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REVIEW ARTICLE

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Antibiotic resistance genes in *Escherichia coli* – literature review

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ABSTRACT
Antimicrobial resistance threatens humans and animals worldwide and is recognized as one of the leading global public health issues. *Escherichia coli* (*E. coli*) has an unquestionable role in carrying and transmitting antibiotic resistance genes (ARGs), which in many cases are encoded on plasmids or phage, thus creating the potential for horizontal gene transfer. In this literature review, the authors summarize the major antibiotic resistance genes occurring in *E. coli* bacteria, through the major antibiotic classes. The aim was not only listing the resistance genes against the clinically relevant antibiotics, used in the treatment of *E. coli* infections, but also to cover the entire resistance gene carriage in *E. coli*, providing a more complete picture. We started with the long-standing antibiotic groups (beta-lactams, aminoglycosides, tetracyclines, sulfonamides and diaminopyrimidines), then moved toward the newer groups (phenicols, peptides, fluoroquinolones, nitrofurans and nitroimidazoles), and in every group we summarized the resistance genes grouped by the mechanism of their action (enzymatic inactivation, antibiotic efflux, reduced permeability, etc.). We observed that the frequency of antibiotic resistance mechanisms changes in the different groups.

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1. Introduction

> There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring 'fastness' [resistance]. (Alexander Fleming 1946)

Fleming's prediction about the development of bacterial resistance remains relevant today. As he articulated in his 1946 book, The Past, Present, and Future of Chemotherapy, bacterial resistance to chemotherapeutic agents is fundamentally encoded in their genetic material (Gálfi et al. 2015). For example, thirty-thousand-year-old metagenomic samples from permafrost soil have been found to contain genes encoding resistance to beta-lactam, tetracycline, and glycopeptide antibiotics (Perry et al. 2016), indicating that these resistance genes – known as antibiotic resistance genes (ARGs) – emerged long before the first antimicrobials were introduced in human medicine. Although the use of penicillin for therapeutic purposes only began in 1942, resistance emerged within just a few years, demonstrating how rapidly bacteria can adapt to antibiotic pressure (Gálfi et al. 2015). It quickly became evident that there would likely be no chemotherapeutic agent to which bacteria would not eventually develop resistance.

The bacterium *Escherichia coli* (*E. coli*), named after its discoverer Theodor Escherich in 1885 (Escherich 1885), is one of the most widely distributed bacterial species worldwide. The first instance where *E. coli* was epidemiologically linked to human disease occurred in 1945 when it was identified as the pathogen responsible for summer diarrhea in infants (Bray 1945). The *E. coli* strains that cause diarrhea were classified as intestinal pathogenic *E. coli* (IPEC) (Köhler and Dobrindt 2011), while those responsible for extraintestinal infections (e.g. bloodstream, urinary tract, joints, meninges, skin) were termed extraintestinal pathogenic *E. coli* (ExPEC), a designation first proposed by Russo and Johnson (Russo and Johnson 2000; Adorján et al. 2021).

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In addition to resistance genes, several genetically encoded virulence factors determine the animal health significance of *E. coli*, particularly in food-producing animals (Adorján et al. 2021; Benmazouz et al. 2024). The identification of virulence factors plays a crucial role in distinguishing *E. coli* as a pathogen. The characterization of virulence factors (e.g. heat-labile toxin, heat-stable toxin, Shiga toxin) has led to the identification of group-specific genes associated with virulence phenotypes, which are used as markers to differentiate the subgroups of IPEC strains. Nowadays, these subgroups can be rapidly identified by PCR through the detection of these group-specific virulence genes, which form the basis for typing or pathotyping (Candrian et al. 1991; Gunzburg et al. 1995; Tornieporth et al. 1995; van Ijperen et al. 2002; Kaper et al. 2004; Fialho et al. 2013). These virulence factors are essential for *E. coli* survival or colonization in a specific environment, leading to overlap in virulence factors among IPEC, ExPEC, and commensal isolates (Johnson JR et al. 2001; Le Gall et al. 2007; Pakbin et al. 2021).

ExPEC is the most common bacterium causing human hospital-acquired infections, particularly urinary tract infections and sepsis (Manges 2016), with an estimated healthcare cost of $1–1.6 billion in the USA (Foxman 2002; Russo and Johnson 2003). Importantly, multiple studies have established a strong link between the contamination of food, particularly poultry products, with ExPEC strains that cause human infection (Lyhs et al. 2012; Agersø et al. 2014; Egervärn et al. 2014; Lazarus et al. 2014; Dewey-Mattia et al. 2018; Farkas et al. 2024). Most studies have found the role of poultry meat to be a much greater risk than that of pork or beef (Johnson JR et al. 2005; Vincent et al. 2010; Bergeron et al. 2012; Reid et al. 2019). Certain ExPEC strains can cause infection both in poultry and in humans (Jørgensen et al. 2019).

Multiple epidemiological studies have revealed the presence of avian ExPEC in both the intestines of healthy poultry and in poultry meat from retail markets (Mellata 2013; Reid et al. 2019). This suggests that specific lineages of human ExPEC may have a reservoir in poultry and poultry meat, making poultry a major potential source of human infections (Manges 2016; Reid et al. 2022; Barnácz et al. 2024). Porcine enteropathogenic *E. coli* strains causing diarrhea have been shown *in vivo* to transfer genes responsible for shiga toxin production with human Stx2 phage (Malik et al. 2012), and cattle are a major reservoir of shiga toxin-producing *E. coli* strains (Mainga et al. 2018).

These observations highlight the need for a clear understanding of the role of *E. coli* in the spread of resistance, especially considering the various antibiotic groups and resistance mechanisms relevant to both animal and public health. The phylogenetic group and virulence factors determine pathogenicity (Regua-Mangia et al. 2010; Garcia et al. 2013; Terlizzi et al. 2017), with studies demonstrating that certain phylogenetic groups display a higher resistance to antimicrobial agents (Denamur et al. 2021), and, correspondingly, increased biofilm production (Miranda-Estrada et al. 2017). For instance, most ExPEC *E. coli* strains belong to the B2 phylogenetic group (Ejrnæs 2011). However, correlations between virulence factors contributing to pathogenicity and the level of antibiotic resistance are not exclusively positive (Ballesteros-Monrreal et al. 2020), as contradictory findings have also been reported (Da Silva and Mendonça 2012; Brennan et al. 2018), warranting further investigation of these associations in future studies.

Li et al. emphasized that phenotypic resistance does not always align with the presence of resistance genes. Specific serogroups are key contributors to severe foodborne diseases, with the acquisition of virulence genes, antimicrobial resistance, and the high prevalence of plasmids exacerbating these concerns (Li Z et al. 2024).

The transmission of ARGs from environmental bacteria to pathogenic bacteria directly associated with humans presents a significant public health risk (Stanton et al. 2020). The majority of studies focus on clinically relevant pathogenic bacterial strains, such as ESBL, *ampC*, and carbapenemase-producing *E. coli*, yet commensal strains are equally crucial in the maintenance of resistance genes (Hennart et al. 2020). The transfer of antimicrobial resistance genes can occur from pathogens to commensals, as well as from commensals or environmental bacteria to the host microbiome (Brinkac et al. 2017; Montassier et al. 2021). Moreover, recent evidence suggests that ARGs may even be transmitted through the air *via* horizontal gene transfer (Yu Y et al. 2021; Lee G and Yoo 2022).

This process is further influenced by the prevalence of bioaerosols, as demonstrated by the reduction in resistant *E. coli* cases during the coronavirus pandemic (ECDC 2022). Antibiotic use is well-documented to increase the frequency of ARGs (Aarestrup et al. 2001; Holman et al. 2019; Skarżyńska et al. 2020). Numerous cases have demonstrated that nonpathogenic bacteria, often overlooked in surveillance programs, act as reservoirs for antimicrobial resistance, with the potential for direct transfer from animals to humans (Barza 2002; Morrison and Rubin 2015). Hospital environments, municipal wastewater, and wastewater treatment plants can accumulate a vast repository of antimicrobial resistance genes (Barancheshme and Munir 2017). Recent studies have confirmed that anthropogenic

environments increase the segregation of ARGs among plasmids and phages, suggesting that human activities significantly contribute to the spread of resistance (de Nies et al. 2022). Examining the interconnections between humans, animals, and the environment through a One Health approach, researchers have documented widespread occurrence of vancomycin resistance genes across diverse settings, as well as a broad distribution of ARGs responsible for resistance to aminoglycosides, macrolides, beta-lactams, and tetracyclines (Li B et al. 2015; Pal et al. 2016).

The evolution of resistance to antibiotics is significantly driven by horizontal gene transfer *via* plasmids, suggesting that plasmid elimination from bacteria could play a vital role in future resistance management strategies (Carattoli 2009; Rozwandowicz et al. 2018), as it could reduce ARG prevalence and sensitize bacteria to antibiotics (Buckner et al. 2018). Gene cassettes embedded in integrons allow for the accumulation of multiple ARGs, which, when incorporated into transposons and plasmids, facilitate horizontal gene transfer (Gillings et al. 2015). The selective pressure from antibiotic use enhances and sustains integron prevalence, thus promoting ARG transfer between species (Barraud and Ploy 2015; Chainier et al. 2017; Lacotte et al. 2017). Therefore, developing a robust risk assessment approach is necessary, one that accounts for ARG carriage on plasmids or phages and considers their presence as mobile genetic elements.

2. Mechanisms of antibiotic resistance

Several resistance mechanisms have been developed by bacteria to certain antibiotics. These main mechanisms are summarized in Figure 1, which will be used as a basis for the following overview of each group of antibiotics.

