INTERNATIONAL JOURNAL OF PHARMACOLOGY, PHARMACOTHERAPEUTICS AND THERAPY
(IJPCTT)
Open Access | Peer-Reviewed Journal
Journal Homepage: https://ijpcttjournal.in/

Volume 1 | Issue 1
2026
Pages: [1-14]

Review Article

Antimicrobial Resistance: Current Challenges, Novel Therapeutic Approaches and the Role of Clinical Pharmacists

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ARTICLE INFO

Published: 12 Nov 2026

Keywords: antimicrobial resistance, antimicrobial stewardship, clinical pharmacist

ABSTRACT

Antimicrobial resistance (AMR) is one of the biggest threats to modern medicine, undermining treatment of common infections, and the safety of surgery, chemotherapy and intensive care. Systematic analyses found that in 2021, bacterial AMR was directly linked to around 1.14 million deaths and associated with 4.71 million deaths globally, with further increases anticipated by 2050. Mechanisms of resistance include enzymatic inactivation of antibiotics, alteration of drug targets, reduced membrane permeability, active efflux, biofilm formation, and acquisition of resistance determinants, either by mutation or horizontal gene transfer. These mechanisms are responsible for the clinical importance of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum β-lactamase-producing and carbapenem-resistant Enterobacterales, and multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Treatment options are dwindling, and many of the newer agents are costly, unevenly available and based on limited trial evidence in the most resistant infections. This narrative review summarises the global burden, resistance mechanisms, priority pathogens and therapeutic challenges; critically appraises novel approaches including new β-lactam/β-lactamase inhibitor combinations, novel antibiotic classes, bacteriophage therapy, antimicrobial peptides, monoclonal antibodies, CRISPR-based antimicrobials, anti-biofilm strategies and immunotherapy, distinguishing approved agents from investigational ones; and describes antimicrobial stewardship and the contrib Gaps in research and implications for practice are identified.

1. Introduction

Antimicrobial resistance (AMR) is the ability of microorganisms to survive exposure to medicines that would ordinarily inhibit or kill them. The term is broader than antibiotic resistance, since it also covers resistance in viruses, fungi and parasites, whereas antibiotic resistance refers specifically to bacteria that withstand antibacterial drugs. This review is concerned mainly with bacterial resistance to antibiotics; the term AMR is retained because it is the one used in surveillance reports and policy documents. A consistent vocabulary is essential for clinical communication. By international consensus, multidrug-resistant (MDR) bacteria are non-susceptible to at least one agent in three or more antimicrobial categories, extensively drug-resistant (XDR) bacteria are non-susceptible to at least one agent in all but two or fewer categories, and pandrug-resistant (PDR) bacteria are non-susceptible to all agents in all categories.[1]

Resistance is a natural evolutionary response to antibiotic exposure, but human activity has accelerated it. Contributing factors include inappropriate or unnecessary prescribing, self-medication and over-the-counter access, incomplete courses, widespread antibiotic use in livestock and agriculture, poor sanitation, weak infection prevention in healthcare facilities, and limited access to rapid diagnostics.[2] Global antibiotic consumption rose by about 65% between 2000 and 2015, with the steepest increases in low- and middle-income countries,[3] and continued to rise through 2018.[4] The COVID-19 pandemic added further pressure: in a rapid review and meta-analysis, roughly 72% of hospitalised patients with COVID-19 received antibiotics, although bacterial co-infection was documented in only a small minority.[5]

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Relevant conflicts of interest/financial disclosures: He author declares no conflict of interest.

The consequences extend beyond treatment failure. Effective antibiotics underpin surgery, obstetric care, neonatal medicine, cancer chemotherapy, organ transplantation and intensive care, and each of these would become more hazardous without reliable antibacterial therapy. The World Health Organization (WHO) has responded with a priority pathogens list to direct research and development,[6,7] a Global Action Plan on AMR,[8] and the AWaRe classification to guide appropriate antibiotic use.[9] Two complementary strategies are central.

Antimicrobial stewardship comprises coordinated interventions that promote the optimal selection, dose, route and duration of antimicrobial therapy, thereby reducing selection pressure. Infection prevention and control (IPC), by contrast, aims to stop transmission of resistant organisms through measures such as hand hygiene, isolation, screening, environmental cleaning and device-care bundles.[10,11] Both are required; neither substitutes for the other.

Clinical pharmacists are well placed to contribute to both strategies because of their expertise in pharmacokinetics, pharmacodynamics, toxicology, drug interactions and medication safety. This narrative review summarises the global burden and mechanisms of AMR, the clinical features of priority resistant pathogens, the limitations of current therapy, and emerging therapeutic approaches, and then examines stewardship and the practical contribution of clinical pharmacists. Emphasis is placed on pharmacotherapeutic decision-making, and approved agents are distinguished from investigational ones throughout.

2. Global Epidemiology and Burden of Antimicrobial Resistance

The largest estimates are those of the Global Research on Antimicrobial Resistance (GRAM) project. In 2019, it estimated that bacterial AMR was directly responsible for 1.27 million deaths and associated with 4.95 million deaths in 204 countries, making AMR a leading cause of death worldwide.[12] The six pathogens with the greatest burden were *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, with methicillin-resistant *S. aureus* (MRSA) alone causing over 100,000 attributable deaths.[12] The attributable mortality rate was highest in western sub-Saharan Africa, followed by other low-resource regions, highlighting the inequity of the burden.[12] An updated analysis for 1990–2021 estimated 1.14 million attributable and 4.71 million associated deaths in 2021.[13] It also recorded a demographic shift: deaths among children younger than five years dropped by more than half between 1990 and 2021, likely reflecting improved infection control, vaccination and sanitation, while deaths among adults aged 70 years and older increased by more than 80%.[13] The forecasts project 1.91 million attributable and 8.22 million associated deaths per year by 2050, which would total about 39 million cumulative attributable deaths between 2025 and 2050.[13] The figures are below the often cited projection of 10 million deaths per year by 2050[14], which was based on different assumptions and is now considered less well-founded. The modelled trajectory is still scary. Both studies rely on patchy surveillance data from many areas, so the confidence intervals are broad.

