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Review Article
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MULTIDRUG-RESISTANT BACTERIAL INFECTIONS: CURRENT MANAGEMENT STRATEGIES AND EMERGING THERAPEUTIC APPROACHES

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ABSTRACT
Multi drug -resistant (MDR) bacterial infections are a growing global health challenge that limit the effectiveness of existing antibiotics and increase patient morbidity and mortality. Effective management involves optimized antimicrobial therapy, combination treatment, rapid diagnostics, infection prevention, and antimicrobial stewardship. Emerging approaches such as bacteriophage therapy, antimicrobial peptides, antivirulence agents, immunotherapy, nanotechnology, plant-derived compounds, and novel antibiotics offer promising alternatives for treating resistant pathogens. Although many of these strategies are still under development, integrating conventional and innovative therapies with rational antibiotic use is essential to improve clinical outcomes and combat the rising threat of antimicrobial resistance.

Keywords: *Multidrug-resistant bacteria (MDR), antimicrobial resistance (AMR), antibiotic resistance, antimicrobial stewardship, combination therapy, rapid diagnostics.*

INTRODUCTION
Antimicrobial resistance (AMR) has emerged as one of the most serious global public health threats of the twenty-first century. The rapid emergence and spread of multidrug-resistant (MDR) bacteria have substantially reduced the effectiveness of many commonly used antibiotics, making the treatment of bacterial infections increasingly challenging. [1]. Factors such as the inappropriate use of antibiotics in human and veterinary medicine, poor infection control practices, and the limited development of new antimicrobial agents have accelerated the evolution of resistant pathogens [2]. As a result, MDR bacterial infections are associated with prolonged hospital stays, increased healthcare costs, higher morbidity, and greater mortality worldwide [3].

The World Health Organization has identified several priority bacterial pathogens, including carbapenem-resistant Gram-negative bacteria, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, and multidrug-resistant *Pseudomonas aeruginosa*, because of their significant clinical impact and limited therapeutic options [4]. These pathogens present major challenges in both community and healthcare settings and require urgent attention for the development of effective treatment strategies.(5)

Current management of MDR bacterial infections extends beyond the use of conventional antibiotics. It involves optimized antimicrobial therapy, combination regimens, rapid diagnostic technologies, antimicrobial stewardship, infection prevention and control measures, and source control [6]. In addition, several innovative therapeutic approaches-including novel antibiotics, bacteriophage therapy, antimicrobial peptides, antivirulence agents, host-directed therapies, immunotherapy, nanotechnology-based drug delivery systems, and plant-derived antimicrobial compounds-are being investigated to overcome resistance and improve patient outcomes [7].

This review discusses the current strategies employed in the management of multidrug-resistant bacterial infections, examines emerging therapeutic approaches, and highlights future perspectives that may help address the growing burden of antimicrobial resistance while preserving the effectiveness of existing and newly developed antimicrobial agents [8].

METHODOLOGY

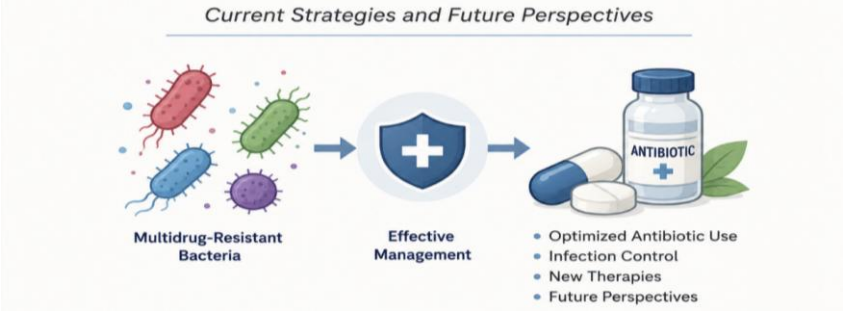

Figure 01: Management of Multidrug-resistance bacterial infection

This review was prepared by collecting information from published research articles, review papers, clinical guidelines, and reports published between 2015 and 2025 [9]. Literature was searched using databases such as PubMed, Google Scholar, Scopus, Web of Science, and Science Direct. Official reports from international health organizations were also included [10]. Studies related to multidrug-resistant bacterial infections, antimicrobial resistance, diagnosis, treatment, antimicrobial stewardship, and new therapies were selected [11]. The collected information was carefully reviewed and summarized to describe the current management strategies, recent advances, challenges, and future perspectives for multidrug-resistant bacterial infections [12].