One of the main and most important mechanisms by which antibiotic resistance develops is through enzymatic degradation or modification of the active substance. This process typically occurs either by inactivation of a key reactive site or by a change in structure. On the other hand, modification of the covalent bonds (e.g. O-phosphorylation, O-ribosylation, O-glycosylation, O-nuleotidylation, O- and N-acetylation) prevents the antibiotic from binding to the target (De Pascale and Wright 2010). Resistance to macrolides occurs through glycosylation, encoded by the *ole* gene (Yang M et al. 2005), the *gimA* gene (Gourmelen et al. 1998) and the *mgt* gene (Cundliffe 1992), similarly to the resistance against rifampicin (Yazawa et al. 1993; Spanogiannopoulos et al. 2012). Furthermore, bacteria can also hydrolyze drugs leading to their decreased activity, while the *vgb* gene inactivates streptogramin-type antibiotics by linearization of the ester bonds of the lactone ring (Mukhtar et al. 2001). In addition, ribolysis inactivation occurs through ADP-ribose coupling from NAD+, encoded by the *arr* genes that result in rifampicin resistance (Quan et al. 1999; Baysarowich et al. 2008). Similarly,

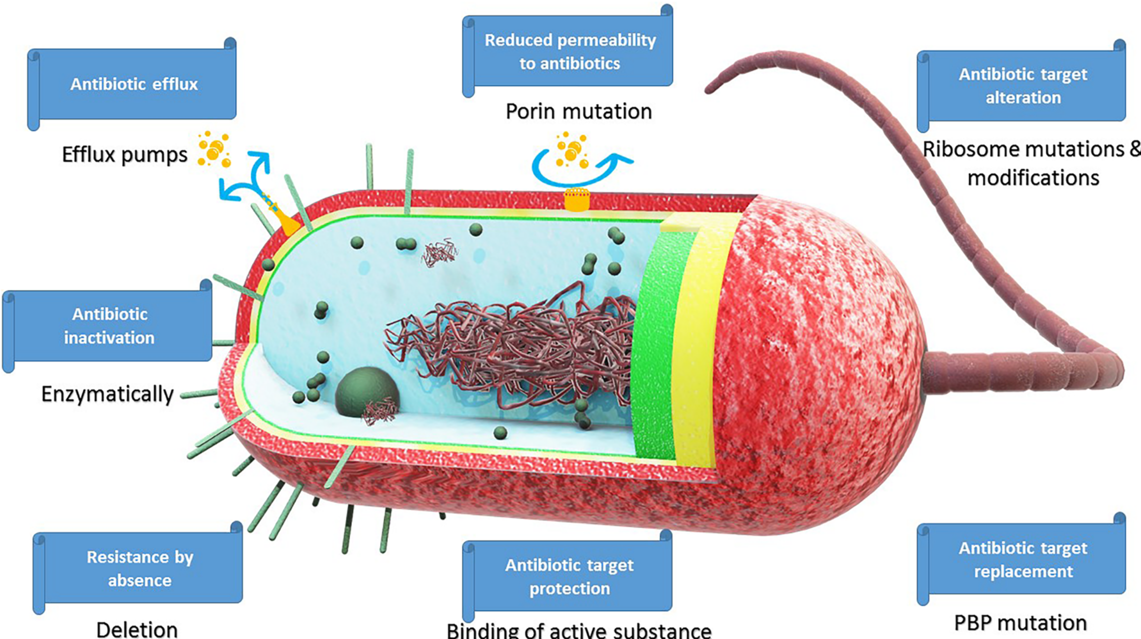

Figure 1. The primary mechanisms contributing to antimicrobial resistance include drug extrusion through efflux pumps, reduced drug entry due to mutations in porin channels, ribosomal mutations, alterations in binding proteins, defense *via* active drug binding, deletion-mediated defects in mechanisms of action, and enzymatic inactivation processes.

metallo-beta-lactamases (Ambler class B), which inactivate the lactam ring using one or two zinc atoms, operate by the same principle (De Pascale and Wright 2010).

Conversely, in the case of Ambler class A, C and D beta-lactamases, a serine residue forms an acyl enzyme intermediate which inactivates the lactam ring by hydrolysis (Mittal et al. 2007; Lister et al. 2009). Hydrolysis also plays a role in the inactivation of fosfomycin (*fos* genes) (Pakhomova et al. 2004), the lactone ring of macrolides (*ere* genes) (Morar et al. 2012) and bacitracin by the *bahA* gene (Pawlowski et al. 2016).

Nucleotidylation is another mechanism contributing to resistance, particularly for lincosamides, where it occurs through the *lnu* and *lin* genes (Leclercq R 2002). This process is similar to the covalent modification of the hydroxyl group on aminoglycosides by ATP-dependent transfer of AMP (*ANT* genes) (Ramirez and Tolmasky 2010). Likewise, phosphorylation (usually by ATP, less frequently by GTP) can inactivate fosfomycin (*fosC* and *fom* genes) using ATP and magnesium (Kobayashi S et al. 2000; Pakhomova et al. 2008), chloramphenicol (*cmlv* gene) by an ATP-dependent kinase (Mosher et al. 1995; Izard and Ellis 2000), aminoglycosides (*APH* genes) by NTP cofactors (Wright and Thompson 1999; Ramirez and Tolmasky 2010), macrolides (*mph* genes) by GTP (Noguchi et al. 1995; Chesneau et al. 2007; Shakya and Wright 2010; Pawlowski et al. 2018), rifampicin by *rph* genes (Yazawa et al. 1994; Stogios et al. 2016) and ciprofloxacin (*crpP* gene) (Chávez-Jacobo et al. 2018).

Additionally, chloramphenicol is inactivated by acetylation through *cat* genes (Schwarz et al. 2004), while aminoglycosidescan receive an acetyl group on the amino groups from acetyl coenzyme A donor substrate by means of *AAC* genes (Ramirez and Tolmasky 2010). Through hydroxylation by a (-OH) group, tetracyclines (*tet* genes) are inactivated (Nguyen et al. 2014). Moreover, the characteristic color of rifampicins is lost by monooxygenase enzyme (Andersen et al. 1997; Hoshino et al. 2010). Antibiotics can be inactivated by complex formation, which prevents antibiotic-target binding, a process that has been described for glycopeptide antibiotics (Mori et al. 2008). Furthermore, Enzymatic chemical inactivation includes beta-lactamase production, whereby resistance is generated by cleavage of the beta-lactam ring (Ambler 1980; Bush et al. 1995; Bush and Jacoby 2010; Pillai et al. 2011).

Another key resistance mechanism is the active expulsion of antibiotics from bacterial cells *via* efflux pumps (Li X-Z and Nikaido 2009). The first such mechanism was reported for tetracyclines in the 1970s (Li X-Z and Nikaido 2004, 2009). It is worth noting that pumps specific to particular drug groups are usually encoded on mobile genetic elements (Butaye et al. 2003). In contrast, multidrug efflux systems are chromosomally encoded in most cases (Poole 2005). The former mechanism involves single-component transporters, such as tetracycline transporters, which act on a limited number of drugs, typically within a single drug class (Levy 1992; Zhanel et al. 2001). The latter, however, requires two additional proteins for their function, and thus can develop a broader range of resistance (Paulsen 2003; Li X-Z and Nikaido 2004; Sun et al. 2014).

Various transporters utilize different energy sources. The transporters of the major facilitator superfamily (MFS), that belong to the single-component transporters, are powered by an electrochemical proton gradient (Pao et al. 1998; Li X-Z and Nikaido 2009). Similarly, small multidrug resistance (SMR) transporters have a total of four transmembrane alpha-helices and an extramembrane domain, are powered by an electrochemical proton gradient (Bay et al. 2008). By contrast, multidrug and toxic compound extrusion (MATE) transporters use the cationic gradient across the membrane as an energy source and mainly associated with fluoroquinolone resistance (Otsuka et al. 2005; Kuroda and Tsuchiya 2009). On the other hand, ATP-binding cassette (ABC) transporters are present in all cells of all organisms and use the energy of ATP hydrolysis (Fath and Kolter 1993). Furthermore, resistance-nodulation-division (RND) transporters are found in both prokaryotes and eukaryotes and derive their energy from the movement of protons across the membrane (Eswaran et al. 2004; Murakami et al. 2006; Blair and Piddock 2009).

Among the various antibiotic target alteration mechanisms, point mutations in DNA resulting in lower binding affinity of the antibiotic, and deactivation of repressors resulting increased gene expression of pumps. For instance, in *E. coli,* for example, these include the fosfomycin resistance genes *glpT*, *uhpT*, *uhpA*, *ptsI* and *cyaA* (Nilsson et al. 2003; Sakamoto et al. 2003; Takahata et al. 2010). Furthermore, the restructuring of bacterial cell wall can also confer antibiotic resistance when D-Ala-D-Lac or D-Ala-D-Ser is incorporated instead of D-Ala-D-Ala in peptidoglycan precursors. This leads to the development of high level resistance to glycopeptides (Marshall et al. 1997; Courvalin 2006). In case of ribosomal alteration conferring antibiotic resistance, the chemical change results in a modification of the target of antibiotics (Leclercq R and Courvalin 1991). Charge alteration, i.e. the reduction or loss of negative charges in the cell wall of Gram-negative bacteria confers resistance to cationic antimicrobials, which require negative charges to bind to the surface of bacteria. These include the reduction of negative charge on the membrane surface by

phosphatase (*pgpB* gene) (Coats et al. 2009) and acetyltransferase of lipid A molecules (Henderson et al. 2017). Increase in the amount of positive charges on the membrane by *mprF* gene (Yang S-J et al. 2010; Peleg et al. 2012) can also confer resistance, and occurs often in case of development of resistance against colistin (Liu Y-Y et al. 2016; Sun et al. 2017). The antibiotic target modifying enzyme leads to resistance through methylation of rRNA (Leclercq R and Courvalin 1991), and is regulated *via* the aforementioned *mprF* gene (Yang S-J et al. 2010; Peleg et al. 2012). This is the principle by which the *armA* and *rmt* genes (Zarubica et al. 2011) for aminoglycosides, the Erm gene (Park AK et al. 2010) for macrolides, the *erm* and *cfr* genes (Park AK et al. 2010; Atkinson et al. 2013) for lincosamides and streptograms, and the *cfr* genes (Atkinson et al. 2013) for phenicols and oxazolidines, all act in methylation processes.

Antibiotic target replacement is the change or substitution of an antibiotic target, often involving the introduction of proteins with similar functions but different structures. Examples include PBP2 proteins, which are responsible for the phenotype of methicillin-resistant *Staphylococcus aureus* (MRSA). These proteins arise from lateral gene transfer, allowing the bacterial cell membrane peptidoglycan synthesis to remain undisturbed even in the presence of beta-lactams (Hartman and Tomasz 1984; Ubukata et al. 1989; Fuda et al. 2004; García-Álvarez et al. 2011; Paterson et al. 2012). Additionally, the *dfr* gene family is responsible for the production of novel dihydrofolate reductase enzymes, leading to trimethoprim resistance (Brolund et al. 2010), while the *sul* gene encodes sulfonamide resistance (Antunes et al. 2005). Furthermore, the gene encoding RNA polymerases is *rpoB*, which is a houskeeping gene and its mutations results in amino acid substitutions that disrupt the binding of rifampicin to the binding site (Jin and Gross 1988).

Antibiotic target protection prevents the active substance from binding to its bacterial target, a mechanism previously described for ribosomal methylases (Wilson et al. 2020). This occurs in case of the fluoroquinolone resistance genes *qnr*, which encode pentapeptide repeat proteins that provide protection by mimicking DNA (Strahilevitz et al. 2009; Wang M et al. 2009). Similarly, the *tet* genes responsible for tetracycline resistance encode proteins that bind to the 30S ribosomal subunit to prevent the ribosomal inhibition by tetracycline antibiotics (Clermont et al. 1997; Roberts 2005).

Resistance *via* decreasing permeability to antibiotics usually occurs through a reduction in number or affinity of porin channels. Additionally, enzymes and other proteins can also directly or indirectly reduce permeability (Cohen et al. 1988; Delcour 2009). For example, in the presence of antibiotics, MarA regulator gene overexpressed in *E. coli*. This gene, in addition to regulating an MDR efflux pump, also reduces the number of porin channels *via* the *ompF* gene, thereby limiting antibiotic entry (Alekshun and Levy 1997; Randall and Woodward 2002).

General bacterial porins (GBP) are found in the outer membrane of Gram-negative bacteria, they function in an energy-independent manner, and they include both cation-selective and anion-selective porins. Their most important representatives are the (classical) porins encoded by *ompF* and *ompC* genes in *E. coli* (Pagès et al. 2008). The gene encoding the outer membrane porin (*opr*) is another type that contribute to imipenem resistance in Gram-negative bacteria (Pagès et al. 2008). The sugar porin family is mainly responsible for the transport of maltodextrins and other sugars across the outer membrane of Gram-negative bacteria, and includes the *lamB* gene in *E. coli*, the reduction of sugar porin reduces the influx of tetracyclines and fluoroquinolones (Makino et al. 1999; Zhang D et al. 2008; Lin et al. 2014).

