

Review article

Antibiotic resistance genes in diabetic foot ulcer microbiomes: Molecular mechanisms and clinical management strategies

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Abstract

Background: Diabetic foot ulcers (DFUs) affect 19.0%–34.0% of patients with diabetes during their lifetime, representing a major global health burden with more than 18 million cases annually. The polymicrobial nature of DFU infections, combined with emerging antibiotic resistance genes, poses considerable clinical management challenges. Methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence reached 84.0% and extended-spectrum beta-lactamase (ESBL) production exceeded 50.0% among Gram-negative isolates in some regions, creating urgent therapeutic concerns.

Objectives: This comprehensive review examines the current understanding of microbial communities in DFUs and their associated resistome, analyzes the molecular mechanisms underlying antibiotic resistance, and evaluates the clinical implications to identify evidence-based management strategies.

Methods: A narrative review was conducted using systematic searches of PubMed/MEDLINE, Embase, Web of Science, and Google Scholar from 2014 to 2025. Search strategies utilized MeSH terms, including “diabetic foot ulcer,” “antibiotic resistance genes,” “microbiome,” and “resistome.”

Result: Analysis revealed extensive resistome diversity, with individual ulcers harboring dozens of distinct resistance determinants. The predominant resistance genes included *mecA* (methicillin resistance, 48.7%–84.0%), *blaCTX-M*, *blaSHV*, *blaTEM* (ESBL production, 26.7%–64.7%), and various fluoroquinolone resistance genes (*qnrS*, 15.4%). Horizontal gene transfer mechanisms facilitate the rapid dissemination of resistance within polymicrobial biofilm communities, thereby substantially affecting treatment outcomes and increasing treatment failure rates.

Conclusion: Antibiotic resistance in DFUs poses a critical challenge that requires urgent, multifaceted approaches. Future directions should prioritize rapid diagnostic technologies, precision antimicrobial approaches, and innovative therapeutic interventions, including antimicrobial photodynamic therapy and bacteriophage treatment, to address this growing threat.

Keywords: Antibiotic resistance genes, antimicrobial resistance, diabetic foot ulcer, microbiome, resistome.

Diabetic foot ulcers (DFUs) represent one of the most devastating complications of diabetes mellitus, affecting approximately 19.0%–34.0% of patients with diabetes during their lifetime and constituting a major global health burden with more than 18 million cases annually worldwide.^(1, 2) The economic impact is substantial, with direct healthcare costs reaching billions annually due to prolonged hospitalizations and

surgical interventions. In contrast, the five-year mortality rate following amputation is 46.0%–57.0%, comparable to that of aggressive cancers.⁽³⁾

The pathogenesis involves complex interactions among compromised immune function, peripheral neuropathy, and microvascular complications, which create microenvironments that favor polymicrobial communities and biofilm formation.⁽⁴⁾ These infections demonstrate remarkable resilience to antimicrobial therapy through synergistic bacterial interactions, quorum sensing, and metabolic cooperation.⁽⁵⁾

Antibiotic resistance has emerged as a crucial threat, with methicillin-resistant *Staphylococcus aureus* (*S. aureus*; MRSA) prevalence reaching up

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to 84.0% and extended-spectrum beta-lactamase (ESBL) producing Gram-negative isolates exceeding 50.0% in some regions.^(6, 7) Horizontal gene transfer mechanisms facilitate the rapid dissemination of resistance within these polymicrobial communities, with individual ulcers harboring dozens of distinct resistance determinants.^(8, 9)

This review synthesizes current knowledge on antibiotic resistance genes in the microbiomes of DFUs, including resistance mechanisms, clinical implications, and therapeutic strategies. The scope encompasses peer-reviewed literature from 2014 to 2025, focusing on molecular epidemiology studies as well as mechanistic investigations to address the urgent need for evidence-based approaches to combat resistance in this vulnerable population.⁽¹⁰⁾

Methods

This comprehensive narrative review was designed to provide an expert synthesis of current knowledge on antibiotic resistance genes in the microbiomes of DFUs.

Reason for the narrative approach

A narrative review approach was selected due to the diverse nature of this field, encompassing molecular, clinical, and epidemiological studies that use fundamentally different methodologies that are unsuitable for meta-analysis. Furthermore, the rapidly evolving genomic technologies and resistance mechanisms require the flexible integration of evidence and expert interpretation to synthesize complex molecular mechanisms with clinical outcomes. Clinical guidance requires integrating mechanistic understanding with practical considerations that go beyond quantitative analysis.

Literature search and selection

Literature searches were conducted using the PubMed/MEDLINE, Embase, Web of Science, and Google Scholar databases, focusing on publications from 2014 to 2025. Search strategies employed MeSH terms and keywords including “diabetic foot ulcer,” “diabetic foot infection,” “antibiotic resistance genes,” “antimicrobial resistance,” “microbiome,” and “resistome.” Priority was given to original research with molecular analysis, clinical studies with resistance characterization, high-impact publications, recent genomic investigations, and studies from diverse geographical regions.

Inclusion criteria comprised: 1) peer-reviewed original research articles, systematic reviews, meta-analyses, or authoritative clinical guidelines published in English between January 2014 and June 2025; 2) studies addressing the microbiome, resistome, antibiotic resistance genes, molecular resistance mechanisms, or antimicrobial management of diabetic foot infections in human subjects; 3) studies reporting microbiological data obtained via culture-based, molecular (PCR, quantitative PCR [qPCR], and multiplex PCR), or sequencing-based (whole-genome sequencing, 16S rRNA sequencing, and shotgun metagenomics) approaches; and 4) reports providing quantitative prevalence data, mechanistic insights, or clinical outcome data relevant to antimicrobial resistance in DFUs. Exclusion criteria comprised: 1) conference abstracts, editorials, commentaries, letters to the editor, and non-peer-reviewed sources; 2) case reports without molecular characterization unless illustrating unique resistance phenotypes of clinical relevance; 3) studies conducted exclusively in non-diabetic chronic wounds without a comparator or extrapolatable data; 4) *in vitro* studies lacking translational implications for clinical practice; and 5) duplicate publications or articles reporting overlapping cohorts.

A total of 352 records were initially identified across the four databases. After removing 89 duplicates, 263 unique records underwent title and abstract screening, of which 173 were excluded for failing to meet the eligibility criteria. The remaining 90 full-text articles were assessed for eligibility, which led to the exclusion of 48 articles for the following reasons: insufficient microbiological characterization ($n = 18$); absence of resistance gene data ($n = 14$); non-diabetic populations ($n = 10$); and language restriction or unavailable full text ($n = 6$). Ultimately, 42 publications were retained as primary references for this narrative review, complemented by additional notable studies cited for historical or mechanistic context. Although not constituting a formal systematic review, this selection process was conducted with explicit, reproducible criteria to enhance methodological transparency and minimize selection bias.

