Multidrug-Resistant Bacterial Infections: Current Treatment Challenges and Emerging Therapeutic Approaches

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Abstract:

Multidrug-resistant (MDR) bacterial infections represent a major and evolving threat to clinical medicine, driven by antimicrobial exposure, transmission within healthcare and community settings, limited diagnostic capacity, and uneven access to effective therapies. Resistance compromises the treatment of common infections and complicates care for patients with sepsis, malignancy, transplantation, major surgery, and other conditions requiring reliable antibacterial coverage. The therapeutic landscape is changing: newer β-lactam/β-lactamase inhibitor combinations, siderophore cephalosporins, pathogen-directed agents, and improved dosing strategies have expanded options for selected resistant organisms. However, these advances are not universal. Treatment remains highly dependent on organism identification, resistance mechanism, infection site, susceptibility testing, pharmacokinetic/pharmacodynamic optimization, and source control. This review summarizes major resistance mechanisms and the clinical challenges encountered in managing infections due to resistant Enterobacterales, Pseudomonas aeruginosa, Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, and selected other pathogens. It discusses contemporary treatment approaches, emerging antibiotics and non-traditional modalities, rapid diagnostics, antimicrobial stewardship, infection prevention, and research priorities. The 2026 Infectious Diseases Society of America guidance and the World Health Organization's 2024 priority pathogen list and 2025 antibacterial pipeline analysis are considered. A central conclusion is that novel agents must be integrated into a coordinated strategy that includes timely microbiology, careful prescribing, surveillance, equitable access, and prevention of transmission.

Keywords: Antimicrobial resistance; Multidrug-resistant bacteria; Carbapenem-resistant Enterobacterales; MRSA; Acinetobacter baumannii; Novel antibiotics; Bacteriophage therapy

1. INTRODUCTION

Antibacterial medicines transformed the management of infectious diseases, enabling safer surgery, cancer chemotherapy, transplantation, and intensive care. Their effectiveness is increasingly threatened by antimicrobial resistance (AMR), in which microorganisms acquire or express mechanisms that reduce susceptibility to drugs that were previously active. Resistance is a biological phenomenon, but its clinical consequences are shaped by prescribing practices, infection prevention, diagnostic access, sanitation, healthcare infrastructure, and the availability of effective medicines. The global burden is substantial. The 2019 analysis by Murray and colleagues estimated that bacterial AMR was directly attributable to approximately 1.27 million deaths and associated with 4.95 million deaths worldwide in that year [1]. These estimates are model-based and should not be interpreted as counts of individually confirmed deaths; nevertheless, they demonstrate the scale of the challenge. Resistant infections can prolong hospitalization, increase treatment costs, and force reliance on agents with less favorable safety profiles. Their impact is particularly pronounced where microbiology laboratories, stewardship services, and newer drugs are limited.

The World Health Organization (WHO) updated its Bacterial Priority Pathogens List in 2024, identifying resistant bacterial groups requiring prioritized research, development, and public health action [2]. Critical priorities include carbapenem-resistant Acinetobacter baumannii (CRAB), carbapenem-resistant Enterobacterales (CRE), third-generation cephalosporin-resistant Enterobacterales, and rifampicin-resistant Mycobacterium tuberculosis. The list is not a treatment guideline; rather, it provides a framework for research and policy. WHO's 2025 GLASS surveillance report further summarizes global resistance prevalence and trends across more than 23 million bacteriologically confirmed cases reported by participating countries. Contemporary clinical decisions must be based on infection syndrome, microbiological results, local epidemiology, and applicable guidelines [3].

The term MDR is also used inconsistently unless a standardized definition is applied. The international expert proposal describes MDR as non-susceptibility to at least one agent in three or more antimicrobial categories; extensively drug-resistant (XDR) isolates remain susceptible to only one or two categories, while pandrug-resistant (PDR) isolates are non-susceptible to all agents in the relevant categories. Definitions are organism-specific and should be applied using appropriate susceptibility testing. This narrative review synthesizes clinically relevant evidence on current treatment challenges and emerging approaches, with an emphasis on the need to pair new therapeutics with stewardship and prevention [4].