This picture is supported by regional data. An estimated 33,110 deaths in the European Union and European Economic Area were attributable to infections with antibiotic-resistant bacteria in 2015, with the burden concentrated among infants and older adults and in healthcare-associated infections.[15] In the U.S., the Centers for Disease Control and Prevention (CDC) reported over 2.8 million antibiotic-resistant infections and over 35,000 deaths annually, pre-pandemic.[16] In 2025, WHO published surveillance data indicating that nearly one in six laboratory-confirmed bacterial infections worldwide was resistant to standard antibiotic treatments.[17] However, reporting remains patchy and many countries did not have the laboratory capacity to provide reliable data to earlier rounds of surveillance. India provides an example of the challenge in a high-burden setting. According to the Indian Council of Medical Research surveillance, Gram-negative pathogens show high levels of resistance, with very little susceptibility to carbapenems in *A. baumannii* and a lot of carbapenem resistance in *K. pneumoniae* and high rates of resistance to third-generation cephalosporins and fluoroquinolones in *E. coli*.[19] The country's first National Action Plan on AMR set out priorities for surveillance, stewardship, infection control and awareness.[20] A common theme in low- and middle-income countries is the coexistence of excess use and lack of access: many patients receive unnecessary antibiotics while others, especially children with sepsis, are unable to access effective ones.[21] Hence, mitigation requires strategies that enhance stewardship and access.

Antimicrobial resistance cannot be understood within the confines of human medicine. Antibiotics are also widely used in food animal production, and resistant bacteria and resistance genes spread between animals, humans and the environment via food, water, waste and direct contact, for example the plasmid-mediated colistin resistance gene mcr-1 was detected in isolates from both animals and humans.[22] The economic consequences are also expected to be large. The Review on Antimicrobial Resistance estimated that if resistance is left unchecked, global output could be reduced by up to US$100 trillion in cumulative terms by 2050, although such projections are subject to considerable uncertainty.[14] Recognition of these cross-sectoral drivers has resulted in national action plans combining surveillance, stewardship, infection prevention, sanitation and responsible agricultural use.[2,8]

3. Mechanisms of Antimicrobial Resistance

Bacteria can be intrinsically resistant, for example, because of low permeability of the Gram-negative outer membrane, or they can acquire resistance by changes due to mutation or gene transfer.[23,24] The principal mechanisms are summarised in Table 1 and illustrated in Figure 1. Often they coexist within a single isolate and this accounts for the frequent observation of simultaneous resistance to several classes of drugs.

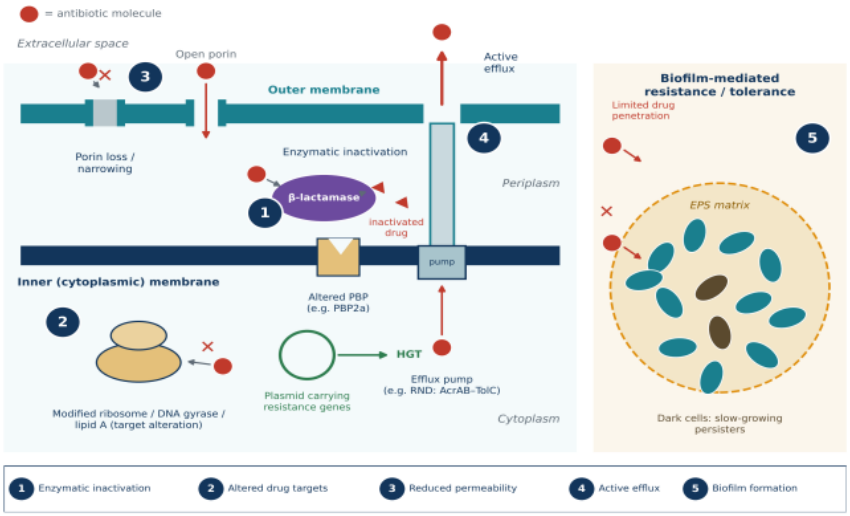


Figure 1. Molecular mechanisms of antimicrobial resistance in Gram-negative bacteria and biofilms: (1) enzymatic inactivation, (2) altered drug targets, (3) reduced membrane permeability, (4) active efflux and (5) biofilm-mediated resistance and tolerance, with horizontal gene transfer (HGT) shown by plasmid transfer. Original schematic prepared by the authors; mechanisms are based on published reviews [23–25].

Table 1. Major antimicrobial resistance mechanisms, molecular basis and clinical implications

Resistance mechanism	Molecular basis	Representative organisms	Antibiotic classes affected	Clinical implications
Enzymatic drug inactivation	β-Lactamases (ESBL, AmpC, KPC, NDM, VIM, IMP, OXA-48-like) hydrolyse the β-lactam ring; aminoglycoside-modifying enzymes acetylate, phosphorylate or adenylate the drug [24,26]	Enterobacterales, *P. aeruginosa*, *A. baumannii*, *S. aureus*	β-Lactams, aminoglycosides, chloramphenicol	Treatment failure with cephalosporins (ESBL); carbapenem resistance with carbapenemases; therapy should follow carbapenemase class [27]
Alteration of drug targets	Low-affinity PBP2a (mecA); D-Ala-D-Lac precursors (vanA/vanB); gyrA/parC mutations; rRNA methylation (erm, cfr); lipid A modification (mcr) [22,28]	MRSA, VRE, Enterobacterales, streptococci	β-Lactams, glycopeptides, fluoroquinolones, macrolides, oxazolidinones, polymyxins	Loss of first-line options; need for alternative agents (e.g. daptomycin, linezolid) and AUC-guided dosing where relevant [29]
Reduced membrane permeability	Loss or reduced expression of outer-membrane porins (OmpF/OmpC, OprD) limits drug entry [30]	Enterobacterales, *P. aeruginosa*, *A. baumannii*	β-Lactams (notably carbapenems), some fluoroquinolones	Carbapenem resistance without a carbapenemase when combined with ESBL or AmpC; often raises MICs moderately
Active efflux pumps	Overexpression of RND, MFS, ABC, SMR and MATE pumps (e.g. AcrAB– TolC, MexAB–OprM, NorA) [31]	*P. aeruginosa*, Enterobacterales, *A. baumannii*, *S. aureus*	Fluoroquinolones, tetracyclines, macrolides, β-lactams, chloramphenicol	Multidrug phenotype; low-level resistance that facilitates selection of higher-level mutants
Biofilm formation	Extracellular matrix, slow growth and persister cells reduce drug penetration and activity [25]	*P. aeruginosa*, *S. aureus*, *Enterococcus*, *A. baumannii*, *E. coli*	Most classes, especially cell-wall-active agents	Relapsing and device-associated infection; frequently needs source control or device removal
Mutation and horizontal gene transfer	Chromosomal mutation; conjugative plasmids, transposons, integrons, transformation and transduction spread resistance genes [32,33]	All major pathogens	All classes	Rapid dissemination of blaCTX-M, blaKPC and blaNDM; co-resistance within the same plasmid; needs infection prevention and control

