WHEN BACTERIA FIGHT BACK: UNDERSTANDING MULTIDRUG RESISTANCE AND ITS GENETIC ROOTS IN PATHOGENIC BACTERIA

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Abstract

Background: Antibiotic resistance was once considered a distant threat; today it is a clinical reality reshaping how we treat even routine infections. Multidrug resistance (MDR)—defined as non-susceptibility to agents across three or more antibiotic categories—has taken hold in hospitals and communities worldwide, leaving clinicians with dangerously few options. Objective: This review explores the genetic machinery behind MDR, examining how bacteria acquire, store, and share resistance genes, and how those genes translate into the mechanisms that defeat our drugs. Methods: We searched Scopus, PubMed, and Web of Science for literature published between 2005 and 2024, prioritizing primary research and authoritative reviews on resistance genetics and mechanisms. Results: MDR arises through four principal strategies: enzymatic drug destruction, active drug expulsion via efflux pumps, alteration of the drug's binding target, and tightening of the bacterial membrane against drug entry. The genes driving these strategies—ranging from bla-family beta-lactamases to mcr colistin-resistance genes—travel efficiently between organisms on plasmids, transposons, and integrons. Conclusion: Addressing MDR demands more than new drugs; it requires an intimate understanding of how bacteria think genetically, because only then can we design interventions that are truly durable.

Keywords: *multidrug resistance; antibiotic resistance genes; horizontal gene transfer; mobile genetic elements; efflux pumps; beta-lactamase; ESKAPE pathogens; resistance mechanisms*

1. Introduction

Not long ago, a severe bacterial infection was a manageable problem—pick the right antibiotic, complete the course, and the patient recovers. That straightforward picture has become increasingly complicated. Bacteria are extraordinary survivors, and decades of antibiotic pressure have pushed them to evolve resistance at a pace that has outstripped our ability to produce new drugs. Today, multidrug-resistant (MDR) organisms are implicated in millions of deaths each year, and projections suggest the toll could reach ten million annually by mid-century if nothing changes [1, 2].

MDR is not a single trick but a layered response—bacteria can simultaneously deploy multiple strategies to neutralize chemically unrelated antibiotics. The organisms that do this most effectively are sometimes grouped under the acronym ESKAPE:

Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. These pathogens dominate hospital-acquired infections worldwide and share the unsettling trait of treating antibiotic exposure as little more than an inconvenience [3]. Within Gram-negative bacteria in particular, carbapenem-resistant strains—once considered a clinical last resort—have become a near-daily challenge in intensive care settings.

What drives all of this is genetics. The capacity of bacteria to resist antibiotics is written into their DNA, sometimes acquired from distant relatives through processes that look almost like deliberate sharing. This review traces that genetic story: how resistance genes arise and what they encode, how they move between organisms, and how their protein products physically defeat antibiotics inside the bacterial cell. Understanding these connections is the first step toward reversing them.

2. Classifying Resistance: More Than a Label

Before examining mechanisms, it helps to establish a shared vocabulary. Clinicians and researchers use three escalating terms to describe how thoroughly a bacterial isolate has escaped antibiotic control. An MDR organism is non-susceptible to at least one drug in three or more antibiotic categories. An extensively drug-resistant (XDR) isolate remains susceptible to just one or two categories. A pandrug-resistant (PDR) strain has crossed the line entirely, showing no susceptibility to anything currently approved [4]. These definitions, proposed by an international expert group, provide a common framework for comparing surveillance data across countries and institutions.

Resistance itself can be intrinsic or acquired. Intrinsic resistance is baked into a species by its biology—Gram-negative bacteria, for instance, are naturally impermeable to vancomycin because the antibiotic is simply too large to cross their outer membrane. Acquired resistance is the real engine of the MDR crisis: individual strains pick up new genetic material, or accumulate mutations, that flip them from susceptible to resistant under antibiotic pressure. It is acquired resistance that travels, spreads, and compounds, and it is the subject of the sections that follow [5].