2. REVIEW APPROACH AND SCOPE

This article is a narrative review rather than a systematic review or meta-analysis. The content was developed from major international guidance documents, WHO priority-pathogen and pipeline publications, landmark randomized trials, and peer-reviewed reviews or primary studies relevant to MDR bacterial infections. Emphasis was placed on therapeutic evidence, mechanisms of resistance, diagnostic and stewardship considerations, and developments available through 2026. The 2026 IDSA guidance is focused on US practice; availability, susceptibility breakpoints, resistance epidemiology, and regulatory status differ across countries. Consequently, drug options discussed here should be interpreted as evidence summaries, not individualized prescribing instructions. Treatment should be selected by qualified clinicians using current local guidelines and susceptibility results.

3. MECHANISMS UNDERLYING MULTIDRUG RESISTANCE

3.1. Enzymatic inactivation

β-lactamases are among the most clinically consequential resistance mechanisms. Extended-spectrum β-lactamases (ESBLs), commonly CTX-M enzymes, hydrolyze many penicillins and cephalosporins. AmpC β-lactamases can be chromosomally encoded or acquired and may be inducible or derepressed, producing resistance to several cephalosporins and complicating treatment during therapy. Carbapenemases include KPC, metallo-β-lactamases such as NDM, VIM and IMP, and OXA-48-like enzymes. Their substrate profiles differ, and the presence of a carbapenemase can predict whether a β-lactamase inhibitor combination is likely to work. Other drug classes are affected by enzymes such as aminoglycoside-modifying enzymes and chloramphenicol acetyltransferases. Enzyme-mediated resistance often coexists with additional mechanisms carried on plasmids or other mobile genetic elements, allowing resistance determinants to spread between bacterial populations [4].

3.2. Altered targets and reduced permeability

Mutations or acquired genes can alter the binding sites of antibiotics. Examples include changes in penicillin-binding proteins in MRSA, ribosomal alterations affecting macrolides or linezolid, and mutations in DNA gyrase or topoisomerase IV associated with fluoroquinolone

resistance. Reduced outer-membrane permeability, loss or alteration of porins, and increased efflux can lower intracellular drug concentrations. In Gram-negative bacteria, the combination of porin loss with β-lactamase production may result in clinically important carbapenem resistance even when a carbapenemase is not detected [4-5].

3.3. Efflux, biofilms, and adaptive tolerance

Efflux pumps actively export antimicrobial compounds and may confer resistance across multiple classes. Biofilms structured bacterial communities embedded in an extracellular matrix are common on devices and at chronic infection sites. Biofilm-associated organisms can exhibit reduced antibiotic penetration, altered metabolic activity, and persister-cell populations. These phenomena are not identical to heritable resistance, but they can contribute to treatment failure and relapse. Foreign-body removal, drainage, debridement, and other forms of source control may therefore be as important as antimicrobial selection.

3.4. Horizontal gene transfer and ecological selection

Plasmids, transposons, integrons, and bacteriophages can facilitate dissemination of resistance genes. Antibiotic exposure selects for resistant organisms by suppressing susceptible populations, while colonization pressure and inadequate infection control promote spread. Broad-spectrum treatment may also disrupt the microbiome and select for organisms such as Clostridioides difficile. Resistance is thus a combined molecular, ecological, and healthcare-system problem rather than a simple consequence of one drug or one pathogen.