3.1 Enzymatic drug inactivation

The main resistance mechanism against β-lactams is enzymatic inactivation. β-Lactamases are classified based on amino acid sequence into Ambler classes A, B, C and D. Class B includes zinc-dependent metallo-β-lactamases (MBLs) such as NDM, VIM and IMP, whereas classes A, C and D are serine enzymes.[26] Extended-spectrum beta-lactamases (ESBLs), especially CTX-M variants, hydrolyse penicillins, cephalosporins and aztreonam and are generally inhibited by classical beta-lactamase inhibitors. Carbapenemases are KPC (class A), MBLs (class B), and OXA-48-like enzymes (class D).[34] AmpC cephalosporinases are chromosomally encoded in several Enterobacterales and in *P. aeruginosa*, but plasmid-borne forms are also common. Besides β-lactams,

aminoglycoside-modifying enzymes (acetyltransferases, phosphotransferases and nucleotidyltransferases) inactivate aminoglycosides and acetyltransferases inactivate chloramphenicol.[24]

3.2 Alteration of drug targets

The antibiotic binds to a specific site on a target. Affinity is reduced by mutation or enzymatic modification of this site, but not necessarily the physiological function of the target. MRSA carries the acquired mecA gene encoding for penicillin-binding protein 2a (PBP2a) with low affinity for most β-lactams. *Enterococci* possess vanA and vanB operons that substitute the D-alanyl-D-alanine terminus of peptidoglycan precursors with D-alanyl-D-lactate, lowering vancomycin binding affinity by approximately 1,000-fold.[28] Fluoroquinolone resistance is usually due to mutations in the quinolone-resistance-determining regions of gyrA and parC, rifampicin resistance is due to rpoB mutations and methylation of 23S or 16S rRNA by Erm or Cfr methyltransferases confers resistance to macrolides, lincosamides and, in the case of Cfr, linezolid.[23,24] Plasmid-mediated mcr genes add phosphoethanolamine to lipid A, which reduces polymyxin binding.[22]

3.3 Reduced membrane permeability

Hydrophilic antibiotics, such as β-lactams and certain fluoroquinolones, enter Gram-negative cells mainly via outer membrane porins. Porins (eg OmpF and OmpC in Enterobacterales, and OprD in *P. aeruginosa*, the entry route for imipenem) limit drug influx by loss, mutation or reduced expression.[30] Loss of porins alone usually results in modest increases in minimum inhibitory concentration (MIC); however, in combination with ESBL or AmpC production, it can result in clinically significant carbapenem resistance in Enterobacterales in the absence of a carbapenemase.[30,35]

3.4 Active efflux pumps

Efflux pumps actively transport antibiotics out of the cell before they can reach inhibitory concentrations. Five major families are recognised, including the resistance-nodulation-division (RND), major facilitator superfamily (MFS), ATP-binding cassette (ABC), small multidrug resistance (SMR) and multidrug and toxic compound extrusion (MATE) families.[31] Gram-negative bacteria have tripartite RND pumps, like AcrAB–TolC in Enterobacterales and MexAB–OprM in *P. aeruginosa*, that span both membranes and extrude various substrates, contributing to intrinsic multidrug resistance.[31,35] Efflux usually confers low level resistance but may increase the mutation frequency required to reach clinically relevant resistance, and overexpression can be selected by one drug and impair several others.

3.5 Biofilm formation

Biofilms are structured communities of bacteria embedded in a self-produced matrix of extracellular polymeric substances. They reduce antibiotic penetration, generate gradients of oxygen and nutrients that result in slow-growing, metabolically inactive cells and contain persister cells that survive lethal drug treatment without harbouring resistance mutations.[25] This is better described as tolerance than resistance because it is phenotypic and reversible, but it is clinically important because it explains relapse in device-related infections, chronic wounds, osteomyelitis and cystic fibrosis lung infection. Biofilm bacteria also show increased horizontal gene transfer and may require antibiotic concentrations far above what can be achieved in tissue.[25]

3.6 Genetic mutations and horizontal gene transfer

Resistance may develop either by spontaneous chromosomal mutation selected by exposure to antibiotics or by acquisition of resistance genes. Horizontal gene transfer happens through conjugation (plasmids and integrative conjugative elements), transformation (free DNA uptake) and transduction (bacteriophage-mediated transfer).[32] Conjugative plasmids, transposons and integrons that carry gene cassettes can transfer multiple resistance determinants among species in a single event, explaining the rapid dissemination of blaCTX-M, blaKPC and blaNDM genes. Such exchanges are favoured in clinical environments with high antibiotic selection pressure and dense microbial populations. [33][33] Antibiotics at sub-inhibitory concentrations can also increase resistance by promoting mutation and gene transfer. In practice mechanisms are not isolated but act together. Porin loss combined with ESBL or AmpC production can lead to carbapenem resistance. In *P. aeruginosa*, efflux overexpression, AmpC derepression and OprD loss are frequently detected in the same isolate .Resistance genes can also be located on the same plasmid so that selection with one antibiotic co-selects resistance to others, which is why restricting a single drug class rarely restores susceptibility to the others. [23,36] The clinical chemist's first step in predicting which alternative agents will retain activity is to recognise the likely mechanism underlying a given resistance phenotype.[24]

4. Major Antimicrobial-Resistant Pathogens

The WHO 2024 bacterial priority pathogens list assigns critical priority to carbapenem-resistant *A. baumannii*, third-generation cephalosporin-resistant Enterobacterales and carbapenem-resistant Enterobacterales, and high priority to, among others, vancomycin-resistant *Enterococcus faecium*, carbapenem-resistant *P. aeruginosa* and MRSA.[7] The pathogens below are discussed in that context.

4.1 Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA is a strain that carries the staphylococcal cassette chromosome mec element encoding PBP2a and is resistant to virtually all β-lactams except the anti-MRSA cephalosporins ceftaroline and ceftobiprole. It is found in healthcare-associated, community-associated and livestock-associated lineages and causes bacteraemia, endocarditis, pneumonia and skin, bone and joint infections.[37] Vancomycin continues to be a first-line agent for serious infections and current consensus guidance recommends area-under-the-curve (AUC) guided dosing, targeting an AUC/MIC ratio of 400–600, rather than trough-based monitoring, to maintain efficacy while minimising nephrotoxicity.[29] Alternatives include daptomycin (not for pneumonia), linezolid and ceftaroline

and are chosen based on infection site, susceptibility and patient factors. Vancomycin-intermediate and heteroresistant strains have been described and high level vancomycin resistance via acquisition of vanA from enterococci is rare but clinically important.[37] MRSA control IPC component includes screening and decolonisation, contact precautions and hand hygiene.[11]

4.2 Vancomycin-resistant *Enterococcus* (VRE)

Most VRE infections are caused by *Enterococcus faecium*, usually in immunocompromised and critically ill patients. They are often also resistant to ampicillin. Resistance is mediated by vanA or vanB gene clusters that modify peptidoglycan precursors. These elements can spread via plasmids and transposons.[28] Colonisation of the gut precedes infection and facilitates transmission, so infection prevention and control and judicious use of antibiotics with anti-anaerobic activity are important. Treatment of invasive VRE infection can be achieved by linezolid and daptomycin (usually in higher doses for bacteraemia), but linezolid resistance, mediated for example by cfr and optrA, and daptomycin non-susceptibility have been reported.[28] Therapy should be based on susceptibility testing and the site of infection. The key IPC measures to limit transmission in the hospital setting are screening of high risk patients and use of contact precautions.[11]

