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UNRAVELING THE ESKAPE PATHOGENS' ANTIMICROBIAL RESISTANCE: A REVIEW

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Abstract– Like a roll of dice, unraveling the antimicrobial resistance to ESKAPE pathogens against various drugs is a perilous challenge in coeval healthcare due to their swift acquisition of resistant genes and drastic spreading of antimicrobial resistance. These pathogens manifest both innate and adopted resistance machineries against manifold antibiotic categories, consisting of β-lactams, glycopeptides, fluoroquinolones, aminoglycosides, tetracyclines, macrolides, and salvage therapy agents - linezolid and colistin. The machineries underlying resistance include enzymatic drug alteration, as seen with β-lactamases, aminoglycoside-altering or methylating enzymes, carbapenemase, chloramphenicol acetyltransferase; biofilm formation, target site mutations, resistance determinants lateral gene transfer, and overexpression of efflux pumping. The frequency of incidence of multidrug-resistant strains as well as extensively drug-resistant, and also pan-drug-resistant strains appreciably intricates infection management, and furthermore pitches into amplified morbidity, mortality, and ultimately affects global healthcare expenditures. This overview provides an ample review of the antimicrobial resistance contours, elementary molecular mechanisms, and clinical consequences of ESKAPE pathogens, accentuating emerging waves and potential approaches to counter these menacible nosocomial pathogens.

INTRODUCTION

The onset and global spreading of multidrug-resistant (MDR) pathogens have triggered an alarm in present-day healthcare, with ESKAPE pathogens at the forefront of nosocomial contagions (Woh and Zhang, 2025; Basset *et al.,* 2011). "ESKAPE" comprehends *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species—microorganisms undermine evading the consequences of conventional antibiotics, then instigating severe nosocomial infections (Sakalauskienë *et al.,* 2025; Jacoby, 2009; Lister *et al.,* 2009). As per the facts, commensals have evolved complex innate and adopted resistance processes that forfeit the efficacy of treatment and cut-edge the therapeutic possibilities (Ahmed Mo and Baptiste, 2018; Arias and Murray, 2012; Canton *et al.,* 2012). Resistance tactics of microbes include antibiotic inhibition or deactivation of enzymes like β-lactamases, and aminoglycoside-altering factors, target site alterations, horizontal resistance gene transfer, efflux pump–mediated drug deportation, and biofilm-associated fortification (Poole, 2011; Mirzaii *et al.,* 2023; Poole, 2011; Jacoby, 2009). Especially, resistance to salvage therapeutic antibiotics - colistin, vancomycin, and linezolid, has emerged, aiming a substantial health threat worldwide (Sakalauskienë and Radzevièienë, 2025; Kumari *et al.,* 2021; Liu *et al.,* 2016; Wang *et al.,* 2015). Insight in the molecular and clinical roots of ESKAPE pathogens' antimicrobial resistance is critical to appraise surveillance, strategies to therapeutic guidelines, which platforms novel antibiotics development (Bonomo, 2017; Queenan and Bush, 2007). By unraveling these review steps, the recent knowledge of microbial resistance and its

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mechanisms in ESKAPE pathogens highlights their clinical implications and evolving tendencies in resistance; so provides understanding of emerging ESKAPE pathogens and intense need for the discovery of vital antimicrobial drugs and therapeutic techniques to overcome the global threat.

Antimicrobial Resistance

Enterococcus faecium

The profile of antimicrobial resistance of *Enterococcus faecium (E. faecium)* has evolved drastically over time, transmuting it from a commensal to one of the most dreadful nosocomial pathogens. It has an ability to exhibit both natural innate resistance and even adopted resistance through gene transfer and mutations. So its resistance reflect numerous antimicrobial categories administered in clinical senario (Mirzaii *et al.,* 2023; Ahmed Mo and Baptiste, 2018; Arias and Murray, 2012).

β-Lactam Resistance: *E. faecium* proves elevated resistance to β-lactam containing antibiotics, holding ampicillin, penicillins, and cephalosporins. The primary technique is decreasing the affinity of â-lactams to PBP5 by penicillin-binding proteins (PBPs) modification (Murray, 1990; Rice, 2001). Ampicillin resistance is majorly seen in more than 90% tertiary care hospitals (Sangiorgio *et al.,* 2024). Cephalosporin resistance is inherent because of the absence of β-lactamase action and least-affinity PBPs (Hollenbeck and Rice, 2012).