Expert synthesis approach

The author has expertise in infectious diseases, clinical microbiology, and molecular diagnostics and conducted a thematic synthesis that involved the critical

evaluation of methodological approaches, the expert interpretation of conflicting findings, and the integration of basic science with clinical outcomes. This approach enabled the comprehensive coverage of resistance mechanisms and clinical manifestations while providing actionable guidance for healthcare practitioners.

DFU microbiome landscape

Normal skin microbiome vs. diabetic foot microbiome

The human skin microbiome is a complex ecosystem that maintains homeostasis and protects against pathogenic invasion. In healthy individuals, the foot microbiome is dominated by Gram-positive bacteria, particularly *Staphylococcus epidermidis* (*S. epidermidis*), *Corynebacterium* species, and *Cutibacterium acnes*, which establish stable communities adapted to the unique environmental conditions of the foot skin.⁽¹¹⁾

Diabetes fundamentally alters this microbial landscape via multiple mechanisms. Hyperglycemia creates an environment rich in glucose and other nutrients that is favorable for the growth of opportunistic pathogens.⁽⁴⁾ The altered pH of diabetic skin, which is typically more alkaline than normal, disrupts the natural antimicrobial properties of the skin barrier. In addition, compromised immune function in patients with diabetes reduces the host's ability to maintain microbial homeostasis, thereby allowing for the expansion of potentially pathogenic species.

Comparative microbiome studies have revealed substantial differences between healthy foot skin and

the diabetic foot environment. Patients with diabetes exhibit reduced microbial diversity, increased abundance of potentially pathogenic species, and altered community structures even without overt infection.⁽¹²⁾ These changes appear to precede ulcer development, suggesting that microbiome dysbiosis may contribute to ulceration risk rather than simply being a result of it. **Figure 1** illustrates the conceptual framework, showing the progression from a normal microbiome to the development of resistance in DFUs.

Polymicrobial nature of diabetic foot infections

Diabetic foot infections are characteristically polymicrobial, with studies consistently demonstrating multiple bacterial species within individual ulcers. Culture-based studies typically identify 2–5 different bacterial species per infection, while molecular techniques often reveal greater microbial diversity, detecting 10–15 distinct bacterial taxa.⁽⁵⁾ This polymicrobial nature has considerable implications for treatment strategies and resistance development.

The microbial communities within DFUs exhibit complex ecological relationships that influence infection progression and treatment responses. Moreover, synergistic interactions between different bacterial species can enhance virulence, with some organisms producing factors that promote the growth or survival of others. For example, facultative anaerobes may create microaerophilic conditions that promote the growth of strict anaerobes, while certain species produce nutrients or growth factors that benefit community members.

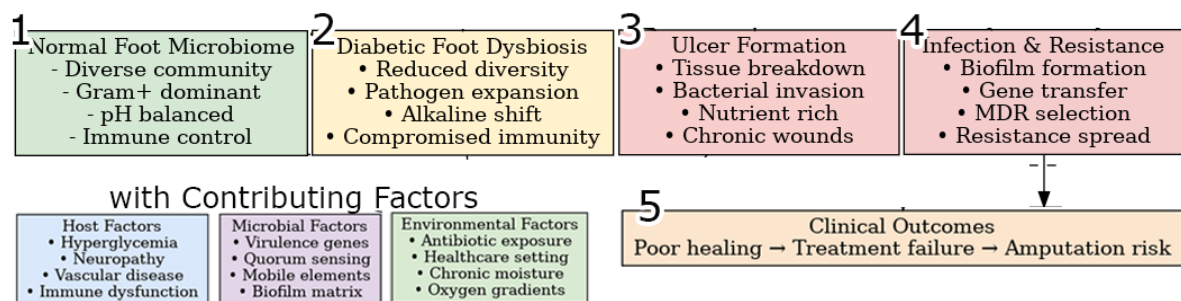


Figure 1. Conceptual framework illustrates the progression from healthy foot microbiome to the establishment of antimicrobial resistance in diabetic foot ulcers. Stage 1 depicts the normal foot microbiome, characterized by diverse, gram-positive-dominant communities with balanced pH and immune homeostasis. Stage 2 shows diabetic foot dysbiosis, marked by reduced microbial diversity, expansion of opportunistic pathogens, alkaline pH shift, and compromised local immunity. Stage 3 represents ulcer formation, in which tissue breakdown, bacterial invasion, nutrient enrichment, and chronic wound conditions converge. Stage 4 illustrates established infection and resistance, involving biofilm formation, horizontal gene transfer, multidrug-resistant clone selection, and resistance gene dissemination. Stage 5 summarizes adverse clinical outcomes—poor wound healing, treatment failure, and increased amputation risk. Three categories of contributing factors—host factors (Hyperglycemia, neuropathy, vascular disease, and immune dysfunction), microbial factors (virulence genes, quorum sensing, mobile genetic elements, and biofilm matrix), and environmental factors (antibiotic exposure, healthcare setting, chronic moisture, and oxygen gradients)—accelerate progression across the cascade. MDR, multidrug resistance.

Competition for resources and ecological niches also shapes the community structure, with dominant species potentially suppressing the growth of others. In addition, antimicrobial therapy can disrupt this competitive balance, potentially leading to the overgrowth of resistant organisms or the emergence of previously minor community members as dominant pathogens.

Predominant bacterial pathogens

The bacterial composition of diabetic foot infections varies considerably depending on factors such as infection severity, prior antibiotic exposure, healthcare setting, and geographic location.⁽¹³⁾ However, certain patterns emerge consistently across studies. Gram-positive cocci, particularly *S. aureus* and *Streptococcus* species, remain the most frequently isolated pathogens, identified in 40.0%–60.0% of infections.⁽¹⁴⁾

Staphylococcus aureus, including methicillin-sensitive and MRSA strains, represents the single most common pathogen in diabetic foot infections. The prevalence of MRSA varies geographically but has increased substantially over the past two decades, with current rates of 15.0%–30.0% in most healthcare settings.⁽¹⁵⁾ Coagulase-negative staphylococci, particularly *S. epidermidis*, are frequently isolated, but their pathogenic importance in polymicrobial infections remains debated.

Gram-negative bacteria play an increasingly important role in chronic or previously treated infections. Enterobacteriaceae, including *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, and *Enterobacter* species, are commonly identified and frequently harbor ESBL genes.⁽¹⁶⁾ Furthermore, *Pseudomonas aeruginosa* (*P. aeruginosa*) is particularly problematic due to its intrinsic resistance to multiple antibiotic classes and its ability to form robust biofilms.

