Huy *Beni-Suef Univ J Basic Appl Sci* (2024) 13:13
https://doi.org/10.1186/s43088-024-00470-4

Beni-Suef University Journal of Basic and Applied Sciences

REVIEW

Open Access

Overcoming *Klebsiella pneumoniae* antibiotic resistance: new insights into mechanisms and drug discovery

Tran Xuan Ngoc Huy[1*]

Abstract

Background Due to antibiotic overuse, numerous organisms have evolved multidrug resistance, a global health crisis. *Klebsiella pneumoniae* (*K. pneumoniae*) causes respiratory, biliary, and urinary infections. It initially impacts individuals with impaired immune systems.

Main body of abstract The treatment of *K. pneumoniae* clones poses significant challenges, highlighting the need for new, more effective pathogen control methods. Our understanding of the natural or acquired antibiotic resistance mechanisms in *K. pneumoniae* is inadequate. Therefore, it is crucial to continue searching for novel compounds to fight against *K. pneumoniae* and to understand its antibiotic resistance processes fully**.**

Short conclusion This review covers *K. pneumoniae* antibiotic resistance in detail. The review also identifies the molecular components of natural or acquired *K. pneumoniae* antibiotic resistance mechanisms. This study further digs into the novel pharmacological targets to offer therapy insights.

Keywords K. pneumoniae, Antibiotic resistance, Drug target

1 Background

Klebsiella pneumoniae is an ubiquitous gram-negative facultative anaerobic bacteria [1]. *K. pneumoniae* lives in many different environments, including the respiratory and gastrointestinal systems of humans and animals [1]. *K. pneumoniae* infection accounts for over 95% of *Klebsiella* infection. *K. pneumoniae* infection can trigger various infections and mostly affect the individuals with weakened immune systems. This particular infection is highly prevalent in medical facilities across the globe [1]. The emergence of genetically modified strains of *K. pneumoniae* that exhibit heightened virulence or demonstrate resistance to antimicrobial agents has become a subject of significant apprehension [1].

The global phenomenon concerning the emergence and progression of multidrug resistance (MDR) in human diseases holds significant significance within the realm of scientific investigation. MDR *K. pneumoniae* has become a significant concern within the healthcare system due to its ability to restrict treatment options. *K. pneumoniae* has two main antibiotic resistance types. The expression of extended-spectrum β-lactamase (ESBL) makes bacteria resistant to cephalosporins and monobactams [1]. In addition, the presence of carbapenemases makes bacteria resistant to most β-lactams, including carbapenems [1]. The aforementioned strains have resulted in an excess of 90.000 infections and 7.000 fatalities within the European region [2].

Colistin and tigecycline, both of which are used as a last-line drugs, are another option for treating CRKp [3]. Last-line drugs have only been effective when used in combination with other medications, not

*Correspondence:
Tran Xuan Ngoc Huy
txn.huy@hutech.edu.vn
[1] Institute of Applied Sciences, HUTECH University, 475A Dien Bien Phu St., Ward 25, Binh Thanh District, Ho Chi Minh City, Viet Nam

alone. However, colistin and tigecycline use has several adverse effects, including nephrotoxicity [4]. New ESBL-producing and CRKp strains are also developing resistance to the last-line antibiotics. Conventional medicines have proved to be ineffective in eradicating these pathogens. So, multidrug resistant infections have posed a significant challenge to public health and the global economy. More seriously, the quantity of antimicrobial drug development initiatives has significantly diminished since the era of remarkable antibiotic discovery due to many factors, including antibiotic resistance, lower profit margins, etc. Therefore, it is necessary to identify new drugs in order to address this pressing public health crisis. Furthermore, our comprehension of the natural or acquired antibiotic resistance of K. pneumoniae remains limited. Hence, it is of outmost significance to continuously explore novel methodologies in combating K. pneumoniae, while concurrently attaining a comprehensive comprehension of the mechanisms underlying K. pneumoniae resistance to currently available pharmaceutical interventions. This review aims to give a comprehensive overview of how K. pneumoniae resists antibiotics. The review also identifies the molecular components contributing to natural or acquired antibiotic resistance mechanism in K. pneumoniae. This research delves deeper into the new pharmacological targets, which can lead to new insights into how to treat K. pneumoniae infections.

