin has the potential to cause ototoxicity and nephrotoxicity.⁷⁰

In the year 2015, a new drug teixobactin was shown to have good efficacy and tolerance in MRSA. This strong bactericidal effect can be explained by its ability of blocking the cell wall synthesis through synergistic inhibition of peptidoglycan and teichoic acid formation, by binding the precursor lipid II and lipid III, causing cell wall injury and the destruction of the bacterial cell. No study in humans has yet been performed. Another newly discovered antibiotic class using a culture-independent approach are the malacins. Malacidin, revealed a calcium-dependent bactericidal in vitro and in vivo effect on Gram-positive bacteria such as *Staphylococcus aureus*, including vancomycin-resistant variants.⁷¹ Although many antibiotic treatments, specifically glycopeptides, are available for DFIs, they are associated with nephrotoxicity, less efficacious results, and a gradual increase in resistance.^{72,73}

Besides the above mentioned parenteral drugs, few traditional oral drugs such as clindamycin, trimethoprim-sulfamethoxazole, doxycycline, and minocycline show clinical efficacy in the treatment of DFIs associated with CA-MRSA. However, clindamycin use is limited because of its bacteriostatic nature and high rate of resistance (both inducible and constitutive) among MRSA clones typically encountered in the hospital setting (HA-MRSA) as well as its ability to predispose to *Clostridium difficile*-associated colitis.⁷⁴ Clindamycin, erythromycin, and amoxicillin/clavulanic acid exhibit high resistance in Gram-positive cocci.⁷⁵

Impaired Microvascular Circulation. Besides antibiotic resistance, the other complication faced in DFI treatment is impaired microvascular circulation, which limits the access of phagocytic cells to the infected area and results in a poor concentration of antibiotics in the infected tissues. However, cellulitis is the most easily treatable and reversible

form of foot infection in patients with diabetes. Deep-skin and soft-tissue infections are also usually curable, but they can be life-threatening and result in substantial long-term morbidity. In India, 16% to 53% of patients with diabetes mellitus have microvascular complications.^{76,77}

Comorbidities. Patients with diabetes are particularly susceptible to foot infection primarily because of neuropathy, vascular insufficiency, and diminished neutrophil function. They are also at a higher risk of macrovascular disease, including hypertension and dyslipidemia. These coexisting factors double the risk for coronary artery disease morbidity and mortality in comparison with the nondiabetic population, thereby making the treatment more challenging.⁷⁸ Diabetic nephropathy is strongly associated with the development of macrovascular complications and with increased cardiovascular mortality. It not only causes renal impairment but has been identified as a contributing factor to atherosclerosis and causes vascular damage at the glomeruli, the retina, and the intima of the arteries. In addition, diabetes is the most significant risk factor for foot amputation among patients with chronic kidney disease.⁷⁸

Antibiotics and Antidiabetic Drug Interactions.

Because the DFI treatment includes both antidiabetic medications and antibiotics to treat infection, it often leads to drug interactions between the 2 classes of drugs and has a clinical impact on the effect of treatment. Most of the antidiabetic drugs are combined with antimicrobials, which are the inhibitors of CYP enzymes: CYP234, CYP2C9, and CYP2C8.

For example, sulfonylureas show drug interaction with fluconazole and miconazole fibrates, which results in elevated risk of hypoglycemia. Similar interaction of sulfonylureas is also reported with clarithromycin. Thiazolidinediones show interaction with other antimicrobials such as ketoconazole and rifampicin, which interferes not only with pharmacokinetic (C_{max} increases) values, but also increases the risk of AEs. DPP4 inhibitors if given in combination with ketoconazole, rifampicin, ritonavir, and clarithromycin, reduce the overall efficacy of antimicrobials. Therefore, while prescribing these combinations, physicians are recommended to perform tight glucose monitoring, dose adjustment requirements, and AE monitoring.^{79,80}

Discussion

Different antibiotics are available to treat DFIs. Only 3 have FDA-approved labeling for DFIs: piperacillin/tazobactam, linezolid, and ertapenem.⁸¹ In 2004, IDSA published a report titled, "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews." This report was based on the weak antibiotic pipeline of the pharmaceutical

companies and a dire need for safe and efficacious drugs that could be approved by the FDA.⁸²

With time, the problem of drug resistance and lack of appropriate antibiotic treatment has only worsened. In India, there is an urgent need for evaluation of MRSA in DFIs, given the fact that India is one of the largest pools of people with diabetes. The clinical need for new antibiotics is clear. The recent discovery of new antibiotic classes and the augmentation of the source pool for further research have brought a glimmer of optimism. But the road to actual clinical benefit might be long, and past experience has taught us that resistance can develop even for very promising molecules. Despite a few hopeful trends, new resistance continues to emerge and proliferate at new sites. There consequently remains a strong need for new antibiotics, particularly those directed against MRSA.