Anaerobic bacteria, including *Bacteroides* species, *Peptostreptococcus*, and *Clostridium* species, are present in 50.0%–80.0% of diabetic foot infections but are often underdetected due to technical challenges in their culture and identification.⁽¹⁷⁾ Recent molecular studies have revealed greater anaerobic diversity than previously appreciated, with important implications for antimicrobial selection.

Biofilm formation and microbial communities

Biofilm formation is a critical virulence mechanism in diabetic foot infections, with studies reporting biofilms

in 60.0%–80.0% of chronic wounds.⁽¹⁸⁾ Biofilms comprise bacterial communities embedded within self-produced extracellular polymeric matrices that protect against host immune responses and antimicrobial agents. The chronic, moist environment of DFUs provides ideal conditions for the development and maturation of biofilms.

The architecture of diabetic foot biofilms is typically complex and heterogeneous, with distinct microenvironments that support different bacterial populations. In addition, oxygen gradients within biofilms create aerobic zones near the surface and anaerobic regions in deeper layers, thereby allowing organisms with different metabolic requirements to co-exist. Nutrient gradients similarly influence bacterial distribution and metabolic activity within the biofilm structure.

Biofilm-associated bacteria exhibit dramatically altered gene expression profiles compared to their planktonic counterparts, with the upregulation of genes involved in stress responses, alternative metabolic pathways, and resistance mechanisms.⁽⁹⁾ These phenotypic changes contribute to the characteristic tolerance of biofilm bacteria to antimicrobial agents, often requiring antibiotic concentrations 100–1,000 times greater than those needed to inhibit planktonic bacteria.

The clinical implications of biofilm formation in diabetic foot infections are profound. Biofilm-associated infections typically exhibit chronic, relapsing patterns with poor responses to standard antimicrobial therapy. The protective nature of the biofilm matrix impedes antibiotic penetration and limits access by host immune cells, thus contributing to persistent infection and delayed wound healing.

Antibiotic resistance genes in DFUs

• Overview of the resistome in diabetic foot infections

The resistome of DFUs encompasses the complete set of antibiotic resistance genes in the microbial communities colonizing these wounds. Recent metagenomic studies have revealed substantial diversity in the resistance gene content, with individual ulcers harboring dozens of distinct resistance determinants.⁽⁵⁾ This extensive resistome reflects the polymicrobial nature of these infections and the selective pressure exerted by frequent antibiotic exposure in patients with diabetes.

Resistance gene abundance in DFUs substantially exceeds that observed in healthy skin microbiomes or other chronic wound types. Comparative studies demonstrate considerably higher densities of resistance genes in diabetic foot infections than in healthy skin microbiomes.⁽¹²⁾ The resistome composition varies notably between patients and even between different sites within individual ulcers, thereby highlighting the heterogeneous nature of these microbial communities.

Temporal studies tracking resistome evolution during treatment reveal dynamic changes in the resistance gene profiles. Initial antibiotic therapy typically leads to selective enrichment of resistant organisms and, subsequently, their associated resistance genes. In contrast, discontinuation of antibiotics may result in gradual shifts toward more diverse microbial communities. However, many resistance genes persist long after antibiotic cessation, which suggests their stable integration into the resident microbiome.

• **Beta-lactamase genes and ESBL producers**

Beta-lactamase genes frequently and critically complicate infections of DFUs. These enzymes confer resistance to beta-lactam antibiotics, including penicillins, cephalosporins, and carbapenems. These antibiotics are the basis of empirical treatment in serious infections. Foot ulcers in patients with diabetes are polymicrobial, exhibiting extensive beta-lactamase genes and multiple enzyme classes with different substrate and inhibitor specificities.

ESBLs, also known as extended-spectrum enzymes, are among the most important concerns as they can hydrolyze broad-spectrum cephalosporins and monobactams. Recent studies of diabetic foot infections have identified various ESBL genes, including *blaCTX-M*, *blaSHV*, and *blaTEM*, with prevalence rates varying substantially across different regions and bacterial species.⁽¹⁹⁻²¹⁾ The distribution patterns of these resistance genes demonstrate considerable geographic and pathogen-specific variation in diabetic foot infections.

Carbapenemase-encoding genes are an emerging threat in diabetic foot infections. Although less prevalent than ESBL genes, they are increasingly becoming clinically important. These enzymes confer resistance to carbapenems, which are typically reserved as last-resort agents for multidrug-resistant infections. NDM-1, *KPC*, and *OXA* types of

carbapenemases are increasingly being reported in isolates from diabetic foot infections, especially in healthcare-associated infections, among patients with prior hospitalization.⁽²²⁾

In a study of *Proteus mirabilis* isolated from diabetic foot infections in Erbil, Iraq, the AmpC-type gene *blaDHA* was detected in 80.0% of isolates, frequently co-occurring with ESBL genes such as *blaTEM* and *blaCTX-M*, thereby highlighting the extensive co-carriage of multiple beta-lactamase determinants within single clinical isolates.⁽²¹⁾ Chromosomal and plasmid-mediated AmpC beta-lactamases further complicate the treatment of diabetic foot infections by conferring resistance to a broad range of beta-lactam antibiotics. Notably, AmpC enzymes are not inhibited by conventional beta-lactamase inhibitors, such as clavulanic acid, which renders standard empirical beta-lactam/inhibitor combinations ineffective against AmpC-producing isolates.

• **Methicillin resistance genes (*mecA* and *mecC*)**

Diabetic foot infections often worsen due to the resistance developed by staphylococci through the *mecA* and *mecC* genes. These genes encode the alternative penicillin-binding protein PBP2a, which exhibits low affinity for beta-lactam antibiotics and confers broad-spectrum beta-lactam resistance. The prevalence of MRSA in diabetic foot infections is 15.0%–30.0% in most healthcare settings, although *mecA* prevalence among *S. aureus* isolates increases up to 84.0% in certain geographical regions.^(7, 23) Molecular typing of *S. aureus* recovered from DFUs in Portugal further demonstrated that *mecA*-positive isolates harbor diverse virulence determinants and clonal profiles that correlate with biofilm-forming capacity and persistence, thus emphasizing the clinical heterogeneity of MRSA diabetic foot infections across geographic settings.⁽²⁴⁾

MecC is a new resistance gene that confers methicillin resistance and may be stealthier than *mecA*, as diagnostic tests can easily overlook it. If *mecC* is present, the strain may display weak resistance and be incorrectly classified as susceptible. Currently, not much is known about the impact of diabetic foot infections caused by *mecC* and how the use of traditional *mecA* resistance therapies influences it. However, based on what is known and the therapies used, it is assumed that resistance mechanisms can lead to outcomes similar to those associated with *mecA*.⁽²⁵⁾