3. The Genetic Toolkit of Resistance

3.1 Resistance Genes and What They Do

Bacteria carry a surprisingly rich collection of genes devoted to surviving antibiotics, and the diversity of those genes reflects the diversity of the drugs they face. For beta-lactams—the penicillins, cephalosporins, and carbapenems—the dominant resistance genes encode beta-lactamases, enzymes that physically break the chemical ring that gives these drugs their activity. The Ambler classification sorts beta-lactamases into four molecular classes. Class A includes the extended-spectrum beta-lactamases (ESBLs) such as CTX-M, SHV, and TEM, which have spread so widely that they are now considered endemic in many hospital environments. Class B encompasses the metallo-beta-lactamases (NDM, VIM, IMP), which can dismantle even carbapenems and represent some of the most clinically concerning resistance mechanisms known.

Class D OXA-type enzymes complete the carbapenem-resistance picture, particularly in Acinetobacter [6].

Aminoglycoside resistance works differently. The key genes—aac, aph, and ant families—encode enzymes that chemically modify the antibiotic itself, adding acetyl, phosphate, or adenyl groups that prevent the drug from latching onto the bacterial ribosome. A separate set of genes (armA, rmtB) go a step further, methylating the ribosome so that even intact aminoglycosides cannot bind. Tetracycline resistance relies on two strategies encoded by tet genes: efflux (tet(A), tet(B)) shuttles the drug out before it can act, while ribosomal protection proteins (tet(M), tet(O)) physically shield the ribosome from tetracycline. Fluoroquinolone resistance, long assumed to depend only on chromosomal mutations, gained a plasmid-borne dimension with the discovery of qnr genes (qnrA, qnrB, qnrS), whose protein products wrap around the bacterial topoisomerases that fluoroquinolones target, reducing drug affinity [7].

Perhaps the most alarming recent addition to the resistance gene catalogue is the mcr family. The mcr-1 gene, first identified in 2015 in livestock and human isolates in China, encodes a phosphoethanolamine transferase that modifies lipid A in the bacterial outer membrane. This modification reduces the binding of polymyxins—colistin in particular—which had been used as a last-resort drug precisely because resistance was thought to be chromosomal and therefore non-transferable. The discovery of plasmid-borne mcr genes (now numbered mcr-1 through mcr-10) shattered that assumption and launched a global surveillance effort [8]. Meanwhile, glycopeptide resistance in enterococci traces to the van gene clusters, which reprogram the bacterium's entire peptidoglycan synthesis pathway to produce a terminal residue that vancomycin cannot recognize. In Staphylococcus aureus, the mecA and mecC genes confer methicillin resistance by encoding an alternative penicillin-binding protein (PBP2a) with a fundamentally different active-site geometry [9].

Table 1. Principal resistance gene families, their encoded functions, and the pathogens in which they are clinically significant

Antibiotic Class	Representative Genes	Mode of Action	Clinically Important Species
Beta-lactams	blaCTX-M, blaNDM, blaKPC, blaOXA-48	Beta-lactam ring hydrolysis	K. pneumoniae, E. coli, A. baumannii
Aminoglycosides	aac(6')-Ib, aph(3'), armA, rmtB	Chemical drug modification; ribosomal methylation	P. aeruginosa, Enterobacteriaceae

Antibiotic Class	Representative Genes	Mode of Action	Clinically Important Species
Fluoroquinolones	qnrA, qnrB, qnrS, aac(6')-Ib-cr	Target shielding; drug acetylation	E. coli, K. pneumoniae
Tetracyclines	tet(A), tet(B), tet(M), tet(O)	Active efflux; ribosomal protection	E. coli, S. aureus, Enterococcus spp.
Glycopeptides	vanA, vanB, vanC	Peptidoglycan terminal modification	E. faecium, E. faecalis
Polymyxins / Colistin	mcr-1 through mcr-10	Lipid A phosphoethanolamine addition	E. coli, K. pneumoniae
Methicillin / Beta-lactams	mecA, mecC	Low-affinity PBP2a substitution	S. aureus (MRSA)

3.2 How Resistance Genes Travel: Mobile Genetic Elements and Gene Transfer

A resistance gene is only as dangerous as its ability to spread, and bacteria have evolved remarkably efficient ways of sharing genetic information. The overarching process is called horizontal gene transfer (HGT), and it encompasses several distinct mechanisms, each with its own set of molecular vehicles.