EPIDEMIOLOGY AND COMMON MULTIDRUG-RESISTANT (MDR) PATHOGENS

Antimicrobial resistance (AMR) is recognized as one of the most pressing global health challenges, contributing to increased illness, death, longer hospital stays, and rising healthcare expenditures [13]. Multidrug-resistant (MDR) bacterial infections are especially common among critically ill patients, individuals admitted to intensive care units, immunocompromised patients, and those with prolonged exposure to broad-spectrum antibiotics [14]. Most clinically important MDR bacteria belong to the ESKAPE group, which are characterized by their ability to evade antimicrobial treatment and persist in healthcare environments [15].

1. Methicillin-Resistant Staphylococcus aureus (MRSA): MRSA is one of the most prevalent Gram-positive multidrug-resistant pathogens worldwide. It is responsible for a wide range of infections, including skin and soft tissue infections, bacteremia, pneumonia, infective endocarditis, and surgical-site infections [16]. Resistance is primarily mediated by the mecA or mecC genes, which encode the altered penicillin-binding protein (PBP2a), resulting in resistance to most β-lactam antibiotics. Although agents such as vancomycin and linezolid remain effective against many strains, MRSA continues to impose a significant global clinical burden [17].

2. Vancomycin-Resistant Enterococcus (VRE)

Vancomycin-resistant Enterococcus, particularly Enterococcus faecium, has become a major cause of hospital-acquired infections, especially among patients in intensive care units and those undergoing oncology or transplant treatment [18]. It commonly causes bloodstream infections, urinary tract infections, intra-abdominal infections, and infective endocarditis [19]. Resistance is mainly associated with the vanA and vanB gene clusters, which reduce the effectiveness of vancomycin. The growing incidence of VRE has considerably narrowed available treatment options and increased the complexity of infection management [20].

3. Extended-Spectrum β-Lactamase (ESBL)-Producing Enterobacterales

ESBL-producing Enterobacterales, particularly Escherichia coli and Klebsiella pneumoniae, have become widespread in both healthcare and community settings [21]. These bacteria produce enzymes capable of inactivating third-generation cephalosporins and aztreonam while generally remaining susceptible to carbapenems [22]. They are frequently implicated in urinary tract infections, bloodstream infections, pneumonia, and intra-abdominal infections. Their increasing prevalence is largely driven by excessive antibiotic use and the transfer of resistance genes through plasmids [23].

4. Carbapenem-Resistant Enterobacterales (CRE)

Carbapenem-resistant Enterobacterales are classified by the World Health Organization as critical-priority pathogens because of their limited treatment options and high mortality rates [24]. Resistance is mainly mediated by carbapenemase enzymes such as KPC, NDM, OXA-48-like, and VIM. The organisms most commonly involved are Klebsiella pneumoniae and Escherichia coli. (25)CRE frequently causes severe infections, including bloodstream infections, ventilator-associated pneumonia, urinary tract infections, and intra-abdominal infections, particularly among hospitalized patients [26].

5. Multidrug-Resistant Pseudomonas aeruginosa

Multidrug-resistant Pseudomonas aeruginosa is an opportunistic Gram-negative pathogen commonly associated with ventilator-associated pneumonia, bloodstream infections, burn wound infections, urinary tract infections, and infections in immunocompromised individuals [27]. Its remarkable ability to develop resistance through mechanisms such as efflux pumps, porin alterations, β-lactamase production, and biofilm formation makes treatment particularly difficult. It remains a major cause of healthcare-associated infections worldwide [28].

6. Multidrug-Resistant Acinetobacter baumannii

Acinetobacter baumannii has emerged as one of the most problematic hospital-acquired pathogens, particularly in intensive care settings [29]. It commonly causes ventilator-associated pneumonia, bloodstream infections, wound infections, and meningitis [30].The organism can survive for prolonged periods in the hospital environment and readily acquires resistance mechanisms, including OXA-type carbapenemases. Carbapenem-resistant A [31]. baumannii is associated with poor clinical outcomes and is considered one of the most difficult MDR pathogens to manage [32].