Typing of staphylococcal cassette chromosome mec (SCCmec) shows that SCCmec types differ in size, genetic content, mobility, and the genetic elements that carry the methicillin-resistance genes. In diabetic foot MRSA isolates, the distribution of SCCmec types diverges from the pattern observed in other clinical settings, which indicates distinct selective factors operating within the wound ecosystem.⁽⁹⁾

Infections of the diabetic foot also feature coagulase-negative staphylococci, which, in addition to other characteristics, carry methicillin-resistance genes with a prevalence greater than that of *S. aureus*. Although considered less virulent than *S. aureus*, these coagulase-negative staphylococci serve as resistance gene reservoirs and contribute to polymicrobial infections, complicating antimicrobial management.⁽²⁶⁾

• Fluoroquinolone and aminoglycoside resistance genes

Diabetic foot infections also include fluoroquinolone-resistant infections, which originate from point mutations in the DNA gyrase and topoisomerase IV genes. In addition to these mutations, a phenomenon known as plasmid-mediated quinolone resistance (PMQR) exists, which includes the resistance genes *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *aac(6')-Ib-cr*, and *qepA*.⁽²⁷⁾ These genes provide weak resistance to fluoroquinolones, but strong resistance can be achieved with additional mutations.

PMQR genes are crucial because they can be transferred between species and are often found alongside other resistance factors on multidrug-resistance plasmids. Infections of the diabetic foot have shown an increase in PMQR genes, notably the *qnrB* and *qnrS* variants, in *Enterobacteriaceae*. These genes can lead to treatment failures with fluoroquinolone antibiotics, increasing resistance to these drugs even when bacterial isolates are identified as sensitive by standard testing.⁽²⁸⁾ A cross-sectional molecular survey of ESBL-producing *E. coli* and *Klebsiella* spp. isolates from a Tunisian diabetic foot infection cohort detected *qnr* determinants in 23.1% of strains (6 of 26 isolates), with *qnrS* as the predominant variant (15.4%; 4 of 26 isolates), thereby highlighting the convergence of ESBL production and plasmid-mediated quinolone resistance within a single mobile genetic context.⁽²⁹⁾

Furthermore, the presence of aminoglycoside resistance genes in diabetic foot infections is notable given the traditional use of aminoglycosides for treating gram-negative organisms in these infections. The most common

aminoglycoside resistance genes, *aac(3)-I*, *aac(6')-I*, *ant(2'')-I*, and *aph(3')-I*, are associated with the enzymatic modification of aminoglycoside antibiotics. These genes are part of mobile genetic elements and are often associated with other resistance genes.⁽³⁰⁾

Poor penetration of aminoglycosides into infected tissues and biofilms substantially worsens the already compromised efficacy of these agents in diabetic foot infections. Therapeutic failures and the emergence of additional resistance mechanisms can result from the infection site failing to achieve the necessary drug levels, even if isolates appear sensitive *in vitro*. In recent years, Lund D, *et al.*⁽³⁰⁾ identified new variants of mobile genetic elements in pathogenic bacteria, linking genomic studies to the discovery of over 7,600 distinct aminoglycoside-modifying enzyme families.

• Multidrug resistance gene clusters

Multidrug resistance (MDR) in diabetic foot infections often results from the accumulation of multiple resistance genes on mobile genetic elements, conferring resistance to three or more antibiotic classes. These MDR clusters are prevalent in gram-negative bacteria, where large plasmids can carry extensive arrays of resistance genes, virulence factors, and metabolic capabilities.⁽⁶⁾ Molecular characterization of multidrug-resistant isolates recovered from DFUs in India revealed concurrent carriage of *bla*-family carbapenemase and ESBL genes alongside aminoglycoside-modifying enzymes within a single mobile cassette, thereby providing direct evidence that DFU niches serve as reservoirs for clinically actionable MDR genotypes.⁽³¹⁾ The clinical consequences of such accumulation extend beyond gram-negative organisms, as glycopeptide resistance has been documented in *S. aureus* and enterococci⁽³²⁾ recovered from DFUs in Indonesia, where *vanA* was detected in 1 of 12 (8.3%) *S. aureus* isolates from a regional cohort, indicating the potential encroachment of vancomycin resistance into community-level diabetic wound flora and raising concerns about the utility of last-resort gram-positive agents.⁽³³⁾

Furthermore, Class I integrons play a crucial role in MDR development by providing a mechanism for capturing and expressing antibiotic resistance gene cassettes. These genetic elements are frequently identified in diabetic foot isolates and typically include multiple resistance genes arranged in tandem arrays. Standard gene cassettes encode resistance to beta-lactams, aminoglycosides, trimethoprim, and chloramphenicol.⁽³⁴⁾

Transposons also contribute substantially to MDR in diabetic foot infections by facilitating the movement of resistance genes between different replicons and bacterial hosts. Composite transposons, containing multiple resistance genes flanked by insertion sequences, are particularly important in disseminating resistance in polymicrobial communities. The clinical implications of MDR in diabetic foot infections are severe and often necessitate the use of last-resort antibiotics with substantial toxicity profiles. MDR infections are associated with prolonged hospital stays, increased healthcare costs, and poorer clinical outcomes, including higher rates of amputation and mortality.⁽³⁵⁾

Molecular mechanisms and clinical implications

• Horizontal gene transfer mechanisms

Horizontal gene transfer (HGT) is the primary mechanism that promotes the dissemination of antibiotic resistance within the polymicrobial communities of DFUs. The unique characteristics of these wound environments, including high bacterial densities, prolonged bacterial contact, and selective antibiotic pressure, create the ideal conditions for genetic exchange between bacterial species.⁽⁸⁾

Conjugation, the most clinically important HGT mechanism, involves direct cell-to-cell transfer of genetic material via pili-mediated connections. The moist, nutrient-rich environment of DFUs facilitates conjugative transfer by promoting bacterial adhesion and pili formation. Previous studies have demonstrated active conjugation within diabetic foot biofilms, with transfer frequencies exceeding those observed in planktonic cultures by several orders of magnitude.

Transformation, involving the uptake of free DNA from the environment, occurs readily in diabetic foot infections due to the presence of lysed bacterial cells and released genetic material. Natural competence varies among bacterial species, but many common foot infection pathogens, including *Streptococcus* species and *Haemophilus influenzae*, readily take up exogenous DNA under appropriate conditions.

Transduction, mediated by bacteriophages, also contributes to genetic exchange in diabetic foot infections, although its quantitative relevance remains unclear. Phage particles are commonly detected in chronic wounds, and several studies have documented the transfer of antibiotic resistance genes via phage-mediated mechanisms in wound-associated bacteria.