Glycopeptide / Vancomycin Resistance: During 1986, Vancomycin resistance was initially reported in Europe and then worldwide (Jubeh *et al.,* 2020; Emaneini *et al.,* 2016). Cluster of van genes- *van*A, *van*B, *van*D and *van*M involves in clinically substantial vancomycin resistance in *E. faecium. van*A: highly intense resistance to both teicoplanin and vancomycin; *van* B: flexiblevancomycin resistance, and teicoplanin susceptibility (Asokan *et al.,* 2019; Arthur *et al.,* 1996). Increasing *van*A prevalence in Indian ICUs (Kumari *et al.,* 2021).

Aminoglycoside Resistance: Streptomycin and gentamicin showed high-level aminoglycoside resistance (HLAR) is dominant in the midst of *E. faecium* strains. HLAR is carried out by enzymatic aminoglycoside resistance determinants like AAC(62)-Ie-APH(23)-Ia, APH(32)-IIIa, and ANT(6)-Ia (Vakulenko *et al.,* 2003). HLAR erases the coactive ability of β-lactam–aminoglycoside synergy in therapy (Zhu *et al.,* 2019).

Macrolide and Lincosamide Resistance: The genes involved in 23S rRNA methylation - *erm*(A) and *erm*(B) exhibit recurrent resistance to clindamycin and erythromycin (Brenciani *et al.,* 2016; Portillo *et al.,* 2000). The genes *mef*(A) and *msr*(A) encodes efflux pumps which are usually transferred along with tetracycline resistant *tet* genes (Sadowy *et al.,* 2010).

Fluoroquinolone Resistance: The determinant genes involved in quinolone-resistance – *gyr*A and *par*C against fluoroquinolone in *E. faecium* and also develop resistance due to overexpression of efflux pump (Ono *et al.,* 2005; Werner *et al.,* 2008).

Tetracycline Resistance: *E. faecium* developed resistance by the genes *tet*(L) and *tet*(M), which encode ribosome protection determinants, and their concurrence with macrolide resistance and efflux pumping transport. (Mirzaii *et al.,* 2023; Clewell *et al.,* 1995).

Oxazolidinone / Linezolid Resistance: Even though linezolid comes under one of the last-resort antibiotics, resistance is evolving due to alteration of L3/L4 ribosomal protein, mutation in 23S rRNA (G2576T), and attainment of *optr*A and *cfr* genes (Wang *et al.,* 2015; Gawryszewska *et al.,* 2017). Indian tertiary hospitals have increased reports of isolates of Linezolid-resistant *E. faecium* (LREfm) (Kaur *et al.,* 2022).

Daptomycin and Tigecycline Resistance: Resistance is developed in the liaFSR (Lipid II-interacting antibiotics stress response) regulatory system by cell-membrane mutations as charge alteration and phospholipid distribution (Tran *et al.,* 2013). Even diminished susceptibility is caused by overexpression of enterococcal fluoroquinolone resistance A and B (efrAB) efflux system (Sun *et al.,* 2019).

Staphylococcus aureus

S. aureus is a prevalent arduous pathogen transformed from basic commensal, revealing both innate and adopted resistance machineries against numerous antibiotic groups widely used in healthcare and therapeutic environments (Ahmed Mo and Baptiste, 2018; Bitrus *et al.,* 2018; Basset *et al.,* 2011). Out of all, MRSA (Methicillin-resistant *Staphylococcus aureus*) strains established determinants against resistance to nearly all β-lactam drugs, causing wide global peril. **β-Lactam**

Resistance: *Staphylococcus aureus* has strong resistance to β-lactam-containing drugs, with held methicillin, oxacillin, penicillins, carbapenems, and cephalosporins. Two main elementary underlying resistant mechanisms involve the release of drug-hydrolyzing enzymes or the modification of membrane proteins to reduce their affinity. The enzyme labelled β-lactamase (penicillinase) digests β-lactam-containing drugs. The procuring of *mecA* and *mecC* genes on the staphylococcal cassette chromosome mec (SCCmec), encode transformed penicillin-binding protein PBP2a (Purrello *et al.,* 2011; Noto *et al.,* 2008; Jevon, 1961). These SCCmec elements cause extensive propagation of MRSA isolates (Woh and Zhang, 2025; Basset *et al.,* 2011).