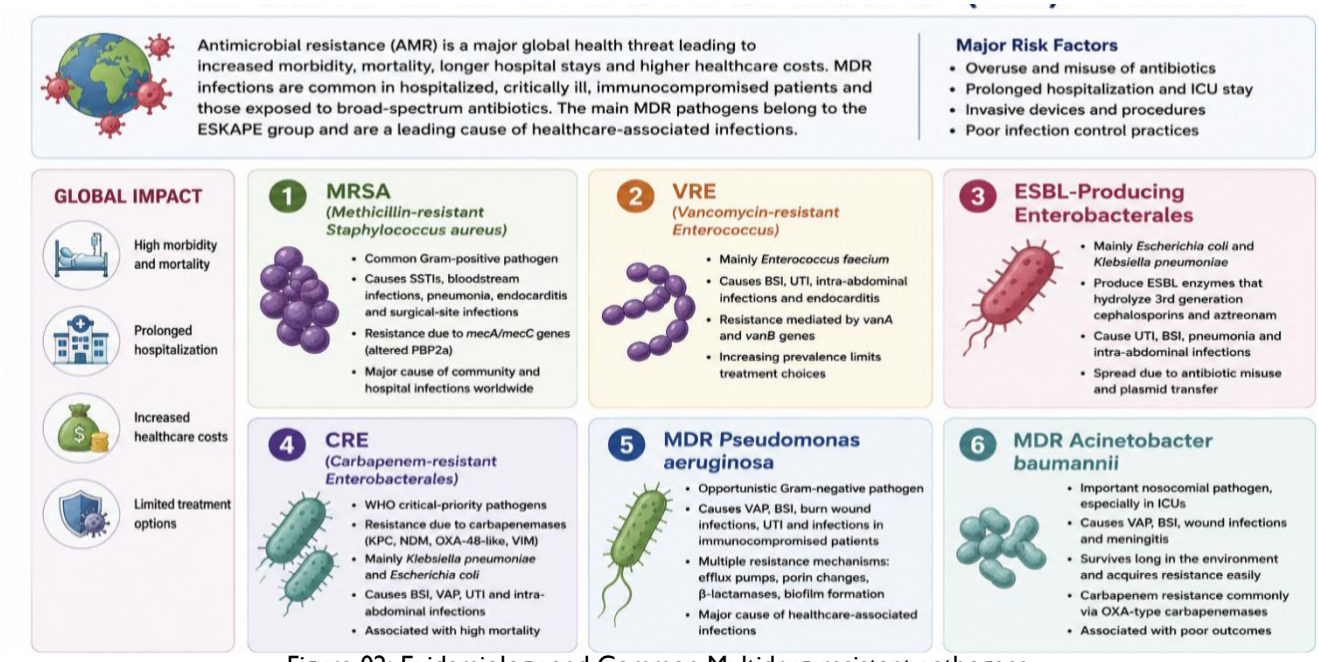

Figure 02: Epidemiology and Common Multidrug-resistant pathogens

MECHANISMS OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance (AMR) occurs when bacteria develop the ability to survive exposure to antibiotics that were previously effective against them. Resistance develops through spontaneous genetic mutations or by acquiring resistance genes from other bacteria via horizontal gene transfer [33].The excessive and inappropriate use of antibiotics in human medicine, veterinary practice, and agriculture has accelerated the emergence and spread of multidrug-resistant (MDR) bacteria [34].

The major mechanisms of antimicrobial resistance include:

1. Enzymatic Inactivation

Some bacteria produce enzymes that destroy or modify antibiotics before they reach their target. Important examples include β-lactamases such as ESBLs and carbapenemases, which inactivate β-lactam antibiotics [35].

2. Modification of Drug Targets

Bacteria can alter the structure of antibiotic target sites, reducing drug binding and effectiveness. For example, MRSA produces an altered penicillin-binding protein (PBP2a), while other bacteria modify ribosomal targets to resist protein synthesis inhibitors [36].

3. Reduced Membrane Permeability

Gram-negative bacteria may decrease the entry of antibiotics by reducing or altering outer membrane porin channels. This limits intracellular drug accumulation and contributes to resistance [37].

4. Active Efflux Pumps

Efflux pump systems actively remove antibiotics from bacterial cells, lowering intracellular drug concentrations and reducing their antibacterial activity [38].

5. Biofilm Formation

Many MDR bacteria form biofilms that protect them from both antibiotics and the host immune system. Biofilms reduce drug penetration and promote persistent or recurrent infections [39].

6. Horizontal Gene Transfer

Resistance genes are transferred between bacteria through plasmids, transposons, and integrons. This process facilitates the rapid dissemination of multidrug resistance across bacterial populations [40].

7. Metabolic Adaptation

Some bacteria survive by protecting antibiotic target sites or utilizing alternative metabolic pathways that bypass the action of antimicrobial agents [41].