4.3 Extended-spectrum β-lactamase-producing Enterobacterales (ESBL)

ESBL-producing *E. coli* and *K. pneumoniae*, mainly CTX-M producers, are common causes of urinary tract, intra-abdominal and bloodstream infections in hospital and community settings.[34] Carbapenems are the drugs of choice for serious infections. In the MERINO trial, 30-day mortality in patients with ceftriaxone-resistant *E. coli* or *K. pneumoniae* bacteraemia was 12.3% with piperacillin-tazobactam and 3.7% with meropenem and non-inferiority of piperacillin-tazobactam was not demonstrated.[38] Current guidance therefore advises against piperacillin-tazobactam and cefepime in serious ESBL infections, even if in-vitro susceptibility is reported, and recommends oral step-down to agents such as trimethoprim-sulfamethoxazole or fluoroquinolones for susceptible isolates once the patient has improved.[27,39] Carbapenem exposure should be avoided in uncomplicated cystitis, for which alternatives exist. Nitrofurantoin, trimethoprim-sulfamethoxazole and fluoroquinolones are among the agents considered for ESBL-producing isolates when susceptibility is confirmed.[27] Stewardship of carbapenems is a priority in itself, because overuse leads to the selection of carbapenem-resistant organisms.

4.4 Carbapenem-resistant Enterobacterales (CRE)

High mortality is observed in CRE infections and the most important mechanism is the production of carbapenemase, in particular KPC, NDM, VIM, IMP and OXA-48-like enzymes.[40,41] The geographic distribution differs. KPC is endemic in parts of the Americas, southern Europe and Asia. NDM and OXA-48-like enzymes are common in South Asia, the Middle East and North Africa.[41] The choice of agent is guided by the class of carbapenemase, so rapid molecular or phenotypic identification is of clinical value. For KPC producers, IDSA guidelines favour ceftazidime-avibactam, meropenem-vaborbactam or imipenem-relebactam. For OXA-48-like producers, it favours ceftazidime-avibactam. For MBL producers, it favours ceftazidime-avibactam plus aztreonam, or cefiderocol.[27] Observational data showed better outcomes and lower nephrotoxicity with ceftazidime-avibactam compared to colistin-based regimens,[42] and the TANGO II trial demonstrated higher clinical cure and less nephrotoxicity with meropenem-vaborbactam compared to best available therapy, although it enrolled few patients.[43] The resistance to colistin with chromosomal mutations or plasmid-borne mcr genes further limits the use of this reserve agent.[22]

4.5 Multidrug-resistant *Pseudomonas aeruginosa*

P. aeruginosa combines intrinsic resistance (low outer-membrane permeability, constitutive efflux and inducible AmpC) with acquired mechanisms including porin loss (OprD), efflux overexpression and carbapenemase production, and is a leading cause of ventilator-associated pneumonia, bloodstream infection in neutropenic patients and chronic lung infection in cystic fibrosis.[36] Resistance may emerge during therapy, particularly with monotherapy. Ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam and cefiderocol are recommended options for infections caused by difficult-to-treat resistant isolates, with selection guided by susceptibility results.[27] Because resistance can develop during treatment, repeat cultures should be considered in patients who fail to improve, and prolonged exposure to a single agent should be avoided where feasible. In chronic infection, biofilm growth and hypermutator phenotypes further complicate eradication.[36]

4.6 *Acinetobacter baumannii*

A. baumannii is an important cause of outbreaks in intensive care units, as it can survive on dry surfaces, is tolerant to desiccation and disinfectants and easily acquires resistance genes.[44] OXA-type carbapenemases coupled with changes in efflux and permeability are the predominant mechanisms for carbapenem resistance. Few agents retain activity and historically therapy depended on polymyxins, tigecycline and high-dose sulbactam. In the phase 3 ATTACK trial, sulbactam-durlobactam, approved for hospital-acquired and ventilator-associated pneumonia caused by the *A. baumannii*-calcoaceticus complex, was non-inferior to colistin for 28-day all-cause mortality (19% vs. 32%) and was associated with less nephrotoxicity, although the numerically lower mortality should be interpreted with caution because both groups also received imipenem-cilastatin.[45] IDSA guidance recommends sulbactam-durlobactam in combination with a carbapenem as the preferred regimen for carbapenem-resistant *A. baumannii* infection.[27] Tigecycline and eravacycline are considered alternatives in some circumstances, but low serum concentrations achieved with tigecycline limit its use in bloodstream infection, and polymyxin-based regimens remain limited by toxicity and uncertain efficacy. Strict environmental cleaning and contact precautions are key for outbreak control.[27,46][44]

5. Current Challenges in Antimicrobial Therapy

The first problem is the limitation of the possibilities of therapy. Some XDR and carbapenem-resistant infections are treated with older narrow therapeutic index drugs. Polymyxins are linked to nephrotoxicity and neurotoxicity, show variable pharmacokinetics and require careful loading and maintenance dosing, so international guidance recommends that their use should be optimised by pharmacokinetic principles.[46] The outlook has improved with newer β-lactam/β-lactamase inhibitor combinations, but each has a defined spectrum. [47] None of them is active against all carbapenemase classes and resistance to ceftazidime-avibactam and cefiderocol have already been reported.[27,47]

Another challenge is diagnostic delay. Conventional culture and susceptibility testing take 2 to 3 days, so initial therapy is empirical and often broad. Molecular rapid diagnostic testing for bloodstream infection has been associated with a shorter time to effective therapy and, when combined with stewardship intervention, a decrease in mortality and length of hospital stay,[48] but availability of these technologies is limited in many settings. The interpretation of susceptibility results also depends upon breakpoints, which are periodically revised by standard-setting bodies.[49] A related issue is penicillin allergy labels: about 10% of patients report a penicillin allergy, but the vast majority are not truly allergic, and the label leads to the use of broader spectrum and often less effective alternatives.[50] The third challenge is variability in pharmacokinetics. Critically ill patients may have subtherapeutic concentrations because of altered volume of distribution, augmented renal clearance, hypoalbuminaemia and extracorporeal support. The DALI study demonstrated that a substantial proportion of patients treated with standard β-lactam doses failed to achieve pharmacodynamic targets, and target non-attainment was associated with a poorer clinical outcome.[51]

Finally, the access environment of the pipeline is not convenient. WHO analysis of the 2023 pipeline identified 97 antibacterial agents in clinical development, but few were innovative and few targeted critical-priority pathogens.[52] Antibiotics are used for short periods and stewardship actively limits their use, so they are not commercially attractive and many large companies have exited the field.[53] The barrier of access to new agents is as important as the discovery: they are expensive and often unavailable in the countries with the highest burden.[21] Management is also made more difficult by shortages of older key antibiotics and the absence of standardised surveillance.