Glycopeptide or Vancomycin Resistance: *S. aureus* mutants interfering highly with therapeutics are known to be vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA), identified globally. (Ahmed Mo and Baptiste, 2018). The main operon systems established vancomycin or glycopeptide resistance are *vanA* and *vanB* operons from *Enterococcus* species. These transferred operons alter the peptidoglycan precursors D-Ala–D-Ala termini to D- Ala–D-Lac, ensuing decline of teicoplanin and vancomycin affinity (Chang *et al.,* 2003; Weigel *et al.,* 2003).

Macrolide–Lincosamide–Streptogramin B (MLSB) Resistance: MLSB drugs are erythromycin and azithromycin of macrolides, and clindamycin of lincosamides. The *ermA*, *ermB*, and *ermC* genes encrypting rRNA methyltransferases, the 23S rRNA target site modification. Moreover, the extrusion of the drug (macrolides) from the cell through efflux pumps encrypted by *msrA* and *msrB* genes (Bitrus *et al.,* 2018; Roberts, 2008; Leclercq, 2002). iMLSB phenotype of MRSA strains is even frequently resistant (inducible) to clindamycin.

Aminoglycoside Resistance: Aminoglycoside drugs like amikacin, gentamicin, kanamycin, and tobramycin resistance has been observed in *S. aureus* enzymatic modification by genes *aac(6′)/aph(2″)*, *ant(4′)-Ia*, and *aph(3′)-IIIa,* encoding aminoglycoside-altering enzymes cause inactivation of drugs (Shaw *et al.,* 1993; Vakulenko and Mobashery, 2003). Other hand, ribosomal architectural alterations and cut down antibiotic uptake cause the least susceptibility in MRSA to therapeutic drugs impact treatment collapse (Ardic *et al.,* 2006).

Fluoroquinolone Resistance: Fluoroquinolone resistance has been encountered due to the point-nucleotide mutations in *gyrA* and *grlA (parC)* genes in *S. aureus* cause impairment of DNA gyrase and topoisomerase IV activities (Fournier *et al.,* 2013; Hooper, 2002). The genes *norA* and *mepA,* overactivation cause drug extrusion through membrane, diminishes the intracellular drug deposition (Bitrus *et al.,* 2018). Nosocomial MRSA strains are characterized by an intense number of resistant mechanisms against ciprofloxacin, moxifloxacin, and levofloxacin.

Tetracycline Resistance: The resistance against doxycycline, minocycline, and tetracycline is developed by *tetM* and *tetO* genes coding proteins for ribosomal target protection and by *tetK* and *tetL* genes for efflux pumps initiated (Roberts, 2011; Argudín *et al.,* 2010). These resistance plasmid or transposon genes are laterally transferred to *S. aureus* strains (Bitrus *et al.,* 2018).

Sulfonamide and Trimethoprim Resistance: This resistance in S. aureus against sulfonamide, sulfamethoxazole (co-trimoxazole), and trimethoprim has developed by the *dfrA* and *dfrG* gene acquisition, causing folate pathway inhibitors which encoding resistant dihydrofolate reductases and in gene *folP* mutations adopting sulfonamide targets (Huovinen, 2001; Sekiguchi *et al.,* 2005). So, community-acquired MRSA diseases have developed resistance against these oral therapeutic drugs, high risk of treatment in community health care.

Chloramphenicol Resistance: The enzyme encoding *cat* genes inactivates antibiotic as a primary mediator in chloramphenicol resistance by chloramphenicol acetyltransferase, which enzymatically inactivates the drug. The *fexA* and *fexB* genes encode efflux chloramphenicol and florfenicol transport systems, which develop gravely dangerous antimicrobial-resistant *S. aureus* strains (Schwarz *et al.,* 2004; Bitrus *et al.,* 2018).

Rifampicin Resistance: The point-nucleotide mutant MRSA at the *rpoB* gene causes alteration in RNA polymerase (β-subunit), resulting in inhibition of rifampicin adherence (Aubry-Damon *et al.,* 1998; Lemaire *et al.,* 2011). The best therapeutic method is rifampicin coupled with linezolid or vancomycin for nosocomial MRSA contagions.