Conjugative plasmids are the workhorses of resistance spread. These are circular DNA molecules—sometimes exceeding 100 kilobases in size—that bacteria transfer directly from cell to cell through physical contact via a channel called a pilus, encoded by type IV secretion systems. A single plasmid can carry resistance genes for multiple antibiotic classes simultaneously, meaning that one transfer event can convert a susceptible strain into an MDR organism virtually overnight. Plasmid incompatibility groups (IncF, IncI, IncN, IncX, and others) define which plasmids can coexist in the same cell, and surveillance data tracking these groups has revealed global transmission networks connecting isolates from livestock, wastewater, and hospital patients across continents [10].

Within the bacterial cell and on plasmids, smaller mobile units called insertion sequences (ISs) and transposons act as molecular cut-and-paste machines, relocating resistance genes between chromosomes and plasmids and sometimes amplifying them in the process. The IS26 element, ubiquitous in Enterobacteriaceae, has been directly implicated in the capture and multiplication of beta-lactamase genes around the world. Class 1 integrons add another layer of sophistication: these genetic platforms recruit small, modular gene cassettes through site-specific recombination, assembling multi-resistance arrays from individual components like building blocks. Entire genomic islands—large stretches of foreign DNA integrated into bacterial chromosomes—can

carry dozens of resistance genes alongside virulence factors, encoding everything a bacterium needs to both cause disease and withstand treatment [11].

Transduction via bacteriophages (bacterial viruses) and natural transformation—the uptake of free DNA fragments from the environment—round out the HGT toolkit. Phage-mediated resistance transfer is well documented in Staphylococcus aureus, while transformation is particularly relevant in naturally competent species such as Acinetobacter baumannii and Streptococcus pneumoniae. In biofilm communities, where cells are densely packed and metabolically active, all three HGT mechanisms operate at elevated rates, turning biofilms into incubators for resistance evolution [12].

4. How Bacteria Actually Defeat Antibiotics

4.1 Destroying the Drug Before It Can Act

The most direct way a bacterium can neutralize an antibiotic is simply to destroy it. Beta-lactamases, the enzymes encoded by bla-family genes, do exactly this: they catalyze the hydrolysis of the beta-lactam ring that is structurally essential to penicillins, cephalosporins, and carbapenems. Once that ring is broken, the drug is inert. NDM-type metallo-beta-lactamases are particularly worrying because they rely on zinc rather than a serine residue in their active site, which makes them structurally incompatible with most currently available beta-lactamase inhibitors. Their rapid international dissemination on promiscuous plasmids has effectively closed carbapenem therapy as an option for a growing number of infections [13].

Chloramphenicol acetyltransferases (CATs) offer another example of enzymatic inactivation, chemically modifying chloramphenicol so it can no longer bind to the ribosomal 50S subunit. Aminoglycoside-modifying enzymes work on a similar principle, adding chemical groups to the antibiotic molecule at positions critical for ribosome contact. The result in each case is the same: a drug that enters the cell exits—or is simply found—in a chemically altered form that has lost all biological activity.

4.2 Pumping the Drug Out

Rather than destroying antibiotics, efflux pumps solve the problem by continuously expelling them. These membrane-spanning protein complexes maintain intracellular drug concentrations below inhibitory levels, effectively giving the bacterium room to breathe even when surrounded by antibiotic. Six major pump families are recognized—RND, MFS, ABC, SMR, MATE, and PACE—and they differ in energy source, substrate range, and structural complexity. The RND family deserves special attention because its members, exemplified by MexAB-OprM in Pseudomonas aeruginosa and AcrAB-TolC in Enterobacteriaceae, form tripartite systems that span both bacterial membranes and can expel a remarkably broad range of structurally diverse compounds [14].