4. MAJOR MDR PATHOGENS AND TREATMENT CHALLENGES

4.1. Extended-spectrum β-lactamase-producing Enterobacterales

ESBL-producing Escherichia coli and Klebsiella pneumoniae are common causes of urinary tract infection, bacteremia, intra-abdominal infection, and healthcare-associated pneumonia. Carbapenems have historically been reliable for serious invasive ESBL infections, but their widespread use contributes to selection pressure for CRE. In uncomplicated cystitis, an active oral option may be appropriate; for pyelonephritis or complicated urinary infection, selection should be guided by susceptibility, clinical severity, renal function, and the ability to achieve adequate tissue exposure. Nitrofurantoin and oral fosfomycin are limited to suitable lower urinary tract infections and should not be used for bloodstream infection or renal parenchymal disease. For invasive infections, the choice of a carbapenem or a suitable newer agent depends on the resistance phenotype and clinical circumstances. Piperacillin-tazobactam or cefepime may appear susceptible in vitro in some cases, yet susceptibility alone does not necessarily establish equivalent clinical reliability for serious ESBL infections. De-escalation should be considered once the pathogen and susceptibility profile are known, with attention to source control and clinical response [5].

4.2. Carbapenem-resistant Enterobacterales

CRE are heterogeneous. Resistance may arise through carbapenemase production, porin changes combined with ESBL or AmpC activity, or other mechanisms. Identifying the enzyme class is useful because newer β-lactam/β-lactamase inhibitor combinations have distinct spectra. KPC-producing organisms may be susceptible to meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-relebactam. OXA-48-like producers may respond to ceftazidime-avibactam if susceptibility is demonstrated. Metallo-β-lactamases such as NDM generally require a different strategy, for example aztreonam protected by avibactam activity delivered through an appropriate combination, or cefiderocol when active.

The 2026 IDSA guidance outlines organism- and mechanism-specific options for CRE, including preferred newer agents and alternatives [5]. The preceding 2024 IDSA guidance similarly

emphasized interpreting antimicrobial susceptibility in conjunction with β-lactamase mechanisms and clinical context [6]. It also emphasizes that combination therapy is not routinely needed once a β-lactam with demonstrated activity has been selected, because evidence for improved outcomes from continued combination treatment is lacking and toxicity may increase. This recommendation should not be generalized without considering severity, pharmacological exposure, susceptibility, and local protocols.

4.3. Difficult-to-treat Pseudomonas aeruginosa

P. aeruginosa has intrinsic resistance traits and readily acquires additional mechanisms, including efflux upregulation, porin changes, AmpC overexpression, target mutations, and biofilm formation. Difficult-to-treat resistance (DTR) is a phenotype that limits commonly used antipseudomonal agents. Newer β-lactams ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam can be valuable, but activity is variable and should be confirmed. Cefiderocol provides another option for selected isolates. Evidence from the phase 3 CREDIBLE-CR trial compared cefiderocol with best available therapy for serious carbapenem-resistant Gram-negative infections, while also highlighting the need for careful interpretation of pathogen-specific outcomes [7].

The current IDSA guidance favors traditional non-carbapenem β-lactams when susceptible and recommends optimized dosing, including prolonged infusion when appropriate, for certain resistant phenotypes. For DTR infections outside the urinary tract, ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam are preferred options in the guidance, with cefiderocol an alternative; ceftolozane-tazobactam is favored for pneumonia in the relevant setting [5]. The ASPECT-NP randomized trial provides comparative evidence for ceftolozane-tazobactam in nosocomial pneumonia [8]. Local resistance patterns and susceptibility testing remain central because no single newer agent reliably covers every resistant isolate.

4.4. Carbapenem-resistant Acinetobacter baumannii

CRAB frequently causes ventilator-associated pneumonia, bloodstream infection, and infections in critically ill patients. Resistance may involve OXA-type carbapenemases, permeability changes, efflux, and additional β-lactamases. Treatment has historically relied on polymyxins, high-dose sulbactam-containing regimens, and other agents, often with uncertain efficacy and considerable toxicity. Polymyxin-associated nephrotoxicity is a major limitation.

Sulbactam-durlobactam represents a pathogen-focused advance. In the phase 3 ATTACK trial, sulbactam-durlobactam was non-inferior to colistin for 28-day mortality in serious infections caused by the Acinetobacter baumannii-calcoaceticus complex, while nephrotoxicity was lower in the sulbactam-durlobactam group [9]. The trial population was predominantly pneumonia, and the results should not be overextended to every infection syndrome. Availability and susceptibility testing may also constrain use. The 2026 IDSA guidance addresses CRAB treatment and stresses the importance of active therapy, combination strategies in selected circumstances, and careful interpretation of evidence [5].