6. Novel Therapeutic Approaches

A broad range of strategies is under development, from improved conventional antibiotics to non-traditional approaches that target virulence, the host or the genetic basis of resistance. Table 2 summarises their mechanisms, evidence and limitations, distinguishing approved agents from those that remain investigational.

Table 2. Novel therapeutic approaches against antimicrobial resistance

Therapeutic approach	Mechanism of action	Representative drug/strategy	Current evidence or development status	Potential clinical application	Major limitations
New-generation antibiotics (approved)	Siderophore-mediated entry (cefiderocol); novel topoisomerase inhibition (gepotidacin); β-lactamase inhibition with PBP targeting (sulbactam-durlobactam)	Cefiderocol; sulbactam-durlobactam; gepotidacin	Approved agents with phase 3 data [45,54,55]	Carbapenem-resistant Gram-negative infection; CRAB; uncomplicated UTI (gepotidacin)	Cost, access, emerging resistance; mortality signal in Acinetobacter subgroup for cefiderocol
β-Lactam/β-lactamase inhibitor combinations	Inhibitor protects partner β-lactam from serine β-lactamases (and some MBLs with newer boronates)	Ceftazidime-avibactam; meropenem-vaborbactam; imipenem-relebactam; cefepime-enmetazobactam; cefepime-taniborbactam	Several approved; cefepime-taniborbactam has phase 3 data and regulatory status should be verified [47,56,57]	KPC- and OXA-48-producing CRE; ESBL-producing UTI; MBL producers (with aztreonam)	No universal MBL activity; resistance emerging; limited head-to-head trials
Novel-class antibiotics (investigational)	Targets such as LPS transport (LptB2FGC) and BamA; cell wall precursors	Zosurabalpin; darobactin; teixobactin; AI-discovered compounds	Preclinical or early-phase [58–61]	Future therapy for CRAB and other Gram-negative pathogens	High attrition; toxicity and pharmacokinetics unknown in humans
Bacteriophage therapy (investigational)	Lytic phages infect and lyse specific bacteria	Personalised phage cocktails; engineered phages	Case series and compassionate use; one negative RCT [62,63]	Salvage therapy for resistant and biofilm-associated infection	Narrow host range, phage resistance, standardisation, regulation
Antimicrobial peptides (mostly investigational)	Membrane disruption; immune modulation	Host-defence peptide analogues (polymyxins are established lipopeptides)	Mostly preclinical or early trials [64,65]	Topical and systemic therapy of resistant pathogens	Toxicity, instability, cost, limited systemic exposure

Therapeutic approach	Mechanism of action	Representative drug/strategy	Current evidence or development status	Potential clinical application	Major limitations
Monoclonal antibodies	Toxin neutralisation, opsonisation, adhesion blockade	Bezlotoxumab (approved, since discontinued); anti-*S. aureus* and anti-*P. aeruginosa* antibodies (investigational)	One approved agent; others in trials [66,67]	Adjunct therapy and prevention of recurrence	Pathogen-specific, cost, need for rapid diagnostics
CRISPR-based strategies (preclinical)	Programmed Cas nuclease cleaves resistance genes or target bacterial DNA	Phage- or plasmid-delivered CRISPR-Cas	Laboratory and animal studies [68,69]	Decolonisation; re-sensitisation to antibiotics	Delivery, escape mutants, off-target effects, regulation
Anti-biofilm approaches (mostly investigational)	Matrix degradation, quorum-sensing inhibition, dispersal, device coatings	Matrix-degrading enzymes; quorum-sensing inhibitors; coatings	Mostly *in vitro* and animal data [70]	Device-related and chronic infection	Lack of standardised assays; heterogeneity; clinical translation
Immunotherapeutic approaches (vaccines licensed for some pathogens; others investigational)	Active immunisation; host-directed immune modulation	Pneumococcal and Hib conjugate vaccines; vaccine candidates for *S. aureus* and Gram-negatives	Established for some pathogens; difficult for others [71]	Prevention of resistant infection and reduction of antibiotic use	Few vaccines against key resistant bacteria; trial failures

6.1 New-generation antibiotics

Cefiderocol is a siderophore cephalosporin that chelates ferric iron and penetrates Gram-negative cells via bacterial iron transport systems, circumventing porin loss and efflux and retaining stability against many β-lactamases. Clinical cure in carbapenem-resistant infections was similar between cefiderocol and best available therapy in the CREDIBLE-CR trial, but all-cause mortality was numerically higher in the cefiderocol arm, predominantly in patients with Acinetobacter infections, thus leaving its role in that pathogen unresolved.[54]

Sulbactam-durlobactam, described above, is the first agent specifically developed for carbapenem-resistant *A. baumannii*.[45] Gepotidacin, a first-in-class triazaacenaphthylene topoisomerase inhibitor, was non-inferior to nitrofurantoin in two phase 3 trials (EAGLE-2 and EAGLE-3) in uncomplicated urinary tract infection and is oral, with a mechanism distinct from fluoroquinolones.[55]

Some structurally novel compounds are in earlier development. Zosurabalpin, a macrocyclic peptide, inhibits the LptB2FGC lipopolysaccharide transporter in carbapenem-resistant *A. baumannii* and demonstrated *in vivo* efficacy in preclinical models.[58] Darobactin targets the outer-membrane protein BamA, [59] teixobactin binds to precursors of cell wall synthesis and did not produce any detectable resistance in laboratory experiments, [60] and machine-learning approaches have identified antibacterial molecules such as halicin and a structural class active against MRSA and VRE in animal models.[61,72] They are still experimental and the failure rate between discovery and approval is high.[73]

6.2 Beta-lactam/beta-lactamase inhibitor combinations

The most fruitful has been the combination of β-lactams with inhibitors that restore activity against resistant organisms. The newer inhibitors avibactam, vaborbactam and relebactam inhibit class A and C enzymes, including KPC, and avibactam also inhibits some class D enzymes such as OXA-48, but none of them inhibits MBLs.[47] In the RESTORE-IMI 1 study, imipenem-relebactam was as effective as colistin plus imipenem for infections that were not susceptible to imipenem, but with fewer side effects, although the numbers were small.[74] In the ALLIUM trial, cefepime-enmetazobactam was superior to piperacillin-tazobactam in complicated urinary tract infection (composite response 79.1% vs 58.9%), relevant for ESBL-producing pathogens.[56] Cefepime-taniborbactam, a boronate inhibitor with some activity against MBLs, showed higher composite success than meropenem in complicated urinary tract infection in the CERTAIN-1 trial [57] and its regulatory status should be verified at the time of use. In addition to the off-label combination of ceftazidime-avibactam with aztreonam, a fixed combination of aztreonam and avibactam is now available in some jurisdictions for MBL producers.[27] Emerging resistance to these combinations, via KPC variants, porin changes and efflux, is a concern.[47]