Furthermore, the MipA interacting protein increases aminoglycoside and fluoroquinolone resistance (Li H et al. 2015). Loss of mildly cation selective porin channels encoded by the *carO* gene results in imipenem and meropenem resistance in *Acinetobacter baumannii* (Mussi et al. 2005). *Lps* genes, that are involved in the synthesis of lipopolysaccharides, are responsible for peptide antibiotic resistance, including resistance against colistin (Hood et al. 2013).

Resistance by absence can occur when the lack of a gene or its product confers resistance, e.g. in case of deletion of a porin gene that prevents the drug from entering the cell. This group includes the *lamB* gene, which is present in *E. coli* and regulates the sugar porin channel responsible for antibiotic entry. Downregulation of this gene increases resistance to chlortetracycline, ciprofloxacin, balofloxacin and nalidixic acid (Makino et al. 1999; Zhang D et al. 2008; Lin et al. 2014). Similarly, the deletion of MipA, an outer membrane protein, increases resistance to kanamycin, nalidixic acid and streptomycin in *E. coli* (Li H et al. 2015).

3. Resistance against Β-lactam antibiotics

Among the resistance mechanisms against β-lactam antibiotics, enzymatic inactivation, i.e. β-lactamase production is clearly the most important in Gram-negative bacteria (Poole 2004). The major resistance genes conferring resistance to β-lactam antibiotics in *E. coli* are summarized in Table 1.

Table 1. Major antibiotic resistance genes (ARGs) in *E. coli* against beta-lactam antibiotics for each group (1–5.) of active substances.

Mechanism	Class	Gene	1.	2.	3.	4.	5.	References
Enzymatic antibiotic inactivation	Class A	*TEM*-type	x	x	ND	x	x	(Datta and Kontomichalou 1965; Sutcliffe 1978; Thomson and Amyes 1993; Bradford 2001; Nordmann and Mammeri 2007; Salverda et al. 2010)
		SHV-type	x	x	x	ND	x	(Prinarakis et al. 1997; Bradford 2001)
		CTX-M-type	x	x	x	ND	x	(Bauernfeind et al. 1990, 1996; Sabaté et al. 2000; Karim et al. 2001; Kumarasamy et al. 2010; Shurina and Page 2021)
		GES-type	x	x	x	x	x	(Vourli et al. 2004; Navon-Venezia et al. 2006; Ortiz de la Rosa et al. 2019)
		KPC-type	x	x	x	x	x	
		VEB-type	ND	x	ND	x	ND	(Poirel et al. 1999)
		TLA-type	ND	x	ND	x	ND	(Silva et al. 2000)
		PER-type	x	x	x	x	x	(Ortiz de la Rosa et al. 2019)
	Class B	*bcII, ccrA*	x	x	x	x	ND	(Yang Y et al. 1992; Osano et al. 1994; Carfi et al. 1995; Lee M-F et al. 2008)
		VIM-type	x	x	x	x	x	(Lee M-F et al. 2008; Ortiz de la Rosa et al. 2019)
		IMP-1,4	x	x	x	x	ND	(Miriagou et al. 2003; Shibata et al. 2003; Kopotsa et al. 2019)
		FEZ-1, gob-1	x	x	x	ND	ND	(Liénard et al. 2008)
		CAU-1	x	ND	x	ND	ND	
		cphA, sfh-1	ND	ND	x	ND	ND	(Saavedra et al. 2003; Liénard et al. 2008)
		NDM	x	x	x	ND	ND	(Yong et al. 2009; Kumarasamy et al. 2010; Hornsey et al. 2011; Kus et al. 2011; Nordmann, Poirel, Toleman, et al. 2011; Nordmann, Poirel, Walsh, et al. 2011; Zhang H and Hao 2011; Paget and Burge 2014)
	Class C	*ampC*	x	x	ND	ND	ND	(Bergström and Normark 1979; Gazouli et al. 1998; Mulvey et al. 2005; Hopkins et al. 2006; Potz et al. 2006; da Silva Dias et al. 2008)
		MOX	x	x	ND	ND	x	(Gonzalez Leiza et al. 1994; Horii et al. 1994; Barnaud et al. 1998; Chirindze et al. 2018)
		DHA	x	x	ND	ND	x	
		FOX	x	x	ND	ND	x	
	Class D	*OXA*	x	x	x	ND	x	(Walther-Rasmussen and Høiby 2006; Evans and Amyes 2014)
		LCR-1	x	x	ND	ND	ND	(Couture et al. 1992)
		LRA-13	x	x	ND	ND	ND	(Allen et al. 2009)
Antibiotic efflux	Class RND	*acrA* *acrB* *tolC*	x	x	ND	ND	ND	(Okusu et al. 1996; Nikaido and Zgurskaya 2001; Källman et al. 2003; Kaczmarek et al. 2004; Li B et al. 2011; Tikhonova et al. 2011; Bohnert et al. 2016; Chetri et al. 2019)
Reduced permeability	Class GBP	*ompF*	x	x	x	x	ND	(Cohen et al. 1988; Alekshun and Levy 1997; Simonet et al. 2000; Randall and Woodward 2002; Delcour 2009)
		ompC	x	x	x	x	ND	(Viveiros et al. 2007)
		ompA	x	x	x	x	ND	(Bialek-Davenet et al. 2014)
Antibiotic target replacement	PBP mutation	*mrdA*	ND	ND	x	ND	ND	(Lange et al. 2019; Ranjitkar et al. 2019)
		ftsI	x	x	ND	ND	ND	(Alm et al. 2015; Misawa et al. 2018; Bellini et al. 2019)

1. penicillins, 2. cephalosporins, 3. carbapenems, 4. monobactams, 5. lactamase inhibitors, ND – not described in this literary summary, x – presence.

3.1. Enzymatic inactivation

As early as 1940, Abraham described an enzyme capable of degrading penicillins, which he named penicillinase (Abraham and Chain 1940). This early discovery laid the foundation for understanding β-lactamase-mediated resistance, which has since been classified into four structural classes (A, B, C, D) according to the Ambler classification (Bush et al. 1995). In case of penicillins and cephalosporins, hydrolytic beta-lactamase inactivation is becoming increasingly common. The process involves various enzymes, with classes A, C, and D inducing the first step of PBP inactivation by forming an acyl enzyme complex *via* a covalent intermediate, while class B beta-lactamases use a water molecule to break the lactam bond with a zinc ion.

Class A beta-lactamases are widely distributed, the most important of the many lactamase genes being *TEM*, *SHV* and *CTX-M*, which are responsible for extended-spectrum beta-lactamases (ESBLs) production. The *TEM* genes are responsible for the hydrolysis of penicillins and first generation cephalosporins, and the *TEM-1* gene may be responsible for ampicillin resistance in *E. coli* in up to 90% of cases (Sutcliffe 1978; Thomson and Amyes 1993; Livermore 1995; Bradford 2001). Several types of *SHV* genes have been shown to be carried by *E. coli* (Bradford et al. 1995; Rasheed et al. 1997). Mutant of these enzymes, such as *TEM-3* and *SHV-5*, exhibit a much broader hydrolytic spectrum, conferring resistance to practically all cephalosporins and penicillins, and termed for this reason ESBLs.

While TEM and SHV enzymes were dominant in conferring β-lactam resistance for years, a phenotypically similar but phylogenetically distinct group, the *CTX-M* enzymes, has now emerged. *CTX-M*-type genes originate from Kluyvera species, which has spread in *E. coli* as a result of multiple gene transfers (Humeniuk et al. 2002; Olson et al. 2005). The *CTX-M* genes encoded on plasmids are named because they hydrolyze cefotaxime more efficiently than ceftazidime, which is the preferred substrate of *TEM* and *SHV* type ESBLs. The first identified type of these genes, *CTX-M-1*, have been isolated from *E. coli* (Bauernfeind et al. 1990, 1996; Sabaté et al. 2000). Also in class A is the *KPC* gene encoding the carbapenemase enzyme, which originates from

Klebsiella pneumoniae, but has now been detected in several species within the *Enterobacteriaceae* family, including *E. coli* (Bratu et al. 2007; Robledo et al. 2011). Class B includes metallo-beta-lactamases, while the chromosomally and plasmid-encoded *ampC* beta-lactamases belong to class C (De Pascale and Wright 2010). In *E. coli*, these factors have great clinical significance when encoded chromosomally, while they are less often a problem when encoded on plasmids (Bergström and Normark 1979), but their plasmid-carried versions have also been reported (Gazouli et al. 1998; Mulvey et al. 2005; Hopkins et al. 2006).

Class D includes oxacillinase (*OXA*) genes (De Pascale and Wright 2010). Extended-spectrum beta-lactamases can be defined in the presence of both *TEM* and *SHV* genes (ESBLs), which can inactivate most beta-lactamase antibiotics, such as cefotaxime and ceftazidime (Page 2008). The first plasmid-encoded *ampC* beta-lactamase gene in *E. coli*, *CFE-1*, was described in Japan in 2004 (Nakano et al. 2004).

The genes that inactivate cephalosporins are from classes A, B and C. Among class A enzymes, genes such as encoded by genes *TEM*, *SHV* (Bradford 2001; de Been et al. 2014; Aleem et al. 2021), *CTX-M* (Bauernfeind et al. 1990, 1996; Sabaté et al. 2000; de Been et al. 2014; Aleem et al. 2021), *GES-5*, *KPC-2* (Shibata et al. 2003; Vourli et al. 2004; Navon-Venezia et al. 2006), *VEB-1* (Poirel et al. 1999), *TLA-1* (Silva et al. 2000) and *PER-1* (Ortiz de la Rosa et al. 2019) play significant roles in hydrolyzing cephalosporins. Among the class B enzyme genes, *bcII*, *ccrA* (Yang Y et al. 1992; Osano et al. 1994; Carfi et al. 1995; Lee M-F et al. 2008), *IMP-1*, *VIM-1* (Poirel et al. 1999; Shibata et al. 2003), *VIM-2* (Lee M-F et al. 2008; Ortiz de la Rosa et al. 2019), *L1*, *FEZ-1*, *gob-1* (Liénard et al. 2008) and *NDM* gene are significant (Yong et al. 2009; Kumarasamy et al. 2010; Hornsey et al. 2011; Kus et al. 2011; Nordmann et al. 2011, 2011; Zhang H and Hao 2011; Paget and Burge 2014; Aleem et al. 2021). Within the genes of class C enzymes, *ampC* gene family (Esterly et al. 2011), namely *ampc1* and *ampH* genes are found in *E. coli* (Crossman et al. 2010). Among the class D enzyme genes, *OXA* (Walther-Rasmussen and Høiby 2006; Evans and Amyes 2014; Aleem et al. 2021), *LCR-1* (Couture et al. 1992) and *LRA-13* genes (Allen et al. 2009) are of high importance.