RISK FACTORS FOR MULTIDRUG-RESISTANT (MDR) BACTERIAL INFECTIONS

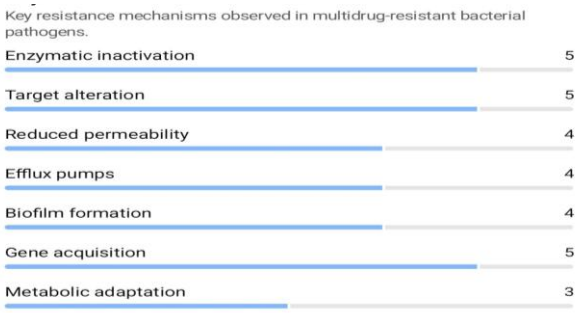

Figure 03: Major mechanisms of antimicrobial resistance

The development of multidrug-resistant (MDR) bacterial infections is influenced by several patient-related, healthcare-related, and environmental factors. Identifying these risk factors is essential for early diagnosis, appropriate antimicrobial therapy, and effective infection prevention [42].

1. Previous Antibiotic Exposure

Prior or prolonged use of broad-spectrum antibiotics is one of the strongest predictors of MDR infections. Inappropriate antibiotic prescribing increases selective pressure, promoting the emergence and spread of resistant organisms [43].

2. Prolonged Hospitalization

Extended hospital stays, particularly in intensive care units (ICUs), increase the risk of exposure to MDR pathogens because of frequent contact with contaminated environments, healthcare workers, and invasive procedures [44].

3. Intensive Care Unit (ICU) Admission

Critically ill patients admitted to ICUs are at greater risk due to severe underlying illness, frequent antibiotic use, invasive devices, and prolonged hospitalization [45].

4. Invasive Medical Devices

The use of mechanical ventilators, urinary catheters, central venous catheters, and other invasive devices provides a route for bacterial colonization and biofilm formation, increasing the likelihood of MDR infections [46].

5. Immunocompromised State

Patients with weakened immune systems, including those with cancer, organ transplants, HIV infection, diabetes, or those receiving immunosuppressive therapy, are more susceptible to infections caused by resistant bacteria [47].

6. Chronic Comorbidities

Underlying diseases such as chronic kidney disease, chronic lung disease, liver disease, and cardiovascular disorders are associated with a higher incidence of MDR bacterial infections because of repeated healthcare exposure and impaired host defences [48].

7. Previous Colonization or Infection with MDR Organisms

Individuals previously colonized or infected with MDR bacteria have an increased risk of recurrent infection and transmission of resistant organisms within healthcare facilities [49].

8. Poor Infection Prevention and Control

Inadequate hand hygiene, improper sterilization of medical equipment, overcrowding, and poor environmental sanitation facilitate the spread of MDR pathogens in hospitals and healthcare settings [50].

9. Advanced Age and Critical Illness

Older adults and critically ill patients are particularly vulnerable because of reduced immune function, multiple comorbidities, and frequent exposure to healthcare interventions [51].

10. Global Travel and Healthcare Exposure

International travel, medical tourism, and transfer of patients between healthcare facilities contribute to the worldwide dissemination of multidrug-resistant bacteria [52].

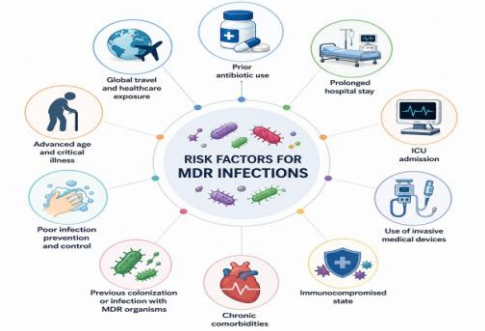

Figure 04: Risk factors for MDR Infections

DIAGNOSIS OF MULTIDRUG-RESISTANT (MDR) BACTERIAL INFECTIONS

Timely and accurate diagnosis is essential for the successful management of multidrug-resistant (MDR) bacterial infections. Early identification of the causative organism and its resistance pattern enables prompt initiation of appropriate antimicrobial therapy and improves patient outcomes [53].

1. Culture and Antimicrobial Susceptibility Testing (AST)

Culture remains the standard method for identifying bacterial pathogens. After isolation, antimicrobial susceptibility testing (AST) determines whether the organism is susceptible or resistant to specific antibiotics, guiding effective treatment selection [54].

2. Rapid Molecular Diagnostics

Rapid diagnostic techniques, such as polymerase chain reaction (PCR) and next-generation sequencing (NGS), quickly detect bacterial pathogens and resistance genes. These methods reduce diagnostic time and support early targeted therapy [55].

3. Biomarkers

Biomarkers including procalcitonin (PCT), C-reactive protein (CRP), white blood cell (WBC) count, and interleukin-6 (IL-6) assist in evaluating bacterial infections and monitoring treatment response. While they cannot directly identify resistant bacteria, they help clinicians make informed decisions regarding antibiotic use [56].