4.5. Methicillin-resistant Staphylococcus aureus

MRSA is resistant to most conventional β-lactams through altered penicillin-binding protein PBP2a, encoded by mecA or related determinants. Treatment depends on syndrome. Vancomycin remains a common option for serious invasive infection, with exposure monitoring and renal safety considerations. Daptomycin is used for bacteremia and selected endovascular infections but is not appropriate for pneumonia because pulmonary surfactant inactivates it. Linezolid may be useful for pneumonia and has excellent oral bioavailability, though prolonged therapy can cause

myelosuppression, neuropathy, and drug interactions. Ceftaroline has activity against MRSA and may be considered in selected situations. Choice should account for infection site, susceptibility, bacteremia clearance, source control, and patient-specific toxicity. Persistent MRSA bacteremia should prompt reassessment for endocarditis, infected devices, metastatic foci, inadequate source control, or reduced antimicrobial activity. Simply adding agents without a structured diagnostic and therapeutic reassessment may not resolve the underlying cause [9-10].

4.6. Vancomycin-resistant Enterococcus

Vancomycin-resistant Enterococcus faecium (VRE) is an important healthcare-associated pathogen, particularly among patients with hematologic malignancy, transplantation, and prolonged hospitalization. Resistance commonly involves van gene clusters that alter peptidoglycan precursors and reduce glycopeptide binding. Linezolid and daptomycin are often considered for invasive VRE infections, depending on susceptibility, site, and clinical context. Daptomycin dosing strategies for serious infections require specialist judgment, and linezolid's hematological toxicity is relevant in patients with pre-existing cytopenias. Colonization alone is not an indication for antibiotic treatment; infection control and antimicrobial stewardship are essential [5].

4.7. Stenotrophomonas maltophilia and other resistant organisms

S. maltophilia possesses intrinsic resistance mechanisms, including β-lactamases, efflux pumps, and reduced permeability, and may be isolated from respiratory samples in patients with complex illness. Distinguishing colonization from true infection is especially important. Therapeutic options historically include trimethoprim-sulfamethoxazole, minocycline, levofloxacin, and other agents according to susceptibility, but resistance and toxicity can complicate management. The 2026 IDSA guidance includes specific suggestions for this organism and cautions against assuming that an isolate from a nonsterile site necessarily represents invasive disease [5]. Drug-resistant Neisseria gonorrhoeae, Salmonella, Shigella, and rifampicin-resistant tuberculosis also remain public health priorities. Their management requires pathogen-specific guidelines, surveillance, and in some cases public health involvement. The principles discussed in this review should not replace disease-specific protocols.

5. CONTEMPORARY THERAPEUTIC STRATEGIES

5.1. Resistance-mechanism-guided antibiotic selection

The shift from broad empiric coverage toward mechanism-informed targeted treatment is one of the most important developments in MDR infection management. A susceptibility report should be interpreted alongside organism identification, infection site, inoculum, pharmacokinetics, and the presence of enzymes such as KPC, OXA-48-like, or NDM. Rapid assays that detect selected resistance genes can inform early decisions, but a negative gene result does not exclude resistance caused by other mechanisms, and gene detection does not always establish phenotypic susceptibility. A practical approach is to obtain cultures before antibiotics when this does not delay urgent treatment, begin empiric therapy based on clinical severity and risk, and promptly narrow or change treatment as microbiology results become available. In severe sepsis, the priority is early administration of a likely active agent; diagnostic stewardship should improve rather than obstruct that goal [7,11].

5.2. New β-lactam/β-lactamase inhibitor combinations

New combinations expand activity against selected Gram-negative resistance mechanisms. Avibactam inhibits many class A and class C β-lactamases and some class D enzymes, but not metallo-β-lactamases. Vaborbactam and relebactam have useful activity against KPC enzymes, while durlobactam inhibits selected class A, C, and D enzymes relevant to Acinetobacter. The β-lactam partner determines the antibacterial spectrum; inhibitor activity cannot be considered in isolation.