Under normal circumstances, cells keep their efflux genes under tight regulatory control to avoid wasting energy. Resistance-relevant overexpression typically occurs when repressor genes (such as mexR, which controls MexAB-OprM) are mutated, or

when global stress responses like the SOS response or the Mar regulon are activated. In P. aeruginosa, the MexXY-OprM pump is specifically induced by aminoglycoside stress, creating a feedback loop in which antibiotic treatment drives the very resistance that makes subsequent treatment harder. The idea of pairing antibiotics with efflux pump inhibitors (EPIs) to restore drug efficacy is scientifically compelling, and several EPIs have shown promise in laboratory settings, though none has yet cleared the hurdles necessary for clinical use [15].

4.3 Changing the Target

A different and elegant bacterial strategy is to alter the molecular target that the antibiotic was designed to hit. This can happen through point mutations that subtly reshape the target's structure, or through the acquisition of a replacement target that performs the same job but is no longer recognized by the drug. Fluoroquinolone resistance through mutations in gyrA and parC illustrates the first approach: each additional mutation incrementally degrades drug binding, and strains with multiple mutations can sustain fluoroquinolone concentrations that would completely inhibit their wild-type ancestors [16].

The mec gene system in MRSA illustrates the second approach. Rather than trying to protect the original penicillin-binding proteins (PBPs) from antibiotic action, the bacterium introduces an entirely new PBP—PBP2a, encoded by mecA—whose active site geometry simply does not accommodate any beta-lactam drug. Cell wall synthesis continues normally using PBP2a while the original PBPs, overwhelmed by the antibiotic, are essentially put out of commission. The bacterium is thus unharmed by drug concentrations that would destroy a susceptible organism. A parallel logic applies to vancomycin resistance in enterococci: the van gene clusters reprogram the entire peptidoglycan synthesis pathway so that the final building block differs by a single chemical substituent—enough to abolish vancomycin binding while maintaining full structural function [9, 17].

4.4 Closing the Door

Gram-negative bacteria have an inherent advantage over Gram-positive ones: an outer membrane that restricts molecular entry. Hydrophilic antibiotics like carbapenems rely on protein channels called porins (OmpC and OmpF in E. coli, OmpK35 and OmpK36 in Klebsiella, OprD in Pseudomonas) to cross this barrier. When bacteria lose or downregulate these channels through mutation or transcriptional repression, antibiotic uptake drops sharply. On its own, reduced permeability produces modest resistance increases; combined with efflux pump overexpression and beta-lactamase production, however, it contributes to a compounding effect that can render a strain insusceptible to an entire antibiotic class [18].

5. A Closer Look at Priority Pathogens

5.1 Klebsiella pneumoniae: A Dangerous Convergence

Among the ESKAPE pathogens, Klebsiella pneumoniae has arguably attracted the most attention in recent years, and for good reason. This bacterium has proven adept at combining resistance and virulence in ways that other MDR organisms have not yet achieved at scale. Historically, hypervirulent K. pneumoniae strains—characterized by large virulence plasmids encoding hypermucoviscosity and iron-acquisition factors—caused devastating community-acquired infections in otherwise healthy individuals across East Asia, particularly liver abscesses that spread to the eye or central nervous system. Classic carbapenem-resistant K. pneumoniae (CRKP), by contrast, was largely a hospital problem. The convergence of both traits—hypervirulence and carbapenem resistance—on single clinical isolates now represents a qualitatively new threat, one that can strike community members with full vigor while remaining virtually untreatable [19].

CRKP most commonly carries blaKPC on IncFII plasmids or blaNDM on IncX3 plasmids, and genomic surveillance has traced global spread to a handful of high-risk clonal lineages—ST258, ST11, and ST147 being the most prominent. These sequence types have essentially become international carriers of resistance determinants, serving as stable platforms onto which new resistance genes are repeatedly acquired.