MANAGEMENT OF MULTIDRUG-RESISTANT (MDR) BACTERIAL INFECTIONS

The management of multidrug-resistant (MDR) bacterial infections requires an integrated approach involving early diagnosis, appropriate antimicrobial therapy, source control, antimicrobial stewardship, and effective infection prevention measures. Initial empirical treatment should be based on the patient's clinical status, local resistance patterns, and risk factors. Once culture and antimicrobial susceptibility testing (AST) results are available, therapy should be optimized by switching to the most appropriate targeted antibiotic. Appropriate dose, route, and duration of treatment, along with removal of infected devices or surgical drainage when required, are essential for successful management [57].

MANAGEMENT STRATEGY	PURPOSE
Early diagnosis	Rapid identification of the pathogen
Culture & AST	Guide targeted antibiotic therapy
Empirical antibiotic therapy	Initial treatment based on local resistance patterns
Targeted therapy	Adjust treatment according to susceptibility results
Combination therapy	Improve efficacy in severe MDR infections
Source control	Drain abscesses, remove infected devices
Antimicrobial stewardship	Promote rational antibiotic use
Infection prevention & control	Prevent transmission through hand hygiene and isolation

Figure 05: General management principles for MDR Bacterial Infections

MANAGEMENT OF SPECIFIC MDR PATHOGENS

MDR Pathogen	First-line Management	Alternative/Advanced Therapy
MRSA	Vancomycin	Linezolid, Daptomycin, Ceftaroline
VRE	Linezolid	High-dose Daptomycin, Combination therapy
ESBL-producing Enterobacterales	Carbapenems (Meropenem, Imipenem, Ertapenem)	Piperacillin–Tazobactam* (selected cases), Cefepime*
Carbapenem-resistant Enterobacterales (CRE)	Ceftazidime–Avibactam, Meropenem–Vaborbactam	Imipenem–Cilastatin–Relebactam, Cefiderocol
MDR *Pseudomonas aeruginosa*	Ceftolozane–Tazobactam	Ceftazidime–Avibactam, Cefiderocol, Imipenem–Relebactam
MDR *Acinetobacter baumannii*	Sulbactam-containing regimen	Cefiderocol, Polymyxins, Tigecycline, Minocycline

Figure 06: Management of Specific MDR Pathogens

Emerging and Future Therapies

The rise of multidrug-resistant (MDR) bacterial infections has encouraged the development of new treatment approaches beyond conventional antibiotics. Several promising therapies are being explored to improve treatment outcomes and reduce antimicrobial resistance [57].

Novel antibiotics: Recently developed antibiotics, such as cefiderocol and newer β-lactam/β-lactamase inhibitor combinations, are effective against many resistant bacteria.

Bacteriophage therapy: Uses viruses that specifically infect and eliminate bacteria, providing a targeted treatment option.

Antimicrobial peptides (AMPs): Natural molecules that destroy bacterial cell membranes and have broad-spectrum antimicrobial activity.

Antivirulence therapy: Reduces bacterial virulence by inhibiting toxin production and biofilm formation rather than directly killing bacteria.

Host-directed therapy: Enhances the body's immune response to improve bacterial clearance.

Nanotechnology: Nanoparticles improve antibiotic delivery, increase drug effectiveness, and reduce adverse effects.

Vaccines and immunotherapy: Help prevent bacterial infections and decrease dependence on antibiotics [59].

CHALLENGES

The management of multidrug-resistant (MDR) bacterial infections is limited by the rapid emergence of resistant bacteria, a shortage of new antibiotics, high treatment costs, delayed diagnosis, and inappropriate antibiotic use. Weak infection control practices and the global spread of resistant pathogens further complicate effective treatment and increase the burden of antimicrobial resistance [60].

CONCLUSION

Multidrug-resistant (MDR) bacterial infections remain a significant global public health concern due to the rapid spread of antimicrobial resistance and the declining effectiveness of existing antibiotics. Successful management relies on timely diagnosis, pathogen-directed antimicrobial therapy, antimicrobial stewardship, effective infection control practices, and appropriate source control. Emerging approaches, including newly developed antibiotics, bacteriophage therapy, antimicrobial peptides, nanotechnology-based drug delivery, and host-directed therapies, show considerable potential for improving treatment outcomes. Future efforts should prioritize the development of innovative therapeutics, expansion of rapid diagnostic technologies, rational antibiotic prescribing, and international collaboration to effectively combat antimicrobial resistance and safeguard the efficacy of antimicrobial agents for future generations.

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