Carbapenem inactivation is particularly concerning, as enzymes from class A, B, and D beta-lactamases can hydrolyze not only carbapenems but also penicillins, cephalosporins, and monobactams (Queenan and Bush 2007). The first gene encoding a class A carbapenemase enzyme (*GES-5*) in *E. coli* was described in Greece in 2004 (Vourli et al. 2004), followed a year later by *KPC-2*, a plasmid-encoded gene, reported in Israel (Navon-Venezia et al. 2006; Adegoke et al. 2020). Among the genes responsible for class B metallo-beta-lactamases in *E. coli*, *IMP-1* was first described in Japan (Shibata et al. 2003), *IMP-4* in Australia (Kopotsa et al. 2019), and *VIM-1* in Greece, all of them being plasmid-encoded genes (Miriagou et al. 2003; Adegoke et al. 2020), and *VIM-2* gene (Lee M-F et al. 2008; Ortiz de la Rosa et al. 2019). In addition, the *FEZ-1*, *gob-1*, *CAU-1*, *cphA* and *sfh-1* genes also encode carbapenem resistance (Liénard et al. 2008). The class D includes members of the *OXA* gene family, which are very often plasmid-encoded genes (Walther-Rasmussen and Høiby 2006; Evans and Amyes 2014).

Among the genes that inactivate monobactams, notable examples include the *TEM* genes (other than *TEM-1*), which belong to class A (Salverda et al. 2010), as well as the *GES-5, KPC-2* (Vourli et al. 2004; Navon-Venezia et al. 2006; Ortiz de la Rosa et al. 2019), *VEB-1* gene (Poirel et al. 1999), *TLA-1* gene (Silva et al. 2000) and *PER-1* (Ortiz de la Rosa et al. 2019) genes. Additionally, class B genes such as *bcII* and *ccrA* also play a significant role (Yang Y et al. 1992; Osano et al. 1994; Carfi et al. 1995; Lee M-F et al. 2008).

Regarding the coding of extended-spectrum beta-lactamases (ESBLs), majority of class A *TEM* genes encode ESBL production from type 3 onwards (Sougakoff et al. 1988; Bradford 2001; Nordmann and Mammeri 2007; Gniadkowski 2008; Salverda et al. 2010; Adegoke et al. 2020; Athanasakopoulou et al. 2021). Several *SHV* types encode ESBL production as well (Bradford 2001; Adegoke et al. 2020), and the *CTX-M* genes (Gniadkowski 2008; Rossolini et al. 2008; Kumarasamy et al. 2010; Händel et al. 2015; Freitag et al. 2017; Adegoke et al. 2020; Aguirre et al. 2020; Kim S et al. 2020; Athanasakopoulou et al. 2021; Carvalho et al. 2021). Plasmid-encoded carriage of the class C *ampC* gene family has also been described (Potz et al. 2006; da Silva Dias et al. 2008; Jamborova et al. 2017; Darphorn et al. 2021), and the importance of *MOX* genes, *DHA* genes, *FOX* genes for *ampC* gene family has been reported as well (Gonzalez Leiza et al. 1994; Horii et al. 1994; Barnaud et al. 1998; Chirindze et al. 2018). ESBL-encoding class D genes include *OXA-11*, *OXA-15*, *OXA-18* and *OXA-45* (Hall et al. 1993; Philippon et al. 1997; Toleman et al. 2003; Walther-Rasmussen and Høiby 2006). In addition, the *VEB-1* gene, first isolated from a Vietnamese patient, has also been described as a gene responsible for ESBL production (Poirel et al. 1999). The ESBL-encoding *TLA-1* gene was isolated from *E. coli* in a patient from Mexico (Silva et al. 2000).

The *TEM*-type includes genes responsible for resistance to β-lactamase inhibitors. The following *TEM*-type

variants belong here (synonym IRT): *TEM-30-41*, *TEM-44-45*, *TEM-50-51*, *TEM-59*, *TEM-68*, *TEM-73-74*, *TEM-76-79* and *TEM-81-84* (Bradford 2001). These *TEM* variants are particularly frequent in *E. coli* (Leflon-Guibout et al. 2000). Among *SHV* genes, *SHV-10* has been shown to be an inhibitor resistant protein (Prinarakis et al. 1997). All variants of *CTX-M* also encode inhibitor resistance (Karim et al. 2001; Shurina and Page 2021). Inhibitor resistance has also been described for the *GES* gene (Ortiz de la Rosa et al. 2019).

3.2. Antibiotic efflux

Efflux pumps are generally divided into five classes, the major facilitator superfamily (MFS), the ATP (adenosine triphosphate)-binding cassette (ABC) family, the resistance-nodulation-division (RND) family, the small multidrug resistance (SMR) family and the multidrug and toxic compound extrusion (MATE) family (Poole 2007). For the ABC family, ATP hydrolysis provides the driving force, while for all the others, the efflux of a proton and a sodium-ion supplies energy (Alekshun and Levy 2007). The RND family is typically found in Gram-negative bacteria (Poole 2004).

Among the RND family, *acrA*, *acrB* and *tolC* genes are responsible for resistance to penicillins (Kaczmarek et al. 2004). In *E. coli,* efflux pumps are also involved in the development of resistance to cephalosporins (Källman et al. 2003). *acrAB-tolC* is a triple RND efflux system that can pump out both cationic, neutral, and anionic substrates, as the genes encoding the multidrug efflux pump have broad substrate specificity. Their role in the efflux of several beta-lactam antibiotics has been described in case of *E. coli*. They do not cross the cytoplasmic membrane, *acrB* connects the pump system at the cell membrane, *tolC* at the outer membrane and *acrA* at the periplasm (Okusu et al. 1996; Nikaido and Zgurskaya 2001; Li B et al. 2011; Tikhonova et al. 2011; Bohnert et al. 2016; Chetri et al. 2019).

3.3. Reduced PERMEABILITY

General Bacterial Porins (GBPs) are resistance genes that are responsible for uptake of beta-lactam drugs, consequently, mutation, lack of expression or absence of the porin protein reduce susceptibility to beta-lactam antibiotics. The principle of *ompF* gene function is that the presence of an antibiotic as a stress factor in *E. coli* triggers the overproduction of the activator protein MarA, which, in addition to activating the efflux pump *acrAB*, induces downregulation of porin channels *via* the *ompF* gene (Cohen et al. 1988; Alekshun and Levy 1997; Randall and Woodward 2002; Delcour 2009; Simonet et al. 2000). SoxS is a regulator in *E. coli* (Miller PF et al. 1994; Ma et al. 1996; White et al. 1997) that functions in a similar way (Nakano et al. 2004; Hopkins et al. 2006; Page 2008), and the same role of RamA has also been described in *E. coli* (George et al. 1995). The *ompC* (Viveiros et al. 2007) and *ompA* genes also have a similar function in *E. coli* (Bialek-Davenet et al. 2014).

3.4. Antibiotic target replacement

Penicillin-binding proteins (PBPs) are transpeptidase enzymes essential for peptidoglycan synthesis, making them a primary target for antibiotic interference. However, bacteria have developed mechanisms to replace or modify these targets, allowing peptidoglycan synthesis to continue even in the presence of beta-lactam antibiotics. A well-documented example is the lateral gene transfer of foreign PBP2 in MRSA strains, which enables the synthesis of cell wall peptidoglycan despite the presence of beta-lactams (Hartman and Tomasz 1984; Ubukata et al. 1989; Lim and Strynadka 2002; Fuda et al. 2004; García-Álvarez et al. 2011; Paterson et al. 2012). In *E. coli*, mutations associated with this resistance mechanism have been identified in the *mrdA* gene, responsible for PBP2 mutation (Lange et al. 2019; Ranjitkar et al. 2019), as well as the *ftsI* gene, which leads to PBP3 mutation (Alm et al. 2015; Bellini et al. 2019). These mutations underline the adaptability of bacterial populations in response to antimicrobial pressure.

4. Resistance against aminoglycoside antibiotics

Aminoglycosides are one of the oldest of the antibiotic groups, yet due to their broad spectrum they still constitute a valuable group of antimicrobials (Block and Blanchard 2022), that are of critical importance for animal health (van Duijkeren et al. 2019). Moreover, *E. coli* strains from food-producing animals may play a role in the horizontal transfer of ARGs (Skyberg et al. 2006; Johnson TJ and Nolan 2009), which can be transferred to human isolates (Chaslus-Dancla et al. 1991; Johnson AP et al. 1994; Nayme et al. 2019). The major resistance genes conferring resistance to aminoglycosides in *E. coli* are summarized in Table 2.

4.1. Enzymatic inactivation

The family of enzymes responsible for the inactivation of aminoglycosides, also called aminoglycoside-

Table 2. Major antibiotic resistance genes (ARGs) in *E. coli* against aminoglycosides for each active substance (1–7).

Mechanism	Class	Gene	1.	2.	3.	4.	5.	6.	7.	References
Enzymatic antibiotic inactivation	Acetyltransferase	*AAC(3)*	ND	ND	ND	x	x	x	x	(Vliegenthart et al. 1991; Miller GH et al. 1997; Vakulenko and Mobashery 2003; Call et al. 2010)
		AAC(6′)	ND	ND	ND	x	x	x	x	
		apmA	ND	ND	ND	ND	x	ND	ND	(Kuriki 1987; Miller GH et al. 1997; Fessler et al. 2011; Bordeleau et al. 2021)
	Nucleotidyl-transferase	*ANT(2′′)* *ANT(4′)*	x	ND	x	x	ND	x	x	(Cox et al. 2015)
	Methyltransferase	*npmA*	ND	ND	x	x	ND	x	x	(Wachino et al. 2007)
		rmt	ND	ND	ND	x	ND	x	x	(Chen et al. 2007; Bodendoerfer et al. 2020; Wangkheimayum et al. 2020)
	Phosphotransferase	*APH(3′)*	ND	ND	x	ND	ND	ND	ND	(Shaw et al. 1993; Hon et al. 1997; Woegerbauer et al. 2014)
		aphA15	x	ND	x	ND	ND	ND	x	(Riccio et al. 2001)
Antibiotic target alteration	Ribosome mutation	*rrsB*	x	x	x	x	ND	x	ND	(Makosky and Dahlberg 1987; Melancon et al. 1988; Brink et al. 1994; Johanson and Hughes 1995; Recht and Puglisi 2001)
		rrnb	x	x	ND	ND	ND	ND	ND	(Yassin et al. 2005)
		rrsH	ND	x	ND	ND	ND	ND	ND	(Sigmund et al. 1984)
		rsmG	x	ND	ND	ND	ND	ND	ND	(Benítez-Páez et al. 2014)
Resistance by absence	MltA	*mipA*	x	ND	ND	ND	ND	ND	ND	(Li H et al. 2015)
Antibiotic efflux	Class MFS	*mdfA*	ND	ND	x	ND	ND	ND	ND	(Edgar and Bibi 1997; Bohn and Bouloc 1998; Heng et al. 2015)
	Class RND	*acrA* *acrD* *tolC*	ND	ND	ND	x	x	ND	x	(Rosenberg et al. 2000; Poole 2004)
		mexXY	ND	ND	ND	x	ND	x	x	(Mine et al. 1999; Hocquet et al. 2003)
	Class SMR	*ykkCD*	x	ND	ND	ND	ND	ND	ND	(Jack et al. 2000)
	Class MATE	*pmpM*	ND	ND	x	x	ND	ND	ND	(He G-X et al. 2004)

1. streptomycin, 2. spectinomycin, 3. neomycin, 4. gentamicin, 5. apramycin, 6. tobramycin, 7. amikacin, ND – not described in this literary summary, x – presence.

modifying enzymes (AMEs) (Garneau-Tsodikova and Labby 2016) include aminoglycoside acetyltransferases that catalyze the transfer of an acetyl group to an amino group present in aminoglycosides using acetyl coenzyme A as a donor substrate (Ramirez and Tolmasky 2010). In case of *E. coli*, the *AAC(3)* and *AAC(6′)* genes have been reported (Vliegenthart et al. 1991; Miller GH et al. 1997; Vakulenko and Mobashery 2003; Call et al. 2010; Bodendoerfer et al. 2020), and the *apmA* gene has been implicated in the development of resistance to apramycin (Kuriki 1987; Miller GH et al. 1997; Fessler et al. 2011; Bordeleau et al. 2021). In the process of nucleotidylation, the *ANT(2′′)* gene is of high importance (Cox et al. 2015). NpmA may similarly be responsible for the development of extensive aminoglycoside resistance in *E. coli,* which is ribosomal methylase (Wachino et al. 2007), and *rmt* genes have also been reported (Chen et al. 2007; Bodendoerfer et al. 2020; Wangkheimayum et al. 2020). The *APH(3*′) gene inactivates neomycin by phosphorylation (Shaw et al. 1993; Hon et al. 1997; Woegerbauer et al. 2014). The *aphA15* gene has been specifically described in *E. coli* and is responsible for resistance to streptomycin, neomycin and amikacin (Riccio et al. 2001).