5.2 Acinetobacter baumannii: Master of Genetic Acquisition

If K. pneumoniae is defined by its virulence potential, A. baumannii is defined by its almost limitless appetite for foreign DNA. Naturally competent and metabolically flexible, this organism accumulates resistance genes at a pace that few others match. Its genome can harbor large resistance islands—integrated chromosomal regions exceeding 80 kilobases—encoding resistances to beta-lactams, aminoglycosides, tetracyclines, and trimethoprim all at once. The AbaR-type resistance islands, named after the element that mediates their insertion and excision, represent some of the densest known concentrations of clinically relevant resistance determinants in any single bacterial chromosome [20].

Carbapenem resistance in A. baumannii is primarily driven by OXA-type beta-lactamases—particularly OXA-23, OXA-40, and OXA-58. An important nuance here is that A. baumannii carries its own intrinsic OXA-51-like gene, which on its own confers only low-level carbapenem resistance. When insertion elements like ISAba1 insert upstream of this gene and provide a strong promoter, expression levels surge and resistance becomes clinically significant. This mechanism—promoter capture by mobile elements—illustrates how the boundaries between intrinsic and acquired resistance are often blurrier than simple classifications suggest.

5.3 Pseudomonas aeruginosa: When Mutation Matters More Than Transfer

Pseudomonas aeruginosa is an organism with one of the largest and most complex genomes among clinically relevant bacteria—roughly 6.3 megabases encoding an intrinsic resistome that already includes multiple efflux pumps, a chromosomal AmpC beta-lactamase, and a selective outer membrane. MDR in P. aeruginosa often arises not

from plasmid acquisition but from the stepwise accumulation of chromosomal mutations: AmpC is derepressed when ampD is mutated, OprD is lost when specific transcriptional regulators are inactivated, and MexAB-OprM or MexXY-OprM is overexpressed when their respective repressors are disrupted. Together, these changes can produce XDR phenotypes in the absence of a single horizontally acquired resistance gene [21].

That said, P. aeruginosa can and does acquire transferable MBL genes (blaNDM, blaVIM, blaIMP) on class 1 integron-bearing plasmids, a phenomenon that is reported with increasing frequency in clinical settings. When plasmid-borne carbapenemases occur in a background that already carries chromosomal MDR mutations, the therapeutic landscape becomes extraordinarily constrained.

5.4 MRSA and VRE: Resistance Through Structural Reinvention

Methicillin-resistant S. aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) represent paradigmatic examples of resistance through target replacement—organisms that have, in effect, rebuilt the structure that antibiotics attack. In MRSA, the Staphylococcal Cassette Chromosome mec (SCCmec) element integrates into the chromosome and imports the mecA or mecC gene. Multiple SCCmec types have been characterized; those found in healthcare-associated MRSA (HA-MRSA, types II and III) tend to carry additional resistance genes for aminoglycosides, macrolides, and tetracyclines, while community-associated MRSA (CA-MRSA, types IV and V) are genetically leaner but often harbor virulence factors that make them effective in immunocompetent hosts [22].

VRE, particularly Enterococcus faecium belonging to sequence type complexes ST17 and ST18, disseminates vanA and vanB on conjugative plasmids anchored by transposons like Tn1546. The clinical significance of VRE extends beyond simple treatment difficulty: in transplant and oncology wards, where vancomycin is routinely used for prophylaxis, VRE colonization can persist for months and seed bloodstream infections that have few remaining treatment options.

6. Who Controls the Controllers: Regulatory Dimensions of MDR

Carrying a resistance gene is one thing; expressing it appropriately is another. Bacteria do not run their resistance machinery at full blast all the time—doing so would be metabolically costly and potentially disruptive. Instead, resistance gene expression is governed by layered regulatory networks that sense the environment and calibrate the response.