These combinations are not interchangeable. The RESTORE-IMI 1 randomized trial evaluated imipenem-relebactam against colistin plus imipenem for imipenem-nonsusceptible infections, contributing clinical evidence for this newer combination. Treatment requires identifying or inferring the mechanism, reviewing susceptibility data, and checking the infection indication and dosing. Resistance can emerge during therapy, including through enzyme changes or increased expression, and therefore clinical failure should trigger repeat cultures and susceptibility reassessment where feasible [10-11].

5.3. Cefiderocol

Cefiderocol is a siderophore cephalosporin that exploits bacterial iron-uptake pathways to enter Gram-negative organisms. It has activity against several resistant non-fermenters and some carbapenemase-producing Enterobacterales, including organisms with metallo-β-lactamases. Its clinical role is nevertheless nuanced. Trial results vary by pathogen and infection setting, and susceptibility testing can be technically challenging. It should be reserved for situations in which the expected benefit is supported by susceptibility and clinical context, with careful monitoring.

5.4. Optimized pharmacokinetics and pharmacodynamics

Antibiotic efficacy is related to exposure relative to the organism's MIC. β-lactams generally benefit from maintaining free-drug concentrations above the MIC for an adequate portion of the dosing interval; prolonged or continuous infusion may help achieve this in critically ill patients. Aminoglycosides and fluoroquinolones are commonly associated with concentration- or exposure-dependent indices. Renal function, augmented renal clearance, fluid shifts, extracorporeal support, and critical illness can substantially alter exposure. Therapeutic drug monitoring (TDM), where available and appropriate, can help individualize selected drugs such as vancomycin and aminoglycosides. Dose optimization should not be confused with indiscriminate dose escalation: toxicity, drug interactions, organ function, infusion compatibility, and validated dosing protocols must be considered [10].

5.5. Combination therapy: when it helps and when it harms

Combination treatment may be justified empirically when the likelihood of resistance is high and no single agent is reliably active, or for specific pathogens and syndromes where evidence or guidance supports it. However, continuing two or more agents after an active, appropriately dosed drug has been identified may increase adverse effects without improving outcomes. The decision should be pathogen- and syndrome-specific rather than a universal response to the MDR label [5].

5.6. Source control and supportive care

Antibiotics cannot reliably compensate for an undrained abscess, obstructed urinary tract, infected prosthesis, necrotic tissue, or infected catheter. Timely drainage, device removal, debridement, and correction of anatomical obstruction are essential. Supportive care for sepsis, organ dysfunction, nutrition, and rehabilitation also influences outcomes. Source control should be evaluated early and revisited if response is inadequate.

6. EMERGING THERAPEUTIC APPROACHES

6.1. Antibiotics in the development pipeline

The WHO 2025 pipeline analysis assessed antibacterial products in clinical and preclinical development using information available through 15 February 2025. The report illustrates a continuing gap between the burden of resistant pathogens and the number of genuinely innovative agents. Many candidates are modifications of established drug classes, which may improve activity against selected resistance mechanisms but can remain vulnerable to cross-resistance. The pipeline also includes non-traditional agents, though development, clinical validation, manufacturing, and

access remain uneven. Novel agents should be evaluated not only by whether they reach regulatory approval but also by whether they address priority pathogens, demonstrate clinically meaningful benefit, have practical diagnostic requirements, and can be made accessible in settings where resistance burden is high. Stewardship plans are needed from the outset to protect their utility [11-12].

6.2. Bacteriophage therapy

Bacteriophages are viruses that infect bacteria. Their potential advantages include narrow targeting, activity against selected resistant isolates, and the possibility of combining phages with antibiotics. Personalized phage cocktails may be developed using isolate-specific testing. Challenges include variable susceptibility, immune neutralization, manufacturing and quality control, regulatory pathways, and limited high-quality randomized evidence. Reviews of phage pharmacokinetics and pharmacodynamics also describe the distinctive complexities of phage dosing, clearance, and resistance emergence. Phage therapy is best considered investigational or a specialized adjunct under appropriate regulatory and clinical oversight rather than routine standard care [13].