4.2. Target alteration

The gene *rrsB* is responsible for ribosome point mutations that result in resistance to multiple aminoglycoside antibiotics, including streptomycin, spectinomycin, neomycin, gentamicin, and tobramycin in *E. coli* (Makosky and Dahlberg 1987; Melancon et al. 1988; Brink et al. 1994; Johanson and Hughes 1995; Recht and Puglisi 2001). Additionally, the presence of the *rrnB* gene specifically confers resistance to streptomycin and spectinomycin by altering ribosomal target sites (Yassin et al. 2005), The *rrsH* gene also contributes to spectinomycin resistance through modifications affecting ribosomal function (Sigmund et al. 1984), Furthermore, mutations in the *rsmG* gene, which

encodes a ribosomal methyltransferase, lead to streptomycin resistance by interfering with the methylation process required for proper ribosomal function (Benítez-Páez et al. 2014).

4.3. Resistance by absence

A special case of aminoglycoside resistance involves deletion-induced gene activation. The MipA is an outer membrane protein, and its deletion results in changes in the cell membrane in a way that increases resistance to kanamycin and streptomycin. The gene has been described in *E. coli*, among others (Li H et al. 2015).

4.4. Antibiotic efflux

Efflux pumps play a crucial role in antibiotic resistance by actively removing antibiotics from bacterial cells, thereby reducing intracellular drug concentrations. The *acrd* gene encodes a hydrophilic efflux pump involved in the development of aminoglycoside resistance (Rosenberg et al. 2000). The efflux pump system encoded by the *acrAD-tolC* genes confers resistance to amikacin, gentamicin and tobramycin in *E. coli* (Rosenberg et al. 2000; Poole 2004). The *pmpM* gene is a multidrug efflux pump of the MATE family that functions as a drug antiporter *via* an H^+, and is responsible for the development of neomycin resistance in *E. coli* (He G-X et al. 2004). The presence of *ykkCD* gene in *E. coli* may decrease the efficacy of streptomycin (Jack et al. 2000). The *mexXY-oprM* multidrug efflux pump has been described in *E. coli* strains showing resistance against gentamicin, tobramycin, and amikacin. It defines a multidrug efflux pump system that develops resistance to fluoroquinolones, tetracyclines, carbapenems and macrolides. Of these, the *mexY* gene encodes a membrane fusion protein, *mexX* is an RND-type membrane protein, and *oprM* is an outer membrane channel (Mine et al. 1999; Hocquet et al. 2003). The *mdfA* gene in *E. coli* is a multidrug efflux pump that leads to the development of neomycin resistance (Edgar and Bibi 1997; Bohn and Bouloc 1998; Heng et al. 2015).

5. Resistance against tetracycline antibiotics

The history of tetracycline also dates back to the early 1940s, with Lederle discovering the first representative, aureomycin, whose first use saved the life of Toby Hockett in 1948 (Nelson and Levy 2011). The major resistance genes conferring resistance to tetracyclines in *E. coli* are summarized in Table 3.

5.1. Enzymatic inactivation

Hydroxylating enzymes can inactivate tetracyclines (Nguyen et al. 2014). In *E. coli* the *tetX* gene encodes a NADPH-dependent oxidoreductase, an enzyme that reduces the efficiency of tetracyclines, requiring NADPH for the inactivation. It is able to inactivate tetracycline and oxytetracycline (Speer et al. 1991; Yang W et al. 2004; Moore et al. 2005; Park J et al. 2017; He T et al. 2019). In *E. coli* the *tetX3* gene, encoded on a plasmid, has been described to inactivate tetracycline. Similarly, the plasmid-carried *tetX4* gene that encodes an enzyme that inactivates tetracycline, is also present in *E. coli*,

Table 3. Major antibiotic resistance genes (ARGs) in *E. coli* against tetracyclines for each active substance (1–5).

Mechanism	Class	Gene	1.	2.	3.	4.	5.	References
Enzymatic antibiotic inactivation	Oxidoreductase	*tetx*	x	x	x	x	x	(Speer et al. 1991; Yang W et al. 2004; Moore et al. 2005; Park J et al. 2017; He T et al. 2019)
		tetX3 *tetX4* *tetX6*	x	ND	ND	ND	ND	(He T et al. 2019; Liu D et al. 2020)
Antibiotic inactivation by complex formation	Sugar porin	*odp1* *lamB*	ND	ND	x	ND	ND	(Makino et al. 1999; Zhang D et al. 2008; Lin et al. 2014)
Antibiotic target alteration	16S rRNA mutation	*rrsB*	x	ND	ND	ND	ND	(Makosky and Dahlberg 1987; Melancon et al. 1988; Brink et al. 1994; Johanson and Hughes 1995; Recht and Puglisi, 2001)
		rrnB	x	ND	ND	ND	ND	(Yassin et al. 2005)
Antibiotic target protection	30S ribosomal subunit	*tetM*	x	x	x	x	x	(Akhtar et al. 2009; Cengiz et al. 2010; Jurado-Rabadán et al. 2014; Hathcock et al. 2019)
		tetW/N/W	x	x	x	x	x	(Leclercq SO et al. 2016)
	ABC-F	*optrA*	x	ND	ND	x	ND	(Wang Y et al. 2015)
		poxtA	x	ND	ND	x	ND	(Antonelli et al. 2018)
Resistance by absence	Sugar porin	*lamB*	ND	ND	x	ND	ND	(Makino et al. 1999; Zhang D et al. 2008; Lin et al. 2014)
Reduced permeability	GBP	*ompF*	x	ND	ND	ND	ND	(Cohen et al. 1988; Delcour 2009)
Antibiotic efflux	Class MFS	*tetA*	x	x	x	x	x	(Aldema et al. 1996; Butaye et al. 2003; Roberts 2003, 2005)
		tetB	x	x	x	x	x	(Roberts 2005; Karami et al. 2006)
		tetC	x	x	x	x	x	(Roberts 2005; Karami et al. 2006; Zhang T et al. 2012; Shin et al. 2015)
		tetD	x	ND	ND	ND	ND	(Changkaew et al. 2014; Shin et al. 2015)

1. tetracycline, 2. oxytetracycline, 3. chlortetracycline, 4. doxycycline, 5. minocycline, ND – not described in this literary summary, x – presence.

and a similar observation was made for the *tetX6* gene (He T et al. 2019; Liu D et al. 2020).

5.2. Antibiotic inactivation by complex formation

The *lamB* gene has been described to interact with the *odp1* gene in complex formation, which is also a mechanism of tetracycline drug inactivation leading to antibiotic ineffectiveness in *E. coli* (Makino et al. 1999; Zhang D et al. 2008; Lin et al. 2014).

5.3. Antibiotic target alteration

Point mutations in the 16S rRNA region of bacteria also provide protection against tetracyclines. The gene that causes point mutations in the ribosome is *rrsB*, which leads to tetracycline resistance in *E. coli* (Makosky and Dahlberg 1987; Melancon et al. 1988; Brink et al. 1994; Johanson and Hughes 1995; Recht and Puglisi 2001). The *rrnB* gene also causes resistance against tetracycline (Yassin et al. 2005).

5.4. Antibiotic target protection

Target protection is achieved by proteins that bind to the 30S ribosomal subunit, thereby preventing tetracycline antibiotics from inhibiting ribosomal function. They are also called ribosome protective proteins. For example, a subfamily of the ATP-binding cassette protein superfamily (ABC proteins), the *ABC-F* genes are responsible for ribosomal protection. These are not involved in efflux pump activity, instead they serve a target defence function (Sharkey et al. 2016; Sharkey and O'Neill 2018). In *E. coli*, the *tetM* gene, which is located on transposable DNA elements, functions in ribosome protection, and is capable of horizontal transfer (Akhtar et al. 2009; Cengiz et al. 2010; Jurado-Rabadán et al. 2014; Hathcock et al. 2019). Furthermore, the *tetW/N/W* is a mosaic tetracycline resistance gene in *E. coli* that encodes a ribosomal protective protein as well (Leclercq SO et al. 2016). Carriage of the *optrA* and *poxtA* genes encoding resistance to tetracycline and doxycycline has been described in *E. coli*, the former from *Enterococcus faecalis* and *Enterococcus faecium* plasmids, the latter from MRSA strains (Wang Y et al. 2015; Antonelli et al. 2018).

5.5. Resistance by absence

The *lamB* gene encodes a sugar porin channel that regulates antibiotic influx in *E. coli*, and its downregulation is responsible for the development of resistance against chlortetracycline (Makino et al. 1999; Zhang D et al. 2008; Lin et al. 2014).

5.6. Reduced permeability

Another mechanism, which has also been described in *E. coli*, is the overexpression of a global activator protein encoded by MarA in the presence of high tetracycline concentration, which, in addition to activating the *acrAB* MDR-type efflux pump, also downregulates the *ompF* gene that regulates porin channel synthesis (Cohen et al. 1988; Delcour 2009).

5.7. Antibiotic efflux

The *tetA* gene encodes an efflux pump in several Gram-negative bacteria, including *E. coli* (Aldema et al. 1996; Butaye et al. 2003; Roberts 2003, 2005; Zhang T et al. 2012). *TetB* gene can confer resistance to tetracycline, oxytetracycline, chlortetracycline, doxycycline and minocycline (Roberts 2005; Karami et al. 2006; Zhang T et al. 2012; Shin et al. 2015). The occurrence of the *tetC* gene in *E. coli* has also been described (Changkaew et al. 2014; Shin et al. 2015), as well as the *tetD* gene which causes tetracycline resistance (Jahantigh et al. 2020).