Two-component regulatory systems (TCSs) are among the most important of these networks. A sensor kinase embedded in the membrane detects signals—osmotic stress, cation concentration, antibiotic presence—and phosphorylates a response regulator that, in turn, adjusts gene expression. The PhoP/PhoQ system in Salmonella and Klebsiella senses magnesium limitation and antimicrobial peptide stress, responding by modifying lipid A to reduce polymyxin affinity. In S. aureus, the VraSR system detects cell wall

stress caused by glycopeptides and upregulates compensatory biosynthesis pathways. Global transcriptional regulators like MarA and SoxS in Escherichia coli coordinate the expression of multiple resistance genes simultaneously, including the AcrAB efflux pump and outer membrane porin-repressing regulators, providing a coordinated, broad-spectrum response to chemical insults [23].

Biofilms add another dimension. When bacteria form communities embedded in a self-produced matrix, they enter a physiological state that is profoundly tolerant of antibiotics—not only because the matrix limits drug diffusion, but because cells within biofilms adopt altered metabolic programs, including downregulation of the same targets that many antibiotics depend upon. Cell-to-cell communication through quorum sensing (QS) governs this transition, regulating the production of the extracellular polymeric substances that hold the biofilm together. Disrupting QS signaling has been proposed as a strategy to prevent biofilm-associated resistance, and it also has the advantage of reducing HGT rates within the community, since gene transfer events are far more frequent in dense biofilm populations than in planktonic cultures [24].

7. Seeing the Problem Whole: Genomics, Surveillance, and New Therapies

Fighting MDR requires knowing where it is and understanding what drives it—two tasks that whole-genome sequencing (WGS) has transformed. A single sequencing run can simultaneously reveal an organism's resistance genotype, virulence gene content, and phylogenetic relationships to isolates collected years earlier on different continents. Bioinformatic tools such as ResFinder, AMRFinder, and CARD extract resistance gene content from sequencing data automatically, while platforms like Pathogenwatch and Microreact display results on geographic maps updated in near-real time. Long-read sequencing technologies, particularly Oxford Nanopore, have added the ability to resolve the full architecture of resistance plasmids—critical information for tracking how specific resistance determinants are spreading and whether they are likely to jump to new hosts [25].

On the therapeutic side, the recognition that bacteria deploy specific genetic mechanisms has inspired targeted countermeasures. The development of next-generation beta-lactam/beta-lactamase inhibitor combinations—ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam—represents a direct genetic response, with each inhibitor designed to neutralize a specific class of enzyme (KPC, OXA-48, and some MBLs) before it can destroy the antibiotic partner. Bacteriophage therapy exploits viruses that evolved specifically to kill bacteria, including MDR strains, and is moving cautiously into clinical trials for chronic and device-associated infections. CRISPR-Cas systems have been proposed as sequence-specific tools to eliminate resistance plasmids from within bacterial populations, delivered either by engineered phages or by other mobile elements. Antimicrobial peptides targeting conserved features of the bacterial membrane—such as lipid A structure—offer additional promise,

particularly against Gram-negative organisms where outer membrane modifications are a key resistance feature [26].

8. Conclusion

Multidrug resistance is, at its core, a genetic problem. Bacteria accumulate resistance genes through mutation and horizontal transfer, organize them on mobile elements that ensure their dissemination, and regulate their expression with impressive sophistication. The clinical consequences—infections that cannot be treated, procedures that become too risky to perform, antibiotics rendered useless after decades of reliable service—are the downstream effects of processes operating at the molecular scale.

The ESKAPE pathogens serve as a vivid illustration of where this genetic adaptability leads when it intersects with human healthcare. Yet the same genetics that makes them so formidable also exposes potential vulnerabilities: plasmids can be targeted, regulatory networks can be disrupted, and enzymatic mechanisms can be circumvented with the right inhibitor. Progress against MDR will come not from any single breakthrough but from sustained investment in understanding how bacterial resistance actually works—at the level of individual genes, regulatory circuits, and the ecological networks through which resistance spreads. Science has made remarkable strides in characterizing all of these; the challenge now is translating that knowledge into therapies, policies, and surveillance systems that can keep pace with bacterial evolution.

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