6.3. Antimicrobial peptides and biologics

Antimicrobial peptides can disrupt bacterial membranes or interfere with essential cellular processes. Their development faces challenges related to toxicity, stability, delivery, cost, and the potential for resistance. Monoclonal antibodies and other biologics may neutralize bacterial toxins, inhibit virulence factors, or support host defense. These strategies can be pathogen-specific and may complement antibiotics, but their clinical utility depends on the target, patient population, and demonstrated outcomes.

6.4. Anti-virulence strategies and microbiome interventions

Anti-virulence approaches seek to reduce pathogenicity without necessarily killing the organism, for example by blocking adhesion, toxin production, quorum sensing, or biofilm formation. Microbiome-based interventions aim to restore colonization resistance and may have a role in preventing recurrence of selected infections. These approaches are conceptually attractive because they may exert different selective pressures than conventional antibiotics, but they require rigorous evaluation for efficacy, safety, durability, and unintended ecological effects.

6.5. Host-directed therapies and vaccines

Host-directed therapies seek to modify immune responses or improve host resilience while antibiotics address the pathogen. Potential targets include inflammatory pathways, immune dysfunction, and tissue damage. Vaccines can prevent infections and reduce antibiotic exposure, indirectly limiting selection for resistance. Their impact is pathogen-specific and depends on uptake, coverage, and effectiveness against circulating strains. Prevention remains one of the most sustainable strategies for reducing the need for antibiotics.

7. RAPID DIAGNOSTICS AND PRECISION MICROBIOLOGY

Conventional culture and susceptibility testing remain foundational, but turnaround time may delay targeted therapy. Molecular panels, nucleic-acid amplification, resistance-gene assays, MALDI-TOF mass spectrometry, and selected phenotypic rapid susceptibility platforms can shorten the interval between specimen collection and actionable results. The greatest value occurs when tests are integrated with clinical interpretation and antimicrobial stewardship feedback. Diagnostic limitations must be recognized. Molecular tests may detect colonization or nonviable organisms, panels cover only selected targets, and resistance genes do not capture every phenotype. Phenotypic susceptibility testing remains important, particularly for novel agents and complex resistance mechanisms. Laboratories should validate methods, communicate critical results promptly, and use locally appropriate breakpoints. A rapid result that is not acted upon may have limited impact.

Programs combining diagnostics with stewardship review, infectious diseases consultation, and clinical pathways can support early escalation when necessary and timely de-escalation when resistance risk is lower [11-13].

8. ANTIMICROBIAL STEWARDSHIP AND INFECTION PREVENTION

8.1. Stewardship interventions

Antimicrobial stewardship promotes the right drug, dose, route, and duration for a documented clinical indication. Core activities include prospective audit and feedback, preauthorization for selected agents, guideline-based empiric pathways, antibiotic time-outs, de-escalation, dose optimization, and monitoring of antibiotic use and outcomes. Stewardship should be collaborative and non-punitive, involving prescribers, pharmacists, microbiologists, nurses, and infection prevention teams. A 48–72-hour review can reassess diagnosis, cultures, clinical trajectory, source control, and continued need for broad-spectrum therapy. Duration should be based on syndrome-specific evidence and response rather than an automatic prolonged course. Unnecessary antibiotics for colonization, viral illness, or contaminated specimens should be avoided [13].

8.2. Infection prevention and surveillance

Hand hygiene, environmental cleaning, isolation or cohorting when indicated, device-care bundles, and adherence to standard precautions reduce transmission. Surveillance helps identify outbreaks, changing resistance patterns, and gaps in infection prevention. Antimicrobial consumption and resistance data should be reviewed together where possible, since trends may reflect prescribing, transmission, or both.