With a rising need for a new antimicrobial agent, the World Health Organization issued a report on priority medicines. The European Medicines Agency and the Federal Drugs Administration decided to amend the assessment process for new antibiotics, work closely with the companies, and provide scientific advice and assistance.⁸³ The introduction of new antibiotics with diverse and novel mechanisms of action can help manage and treat DFIs.

In the past few decades, various antibiotics have been researched against MRSA. There are very few pharma companies involved in inventing new chemical entity antibiotics for multidrug-resistant infections. WCK 771, an arginine salt of levonadifloxacin is an intravenously administered benzoquinolizine antibiotic. Alalevonadifloxacin (also known as WCK 2349) is the oral ester prodrug of WCK 771. Levonadifloxacin is a broad-spectrum antibacterial agent, which targets DNA gyrase along with topoisomerase IV in both Gram-positive and -negative bacterial strains, including MRSA, VISA/glycopeptide-intermediate *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, and levofloxacin/moxifloxacin-resistant staphylococci. It is capable of inhibiting multidrug efflux pumps, including Nor A pump associated with quinolone resistance, in *P aeruginosa*, *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Moreover, it has an excellent activity against *Staphylococcus aureus* Biofilms along with an enhanced antibacterial potency in acidic medium. Currently, the molecule has completed a phase III study for acute bacterial skin and skin structure infections in India.

Conclusion

Diabetes and its associated complications, particularly DFI, are one of the major health care burdens in India. DFIs are predominantly polymicrobial, and *Staphylococcus aureus*, including MRSA, is the major pathogen isolated. Its pathophysiology is complex, and there are many challenges in managing DFIs, which ranges from the severity of infection

to the comorbidities of patients. Systemic antibiotics are the cornerstone in the management of DFIs. However, the increasing multidrug resistance and safety profile of current anti-MRSA agents have forced clinicians to reevaluate treatment options. Therefore, a vigorous effort is continuously needed to not only develop a strict antimicrobial stewardship program, but also research novel antimicrobial agents that could combat the increasing multidrug-resistant MRSA pathogens in DFI patients.

Appendix

IDSA Recommendations for the Management of DFI With MRSA

- Clinically uninfected wounds should not be treated with antibiotic therapy.
 - Antibiotic therapy should be prescribed for all infected wounds, but patients should be cautioned that this is often insufficient unless combined with appropriate wound care.
 - An empirical antibiotic regimen should be selected by clinicians based on the severity of the infection and the likely etiological agent(s):
 - For mild to moderate infections in patients who have not recently received antibiotic treatment, a therapy just targeting aerobic gram-positive cocci is sufficient.
 - For most severe infections, starting broad-spectrum empirical antibiotic therapy, pending culture results and antibiotic susceptibility data is recommended.
 - Empirical therapy directed at *P aeruginosa* is usually unnecessary except for patients with risk factors for true infection with this organism.
 - Consider providing empirical therapy directed against MRSA in a patient with a prior history of MRSA infection, when the local prevalence of MRSA colonization or infection is high, or if the infection is clinically severe.
 - Definitive therapy should be recommended based on the results of an appropriately obtained culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empirical regimen.
 - Clinicians can probably use highly bioavailable oral antibiotics alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections.
 - Antibiotic therapy should be continued until, but not beyond, resolution of findings of infection, but not through complete healing of the wound.
 - An initial antibiotic course for a soft-tissue infection of about 1 to 2 weeks for mild infections and 2 to 3 weeks for moderate to severe infections is suggested.
- In the case of MRSA infections, DFIs should be empirically treated with an antibiotic regimen that covers MRSA in the following situations:
 - The patient has a history of previous MRSA infection or colonization within the past year.
 - The local prevalence of MRSA (i.e., percentage of all *Staphylococcus aureus* clinical isolates in that locale that are methicillin resistant) is high enough (perhaps 50% for a mild and 30% for a moderate soft-tissue infection) that there is a reasonable probability of MRSA infection.
 - The infection is sufficiently severe that failing to empirically cover MRSA while awaiting definitive cultures would pose an unacceptable risk of treatment failure.
 - For bone infections, it is recommended to obtain a specimen of bone when there is concern that MRSA is a pathogen.

Authors' Note

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