6. Resistance against phenicols

Florfenicol is mainly used to treat bacterial infections in farm animals. Because of this and its widespread use, florfenicol can enter the food chain and potentially contribute to food-borne diseases. The first resistance gene was detected in a fish pathogen in 1996 and was identified in the genome of *Salmonella enterica* shortly afterwards (Kim E and Aoki 1996; Arcangioli et al. 1999; White et al. 2000). Its occurrence in *E. coli* was soon reported, highlighting the potential for cross-species transfer of resistance genes (Keyes et al. 2000; Bischoff et al. 2002; Doublet et al. 2002; Blickwede and Schwarz 2004; Du et al. 2004). The major resistance genes conferring resistance to phenicols in *E. coli* are summarized in Table 4.

6.1. Enzymatic inactivation

The cat genes enzymatically inactivate chloramphenicol by the addition of an acyl group. Among these, the most notable members are *catB* (*catB2*, *catB3*, *catB4*) and *catII* genes, which have been described in *E. coli* (Murray et al. 1990; Parent and Roy 1992; Villa et al. 2002; Tennstedt et al. 2003; Wang M et al. 2003;

Table 4. Major antibiotic resistance genes (ARGs) in *E. coli* against phenicols for each active substance (1–3).

Mechanism	Class	Gene	1.	2.	3.	References
Enzymatic antibiotic inactivation	Acetyltransferase	*catB*	x	ND	ND	(Murray et al. 1990; Parent and Roy 1992; Villa et al. 2002; Tennstedt et al. 2003; Wang M et al. 2003; Schwarz et al. 2004)
		catII	x	ND	ND	
	Methyltransferase	*cipA*	x	x	x	(Atkinson et al. 2013)
Antibiotic target alteration	23s rRNS	*ND*	x	ND	ND	(Ettayebi et al. 1985)
Antibiotic efflux	Class MFS	*cmlA*	x	ND	x	(Bissonnette et al. 1991; Stokes and Hall 1991; Keyes et al. 2000)
		flo	x	ND	x	(Keyes et al. 2000; White et al. 2000; Schwarz et al. 2004; Poole 2005)
		ppflo	x	ND	x	
		floR	x	ND	x	
		mdtM	x	ND	ND	(Holdsworth and Law 2013)

1. chloramphenicol, 2. thiamphenicol, 3. florfenicol, ND – not described in this literary summary, x – presence.

Schwarz et al. 2004; Wang CG et al. 2013). *CipA* is a *cfr*-like gene that inactivates florfenicol by methylation in *E. coli* (Atkinson et al. 2013).

6.2. Antibiotic target alteration

Resistance to chloramphenicol in *E. coli* can also arise from a point mutation in 23S rRNA, but this gene is not specifically named in the literature (Ettayebi et al. 1985).

6.3. Antibiotic efflux

The *cmlA* gene encodes florfenicol and chloramphenicol resistance through an efflux pump mechanism well-documented in *E. coli* (Bissonnette et al. 1991; Stokes and Hall 1991; Keyes et al. 2000). The same properties have been reported about the *flo* gene (Keyes et al. 2000; White et al. 2000; Poole 2005). Other names used in the literature are *pp-flo* and *floR*, genes with 96–100% nucleotide sequence identity (Keyes et al. 2000; White et al. 2000; Schwarz et al. 2004; Poole 2005). The *mdtM* gene is a multidrug efflux pump, also described in *E. coli*, that leads to chloramphenicol resistance (Holdsworth and Law 2013).

7. Resistance against peptide antibiotics

The major resistance genes conferring resistance to peptide antibiotics in *E. coli* are summarized in Table 5. Peptide antibiotics target key processes in bacterial cells, making resistance mechanisms against them particularly concerning.

7.1. Enzymatic inactivation

The *uppP* (*bacA*), *ybjG*, *yeiU* and *pgpB* genes, also described in *E. coli*, encode an undecaprenyl phosphatase enzyme responsible for the incorporation of lipids into the bacterial envelope during glycan biosynthesis. Since peptide antibiotics target the proteins involved in this process, the presence of these genes can lead to bacitracin resistance (El Ghachi et al. 2004, 2005; Tatar et al. 2007). In *E. coli*, a point mutation has been described resulting in the generation of a *waaL* gene that attaches peptidoglycans to the cell surface, acting as a decoy that binds vancomycin, thereby contributing to antibiotic resistance (Han et al. 2012; Ruan et al. 2012; Grabowicz et al. 2014).

7.2. Reduced permeability

In *E. coli,* the *pmrC* (*eptA*) genes modify the lipid layer by the addition of 4-amino-4-deoxy-L-arabinose and phosphoethanolamine, which decreases the positive charge shift of the cell membrane and reduces polymyxin binding, resulting in resistance development (Gunn et al. 1998; Lee H et al. 2004). The *mcr* genes also alter the lipid layer by the addition of a phosphoethanolamine, which inhibits colistin binding to the cell membrane through reduced negative charges. The mcr family includes the genes *mcr-1*, *mcr-2*, and *mcr-3*, which have been previously isolated from *E. coli* (COMBAT consortium, 2016; Di Pilato et al. 2016; Liu Y-Y et al. 2016; Xavier et al. 2016; Sun et al. 2017; Yin et al. 2017). More recently, *mcr-4* and *mcr-5* genes have also been detected in this bacterium (Timmermans et al. 2021).

General Bacterial Porins encompass porin channels that show reduced sensitivity to peptide antibiotics. This reduced sensitivity may arise from mutations in the porin protein, the absence of porin protein, or a lack of gene expression. Additionally, the outer membrane proteases *ompT* and *ompP* are regulators in *E. coli* that can reduce the efficacy of cationic peptide antibiotics by mutating porin channels (Hui et al. 2010; Mišić et al. 2021).

7.3. Antibiotic efflux

The *yojI* gene is an efflux pump capable of removing peptide antibiotics from *E. coli*. This mechanism allows

Table 5. Major antibiotic resistance genes (ARGs) in *E. coli* against peptide antibiotics for each active substance (1–5).

Mechanism	Class	Gene	1.	2.	3.	4.	5.	References
Enzymatic antibiotic inactivation	Undecaprenyl pyrophosphatase	*uppP (bacA)* *ybjG* *yeiU* *pgpB*	x	x	x	x	ND	(El Ghachi et al. 2004, 2005; Tatar et al. 2007)
	Glycosyltransferase	*waaL*	ND	ND	ND	ND	x	(Han et al. 2012; Ruan et al. 2012; Grabowicz et al. 2014)
Reduced permeability	Phospho-ethanol-amine transferase	*pmrC (eptA)*	ND	x	x	x	ND	(Gunn et al. 1998; Lee H et al. 2004)
		mcr-1 *mcr-2* *mcr-3*	ND	x	x	x	x	(COMBAT consortium, 2016; Di Pilato et al. 2016; Liu Y-Y et al. 2016; Xavier et al. 2016; Sun et al. 2017; Yin et al. 2017)
		mcr-4 *mcr-5*	ND	x	x	x	ND	(Timmermans et al. 2021)
	GBP	*ompT* *ompP*	ND	ND	ND	ND	ND	(Hui et al. 2010; Mišić et al. 2021)
Antibiotic efflux	Class ABC	*yojI*	ND	ND	ND	ND	ND	(Delgado et al. 2005)

1. bacitracin, 2. polymyxin B, 3. polymyxin E (colistin), 4. polymyxin M, 5. vancomycin, ND – not described in this literary summary, x – presence.

the bacteria to develop resistance to microcin antibiotics and requires the TolC outer membrane protein for its function (Delgado et al. 2005).

8. Resistance against sulfonamides and diaminopyrimidine antibiotics

The major resistance genes conferring resistance to sulfonamide and diaminopyrimidine antibiotics in *E. coli* are summarized in Table 6. These antibiotics act by disrupting folic acid synthesis, a critical metabolic pathway in bacteria, making resistance to them particularly concerning.

8.1. Antibiotic target alteration

In *E. coli*, the *folP* gene is the result of a point mutation that prevents the inhibition of dihydropteroate synthase enzyme during folic acid synthesis. This mutation effectively interferes with the binding of sulfonamides, such as sulfathiazole, thus conferring resistance (Vedantam et al. 1998).

8.2. Antibiotic target replacement

The *sul* genes (*sul1*, *sul2*, *sul3*, *sul4*) in *E. coli* encode alternative forms of dihydropteroate synthase, which exhibit reduced sensitivity to sulfonamides. This mechanism represents a classic case of target substitution, whereby the drug's binding site is altered to prevent effective inhibition (Perreten and Boerlin 2003; Sáenz et al. 2010; Razavi et al. 2017; Jiang et al. 2019). The plasmid-carried *dfr* genes encode alternative proteins that are less sensitive to trimethoprim, thereby promoting resistance development in *E. coli* (Grape et al. 2007; Brolund et al. 2010; Suhartono et al. 2016).

8.3. Antibiotic efflux

The plasmid-encoded *oqxAB* genes encode an efflux pump system that actively exports trimethoprim out of *E. coli* cells. By reducing intracellular drug concentrations, this efflux mechanism significantly contributes to trimethoprim resistance (Kim HB et al. 2009; Zhao J et al. 2010).

9. Resistance against fluoroqinolone antibiotics

The major resistance genes conferring resistance to fluoroquinolone antibiotics in *E. coli* are summarized in Table 7. Fluoroquinolones target DNA gyrase and topoisomerase IV, essential enzymes involved in DNA replication, making resistance to these antibiotics a critical concern for public health.

9.1. Enzymatic antibiotic inactivation

Fluoroquinolone resistance caused by the acetyltransferase enzyme encoded by the *AAC(6')-Ib-cr* gene has been described in *E. coli* against norfloxacin and ciprofloxacin. This enzymatic modification represents a direct inactivation mechanism contributing to reduced antibiotic efficacy (Robicsek et al. 2006; Jones-Dias et al. 2016; Machuca et al. 2016; Alsharapy et al. 2018).

9.2. Antibiotic target alteration

The DNA gyrase enzyme is responsible for the cleavage of the DNA double helix and is the target of fluoroquinolone antibiotics. A point mutation of the *gyrA* enzyme in *E. coli* however can prevent fluoroquinolones from binding to the alpha subunit of DNA gyrase, thus contributing to the development of resistance

Table 6. Major antibiotic resistance genes (ARGs) in *E. coli* against sulfonamides and diaminopyrimidines for each active substance (1–6).

Mechanism	Class	Gene	1.	2.	3.	4.	5.	6.	References
Antibiotic target alteration	Dihydropteroate synthase	*folP*	x	x	x	x	x	ND	(Vedantam et al. 1998)
	Dihydrofolate reductase	*dfr*	ND	ND	ND	ND	ND	x	(Grape et al. 2007; Brolund et al. 2010; Suhartono et al. 2016)
Antibiotic target replacement	Dihydropteroate synthase	*sul1* *sul2* *sul3* *sul4*	x	x	x	x	x	ND	(Perreten and Boerlin 2003; Sáenz et al. 2010; Razavi et al. 2017; Jiang et al. 2019)
Antibiotic efflux	Class RND	*oqxAB*	ND	ND	ND	ND	ND	x	(Kim HB et al. 2009; Zhao J et al. 2010)

1. sulphaguanidine, 2. sulfadimidine, 3. sulfamethoxazole, 4. sulphadimethoxine, 5. sulphamethoxypyrazine, 6. trimethoprim, ND – not described in this literary summary, x – presence.

Table 7. Major antibiotic resistance genes (ARGs) in *E. coli* against fluoroquinolone antibiotics for each active substance (1–10).