2 Main text

2.1 Antimicrobial resistance

2.1.1 Intrinsic resistance

Since *K. pneumoniae* is antibiotic-resistant, standard treatments are less effective. *K. pneumoniae* generates intrinsic resistance to antibiotics through the following mechanisms: enzymatic antibiotic inactivation and modification, porin loss, enhanced antibiotic efflux pump expression, and biofilm development (see Fig. 1) [5, 6]. Table 1 gives a summary of natural resistance mechanisms in *K. pneumoniae*.

2.1.2 Antibiotic modifying or inactivating enzyme

K. pneumoniae often develops resistance to antibiotics due to medication modification. Currently, the most usual way to treat *K. pneumoniae* infection in the clinic is β-lactam antibiotics. β-lactam antibiotics kill bacteria by covalently attaching to Penicillin-binding proteins (PBPs), which are necessary for peptidoglycan cross-linking formation in bacteria [9]. This stops the bacteria from making cell walls. *K. pneumoniae* makes an enzyme called β-lactamase to get around this. β-lactamase

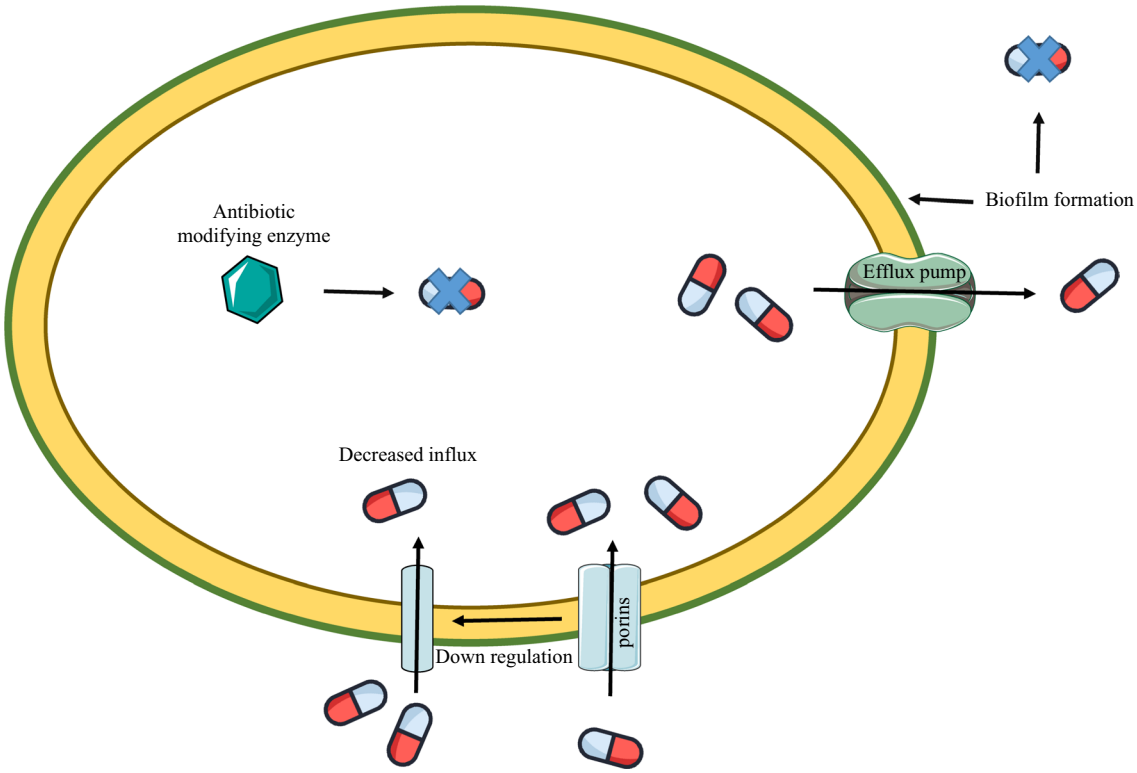

Fig. 1 Mechanisms of *K. pneumoniae* innate antibiotic resistance

Table 1 The intrinsic antibiotic resistance mechanisms in *K. pneumoniae*

Resistance mechanism	Antibiotic class	References
Antibiotic modifying or inactivating enzyme	β-Lactam	[9–12, 15, 16]
Bacterial influx	β-lactam and fluoroquinolones	[7]
Efflux pump	β-lactam, macrolides, fluoroquinolones, and tetracycline	[7]
Biofilm formation	Aminoglycoside, penicillin, and quinolone	[8]

hydrolyzes the β-loop of β-lactam. This is a key resistance mechanism. Cephalosporinases (AmpC), ESBLs, and carbapenemases are the three subtypes of β-lactamases [10–13]. ESBLs are plasmid-based antibiotic resistance mechanisms. The *bla*SHV-2 and *bla*TEM-3 were found in *K. Pneumoniae* [14, 15]. They are viral carrier ESBL mutant genes [15]. Clavulanic acid stops ESBL genes from working against carbapenems in a way that is called "extended-spectrum". Since plasmids and transposons that create *bla* CTX-M-type ESBLs are simple to obtain, it slowly superseded TEM and SHV as the primary genotype. Horizontal gene transfer also happened with *bla* PER, *bla* SFO, *bla* TLA, *bla* OXA, *bla* GES, *bla* VEB, and *bla* KLUC-5 [16]. For ESBL-producing bacterium infections, carbapenems have long been the preferred choice [14]. From first to third-generation cephalosporins, cephalomycin, and enzyme inhibitors, AmpC is resistant [12]. The bacteria contains over 40 AmpC genotypes, which can swiftly disseminate among various strains via plasmid-mediated mechanisms [14].

2.1.3 Bacterial influx

A group of outer membrane proteins called porins is highly prevalent in the outer membrane [17]. The regulation of flux is accomplished through the formation of channels that traverse the outer membrane, facilitating the transport of molecules across the lipid bilayer membranes [17]. Antibiotics with paramount therapeutic importance, such as β-lactams and fluoroquinolones, can diffuse across porins thanks to the small hydrophilic molecules (<600 Da) [17]. They protect bacterial cells by acting as receptors for bacteriophages and bacteriocins [18]. Pore-forming proteins, which comprise the bulk of the outer membrane, contribute to bacterial pathogenicity by aiding in processes including adhesion, invasion, and resistance to serum [18]. Loss of porins in ESBL-generating bacteria may contribute to antibiotic resistance and enable the selection of additional resistance mechanisms [19]. Porins expressed by *K. pneumoniae* under host-body conditions aid in outer membrane stability and have a role in bacterial protection against defensins and other antimicrobial peptides produced by the immune system [20]. Altering the porin type, expression level, or function may limit cell drug uptake [20]. The porins LamB, OmpK26, PhoE, OmpK35, OmpK36 and KpnO contributes significantly to innate drug resistance [7].