• Mobile genetic elements and plasmid-mediated resistance

Mobile genetic elements are the primary vehicles for the dissemination of antibiotic resistance genes in diabetic foot infections. Plasmids, as the most important mobile elements, exist as autonomous genetic units capable of replication and transfer between bacterial cells. Large conjugative plasmids commonly isolated from diabetic foot infections often harbor multiple resistance genes, thereby forming single genetic units that confer MDR phenotypes.⁽⁸⁾

Plasmid incompatibility groups provide insights into the epidemiology and transfer characteristics of resistance plasmids. IncF plasmids are particularly prevalent in *Enterobacteriaceae* from diabetic foot infections, are associated with the carriage of ESBL genes, and exhibit high transfer frequencies under selective pressure. IncI and IncN plasmids also contribute substantially to the dissemination of resistance genes in these infections.⁽⁶⁾

Transposons represent another crucial class of mobile genetic elements that can move between DNA molecules within bacterial cells. Composite transposons, such as *Tn1546*, which carry vancomycin resistance genes, can transfer complex resistance phenotypes as single genetic units. The activity of transposases in diabetic foot bacterial communities facilitates the ongoing genetic rearrangement and mobilization of resistance genes.⁽²⁶⁾

Although individually small, insertion sequences play an important role in the mobility of resistance genes by providing recombination sites and promoting genetic instability. The accumulation of insertion sequences in antibiotic-resistant bacteria from diabetic foot infections suggests ongoing selective pressure and genetic adaptation within these microbial communities.⁽⁹⁾

• Effect on treatment outcomes and wound healing

Antibiotic resistance considerably influences clinical outcomes in diabetic foot infections, with resistant infections associated with prolonged healing times, extended hospital stays, and higher healthcare costs. Patients with resistant infections are more likely to experience treatment failure and require additional interventions, such as surgical debridement or amputation.⁽¹⁰⁾

The relationship between antibiotic resistance and wound healing is complex and multifactorial. Resistant organisms often exhibit enhanced virulence

characteristics and biofilm-forming capabilities that directly impair the healing process. The limited therapeutic options for resistant infections may necessitate the use of antibiotics with suboptimal tissue penetration or substantial adverse effects that indirectly affect healing.

MRSA infections in particular demonstrate poor outcomes, with higher rates of amputation than methicillin-sensitive infections. The enhanced pathogenicity of many MRSA strains, combined with limited therapeutic options, contributes to more severe tissue destruction and impaired healing responses.⁽²³⁾

Gram-negative resistance, particularly ESBL production, is associated with increased mortality in diabetic foot infections. ESBL-producing infections are associated with higher mortality than infections caused by susceptible organisms, reflecting the severity of illness and the challenges of achieving effective antimicrobial therapy.⁽¹⁶⁾

• Diagnostic challenges and molecular detection methods

Traditional culture-based diagnostic methods face considerable limitations in detecting and characterizing antibiotic resistance in diabetic foot infections. The polymicrobial nature of these infections, the presence of fastidious organisms, and the influence of biofilm formation on bacterial growth characteristics can lead to the incomplete isolation of organisms and inaccurate resistance profiles.⁽³⁶⁾

Molecular diagnostic methods offer substantial advantages for detecting resistance, providing rapid, sensitive, and specific identification of resistance genes regardless of organism viability or culture characteristics. PCR-based assays for specific resistance genes, such as *mecA* for methicillin resistance or *blaCTX-M* for ESBL production, can provide clinically actionable information within hours rather than the days required for conventional culture testing (**Table 1**).⁽³⁷⁾

Furthermore, next-generation sequencing (NGS) technologies enable comprehensive characterization of the resistome, providing detailed information about resistance gene diversity, abundance, and genetic context. Whole-genome sequencing of bacterial isolates can identify novel resistance mechanisms, track transmission patterns, and accurately predict resistance phenotypes.⁽³⁷⁾

Point-of-care diagnostic devices are an emerging frontier in resistance detection, potentially enabling rapid resistance screening in outpatient settings. These devices could facilitate the appropriate selection of empirical therapy and reduce unnecessary use of broad-spectrum antibiotics, thereby contributing to antimicrobial stewardship efforts.⁽¹⁰⁾

Therapeutic strategies and management

• Current antimicrobial treatment approaches

The contemporary antimicrobial management of diabetic foot infections requires careful consideration of infection severity, likely pathogens, local resistance patterns, and patient-specific factors. Current guidelines recommend empirical therapy selection based on infection classification. Mild infections are typically managed with oral agents targeting gram-positive cocci, whereas moderate-to-severe infections require broad-spectrum parenteral therapy covering gram-positive and gram-negative pathogens.⁽¹⁰⁾

For mild infections in patients without risk factors for resistance, oral agents such as clindamycin, trimethoprim-sulfamethoxazole, or fluoroquinolones provide appropriate coverage for common gram-positive pathogens. However, the increasing prevalence of resistance to these agents necessitates the careful consideration of local epidemiology and prior patient exposure.

Moderate-to-severe infections typically require hospitalization and parenteral antimicrobial therapy. Beta-lactam/beta-lactamase inhibitor combinations, such as piperacillin-tazobactam or ampicillin-sulbactam, provide broad-spectrum coverage, including against anaerobic organisms. However, these agents may be inadequate in settings with high ESBL prevalence, thereby necessitating carbapenem use as first-line therapy.

Furthermore, MRSA coverage in diabetic foot infections requires careful risk assessment. Vancomycin, linezolid, or daptomycin is recommended for patients with risk factors, including a previous MRSA infection, recent hospitalization, or residence in a long-term care facility. The choice between agents depends on infection severity, renal function, and the ability to achieve adequate tissue concentrations.

Figure 2 presents a comprehensive clinical decision algorithm for antimicrobial therapy selection in diabetic foot infections.