Mechanism	Class	Gene	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	References
Enzymatic antibiotic inactivation	Acetyltransferase	*AAC(6′)-Ib-cr*	x	x	ND	ND	ND	ND	ND	ND	ND	ND	(Robicsek et al. 2006; Jones-Dias et al. 2016; Machuca et al. 2016; Alsharapy et al. 2018)
Antibiotic target alteration	DNA gyrase subunit	*gyrA*	x	x	x	x	x	x	x	x	x	x	(Cullen et al. 1989; Yoshida et al. 1990; Oram and Fisher 1991; Reece and Maxwell 1991; Heisig et al. 1993; Vila et al. 1994; Drlica and Zhao 1997; Nawaz et al. 2015; Cheng et al. 2020; Umeda et al. 2020; Kim J-H et al. 2021; Zhao Q et al. 2021)
		gyrB	x	x	x	x	x	x	x	x	x	x	(Yoshida et al. 1991; Hopkins et al. 2005)
	Topoisomerase subunit	*parC* *parE*	x x	x x	x x	x x	x x	x x	x x	x x	x x	x x	(Dasgupta et al. 2018; Gulyás et al. 2019; Umeda et al. 2020)
Antibiotic target protection	PMQR	*qnr*	x	x	ND	ND	ND	ND	x	x	x	ND	(Tran and Jacoby 2002; Nordmann and Poirel 2005; Juraschek et al. 2021)
Antibiotic efflux	Class MFS	*mdfA*	x	x	ND	ND	ND	ND	ND	ND	ND	ND	(Mirzaii et al. 2018
	Class RND	*acrAB-tolC*	ND	x	ND	ND	ND	ND	ND	ND	ND	ND	(Yu EW et al. 2003; Li X-Z and Nikaido 2004, 2009)
	Regulator	Mar	x	x	x	x	x	x	x	x	x	x	(Maneewannakul and Levy 1996; Okusu et al. 1996; Alekshun and Levy 1997; Oethinger et al. 1998; Randall and Woodward 2002)

1. norfloxacin, 2. ciprofloxacin, 3. ofloxacin, 4. enrofloxacin, 5. marbofloxacin, 6. pefloxacin, 7. levofloxacin, 8. sparfloxacin, 9. gatifloxacin, 10. trovafloxacin, ND – not described in this literary summary, x – presence.

(Cullen et al. 1989; Yoshida et al. 1990; Oram and Fisher 1991; Reece and Maxwell 1991; Heisig et al. 1993; Vila et al. 1994; Drlica and Zhao 1997; Nawaz et al. 2015; Cheng et al. 2020; Umeda et al. 2020; Kim J-H et al. 2021; Zhao Q et al. 2021). The *gyrB* mutation is much less common, the main reason being that the *gyrA* mutation causes a higher minimum inhibitory concentration value increase, which puts much more evolutionary selection pressure (Yoshida et al. 1991; Hopkins et al. 2005). A point mutation in the *parC* gene in *E. coli* contributes to fluoroquinolone resistance as it can prevent binding of the antibiotic to the *parC* subunit of topoisomerase IV. The *parE* gene is also the result of a point mutation (Dasgupta et al. 2018; Gulyás et al. 2019; Umeda et al. 2020).

9.3. Antibiotic target protection

The *qnrA*, *qnrB* and *qnrS* genes found in *E. coli* encode proteins belonging to the pentapeptide repeat family. These proteins protect DNA gyrase and topoisomerase IV against quinolone compounds by mimicking DNA and thereby shielding these enzymes from the effects of fluoroquinolone antibiotics (Tran and Jacoby 2002; Nordmann and Poirel 2005; Rezazadeh et al. 2016; Mirzaii et al. 2018; Juraschek et al. 2021).

9.4. Antibiotic efflux

Efflux pump systems play a significant role in fluoroquinolone resistance in *E. coli*. The *acrAB-tolC* efflux pump complex is well-characterized, with ciprofloxacin-binding sites identified within the system, indicating its role in actively exporting fluoroquinolones from the cell (Yu EW et al. 2003; Li X-Z and Nikaido 2004, 2009). The *mdfA* gene also encodes an efflux pump capable of contributing to fluoroquinolone resistance (Yang S et al. 2003). Multidrug resistance mediated by *mar* genes involves stress-induced upregulation of the *acrAB-tolC* efflux pump, thereby promoting

resistance not only against fluoroquinolones but also against other antibiotics, including beta-lactams, tetracyclines, and phenicols (Maneewannakul and Levy 1996; Okusu et al. 1996; Alekshun and Levy 1997; Oethinger et al. 1998; Randall and Woodward 2002).

10. Resistance against nitrofuran antibiotics

The major resistance genes conferring resistance to nitrofuran antibiotics in *E. coli* are summarized in Table 8.

10.1. Antibiotic target alteration

In *E. coli*, the nitroreductase encoded by *nfsA* gene is an important oxygen-sensitive enzyme, that uses only NADPH and leads to resistance against nitrofurantoin and furazolidone (Race et al. 2005; Sandegren et al. 2008; Ho et al. 2016). In comparison, *nfsB* encodes a nitroreductase with a lower oxygen sensitivity that can utilize both NADH and NADPH (Whiteway et al. 1998; Sandegren et al. 2008; Ho et al. 2016).

11. Resistance to other antibiotic groups

This section focuses on antibiotic groups that are not typically used to treat *E. coli* infections but have been found to carry resistance genes. Although these antibiotics may not be the primary choice for treatment, the presence of their resistance genes on mobile genetic elements (MGEs), including plasmids and phages, poses a significant risk of horizontal gene transfer to other members of the gut microbiome. Such transfer events can contribute to the broader dissemination of resistance.

11.1. Macrolides

Although macrolides are not typical first-line agents against *E. coli*, their use may be required as alternative therapeutic options in cases of extensicely drug resistant (XDR) *E. coli* (Farrar 1985; Ochoa et al. 2009; Gonzales et al. 2013). Macrolides can be viable alternatives for the treatment of diarrhea caused by *E. coli* (Lübbert 2016; Gomes et al. 2017). Additionally, it is important to highlight that *E. coli* may act as a

Table 8. Major antibiotic resistance genes (ARGs) in *E. coli* against nitrofuran antibiotics for each active substance (1–4).

Mechanism	Class	Gene	1.	2.	References
Antibiotic target alteration	Nitro-reductase	*nfsA*	x	x	(Race et al. 2005; Sandegren et al. 2008; Ho et al. 2016)
		nfsB	x	x	(Whiteway et al. 1998; Sandegren et al. 2008; Ho et al. 2016)

1. nitrofurantoin, 2. furazolidone, x – presence.

Table 9. Major antibiotic resistance genes (ARGs) in *E. coli* against macrolides for each active substance (1–5).

Mechanism	Class	Gene	1.	2.	3.	4.	5.	References
Enzymatic antibiotic inactivation	Methyltransferase	*ermA*	x	x	x	x	x	(Atkinson et al. 2017; Gomes et al. 2019)
		ermB	x	x	x	x	x	(Yu L et al. 1997; Hajduk et al. 1999; Min et al. 2008; Palma et al. 2017)
		ermC	x	x	x	x	x	(Feder et al. 2008; Gomes et al. 2019)
	Phosphotransferase	*mphA*	x	ND	ND	x	x	(Noguchi et al. 1995; Chesneau et al. 2007; Shakya and Wright 2010; Pawlowski et al. 2018; Gomes et al. 2019)
		mphB	x	x	x	x	x	(Kono et al. 1992; Noguchi et al. 1996, 1998; Chesneau et al. 2007; Pawlowski et al. 2018)
	Esterase	*ereA*	x	ND	ND	ND	x	(Ounissi and Courvalin 1985; Morar et al. 2012)
Antibiotic target alteration	23s rRNS	ND	x	ND	ND	ND	x	(Sigmund et al. 1984; Ettayebi et al. 1985; Douthwaite 1992; Vannuffel et al. 1992; Xiong et al. 1999; Vester and Douthwaite 2001)
Antibiotic target protection	ABC proteins	*ABC-F* *msrA* *vgaA* *lsaA*	ND	ND	ND	ND	ND	(Tessé et al. 2013; Sharkey et al. 2016; Sharkey and O'Neill 2018)
Antibiotic efflux	Class MFS	*mefA*	x	ND	ND	ND	ND	(Ojo et al. 2004; Gomes et al. 2019)
		mefB	x	ND	ND	ND	ND	(Ojo et al. 2004; Liu J et al. 2009; Gomes et al. 2019)
	Class ABC	*msrA*	x	ND	ND	ND	ND	(Gomes et al. 2017, 2019)
		msrD	x	ND	ND	ND	ND	(Gomes et al. 2017, 2019)
		macAB-tolC	x	ND	ND	x	ND	(Sharff et al. 2001; Kobayashi N et al. 2003; Koronakis 2003; Nishino et al. 2006, 2006; Xu et al. 2009; Yum et al. 2009; Xu et al. 2010)
	Class RND	*acrA* *acrD* *tolC*	x	ND	ND	ND	x	(Chollet et al. 2004; Pagès et al. 2005)

1. erythromycin, 2. spiramycin, 3. tylosin, 4. tylvazolin, 5. tilmicosin, 6. tulathromycin, 7. gamithromycin, 8. tildipirosin, 9. azithromycin, 10. clarithromycin, ND – not described in this literary summary, x – presence.

reservoir for plasmid-encoded genes responsible for macrolide resistance, which has significant implications (Phuc Nguyen et al. 2009). The key resistance genes that confer macrolide resistance in *E. coli* are summarized in Table 9.

The *ermB* gene encodes a ribosomal methylase that causes enzymatic inactivation of macrolides by dimethylating a single adenine in the 23S rRNA. This methylation prevents the binding of macrolides to the ribosome, leading to high-level resistance and cell survival. When erythromycin binds to the leader peptide, it induces a conformational change that triggers the expression of this gene. The presence of the *ermB* gene in *E. coli* has been documented in several studies (Chassy and Thompson 1983; Yu L et al. 1997; Hajduk et al. 1999; Min et al. 2008; Palma et al. 2017). Similarly, the *ermA* and *ermC* genes, which also encode ribosomal methylases, have been identified in *E. coli* (Feder et al. 2008; Atkinson et al. 2017; Gomes et al. 2019). Additionally, the *mphA* gene encodes an enzyme that inactivates 14-membered macrolide antibiotics through GTP-dependent phosphorylation of the 2′-OH group in the desosamine sugar moiety of the molecule (Noguchi et al. 1995; Chesneau et al. 2007; Shakya and Wright 2010; Pawlowski et al. 2018; Gomes et al. 2019). This gene has been shown to confer azithromycin resistance in *E. coli* (Xiang et al. 2020). The *mphB* gene acts in a similar manner, primarily inactivating 14- and 16-membered macrolides in *E. coli* and other bacteria (Kono et al. 1992; Noguchi et al. 1996, 1998; Boerlin et al. 2001; Leclercq R and Courvalin 2002; Chesneau et al. 2007; Pawlowski et al. 2018). Another resistance gene, *ereA*, encodes an esterase enzyme that hydrolyzes the lactone ring of macrolides, thereby inactivating the antibiotic. The *ereA* gene is also present in *E. coli* (Ounissi and Courvalin 1985; Morar et al. 2012).