6.3 Bacteriophage therapy

Bacteriophages are viruses that infect bacteria. Lytic phages kill their hosts regardless of the antibiotic resistance profiles. They have narrow host ranges, which spares the microbiota, but generally requires matching a phage or cocktail to the patient's isolate. Compassionate-use cases have included a patient with disseminated *A. baumannii* infection treated with a personalised phage cocktail [76], and a patient with disseminated *Mycobacterium abscessus* infection treated with engineered phages .[77] In a retrospective review of 100 consecutive personalised cases, clinical improvement was reported in 77% and bacterial eradication in approximately 61%; however, the design was observational and uncontrolled.[62] The single randomised, placebo-controlled trial of intravesical phages in transurethral prostate resection did not demonstrate efficacy compared to placebo or standard antibiotics .The major obstacles are phage standardisation, resistance development, immune responses, pharmacokinetics at the

site of infection, and regulatory structures. Phage therapy is not an established standard treatment yet.[75]

6.4 Antimicrobial peptides

Antimicrobial peptides are short, usually cationic and amphipathic molecules that disrupt bacterial membranes and, in many cases, modulate host immunity.[65] Their broad activity and low propensity to select for resistance *in vitro* are attractive, but clinical translation has been limited by toxicity, proteolytic instability, poor systemic exposure and cost of manufacture.[64] Most candidates have not progressed beyond early clinical trials, and the polymyxins, which are natural lipopeptides, remain the main clinically established peptide antibiotics.

6.5 Monoclonal antibodies

Monoclonal antibodies can neutralise toxins or virulence factors, promote opsonophagocytosis or block bacterial adhesion, and they offer high specificity without perturbing the microbiota.[67] Bezlotoxumab, which neutralises *Clostridioides difficile* toxin B, reduced recurrent infection in the MODIFY trials,[66] but it has since been discontinued commercially, illustrating the commercial fragility of this class. Antibodies directed at *S. aureus* and *P. aeruginosa* virulence factors are in development.[67] Their value is likely to be adjunctive and pathogen-specific, depending on rapid identification of the infecting organism.

6.6 CRISPR-based antimicrobial strategies

CRISPR-Cas systems can be programmed to cleave specific DNA sequences. When delivered into bacteria through phage capsids or conjugative plasmids, Cas nucleases can selectively kill bacteria carrying a target sequence or eliminate resistance genes, thereby re-sensitising populations to antibiotics.[68,69] Foundational work showed sequence-specific killing of pathogenic and antibiotic-resistant *E. coli* and *S. aureus*.[68,69] The evidence remains largely preclinical. Efficient in-vivo delivery, escape mutants, off-target effects, biosafety and regulatory pathways must be addressed before clinical use.

6.7 Anti-biofilm approaches

Anti-biofilm strategies include matrix-degrading enzymes, quorum-sensing inhibitors, dispersal agents, surface coatings for medical devices, and combinations that pair conventional antibiotics with agents that improve penetration or reactivate persister cells.[70] Many have shown activity in laboratory models, but standardised biofilm assays are lacking, and translation to patients has been difficult because biofilm infections are heterogeneous and often require device removal. Surgical source control and appropriately selected, prolonged antibiotic therapy therefore remain the cornerstones of management, while anti-biofilm agents are mostly investigational.[25,70]

6.8 Immunotherapeutic approaches

Immunological approaches to limit resistance include vaccines that prevent infections and reduce the use of antibiotics; pneumococcal and *Haemophilus influenzae* type b conjugate vaccines have been linked to reductions in resistant invasive disease.[71] Development of vaccine against several important resistant pathogens, such as *S. aureus*, has been challenging and no vaccine is available for the Gram-negative ESKAPE pathogens.[71] Other host-directed approaches (e.g., cytokine therapies to reverse immune dysfunction in sepsis) remain experimental. Passive immunotherapy has been discussed above.[67]

The evidence for new agents overall has important limitations that should temper enthusiasm. Many approvals are based on non-inferiority trials in complicated urinary tract infection, intra-abdominal infection or pneumonia, in which relatively few patients had infections due to the most resistant organisms, and comparators have differed between trials. Studies on the pathogen in carbapenem-resistant infection are small and frequently descriptive.[56,57,74][43,54] Thus, newer agents should be used where they are most needed, guided by mechanism and local susceptibility, and monitored for emerging resistance, because the indiscriminate use of newly approved drugs will erode their value as quickly as it did for earlier classes.[27,73]

7. Antimicrobial Stewardship Programs

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal drug regimen, including dose, duration and route of administration.[10] It differs from IPC, which prevents transmission of organisms between patients, although the two are mutually reinforcing: stewardship lowers selection pressure and IPC limits the spread of resistant strains that have already emerged.[10,11]

Core stewardship strategies include prospective audit and feedback, formulary restriction and preauthorisation, evidence-based local guidelines and order sets, de-escalation, IV-to-oral conversion, dose optimisation, and evaluation of penicillin allergy labels. Diagnostic stewardship, which optimises testing and the reporting of results, supports these strategies.[10,50] Biomarker-guided approaches may also help: procalcitonin-guided therapy in acute respiratory infection reduced antibiotic exposure without an adverse effect on mortality.[78] The WHO AWaRe classification groups antibiotics into Access, Watch and Reserve categories, so that the choice of agent can be audited and national use targets set.[9] Evidence of benefit is reasonably robust, though heterogeneous. A Cochrane review found that interventions to improve hospital antibiotic prescribing increased compliance with policy and reduced the duration of treatment, with no increase in mortality.[79] A systematic review and meta-analysis showed that stewardship reduced the incidence of infection and colonisation with multidrug-resistant Gram-negative bacteria, ESBL producers, MRSA and *Clostridioides difficile*, with the greatest effect for multifaceted interventions that included infection control measures.[80] Hospital-based programmes have also been associated with reduced antimicrobial consumption and costs.[81] Limitations include variation in study design, reliance on process outcomes, uncertain long-term sustainability and limited data from low-resource settings. Programmes require institutional support, adequate staffing and information technology to function well.[10]

8. Role of Clinical Pharmacists in Combating AMR

Guidelines identify the clinical pharmacist, with training in infectious diseases, as a core member of the stewardship team alongside the infectious diseases physician, the clinical microbiologist and the IPC practitioner.[10] The pharmacist's contribution spans the whole antimicrobial treatment pathway, as summarised in Figure 2.