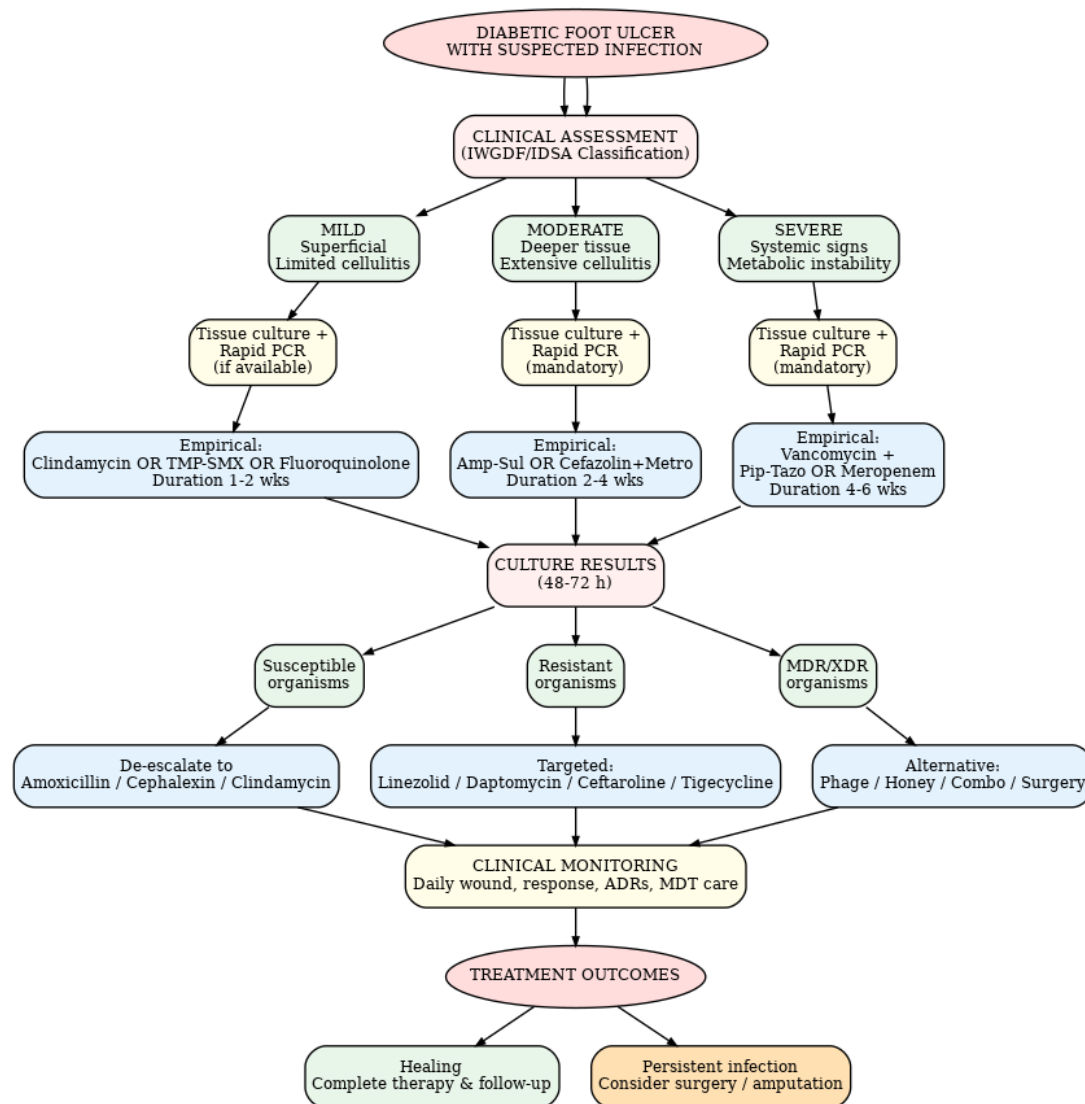


Figure 2. Clinical decision algorithm for the selection of antimicrobial therapy in diabetic foot infections. Following initial clinical assessment using the IWGDF/IDSA classification, infections are stratified as mild (superficial, limited cellulitis), moderate (deeper tissue, extensive cellulitis), or severe (systemic signs, metabolic instability). A tissue culture combined with rapid PCR is recommended for moderate and severe infections and is optional for mild infections. Empirical antibiotic regimens are selected by severity: clindamycin, trimethoprim–sulfamethoxazole, or fluoroquinolone for 1–2 weeks for mild infection; ampicillin–sulbactam or cefazolin plus metronidazole for 2–4 weeks for moderate infection; and vancomycin plus piperacillin–tazobactam or meropenem for 4–6 weeks for severe infection. Culture results obtained at 48–72 h guide subsequent therapy: de-escalation (amoxicillin, cephalexin, or clindamycin) for susceptible organisms; targeted therapy (linezolid, daptomycin, ceftaroline, or tigecycline) for resistant organisms; and alternative or adjunctive approaches (bacteriophage therapy, medical-grade honey, combination regimens, or surgical intervention) for multidrug- or extensively drug-resistant organisms. Daily clinical monitoring of wound status, treatment response, adverse drug reactions (ADRs), multidisciplinary team (MDT) care, informs the treatment outcomes, which are classified as healing (with therapy completion and structured follow-up) or persistent infection (which should prompt the consideration of surgical management or amputation).

• Novel antimicrobial agents and combination therapies

The emergence of extensive antibiotic resistance has spurred the development of novel antimicrobial agents designed to overcome the common resistance mechanisms. Ceftaroline, a fifth-generation

cephalosporin with activity against MRSA, represents an important addition to the antimicrobial armamentarium for diabetic foot infections. Clinical trials demonstrated efficacy comparable to that of vancomycin plus aztreonam, with potentially improved tolerability.⁽¹⁰⁾

Ceftolozane–tazobactam combines a novel cephalosporin with a beta-lactamase inhibitor, thereby enhancing its activity against MDR *P. aeruginosa* and ESBL-producing *Enterobacteriaceae*. This combination exhibits promise for diabetic foot infections involving gram-negative organisms with complex resistance patterns.

Combination therapy approaches offer potential advantages in treating resistant diabetic foot infections, including synergistic antimicrobial effects, reduced development of resistance, and improved penetration into biofilms. Beta-lactam combinations with aminoglycosides or fluoroquinolones may enhance their activity against gram-negative pathogens. In contrast, combination regimens targeting gram-positive and gram-negative organisms can address the polymicrobial nature of these infections.

Novel drug delivery systems, including antibiotic-loaded nanoparticles and sustained-release formulations, provide improved drug penetration into infected tissues and biofilms. These approaches may overcome pharmacokinetic limitations that contribute to treatment failures in diabetic foot infections.

• Non-antibiotic therapeutic options

Recognition of the limitations of antimicrobial therapy alone has prompted the investigation of alternative and adjunctive treatment modalities for diabetic foot infections. Antimicrobial photodynamic therapy uses photosensitizing compounds that are activated by specific wavelengths of light to generate reactive oxygen species that destroy bacterial cells. This approach has exhibited potential against biofilm-associated infections and antibiotic-resistant organisms.⁽³⁸⁾

Bacteriophage therapy is an early-20th-century treatment modality that uses naturally occurring bacterial viruses to target specific pathogens. Phage therapy offers several theoretical advantages, including specificity for target organisms, the ability to replicate at sites of infection, and the lack of cross-resistance with conventional antibiotics. Recent clinical trials have demonstrated its potential efficacy in diabetic foot infections, particularly those involving MDR organisms.⁽³⁹⁾

Medical-grade honey, particularly manuka honey, demonstrates broad-spectrum antimicrobial activity and wound healing properties. Clinical studies in DFUs show improved healing rates and reduced infection when honey is used as an adjunct to conventional

therapy. The antimicrobial mechanisms of honey include osmotic effects, hydrogen peroxide production, and methylglyoxal activity.⁽⁴⁰⁾