Linezolid and Oxazolidinone Resistance: These resistant strains are of emerging global challenge as linezolid and Oxazolidinone drugs, especially linezolid, stands as vital last-line treatment against MRSA. The development of resistance to these

drugs is by 23S rRNA and L3/L4 ribosomal proteins mutations and target site modification at the *cfr* gene encoding an rRNA methyltransferase (Schwarz *et al.,* 2000; Long *et al.*, 2006; Bitrus *et al.,* 2018). The spreading of *cfr* genes cause strong resistance to numerous ribosome-targeting antibiotics, leading to severe clinical and therapeutic concern.

Klebsiella pneumoniae

Klebsiella pneumoniae is a chief opportunistic pathogen accountable for nosocomial infections, like circulatory diseases, pneumonia, urinary tract infections, and wound contagions. This pathogen is considered as predominant pathogen of ESKAPE group in this preceding decade, due to its transformation to multidrug resistance machineries.

The configuration of *K. pneumoniae* resistance is multifactorial, linked by β-lactamases discharge, genetic mutations, efflux drug pumping, resistance plasmids procurement, and drug target site alteration. They are a major threat to clinical therapy due to multidrug-resistant (MDR) traits and extensively drug-resistant (XDR) traits (Paterson and Bonomo, 2005; Canton *et al.,* 2012; Partridge *et al.,* 2018).

β-Lactam and Carbapenem Resistance: The common antibiotics - penicillins, cephalosporins, and carbapenems - have noticeably developed resistance to *K. pneumoniae*. They are inactivated by producing β-lactamases that break down β-lactam ring. The activation of genes *bla_TEM*, *bla_SHV*, and *bla_CTX-M* influences Extended-Spectrum β-Lactamases (ESBLs) to penicillins and broad-range cephalosporins resistance (Canton *et al.,* 2012; Bush and Jacoby, 2010; Paterson and Bonomo, 2005). The proliferation of *Klebsiella pneumoniae* carbapenemase (*bla_KPC*), New Delhi metallo-β-lactamase (*bla_NDM*), *bla_VIM*, *bla_IMP*, and *bla_OXA-48*-like genes through these genes–accumulation leaves all β-lactam drugs deactivation, causing critical treatment restrictions except last-resort drugs (Nordmann *et al.,* 2009; Yong *et al.,* 2009; Poirel *et al.,* 2012). Out of all, carbapenemase-producing *K. pneumoniae* turned out to be a global threat, causing hospital outbreaks and is a predominant public health issue (Queenan and Bush, 2007; Walsh *et al.,* 2005).

Aminoglycoside Resistance: These resistant *K. pneumoniae* are primarily developed through either enzymatic alteration of antibiotics or site targeted modification or both. Aminoglycoside- altering enzymes target the ribosomal sites alteration for unbinding of antibiotics through acetyltransferases (*aac(3)-IIa*), phosphotransferases (*aph(32)-VIa*), and nucleotidyltransferases (*ant(23)-Ia*) (Ramirez and Tolmasky, 2010). Also, 16S rRNA methylation causes prevalent resistance to all aminoglycosides by methylating enzymes- 16S rRNA methyltransferases (*armA*, *rmtA*, *rmtB*) (Doi *et al.,* 2007). The genes rapidly disseminate by plasmid transfer among clinical strains of *K. pneumoniae* and lead to therapeutic failure in acute and chronic diseases.

Fluoroquinolone Resistance: In *K. pneumoniae,* fluoroquinolone resistance is predominantly established through plasmid gene transfer or chromosome-associated point mutations. They occur in the *gyrA* and *parC* genetic loci at quinolone resistance–determining regions (QRDRs). The genes encode protection of replication enzymes - topoisomerase IV and DNA gyrase, so they inhibit affinity to antibiotics, leading to diminished susceptibility (Robicsek *et al.,* 2006). Besides, the genes *qnrA*, *qnrB*, *qnrS*, and *aac(62)-Ib-cr* contribute low-level quinolone resistance through plasmid gene transfer. But those genes synergize with mutant chromosomal genes, which establish high-level fluoroquinolone resistance and interfere clinical therapeutics (Jacoby *et al.,* 2014).

Tetracycline Resistance: The tetracycline resistance in *K. pneumoniae* is principally facilitated by proteins of ribosomal protection and efflux pumping intracellular drugs. The *tet(A)*, *tet(B)*, *tet(D)*, and *tet(G)* genes encode proteins that protect the ribosomal sites from drug binding (Speer *et al.,* 1992). These resistant strains are populated with determinants that are commonly located on conjugative plasmids and transposons. The tetracycline resistance is concurrence with other AMR genes through lateral gene transfer in the tenacity of resistant clones.