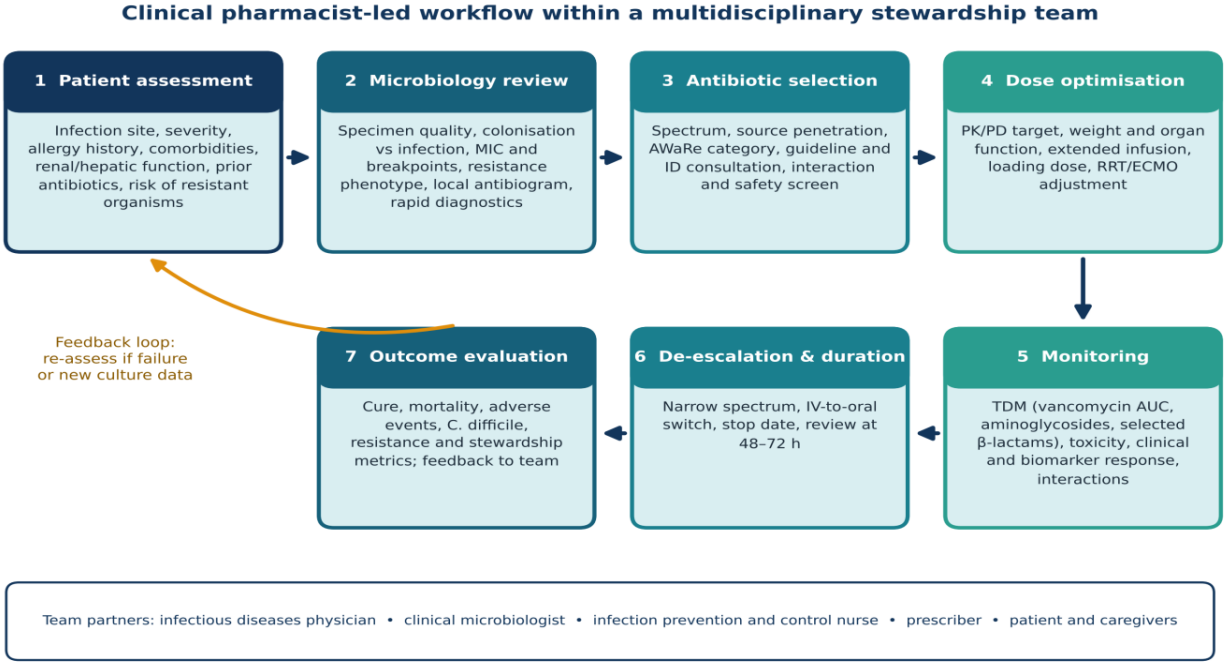


Figure 2. Clinical pharmacist's role in antimicrobial stewardship: a seven-step workflow from patient assessment to outcome evaluation, with feedback to reassess therapy. Original schematic prepared by the authors; components are based on stewardship and pharmacokinetic guidance [10,29,82].

8.1 Antibiotics selection and optimisation

Pharmacists evaluate if an antibiotic is appropriate, if the choice aligns with local antibiograms, guidelines, patient allergy history and risk factors for resistant organisms, and if a narrower alternative in the Access category will suffice. They also provide empirical regimens reflecting infection source and severity, and they highlight combination therapy lacking supporting evidence.[9,10] Special consideration should be given to allergy history as the structured assessment enables safe use of first-line β-lactams in many patients labelled as penicillin allergic without verification.[50] Pharmacists also consult infectious disease specialists early when the pathogen is highly resistant and the choice of agent is complex.

8.2 Personalising the dose

Dosing should be based on the pharmacodynamic index for each class: time above MIC for beta-lactams, peak concentration/MIC for aminoglycosides, and AUC/MIC for vancomycin and fluoroquinolones. Pharmacists make adjustments of doses for body weight, obesity, augmented renal clearance, extracorporeal support, and renal replacement therapy.[51,82] An example of a pharmacokinetically driven approach is the use of prolonged or continuous infusion of β-lactams. In critically ill patients with sepsis, the BLING III trial found a lower 90-day mortality with continuous infusion compared with intermittent dosing, and the finding is influencing practice, although it needs to be considered when considering logistic constraints such as drug stability and queue access.[83] Loading doses are important for agents such as polymyxins and are given regardless of renal function with maintenance doses then being adjusted.[46]

8.3 Renal and hepatic dose adjustment

Many antibiotics, including β-lactams, aminoglycosides, vancomycin and fluoroquinolones, are renally eliminated, so doses must follow renal function. Creatinine-based estimates may be unreliable in acute kidney injury, extremes of body composition and critical illness, and pharmacists should interpret them in clinical context and avoid delaying the first effective dose. Hepatic impairment requires dose reduction for a smaller group of agents, such as tigecycline in severe hepatic impairment, and extra caution with hepatotoxic drugs. Avoiding nephrotoxic combinations is also a pharmacist responsibility, and renal function should be reassessed frequently during therapy with potentially nephrotoxic drugs such as aminoglycosides, vancomycin and polymyxins.[46,82]

8.4 Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) personalises drug exposure for drugs with a narrow therapeutic index or large variability. Pharmacists lead AUC-guided vancomycin dosing,[29] aminoglycoside monitoring and β-lactam monitoring where assays are available in critically ill patients.[82] Polymyxin dosing is complicated by assay limitations and nephrotoxicity, with consensus guidance describing loading doses and pharmacokinetic-based

maintenance.[46] In practice, TDM is most useful when it is linked to clear action, with samples taken at the right time, concentrations interpreted against the pharmacodynamic target and documented dose changes communicated to the prescriber.[82]

8.5 Drug interaction assessment

Antibiotics interact through enzyme induction and inhibition, QT prolongation, chelation, protein binding and additive toxicity. Rifampicin induces many cytochrome P450 enzymes, macrolides such as clarithromycin inhibit CYP3A4, fluoroquinolones chelate polyvalent cations and prolong the QT interval, and trimethoprim-sulfamethoxazole can cause hyperkalaemia with renin-angiotensin system inhibitors. Linezolid carries a serotonin syndrome warning, but a population-based cohort study found a low absolute risk in older adults taking antidepressants, which supports individualised assessment instead of reflex avoidance.[84]

8.6 IV-to-oral conversion

Early switch to oral therapy decreases length of stay and line related complications. Eligible candidates are clinically improving, haemodynamically stable, enterally feeding and have a pathogen susceptible to an oral agent with good bioavailability. The OVIVA trial showed that oral therapy was non-inferior to IV therapy for bone and joint infection, challenging the standard preference for long IV treatment.[85] Pharmacists are able to add criteria for automatic IV-to-oral review to prescribing systems, to identify eligible patients at approximately 48–72 hours, without reliance on individual recall.[10]