Furthermore, silver-based antimicrobial dressings provide sustained antimicrobial activity and may be particularly beneficial for superficial infections or prophylaxis in high-risk ulcers. However, concerns about cytotoxicity and potential for resistance development require careful consideration in their clinical application.⁽⁹⁾

• Wound care and multidisciplinary management

The effective management of diabetic foot infections extends beyond antimicrobial therapy to encompass comprehensive wound care and multidisciplinary interventions. Surgical debridement remains a cornerstone of treatment by removing necrotic tissue, reducing bacterial load, and improving antibiotic penetration. The extent and frequency of debridement should be individualized based on the infection severity and tissue viability.⁽¹⁰⁾

Offloading, which is the redistribution of pressure away from infected areas, is critical for healing diabetic foot infections. Total contact casting, removable cast walkers, and specialized footwear can reduce the pressure and shear forces that impede healing. Patient education and compliance with offloading recommendations substantially affect treatment outcomes.⁽²⁾

Advanced wound care modalities, including negative pressure wound therapy, hyperbaric oxygen, and growth factor applications, may be more beneficial for selected patients. These interventions can improve local tissue oxygenation, promote angiogenesis, and accelerate the wound healing process.⁽⁴¹⁾

In addition, glycemic control optimization is fundamental to the successful treatment of infections, as hyperglycemia impairs immune function and wound healing. Multidisciplinary teams involving endocrinologists, wound care specialists, podiatrists, and infectious disease specialists provide comprehensive care that addresses all aspects of diabetic foot infections.⁽¹⁰⁾

Future directions and recommendations

• Emerging technologies

NGS technologies are revolutionizing our understanding of the microbiology and resistance mechanisms of diabetic foot infections. Whole-genome

sequencing of bacterial isolates provides comprehensive information about the resistance genes, virulence factors, and phylogenetic relationships, which can inform treatment decisions and infection control measures. Real-time sequencing platforms may soon enable rapid, comprehensive pathogen characterization directly from clinical samples.⁽³⁶⁾

Furthermore, metagenomic approaches offer insights into the complete microbial communities within DFUs, including unculturable organisms and their functional capabilities. Shotgun metagenomics can simultaneously identify all microorganisms present and characterize their collective resistome, thereby providing a comprehensive picture of antimicrobial resistance potential within the wound environment.⁽³⁷⁾

Artificial intelligence (AI) and machine learning applications have the potential to improve diagnostic accuracy and optimize treatment in diabetic foot infections. AI algorithms can integrate clinical, microbiological, and genomic data to predict treatment outcomes, identify optimal antimicrobial regimens, and forecast patterns of resistance development. Machine learning models may enable personalized treatment recommendations based on individual patient characteristics and local epidemiological patterns.⁽³⁷⁾

Moreover, long-read sequencing technologies are improving our ability to characterize mobile genetic elements and understand the genetic context of resistance genes. These approaches can identify complete plasmid sequences, resolve complex genomic rearrangements, and track HGT events in real time.⁽⁸⁾

• **Personalized medicine and precision therapy**

The future of diabetic foot infection management lies in personalized medicine approaches that tailor interventions to the individual patient characteristics, pathogen profiles, and host-microbe interactions. Pharmacogenomic testing may identify patients with altered drug metabolism or increased susceptibility to adverse effects, thereby enabling dosing optimization and drug selection tailored to individual genetic profiles.⁽⁴⁾

Precision antimicrobial therapy, guided by rapid molecular diagnostics and AI-assisted decision support systems, could substantially improve treatment outcomes while reducing unnecessary antibiotic exposure. The real-time monitoring of treatment response through biomarker analysis or continuous wound assessment may enable dynamic therapy adjustments based on clinical progress.⁽⁴²⁾

Furthermore, host immune profiling may identify patients with specific immune deficiencies or inflammatory patterns that require targeted interventions. Immunomodulatory therapies could enhance host defense mechanisms, while conventional antimicrobials address the infectious burden.⁽⁴¹⁾

Microbiome restoration strategies, including targeted probiotics or fecal microbiota transplantation, may assist in restoring healthy microbial communities and preventing infection recurrence. These approaches could be particularly beneficial in patients with recurrent infections or a history of extensive antibiotic exposure.⁽²⁾

• **Prevention and antimicrobial stewardship**

Antimicrobial stewardship programs for diabetic foot infections are urgently required to optimize antibiotic use and prevent the development of resistance. These programs should incorporate infection-prevention strategies, diagnostic stewardship, and treatment-optimization protocols tailored to the unique characteristics of diabetic foot infections.⁽¹⁰⁾

Prevention strategies should address the primary prevention of foot ulceration and the secondary prevention of infection in established ulcers. Primary prevention includes patient education, foot care programs, appropriate footwear, and regular podiatric assessment. Secondary prevention focuses on early ulcer recognition, appropriate wound care, and the judicious use of antimicrobial agents.⁽²⁾

Rapid diagnostic testing implementation could considerably improve antimicrobial stewardship by enabling targeted therapy selection and reducing the use of broad-spectrum antibiotics. Moreover, point-of-care resistance testing may enable immediate therapy optimization and reduce the selective pressure that drives resistance development.⁽⁹⁾

Surveillance programs tracking resistance trends in diabetic foot infections are essential for guiding empirical therapy recommendations and identifying emerging resistance threats. These programs should integrate data from multiple healthcare settings and geographical regions to provide comprehensive epidemiological insights.⁽⁶⁾

• **Research gaps and future priorities**

There are several critical research gaps that must be addressed to advance our understanding and management of antibiotic resistance in diabetic foot infections. Long-term prospective studies that track

the evolution of resistance in individual patients are required to understand the dynamics of resistance development and to identify intervention opportunities.⁽⁹⁾

The role of the local wound environment in promoting the development of resistance requires further investigation. Studies examining the influence of wound characteristics, biofilm formation, and host factors on the expression and transfer of resistance genes could identify novel therapeutic targets.⁽¹⁸⁾

Standardization of diagnostic approaches for diabetic foot infections is urgently needed to enable meaningful comparison between studies and the development of evidence-based treatment guidelines. This includes the standardization of sampling techniques, molecular diagnostic methods, and resistance detection protocols.⁽³⁷⁾

In addition, clinical trials evaluating antimicrobial agents for diabetic foot infections are needed, as many current treatment recommendations are based on extrapolation from other infection types. These trials should incorporate modern diagnostic techniques and consider the unique challenges of treating biofilm-associated polymicrobial infections.⁽³⁹⁾

• Clinical practice recommendations

Based on the current evidence and emerging trends, several clinical practice recommendations can be made to manage antibiotic resistance in diabetic foot infections. First, empirical antimicrobial therapy should be guided by local resistance patterns and individual patient risk factors, with regular review and adjustment based on the patient's culture results and clinical response.⁽¹⁰⁾