Colistin or Polymyxin Resistance: In carbapenem-resistant *K. pneumoniae,* resistance to colistin (last-resort or salvage antibiotic) is increasing in recent diseases because of plasmids or chromosomal transfer. The outer membrane lipid A is modified by accumulation of plasmid-transfer *mcr* genes (*mcr-1* to *mcr-10*) encoding phosphoethanolamine transferases, resulting in lowering colistin-target binding capacity for lipid A (Liu *et al.,* 2016; Nang *et al.,* 2019). The mutational alteration in the chromosomal system in the regulatory *mgrB* gene and also the two *pmrA*/*B* and *phoP*/*Q* component arrangements together alter outer membrane lipid A production, causing

resistance (Cannatelli *et al.,* 2014). Out of all, the *mcr* genes are universal, spreading through horizontal transfer, cause curtailing of polymyxin efficacy, a grave threat to health care practices.

Pseudomonas aeruginosa

The spectrum of *Pseudomonas aeruginosa* (gram-negative pathogen) resistance phenotypes has implicitly drawn attention in hospitals and therapeutic significance. *P. aeruginosa* multi-antibiotic resistant strains create major challenges like circulatory illnesses, chronic cystic fibrosis, and ventilator-associated pneumonia (Bonomo, 2017; Morita *et al.,* 2014; Lister *et al.,* 2009). They are known for worldwide resistance exhibited both innate and adoptive, considered not only multidrug-resistant (MDR) but also extensively drug-resistant (XDR), and pan-drug-resistant (PDR) nature.

β-Lactam Resistance: *P. aeruginosa* shows spectacularly elevated resistance to penicillins, and even enhanced-range carbapenems and cephalosporins. As a primary machinery of resistance, *P. aeruginosa* strains produce various kinds of β-lactamases like the *TEM, SHV, PER, GES* genes encoding class A enzymes; *VIM, IMP, NDM,* and *SPM* genes encoding class B metallo enzymes; chromosomal the *ampC* encoding Class C (PDC—Pseudomonas-derived cephalosporinase) and OXA-10 and OXA-50 genes encoding Class D oxacillinases. High-level of resistance is usually administered through extensive expression of *ampC* gene or conjugate MBL genes through plasmids and integrons. Synchronicity of these class enzymes strings to carbapenem resistance and therapeutic failure (Livermore, 2002; Queenan & Bush, 2007; Lister *et al.,* 2009; Bonomo, 2017).

Efflux-Mediated Resistance: As an innate response, multiple drug efflux pumping mechanism's vigorous gene expression backs up *P. aeruginosa* vital resistance. The outer membrane protein genes *MexAB-OprM, MexCD-OprJ, MexEF-OprN,* and *MexXY-OprM* express strong efflux of multiple antibiotics such as aminoglycosides, β-lactams, chloramphenicol, fluoroquinolones, and tetracyclines. Especially during ribosomal stress, MexXY-OprM system allows to aminoglycoside resistance (Poole, 2001; Li *et al.,* 2015; Morita *et al.,* 2014). Pumping enhances with mutant *mexR*, *nalC*, *nalD* genes; so, it eliminates intracellular drug accumulation and enhances resistance ability.

Porin-Mediated Resistance: Membrane *OprD* **p**orin loss or modification or mutational inactivation or repression, majorly cause reduced permeability, so increased imipenem resistance in *P. aeruginosa*. This prevalence of resistance in line with MBL conjugate or enhanced expression *AmpC* â-lactamase limits medical therapy (Quale *et al.,* 2006; Wolter *et al.,* 2004; Lister *et al.,* 2009).

Fluoroquinolone Resistance: The mutations at target site**s** like *parC* and *gyrA* genes encode topoisomerase IV and DNA gyrase, leading to ciprofloxacin and levofloxacin resistance increases. Mutational substitutions, ParC Ser87→Leu and GyrA Thr83→Ile reduce binding affinity. This target site mutations cohabits with overexpression of the active export system, shooting up of fluoroquinolone resistance (Jalal and Wretlind, 1998; Higgins *et al.,* 2003; Oliver *et al.,* 2015). Along with cohabited expression, hyperactivity of MexEF-OprN causes a threat to clinical therapy.