8.3. One Health and community action

AMR is connected across human health, animal health, food systems, and the environment. Responsible antimicrobial use in agriculture, wastewater management, infection prevention in community settings, vaccination, and access to quality-assured medicines are important components of a One Health response. Policies must avoid creating barriers that prevent patients with genuine bacterial infections from receiving timely effective treatment.

9. PRACTICAL FRAMEWORK FOR MANAGEMENT

The following framework summarizes a disciplined approach to suspected MDR bacterial infection. It is intended as a conceptual aid and does not replace local protocols or specialist decision-making.

Table: 1 Selected MDR pathogens, resistance mechanisms143-153**, and therapeutic considerations.**

Pathogen / phenotype	Common resistance mechanisms	Selected treatment considerations (susceptibility- and syndrome-dependent)
ESBL-producing Enterobacterales	ESBL enzymes (often CTX-M); plasmid co-resistance	Carbapenems for serious invasive infections; selected oral agents for uncomplicated lower UTI only when active and appropriate; narrow therapy once results available.
CRE (KPC)	KPC carbapenemase; porin changes	KPC-active newer β-lactam/inhibitor options (e.g., meropenem-vaborbactam, ceftazidime-avibactam, imipenem-relebactam) when susceptible.
CRE (NDM / other MBL)	Metallo-β-lactamase; often co-resistance	Mechanism-specific options such as aztreonam-based protected strategies or cefiderocol when susceptibility is confirmed; specialist consultation is valuable.
DTR P. aeruginosa	Efflux, porin loss, AmpC, target mutations	Test newer antipseudomonal β-lactams and cefiderocol; optimize infusion and dose; use active agent based on infection site.
CRAB	OXA carbapenemases, permeability changes, efflux	Sulbactam-durlobactam where available and appropriate; sulbactam-containing regimens or alternatives per current guidance and susceptibility.

Pathogen / phenotype	Common resistance mechanisms	Selected treatment considerations (susceptibility- and syndrome-dependent)
MRSA	PBP2a (mecA/mec-related)	Vancomycin for selected serious infections; linezolid for appropriate pneumonia cases; daptomycin for bloodstream/endovascular disease but not pneumonia.
VRE E. faecium	van gene clusters altering target	Linezolid or daptomycin when susceptible; differentiate colonization from infection; monitor adverse effects and optimize dosing.
S. maltophilia	Intrinsic β-lactamases, efflux, reduced permeability	Assess whether isolate represents infection; select treatment from susceptibility and current guidance, considering combination/alternative approaches as warranted.

Table: 2 Newer antibacterial agents and their broad clinical positioning.

Agent / combination	Key activity or rationale	Important limitations / cautions
Ceftazidime-avibactam	Selected KPC and OXA-48-like CRE; some resistant P. aeruginosa	Not active against metallo-β-lactamases; resistance can emerge.
Meropenem-vaborbactam	KPC-producing CRE	Does not inhibit NDM/VIM/IMP; requires susceptibility and appropriate infection context.
Imipenem-relebactam	Selected KPC and resistant P. aeruginosa	Spectrum is mechanism-dependent; susceptibility testing required.
Ceftolozane-tazobactam	Selected resistant P. aeruginosa; certain Gram-negative infections	Not a universal CRE agent; check susceptibility.
Cefiderocol	Selected resistant Gram-negative organisms including some MBL producers and non-fermenters	Clinical evidence varies by pathogen; laboratory testing can be challenging; reserve according to indication.
Sulbactam-durlobactam	CRAB, targeting relevant β-lactamases while sulbactam acts on Acinetobacter	Access and susceptibility may vary; trial evidence predominantly severe pneumonia.
Aztreonam protected by avibactam activity (co-administered or fixed-combination strategy depending on region)	Potential option for MBL-producing Enterobacterales	Regulatory status and availability vary; specialist-directed use and susceptibility support needed.