Rapid diagnostic testing should be implemented wherever possible to enable targeted therapy and reduce the unnecessary use of broad-spectrum antibiotics. This includes phenotypic susceptibility testing and molecular methods for resistance gene detection.⁽⁹⁾

Moreover, combination therapy should be considered for severe infections involving MDR organisms, with careful attention to potential synergistic effects and toxicity profiles. Therapy duration should be individualized based on clinical response and infection severity rather than rigid protocol adherence.⁽⁶⁾

Multidisciplinary care teams should address all aspects of diabetic foot infection management, including antimicrobial optimization, wound care,

glycemic control, and patient education. Regular case review and consultation with infectious disease specialists can improve treatment outcomes and reduce the development of resistance.⁽¹⁰⁾

Finally, patient education on infection prevention, medication adherence, and the importance of completing prescribed antimicrobial courses is essential for optimizing individual outcomes and reducing the development of community resistance.⁽²⁾

Conclusion

Antibiotic resistance in DFUs is a critical, evolving challenge that requires urgent, multifaceted approaches. The polymicrobial nature of these infections, combined with unique wound environments and patient characteristics, creates ideal conditions for the development and dissemination of resistance. Current evidence indicates alarming trends of rising rates of resistance among common pathogens, with MRSA prevalence reaching up to 84.0% and ESBL production exceeding 50.0% among gram-negative isolates in some regions, thus necessitating immediate action to preserve effective treatment options.

The resistome of DFUs encompasses diverse resistance mechanisms affecting all major antibiotic classes, with HGT facilitating rapid dissemination within microbial communities. Resistance substantially affects clinical outcomes, with resistant infections associated with prolonged healing times, increased complications, and higher healthcare costs. These findings highlight the importance of preventing resistance and optimizing antimicrobial stewardship in clinical practice.

Future directions should prioritize rapid diagnostic technologies, novel therapeutic approaches, and personalized treatment strategies. Integrating genomic technologies, AI, and precision medicine offers innovative opportunities to improve patient outcomes while combating the development of resistance. However, realizing these advances requires sustained research investment, healthcare system adaptation, and coordinated efforts from clinicians, researchers, and policymakers to preserve effective therapeutic options for patients with diabetes facing this devastating complication.

Table 1. Prevalence of major antibiotic resistance genes in diabetic foot ulcers.

Gene	Antibiotic class	Prevalence (%)	Sample size	Study design	Detection method	Study region	Associated organism	Reference
<i>mecA</i>	β-lactams (methicillin)	48.7	n = 41 <i>S. aureus</i> isolates (of 53 staphylococci)	Cross-sectional	PCR; PFGE; MLST; E-test	Portugal	<i>S. aureus</i>	Mottola C, et al., 2016
<i>mecA</i>	β-lactams (methicillin)	84.0	n = 50 patients	Cross-sectional	PCR; disk diffusion	Pakistan	<i>S. aureus</i>	Chaudhry WN, et al., 2016
<i>blaNDM-1</i>	Metallo-β-lactamase	52.9	n = 480 patients; 70 isolates; 19 ESBL producers; 43 MBL producers	Cross-sectional	Multiplex PCR	India	<i>Acinetobacter baumannii</i>	Khan DM, et al., 2025
<i>blaDHA</i>	β-lactams (AmpC)	80.0	n = 84 patients; 18 isolates	Cross-sectional	PCR; combined-disc; DDST	Iraq	<i>Proteus mirabilis</i>	Fattah Hamid S, et al., 2020
<i>blaTEM</i>	β-lactams (ESBL)	52.9	n = 480 patients; 70 isolates; 19 ESBL producers	Cross-sectional	Multiplex PCR	India	<i>A. baumannii</i>	Khan DM, et al., 2025
<i>blaTEM</i>	β-lactams (ESBL)	64.7	n = 400 patients; 70 isolates; 17 ESBL producers	Cross-sectional	PCR; Kirby-Bauer; DDST; MIC; MHT	India	<i>A. baumannii</i>	Khan DM, et al., 2018
<i>blaSHV</i>	β-lactams (ESBL)	29.4	n = 400 patients; 70 isolates; 17 ESBL producers	Cross-sectional	PCR; Kirby-Bauer; DDST; MIC; MHT	India	<i>A. baumannii</i>	Khan DM, et al., 2018
<i>qnrS</i>	Fluoroquinolones (PMQR)	15.4	n = 26 isolates	Cross-sectional	MALDI-TOF; PCR; sequencing	Tunisia	<i>E. coli & Klebsiella spp.</i>	Arfaoui A, et al., 2024
<i>vanA</i>	Glycopeptides	8.3	n = 32 patients; 12 <i>S. aureus</i> isolates; 2 VRSA	Cross-sectional	PCR; MIC	Indonesia	<i>S. aureus</i>	Soleha TU, et al., 2024
<i>blaOXA</i>	β-lactams	52.6	n = 42 patients; 142 isolates; 38 MDR isolates	Cross-sectional	PCR; disk diffusion	India	<i>MDR bacteria (mixed species)</i>	Shahi SK, et al., 2016
<i>blaCTX-M</i>	β-lactams (ESBL)	26.7	n = 84 patients; 18 isolates	Cross-sectional	PCR; combined-disc; DDST	Iraq	<i>P. mirabilis</i>	Fattah Hamid S, et al., 2020

AmpC, ampicillin C-type cephalosporinase; AST, antimicrobial susceptibility testing; DDST, double-disc synergy test; ESBL, extended-spectrum β-lactamase; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MHT, modified Hodge test; MIC, minimum inhibitory concentration; MLST, multilocus sequence typing; PCR, polymerase chain reaction; PFGE, pulsed-field gel electrophoresis; PMQR, plasmid-mediated quinolone resistance; All studies cited in this table examined diabetic foot ulcer or diabetic foot infection cohorts directly; the qnr-related entry for Arfaoui A, et al. (2024) reports the predominant variant (qnrS) detected in 4 of 26 Enterobacteriaceae from diabetic foot infections in Tunisia, with qnrB additionally detected in 2 of 26 isolates.

Author contributions

FAP contributed substantially to the study concept and design, data acquisition, literature review, and data analysis and interpretation. FAP contributed to drafting the manuscript. FAP edited the manuscript critically for important intellectual content. The author approved the final version submitted for publication and takes responsibility for statements made in the published article.

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Ethical approval

Not applicable.

Conflict of interest statement

The author declares that there are no competing interests.

Data sharing statement

The present review is based on the references cited. All data generated or analyzed during the present study are included in this published article and the citations herein. Further details, opinions, and interpretation are available from the corresponding author on reasonable request.

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