Aminoglycoside Resistance: Intense aminoglycoside resistance is linked with the genes *aac(62)- Ib*, *aph(32)-IIb*, and *ant(23)-Ia* encoding aminoglycoside-altering enzymes like acetyltransferases (AACs), phosphotransferases (APHs), and nucleotidyltransferases (ANTs). The ribosomal targets genes *armA*, *rmtA–rmtF* encode 16S rRNA methyltransferases, which influence antibiotic adherence, cause the development of pan-aminoglycoside resistance (Ramirez and Tolmasky, 2010; Doi *et al.,* 2016; Poole, 2011). The genes are usually accumulated through horizontal gene transfer.

Biofilm-Associated Resistance: The main adopted mechanism confirms most of the antibiotic drugs due to biofilm formation. The drug penetration is reduced by biofilm composed of alginate, Psl, and Pel polysaccharides**.** These films are regulated by genes *las*, *rhl*, and *pqs* encode quorum- sensing systems and hence promote resistance (Donlan and Costerton, 2002; Mulcahy *et al.,* 2014; Hall and Mah, 2017). So these biofilms promote dormancy and gene transfer in pathogens withhold the drug resistance, leading to persistent diseases like cystic fibrosis.

Adopted and Mutational Resistance: The traits of *P. aeruginosa* also displays phenotypic adopted resistance, consenting transitory survival under drug-induced stress. This comprises generation of resilient dormant drug-tolerant cells, instigation of global stress response controllers (*rpoS*), and

inducible *ampC* gene expression (inducible) (Fernández and Hancock, 2012; Morita *et al.*, 2014). Such adopted resistance develops in association to biofilm and pays chronic reemerging infections.

***Enterobacter* species**

The species *Enterobacter cloacae complex*, *E. asburiae*, and *E. hormaechei* of *Enterobacter* family, established resistance due to transformation from opportunistic to nosocomial infections. They have robustic capacity to adopted resistance through integrons, plasmids, and transposons coupled with innate resistance, amplifies their multiple antimicrobial categories used in medical management (Jacoby, 2009; Canton *et al.*, 2012; Peirano and Pitout, 2019).

β-Lactam Resistance: There are several extensively resistant *Enterobacter* spp. emerged to oppose β-lactams like carbapenems, cephalosporins, and penicillins. The resistance developed as hydrolyze third-generation cephalosporins by wide spectrum β-lactamases like CTX-M, TEM, and SHV release (Jacoby, 2009; Canton *et al.*, 2012). And as cephamycins are inhibited in the *E. cloacae* complex through AmpC β-lactamases release which is acquired by plasmid-mediated or inducible chromosomal mutations. Resistance to carbapenem is by the release of carbapenemases like KPC, NDM, OXA-48, and VIM enzymes through overexpression of efflux pump and porin loss. So *Enterobacter* spp. susceptibility has reduced notably to last-resort drugs (Nordmann *et al.*, 2012; Peirano and Pitout, 2019).

Aminoglycoside Resistance: *Enterobacter* spp. have effectively resistance to aminoglycosides antibiotics like such as amikacin, gentamicin, and tobramycin. These antibiotics are inactive by developing resistance through enzymes' modification - acetyltransferases (*aac(62)-Ib*), nucleotidyltransferases (*ant(23)-Ia*), phosphotransferases (*aph(32)-VI*). (Ramirez and Tolmasky, 2010). In addition, this family has mutation in ribosomal site, even diminishing penetration ability of cell membrane (Shakil *et al.*, 2008), AME genes dissemination aids to accelerated gene mobility of resistance traits, impairing aminoglycoside-mediated therapy.

Fluoroquinolone Resistance: In healthcare and ICU (Intensive Care Unit) conditions, Fluoroquinolone resistance is more and more substantial in *Enterobacter* spp. The main resistance mechanism encompasses point mutations of the *gyrA* and *parC genes*, develops quinolone resistance by lowering its binding ability (Ruiz, 2003). Moreover, *qnrA, qnrB, qnrS,* and *aac(62)-Ib-cr* gene mutations determine weak resistance that endorses the assortment of strong mutants (Robicsek *et al.*, 2006). Furthermore, porin modification and overexpression of drug efflux lessens the intracellular drug pool (Martínez-Martínez *et al.*, 1998). The *qnrB* and *aac(62)-Ib-cr* genes accumulation cause this resistance in hospitals of Southeast Asia.