2.1.4 Efflux pump

Bacteria heavily depend on their efflux capability as a means of defense to adapt and ensure survival within their environment. The defense mechanism in question assumes a pivotal function in the restriction of drug buildup within bacterial cells. Membrane efflux pumps release antimicrobials from the cell into the surrounding medium, reducing the concentration of medicines inside the cell. Efflux pumps is critical to how drug resistance develops [21–23]. Overexpression of efflux pumps to deal with a rising drug concentration within the cell and/or the accumulation of mutations in the pumps that improve their ability to expel the drug are two possible ways [24]. Efflux pumps become ready to rid the body of harmful substances. Inferred from whole genome sequencing data, over 30 genes or operons for MDR efflux pumps are present on the *Klebsiella* chromosome [25]. *Klebsiella* has many MDR efflux pumps comprising the major facilitator superfamily, resistance-nodulation-division, small multidrug resistance, and toxin extrusion families. [20]. Bacterial innate and acquired antibiotic resistance depends on resistance-nodulation-division efflux pumps. Both TolC and AcrA are known to interact with various resistance-nodulation-division and significant facilitator superfamily pharmacological efflux pumps, demonstrating that they are multi-compatible compounds [26]. TolC, an outer membrane component, is connected with the AcrAB pump, the most thoroughly investigated efflux mechanism to date. Clinically significant efflux systems in *Klebsiella* include the AcrAB-TolC pump complex, which is responsible for the energy-dependent expulsion of drugs [20]. Since AcrAB substrates can have negative or positive charges, the protein only needs a hydrophobic region to enter the phospholipid bilayer to transport the medication [20]. The active efflux system AcrAB-TolC can exocytose several medicines, such as β-lactams, macrolides, fluoroquinolones, and tetracycline [20].

2.1.5 Biofilm formation

K. pneumoniae exhibits a propensity for biofilm formation, with structures such as capsules and pili playing

crucial roles in facilitating this process [21]. Antibiotic penetration is hindered by biofilms because they slow bacterial growth, promote the development of persister cells, and allow for the dissemination of genetic material [21]. Microorganisms that produce an exo-polymeric matrix cling to an inanimate or living surface to form a biofilm. This matrix contains polysaccharides, proteins, and extracellular DNA [22]. Biofilms are characterized by osmotic barrier properties and antimicrobial drug resistance. Biofilm formation in *K. pneumoniae* leads to a decreasing in the gentamicin, ampicillin, and ciprofloxacin susceptibility [8]. The development of biofilms and resistance to colistin have been linked [23].

2.1.6 Acquired resistance

The β-lactam antibiotic class is commonly used to treat *K. pneumoniae* infection. Other antibiotics must be used when patients are infected with multidrug-resistant or extended-duration *K. pneumoniae*. However, drug resistance can develop when these antibiotics are administered clinically. Table 2 gives a summary of acquired resistance mechanisms in *K. pneumoniae.* Instead of relying on chromosomal gene alterations, horizontally acquired accessory antimicrobial resistance (AMR) genes appear responsible for most *K. pneumoniae* resistance. These are often carried by plasmids, though they can be integrated into the chromosome.

2.1.7 Carbapenem resistance

The ESBL-producing *K. pneumoniae* has increased carbapenem use dramatically. They may have resulted from carbapenem selective pressure. Plasmid-regulated carbapenem enzymes remain the most worrisome multidrug resistance route. The serine-based class β-lactamase (KPC) is the most prevalent and potentially lethal carbapenemase. KPCs is associated with CG258, a clonal subgroup [24, 25]. Both ST258 and ST11 are widespread in Asia, but ST258 is more common in Europe and the Americas [25–29]. *Bla* KPC genes use a unique Tn4401 transposition form to transfer onto other plasmids and spread clonally [30, 31]. High mortality rates and difficulty treating carbapenemase-producing *Enterobacteriaceae* are consequences of the widespread of resistance genes of this sort. Most β-lactamase inhibitors are ineffective against KPCs, making treatment difficult. The chromosomal translocation of carbapenemase-encoding genes from plasmids complicates these resistances [32]. CRKP presents significant challenges in clinical practice [14].

K. pneumoniae adaptability in attaching β-lactamase genes to transportable plasmids aids in the dissemination of AmpC-like cephalosporinase in these species [33, 34]. The presence of *bla* AmpC in *K. pneumoniae* and gene expressing deletions or improved efflux, comparable to *bla* ACT-1, lead to β-lactam antibiotic resistance. Increased copies or promoter strength can easily express genes on plasmids, resulting in carbapenem resistance [33]. Some *K. pneumoniae* strains may carry many lactamase genes, such as SHV, AmpC, KPC, and β-lactamase inhibitors. The effects of many resistance genes present in the same strain are additive. While Vim, NDM, and IMP are impossible to exhibit resistance to aztreonam, their presence can facilitate the development of such resistance in the presence of ESBL or AmpC.