10. KEY UNRESOLVED CHALLENGES

Despite therapeutic progress, several barriers persist. First, resistance surveillance is uneven and may underrepresent community settings or regions with limited laboratory capacity. Second, diagnostic turnaround and availability of resistance-mechanism testing remain inconsistent. Third, newer drugs may be expensive, unavailable, or difficult to access in resource-limited settings. Fourth, clinical trials often enroll selected populations and may be underpowered for uncommon pathogen-specific outcomes. Fifth, resistance to newly introduced agents can emerge, particularly when use is widespread or exposure is suboptimal. Regulatory approval, guideline recommendation, and real-world availability are distinct. A drug may be approved in one jurisdiction but not another; laboratory breakpoints may differ; and national formularies can lag behind evidence. Thus, treatment recommendations should be contextualized, and international guidance should be adapted rather than copied without assessment. Another challenge is the balance between preserving new antibiotics and ensuring access for patients who need them. Stewardship should prevent unnecessary use, not create delays in treating severe infections. Equity-focused approaches should pair access programs with surveillance, diagnostic capability, and health-system strengthening.

11. DISCUSSION

The treatment of MDR bacterial infection has moved beyond reliance on a small set of older broad-spectrum agents. Novel β-lactamase inhibitors, siderophore cephalosporins, and pathogen-specific approaches provide clinically meaningful options for selected resistant phenotypes. Nevertheless, therapeutic success depends on a series of connected decisions: recognizing infection rather than colonization, collecting appropriate specimens, identifying the organism and resistance mechanism, selecting an active agent, achieving adequate exposure, controlling the source, and reassessing the response. The 2026 IDSA guidance illustrates the growing precision of treatment recommendations for resistant Gram-negative pathogens. Such guidance reflects a dynamic evidence base and a need to interpret susceptibility data rather than treat resistance labels as interchangeable. It is also explicitly region-focused, underscoring that epidemiology and drug access shape practical decisions. In parallel, the WHO priority pathogen list directs attention to pathogens that threaten public health and require coordinated R&D [2].

The 2025 WHO pipeline report provides a useful snapshot of candidate development, but a pipeline count alone cannot guarantee innovation, clinical success, or equitable availability. A major clinical principle is that antibiotic escalation is not a substitute for diagnostic reassessment. Persistent fever or bacteremia may reflect an uncontrolled focus, an infected device, inadequate dosing, an incorrect diagnosis, or a complication such as endocarditis. Repeating cultures, imaging when indicated, and source control can be more consequential than empirically adding another drug. Similarly, the detection of a resistant organism in a respiratory or urine specimen should be interpreted in the clinical context, since colonization may be mistaken for infection.

New drugs also require stewardship. Protecting their utility means avoiding unnecessary exposure while promptly using them when they are the most appropriate active treatment. Programs should measure not only antibiotic consumption but also clinical outcomes, toxicity, resistance trends, time to active therapy, and adherence to source-control and diagnostic practices. Pharmacists and microbiologists have pivotal roles in dose optimization, susceptibility interpretation, and feedback. Emerging non-traditional approaches including phages, biologics, anti-virulence strategies, and microbiome interventions may broaden future options. Their promise should be balanced against limited comparative evidence, manufacturing complexity, and regulatory challenges. Clinical research should prioritize robust outcomes, pathogen-specific analyses, accessible diagnostic pathways, and settings with high resistance burdens. The best long-term strategy is therefore multifaceted: innovation in medicines, strengthened diagnostics, infection prevention, responsible prescribing, surveillance, and equitable access.

CONCLUSION

Multidrug-resistant bacterial infections remain a formidable clinical and public health challenge, but the therapeutic landscape is evolving. Mechanism-guided selection of newer antibiotics, optimized pharmacokinetic/pharmacodynamic dosing, rapid diagnostics, and timely source control can improve the likelihood of effective treatment in selected infections. At the same time, new agents do not eliminate the need for careful microbiological interpretation, stewardship, and infection prevention. The development pipeline remains insufficiently aligned with all priority pathogens, and access to effective drugs and diagnostics is uneven. Sustainable progress will require coordinated clinical, laboratory, public health, research, and policy action. In practice, the most effective response is not simply to develop another antibiotic, but to ensure that each effective agent is used appropriately, reaches the patient who needs it, and remains useful for as long as possible.

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