In *E. coli*, a point mutation in the 23S rRNA has been shown to confer resistance to clarithromycin and erythromycin by altering the antibiotic target. However, the specific gene responsible for this mutation is not explicitly named in the literature (Sigmund et al. 1984; Ettayebi et al. 1985; Douthwaite 1992; Vannuffel et al. 1992; Xiong et al. 1999; Vester and Douthwaite 2001).

ABC-F genes, while not associated with the transmembrane domain and therefore not involved in efflux activity, play a role in ribosomal (target) protection. The proteins encoded by these genes bind to the ribosome, protecting its translation mechanism. Although the related *msrA*, *vgaA*, and *lsaA* genes have been identified in *E. coli*, they are unable to establish ribosomal protection in this bacterium (Tessé et al. 2013; Sharkey et al. 2016; Sharkey and O'Neill 2018).

The *mefA* gene encodes an efflux pump that contributes to macrolide resistance in *E. coli* (Ojo et al. 2004; Gomes et al. 2019). Similarly, the *mefB* gene, located near the *sul3* gene, also encodes a macrolide efflux pump (Ojo et al. 2004; Liu J et al. 2009; Gomes et al. 2019). The *msrA* and *msrD* genes are part of the ABC family of efflux pump genes (Gomes et al. 2017, 2019). The *macAB-tolC* efflux system in *E. coli* is an ABC-type complex pump that, among other functions, leads to erythromycin resistance. This complex includes MacA (a membrane fusion protein), MacB (an ABC transporter capable of exporting 14- and 15-membered macrolides), and TolC (a component of a multidrug efflux complex) (Sharff et al. 2001; Kobayashi N et al. 2003; Koronakis 2003; Nishino et al. 2006; Xu et al. 2009; Yum et al. 2009; Xu et al. 2010). Additionally, the efflux pump system encoded by the *acrAD-tolC* genes in *E. coli* is responsible for resistance to various antibiotics, including macrolides (Chollet et al. 2004; Pagès et al. 2005).

11.2. Lincosamides and pleuromutilins

The major resistance genes conferring resistance to lincosamides and pleuromutilins in *E. coli* are summarized in Table 10. These resistance mechanisms involve enzymatic inactivation, target modification, ribosomal protection, and efflux systems.

In case of lincosamides, enzymatic inactivation by methylation as a mechanism of resistance conferred by *erm* genes *ermB* and *ermT*. These genes encode enzymes responsible for the methylation of the 23S ribosomal RNA, thereby preventing antibiotic binding and conferring resistance (Tannock et al. 1994; Yu L et al. 1997; Hajduk et al. 1999; Roberts et al. 1999; Min et al. 2008; Park AK et al. 2010). The *lnuD* (*linD*) gene is a plasmid-encoded gene responsible for inactivation by nucleotidylation that has also been described in *E. coli* (Petinaki et al. 2008). The *lnuF* (*linF*) gene, which encodes an integron-mediated nucleotidyltransferase enzyme has been isolated from *E. coli* (Heir et al. 2004). Resistance to pleuromutilins in *E. coli* can occur *via* methylation conferred by *cfr* genes (Kehrenberg et al. 2005; Long et al. 2006).

For lincosamides, mutations in the 23S rRNA of *E. coli* cause resistance, but this is not specifically named in the literature (Douthwaite 1992). This mutation has also been reported to cause resistance against pleuromutilins in *E. coli* (Bøsling et al. 2003; Kosowska-Shick et al. 2006; Gentry et al. 2007; Long et al. 2009; Li B-B et al. 2010).

Similarly to tetracyclines and macrolides, *ABC-F* genes are involved in ribosomal protection against lincosamides and pleuromutilins. These genes encode proteins that bind to the ribosome, thereby preventing

Table 10. Major antibiotic resistance genes (ARGs) in *E. coli* against lincosamides and pleuromutilins for each active substance (1–4).

Mechanism	Class	Gene	1.	2.	3.	4.	References
Enzymatic antibiotic inactivation	Methyltransferase	*ermB* *ermT*	x	x	ND	ND	(Tannock et al. 1994; Yu L et al. 1997; Hajduk et al. 1999; Min et al. 2008; Roberts et al. 1999; Park AK et al. 2010)
		cfr	x	x	x	x	(Kehrenberg et al. 2005; Long et al. 2006)
	Nucleotidyl-transferase	*InuD (linD)*	x	x	ND	ND	(Petinaki et al. 2008)
		InuF (linF)	x	x	ND	ND	(Heir et al. 2004)
Antibiotic target alteration	23s rRNS	*ND*	x	x	x	x	(Douthwaite 1992; Bøsling et al. 2003; Kosowska-Shick et al. 2006; Gentry et al. 2007; Long et al. 2009; Li B-B et al. 2010)
Antibiotic target protection	ABC proteins	*ABC-F* *msrE* *vgaA* *lsaA*	x	x	x	x	(Bonnin et al. 2013; Tessé et al. 2013; Sharkey et al. 2016; Sharkey and O'Neill 2018)
Antibiotic efflux	Class RNS	*acrAB-tolC*	ND	ND	x	x	(Okusu et al. 1996; Nikaido and Zgurskaya 2001; Wehmeier et al. 2009; Li B-B et al. 2011; Tikhonova et al. 2011; Eicher et al. 2012; Bohnert et al. 2016; Schuster et al. 2019; Chetri et al. 2019)
	Class ABC	*vgaA*	x	x	ND	ND	(Novotna and Janata 2006; Tessé et al. 2013)
	Subunit	*emr*	x	x	ND	ND	(Lomovskaya and Lewis 1992; Kehrenberg et al. 2004; Liu J et al. 2009; Malbruny et al. 2011; Kumar et al. 2016; Afridi et al. 2020)
		lsaB	x	x	ND	ND	
		mefB	x	x	ND	ND	

1. lincomycin, 2. clindamycin, 3. tiamulin, 4. valnemulin, ND – not described in this literary summary, x – presence.

antibiotics from inhibiting the translation mechanism. The *msrE*, *vgaA* and *lsaA* genes are carried by *E. coli*, but are not able to establish ribosomal protection in the bacterium (Bonnin et al. 2013; Tessé et al. 2013; Sharkey et al. 2016; Sharkey and O'Neill 2018).

In case of lincomycins, the presence of *vgaA* gene has been described in *E. coli*, which encodes an efflux pump that contributes to the development of resistance (Novotna and Janata 2006; Tessé et al. 2013). The *emr* genes encode macrolide-lincosamide-streptogramin resistance in *E. coli*, and the *lsaB* and *mefB* genes play a similar role (Lomovskaya and Lewis 1992; Kehrenberg et al. 2004; Liu J et al. 2009; Malbruny et al. 2011; Kumar et al. 2016; Afridi et al. 2020). The *acrAB-tolC* triple RND efflux system, a multidrug efflux pump against pleuromutilins, is able to induce resistance in *E. coli* against this drug group. Among these, the importance of *acrB* gene is the highest, which is located on the cell membrane. In addition, the significance of *mdtF* and *acrF* inner membrane transporters should be highlighted (Okusu et al. 1996; Nikaido and Zgurskaya 2001; Wehmeier et al. 2009; Li B et al. 2011; Tikhonova et al. 2011; Eicher et al. 2012; Bohnert et al. 2016; Schuster et al. 2019; Chetri et al. 2019).

11.3. Rifamycins and mupirocin

The major resistance genes conferring resistance to rifamycin antibiotics and mupirocin in *E. coli* are summarized in Table 11. Resistance mechanisms include enzymatic inactivation, point mutations, and gene overexpression.

Resistance to rifamycin antibiotics in *E. coli* can occur through the presence of plasmid-carried *arr* genes. These genes encode a ribosyltransferase enzyme that inactivates rifamycin antibiotics through ADP-ribosylation, thereby preventing the antibiotic from binding to its target. The presence of *arr* genes in *E. coli* has been reported in several studies (Baysarowich et al. 2008; Tribuddharat and Fennewald 1999; Baumert et al. 2020).

In *E. coli*, a point mutation in the *rpoB* gene has been described that leads to resistance to rifampicin. The *rpoB* gene encodes RNA polymerases, and mutations lead to amino acid changes that interfere with the binding of rifampicin to its target site. These mutations can either directly affect the amino acids in contact with rifampicin or indirectly alter the structure of the binding site, reducing the antibiotic's effectiveness (Jin and Gross 1988; Kothary et al. 2013; Huseby et al. 2020).

Another mechanism of rifampicin resistance involves the *dnaA* gene, which encodes a protein responsible for initiating chromosome replication. Overexpression of this gene disrupts the activity of rifampicin at the RNA polymerase transcription site, leading to resistance (Pierucci et al. 1987; Flåtten et al. 2009; Salguero et al. 2011).

No gene encoding mupirocin resistance in *E. coli* has been described yet in the literature. This suggests that

Table 11. Major antibiotic resistance genes (ARGs) in *E. coli* for rifamycin antibiotics and mupirocin for each active substance (1–4).

Mechanism	Class	Gene	1.	2.	3.	4.	References
Enzymatic antibiotic inactivation	Ribosyl-transferase	*arr-2* *arr-3*	x	x	x	ND	(Baysarowich et al. 2008; Tribuddharat and Fennewald 1999; Baumert et al. 2020)
Antibiotic target alteration	Beta-subunit of RNA	*rpoB*	x	x	x	ND	(Jin and Gross 1988; Kothary et al. 2013; Huseby et al. 2020)
	Replication initiation protein	*dnaA*	x	x	x	ND	(Pierucci et al. 1987; Flåtten et al. 2009; Salguero et al. 2011)

1. rifampicin, 2. rifabutin, 3. rifaximin, 4. mupirocin, ND – not described in this literary summary, x – presence.

resistance to mupirocin in *E. coli* is either absent or remains to be identified, requiring further investigation.

12. Conclusion

The increasing prevalence of antimicrobial resistance (AMR) in *E. coli* poses a critical and escalating threat to both human and animal health worldwide. This literature review highlights the extensive array of ARGs present in *E. coli*, underscoring the bacterium's ability to resist nearly all major classes of antibiotics. The most concerning mechanism is the enzymatic degradation of antibiotics, exemplified by the role of ESBLs in nosocomial infections. ESBL-producing *E. coli* strains represent a particularly severe threat due to their ability to rapidly exchange genetic material across species boundaries, further exacerbating the global AMR crisis.

The review also emphasizes the role of *E. coli* as a reservoir for resistance genes, especially those encoded on mobile genetic elements such as plasmids and phages, which facilitate horizontal gene transfer. This capacity not only bridges the gap between animal and human health but also underscores the urgent need for intervention strategies aimed at breaking the chain of transmission. The presence of ARGs in *E. coli* from food-producing animals and their potential transmission to human pathogens through the food chain represent a critical public health concern with far-reaching implications.

The findings presented in this review underscore the pressing necessity for comprehensive surveillance, robust stewardship strategies, and innovative therapeutic approaches to mitigate the spread of AMR in E. coli. A coordinated, interdisciplinary effort encompassing human, animal, and environmental health sectors is essential to address this growing "silent pandemic" effectively. Immediate action is required to implement targeted intervention strategies that will not only curb the dissemination of resistance genes but also preserve the efficacy of existing antibiotics for future generations.

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