2.1.8 Aminoglycoside resistance

The armA gene family in *K. pneumoniae* is expressed by plasmids, and while drug-modifying enzymes can reduce its activity, 16S rRNA methylase is resistant to virtually all aminoglycosides [35]. Chromosomal genes affect *K. pneumoniae* resistance to aminoglycoside antibiotics, which alter cell permeability by mutating the AcrAB-TolC and KpnEF efflux pump systems and deleting the putative protein KpnO. The former had heavy tobramycin and gentamicin resistance, while the latter had heavy vancomycin and mild streptomycin resistance. This implies that aminoglycosides represent cell channels. Lost pore protein KpnO caused tobramycin, streptomycin, and spectinomycin resistance [36].

Table 2 The acquired antibiotic resistance mechanisms in *K. pneumoniae*

Target gene	Antibiotic class	References
*bla*SHV, *bla*TEM, *bla*CTX, *bla*KLUC-5, *bla*SFO, *bla*GES, *bla*PER, *bla*VEB, *bla*TLA, *bla*KPC *bla*NDM, *bla*VIM, *bla* IMP, *bla*OXA, *bla*CMY, *bla*DHA, *bla*FOX, and *bla*MOX	β-lactam	[8, 32, 33, 40, 41]
aac, aph, ant, AcrAB-TolC, kpnEF, and KpnO		
AcrAB-TolC, OqxAB, RarA, RamA, RamR, AcrR, rpsJ, 16S rRNA methylase, and tetA	Tigecycline	[7]
DNA gyrase, topoisomerase IV, mpK36, acrAB, kdeA, OqxAB, and aa(6')-Ib-cr	Quinolone	[7]
phoPQ, pmrA, pmrD, mcr-1, and mgrB	Polymyxin	[7]
fos	Fosfomycin	[7]

2.1.9 Tetracycline resistance

The novel tetracycline antibiotic tigecycline shows broad-spectrum efficacy against ESBL-producing bacteria [37]. Antibiotic resistance is mostly caused by the Oqx-AB, Ade-ABC efflux pumps, Tet(A) mutant, KpgABC, and ribosomal protein. This antibiotic's resistance gene lies on the chromosome and alters cell permeability and ribosomal targets [14]. The rpsJ gene encodes ribosomal protein S10, a 30S subunit component. It is close to the main binding site for tetracycline and tigecycline in the 30S subunit of the ribosome. Among three discovered *K. pneumoniae*-resistant tigecycline strains, one of them showed a point mutation in the rpsJ gene which closes the tigecycline target in the 30S subunit [38]. Thus, the S10 ribosomal protein alternation may be the new mechanism. Ribosomal proteins S3, S13, and S10 lie near the tetracycline-ribosomal subunit binding domain, and S3 maintains the site's structural integrity [39]. The S3 protein structural mutation may also produce tigecycline resistance. RpsJ gene mutation can cause tigecycline resistance without efflux pump participation, according to studies [14].

2.1.10 Quinolone resistance

Quinolone antibiotics inhibit topoisomerases, which prevent bacterial DNA replication [40]. Alterations in the target gene boosted MDR efflux production, and enzyme and protein alterations made *K. pneumoniae* fluoroquinolone-tolerant [40]. With chromosomal resistance mechanisms, topoisomerase IV and DNA gyrase bind quinolones. OqxAB is present in numerous bacteria and is connected to plasmid-mediated quinolone resistance [41]. Other quinolone resistance genes include the plasmid-mediated determinant in *Enterobacteriaceae* species. These gene protein family protects DNA gyrase and topoisomerase IV from quinolones. Quinolone modification is expected to only occur in *K. pneumoniae* via plasmid-mediated quinolone resistance gene aa(6')-Ib-cr [42]. Other antibiotics and restricted quinolones with the enzyme's substrate can also be inactivated by aa(6')-Ib-cr [42]. It was also found on chromosomes recently. Plasmid-mediated quinolone resistance gene expression promotes chromosomal genetic alterations and mild to moderate quinolone resistance [41].