8.7 De-escalation and duration optimisation

When cultures return, chemists advise narrowing the spectrum and documenting a stop date or review at 48-72 hours. Trials support shorter courses. In uncomplicated Gram-negative bacteraemia with source control and clinical response, 7 days was non-inferior to 14 days.[86] The principle that less is often enough is gaining acceptance,[87] but recognising that complicated infections, undrained collections and immunosuppression may require longer therapy. Procalcitonin can support early discontinuation in respiratory infection.[78]

8.8 Patient education and adherence

Pharmacists educate patients on the importance of taking antibiotics exactly as prescribed, the absence of benefit in viral illness, the dangers of sharing or storing leftover antibiotics, and the importance of vaccination and hand hygiene. They also implement regulatory controls in community practice such as restricting selected antibiotics to prescription only supply under Schedule H1 in India. They can discourage requests for antibiotics without a clinical indication.[20] Clear instructions and counselling on adverse effects and missed doses support treatment success and reduce selection pressure, which is linked to better adherence.

8.9 Microbiology report interpretation

Pharmacists are well-placed to distinguish between colonisation and infection, interpret MICs against current breakpoints, recognise resistance phenotypes (e.g. ESBL, carbapenemase production), and understand categories such as susceptible, susceptible-dose dependent, intermediate and resistant.[49] They use cumulative antibiograms to guide empirical therapy, and they support the implementation of rapid diagnostic results, which are most effective when paired with timely stewardship review.[48] Selective reporting of susceptibility results can be negotiated with the laboratory to guide prescribers to narrower agents.

8.10 Participation in multidisciplinary stewardship teams

Pharmacists are involved in guideline development, prospective audit and feedback, formulary decisions, drug-use evaluation, penicillin allergy assessment and education of prescribers.[10,50] Stewardship and infection control are linked through collaboration with microbiologists, infectious diseases physicians and IPC teams.[10] Much of the published data on pharmacist led activity is from multi-faceted programs making it difficult to isolate the independent effect of pharmacists. Rigorous evaluation with patient centred outcomes is still required.

9. Clinical Applications and Therapeutic Considerations

The evidence must be translated into practice with attention to syndrome, pathogen, host and setting. There are three principles. First, a resistant infection should be treated pathogen-directed and mechanism-directed. Carbapenems remain the preferred treatment for bloodstream infection caused by ESBL-producing Enterobacterales, whereas for CRE, the choice of ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam or cefiderocol should be informed by the carbapenemase type.[27,38,39] Second, combination therapy needs to be justified, not automatic. Clinical failure at 14 days in severe carbapenem-resistant Gram-negative infection was not improved by the addition of meropenem to colistin in the AIDA trial. Therefore, combination use should be based on specific indications, such as the guidance-supported pairings for CRAB and MBL producers.[27,88] Third, the drug choice is as important as the source control, duration, and avoidance of treatment of non-infective states; for instance, asymptomatic bacteriuria should generally not be treated outside defined exceptions, thereby preventing unnecessary antibiotic exposure.[89]

These principles lead to syndrome-specific problems. For hospital-acquired and ventilator-associated pneumonia, empiric regimens should reflect local MRSA and resistant Gram-negative bacilli prevalence and be narrowed when cultures are available.[10,27] Oral step-down is feasible in complicated urinary tract infection when the isolate is susceptible and the patient has improved. Newer agents with oral or intravenous formulations expand options for resistant uropathogens.[55,56] In bloodstream infection, source control, appropriate empirical coverage and an evidence-based duration are important, and shorter courses are supported for selected uncomplicated Gram-negative cases.[86] Special populations require individualisation: dose requirements vary in neonates and children, pregnancy restricts some classes, renal impairment alters elimination and the increasing proportion of burden in adults over 70 years of age emphasises the importance of

polypharmacy and interaction screening in older patients.[13,84]

Sicherheit und Individualisierung sind gleichermaßen wichtig. The choice of agent should consider the patient's allergy history, renal and hepatic function, pregnancy status, age, drugs interacting with it and the risk of adverse effects like nephrotoxicity, neurotoxicity, QT prolongation and *Clostridioides difficile* infection. Experimental measures such as phage therapy should be limited to specialist-led compassionate use or clinical trials with appropriate governance as the evidence base is not yet sufficient for routine practice [10,46].[63,75] The realities of availability, cost and diagnostic capacity may determine what can be delivered in low-resource settings. Local antibiograms, essential medicines lists and the AWaRe framework are the pragmatic basis for guidance.[9,21]

10. Research Gaps and Future Perspectives

Practice is limited by several evidence gaps. There are few randomised trials in carbapenem-resistant *A. baumannii* and MBL-producing infections which are often small with mortality or composite end-points that are difficult to compare. Many newer agents have been approved on the basis of limited pathogen-specific data.[27,45,54] Sparse pharmacokinetic and pharmacodynamic data exist in children, pregnancy, obesity, renal replacement therapy and extracorporeal support, and dosing in these groups is based on extrapolation.[51,82] Further randomised evaluation is needed to assess the impact of rapid diagnostics and TDM on patient-centered outcomes, and implementation research is needed to adapt stewardship and pharmacist-led models to low-resource settings.[21,48]

Priority areas for discovery and development include new classes active against Gram-negative bacteria, standardised frameworks for phage therapy and CRISPR-based tools, and validation of artificial intelligence-guided discovery in clinical development.[61,73,75] Also economic reform is needed, since new agents need to be developed and used in an equitable way, requiring sustainable models that break the link between revenue and sales volume and ensure access throughout all regions.[14,21,52] Strengthened surveillance, including genomic surveillance and a One Health approach across the human, animal and environmental sectors, is needed to detect and contain emerging resistance.[8,12]

11. Conclusion

AMR is a growing and unevenly distributed threat driven by a number of interacting resistance mechanisms and the pressure of antibiotic use. Recent availability of new drugs, particularly newer β-lactam/β-lactamase inhibitor combinations, cefiderocol and sulbactam-durlobactam, have improved treatment options for carbapenem-resistant infections, but these drugs are not universally available, do not cover all resistance mechanisms and are vulnerable to the development of resistance. Non-traditional approaches including phage therapy, antimicrobial peptides, monoclonal antibodies, CRISPR-based antimicrobials, anti-biofilm agents and vaccines are promising but mostly investigational and should not be offered as established treatments. Clinical chemists are involved in antibiotic selection, dose individualisation, therapeutic drug monitoring, interaction screening, de-escalation, duration optimisation, patient education and stewardship teams. Innovation, equitable access, and stewardship and infection prevention, remain the most practical ways of limiting the impact of AMR and protecting existing antibiotics.

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