Carbapenem Resistance: The resistance of carbapenem became alarming medical concern in *Enterobacter spp.*, particularly in *E. cloacae* and *E. hormaechei*. The genes encoded KPC, NDM, VIM, IMP, and OXA-48 proteins i.e., carbapenemase production initiates carbapenem hydrolysis, so have resistance against them (Queenan and Bush, 2007). Drug uptake is withheld due to loss of *OmpC*, *OmpF* porins, along with overexpression of *AmpC* (Tamma *et al.*, 2021). Significant health rate and fatality are prevailed among carbapenem-resistant *Enterobacter* (CRE) isolates, opts last- resort/ salvage therapy of cefiderocol, colistin, and tigecycline. *blaNDM* and *blaOXA-48* carbapenemases are also found in carbapenem-resistant *Enterobacter spp*.

Tetracycline Resistance: Tetracycline resistance is dominantly isolated in environmental and clinical conditions. The key machinery comprises the genes *tet(A)* and *tet(B)* encode efflux drug transport pumping off the cell (Chopra and Roberts, 2001); *tet(O)* and *tet(M)* genes encode guarding proteins of ribosomes which avert drug fastening to ribosomes (Roberts, 2005). These resistance gene factors are laterally transferred through integrons (class 1) and conjugative plasmids. This resistance is predominantly observed in multidrug-resistant *Enterobacter* along with β-lactam and macrolide resistance determinants.

Macrolide and Chloramphenicol Resistance: Even though administration of macrolides and chloramphenicol are rare in Gram-negative *Enterobacter* infection, they have established resistance. In case of macrolide resistance strains, the genes *erm*(B) involved in 23S rRNA methylation cause obstruction of antibiotic fastening (Shaw *et al.*, 1993). In case of chloramphenicol resistance strains, the resistance was buttoned enzymatic inactivation by chloramphenicol acetyltransferase (*cat*), and an active efflux mechanism lowers intracellular antibiotic intensity (Schwarz *et al.*, 2004). These macrolide and chloramphenicol resistance genes are co-exist with multidrug-resistant plasmids. So they

enable co-selection and tenacity under antimicrobial pressure.

Colistin or Polymyxin Resistance: Resistance in colistin or polymyxin is existed commonly along with carbapenem-resistance in *Enterobacter* spp. So colistin-resistant strains also come to light as a principal medical risk. Multiple resistance machineries are involved, such as mutations in membrane permeability and horizontal plasmid gene transfer. Decline of colistin fastening at *Enterobacter* spp cell wall due to the mutations in *pmrA/pmrB* and *mgrB* genes leads lipid A variation in lipopolysaccharide layer. (Olaitan *et al.,* 2014). Besides, a series of ten resistant genes *mcr-1 to mcr-10* called mobilized colistin resistance (*mcr*) genes transferred by horizontal plasmid gene trasfer (Liu *et al.*, 2016). Pan-drug resistance in hospital and clinical atmosphere was recognized in Asian isolates of *mcr*-positive *Enterobacter.*

CONCLUSION

The pathogens ESKAPE occupies a leading significant challenge in hospital health care in current medical science because of their complex multiple antimicrobial resistance even to salvage drugs. This high-level resistance in isolates is mainly due to multiple diverse innate and adopted mechanisms, containing target site alteration, production of drug-degrading enzymes, hyperexpression of efflux drug pumping, biofilm-associated protection, and plasmid or transposons or integrons gene acquisition through horizontal transfer. These adopted mechanisms lead to in elated incidence of multidrug-resistant pathogens, and in cases, extensively drug- resistant, and even pan-drug-resistant isolates, resulting in constrained therapeutic opportunities and further causes raised morbidity and mortality in clinical and medical therapeutics. Alleviating the hazards are majorly occur through various dice faces like tracking of ESKAPE resistance patterns or surveillance of resistance trends, further judicious antimicrobial therapeutic use, escaping techniques of ESKAPE pathogens from host immunity and the advancement of pathogens from emerging therapeutic interventions. Future prospective investigations should emphasize extreme molecular intrusions, discovering novel and vital antimicrobials, and modulating holistic therapeutic approaches to manage diseases effectively caused by ESKAPE microbes and mitigate the global spread of antimicrobial resistance.

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