2.1.11 Other antibiotic mechanisms

Polymyxin resistance in *K. pneumoniae* is usually caused by mutations in regulative genes such as mgrB, which regulates bacterial lipid A, a polymyxin antibiotic target, reducing polymyxin interaction [43–45]. *K. pneumoniae* BSI isolates in China rarely include mcr-1, although *E. coli* does. America had its first mcr-1 case in 2016 [46].

Fosfomycin, an ancient antibiotic, is now used to treat MDR bacterial infections [47]. With increased fosfomycin use, resistant strains are emerging. Amino acid replacement or overexpression of MurA, deficient or reduced expression of GlpT and UhpT, and the fos gene, which encodes a glutathione S-transferase-activated enzyme that inactivates fosfomycin, constitute fosfomycin resistance mechanisms [48]. The fosA3 gene has been identified as the primary determinant responsible for conferring fosfomycin resistance in carbapenem-resistant *K. pneumoniae* (CRKp). The horizontal transferability of this resistance mechanism observed through plasmids that are frequently encountered within hospital settings [49]. The CRKp strains that exhibited resistance to fosfomycin and lacked the FosA3 gene were found to possess mutations in the MurA gene and the glpT transporter [49].

2.1.12 Potential drug targets of K. pneumoniae

As multidrug-resistant *Klebsiella* cases multiply and antimicrobial medication activity decreases, global clinical issues arise. *Klebsiella* infections were treated with β-lactam antibiotics, but the advent of hypervirulent and MDR forms has rendered these treatments ineffective [50]. Identifying new medicines and medication combinations to treat these fatal illnesses is urgent.

Identifying pharmacological targets requires microorganism genomic data. Pathogenic microorganism entire genomes and virulence-causing genes can be sequenced first. Next, subtractive genomic methods can exclude homologous proteins and identify the pathogenic non-homologous protein lacking in the host [51]. Researchers searched for *K. pneumoniae*-host homologous proteins using in silico methods like Blastp and BLAT [52]. Selecting non-homologous proteins not found in humans reduces cross-reactivity and adverse effects. The database of essential genes can identify pathogen-survival genes. Use the KEGG pathway database to analyze the shortlisted genes and proteins pathways [53]. Most identified therapeutic target candidates with promising drug development prospects participate in important biosynthetic activities such as peptidoglycan, fatty acids, pyrimidine deoxyribonucleotides, pyrimidine deoxyribonucleotides, LPS, and purine nucleotides.

In addition to druggable, essential, and conserved enzymes, the metabolic enzymes FabB, FabI, and FabH which are involved in fatty acid biosynthesis, are interesting targets. FabI, a crucial focal point, exhibits immense potential as a target for pioneering therapeutic interventions against bacterial pathogens [54]. By facilitating the incorporation of two carbon atoms derived from malonyl-acyl carrier protein (ACP) into an acyl acceptor, the enzyme FabB effectively mediates a diverse range of

acyl-ACP elongation reactions within the type II fatty acid elongation cycle [55]. The enzyme FabH initiates the process of fatty acid synthesis by incorporating a two-carbon acyl acceptor from malonyl-ACP into the initial condensation step [56]. FabH controls total fatty acid synthesis. This enzyme acts as a synthase and transacylase for acetyl-CoA. The FabH enzyme's acetyl-CoA substrate selectivity controls straight-chain fatty acid production [57]. It can utilise propionyl-CoA less efficiently. In the subsequent step, FabI enzymatically catalyzes the reduction of a carbon–carbon double bond within an enoyl moiety that is covalently linked to an acyl carrier protein [54]. This process occurs within the fatty acid elongation cycle, which is crucial for lipid metabolism and biotin synthesis [54]. LPS production is essential for bacterial cell wall lipid development. LpxA, LpxB, LpxC, and LpxD are potential drug targets [58, 59].

MurG is a crucial component in the process of cell wall formation [60]. Simultaneously, MurF actively participates in the process of cell wall biogenesis [61]. Important targets, including aspartate semialdehyde dehydrogenase, synthesize L-lysine, L-threonine, L-methionine, and L-homoserine. An important membrane ATPase, SecA, powers Sec-dependent protein translocation. YajC and SecYEG form an oligomer. By helping bacteria secrete proteins, poisons, and virulence factors, SecA was crucial to their survival [62]. Thus, making it an ideal antibacterial target. Since SecA is a membrane protein, developing SecA inhibitors allows easy access without entering the cytoplasm [63].

Targeting histidine kinase Bacterial two-component system receptor includes EvgS. Acid and drug resistance are linked to EvgS/EvgA bacterial two-component system receptor in *E. coli* [64]. A slight acidity increase activates EvgS, which phosphorylates EvgA. EvgS/EvgA activation promotes several acid-resistance genes and gives bacteria acid resistance [65]. Secretion of hazardous chemicals such antibiotics, dyes, disinfectants, host-produced bile, hormones, and defense compounds depends on TolC [65]. TolC is involved in exporting extracellular proteins [66]. QseC, a receptor belonging to the bacterial two-component system, presents itself as an alluring subject for further investigation. Epinephrine and norepinephrine activate this QseC kinase [67].

3 Conclusion

Global drug-resistant *K. pneumoniae* infections have increased. Previously, nothing was known about *K. pneumoniae*, which infects the brain, liver, circulation, lungs, and bladder. Despite its century-old discovery, the pathogen's virulence mechanisms are unknown. The host immune responses against *K. pneumoniae* infection is also poorly defined. Current antibiotic regimens are nearly untreatable due to the widespread of MDR and hypervirulent clones. Numerous studies have explored ESBLs, carbapenemase, or AmpC target change, porin loss and mutation, efflux pump overexpression, and horizontal diffusion of mobile gene elements in resistance mechanisms. So far, nothing is known about how biofilm development governs antibiotic resistance in *K. pneumoniae*. Fatty acids, LPS, peptidoglycan, pyrimidine deoxyribonucleotides, and purine nucleotides are promising targets against *K. pneumonia* via high-throughput analysis. These targets meet most pharmacological targeting criteria, including a host gene absence for their homolog. The chosen targets require numerous steps to design and produce inhibitors.

Abbreviations

K. pneumoniae	*Klebsiella pneumoniae*
ESBL	Extended-spectrum β-lactamase
CRKp	Carbapenem-resistant *K. pneumoniae*
MDR	Multidrug resistance
KPC	Serine-based class β-lactamase

Acknowledgements
Not applicable.

Author contributions
All authors participated in the collection of data, writing, reviewing, and editing the manuscript. All authors read and approved the final manuscript.

Funding
This research received no external funding.

Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 18 October 2023 Accepted: 29 January 2024
Published online: 04 February 2024

References

1. Paczosa MK, Mecsas J (2016) Klebsiella pneumoniae: going on the offense with a strong defense. Microbiol Mol Biol Rev 80:629–661
2. Gasser M, Zingg W, Cassini A, Kronenberg A, Center for Antibiotic Resistance S, (2019) Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in Switzerland. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(18)30708-4
3. Goodrum KJ (1987) Stimulation of complement component C3 synthesis in macrophagelike cell lines by group B streptococci. Infect Immun 55:1101–1105

4. Ordooei Javan A, Shokouhi S, Sahraei Z (2015) A review on colistin nephrotoxicity. Eur J Clin Pharmacol 71:801–810
5. Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi KR (2019) Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Front Microbiol. https://doi.org/10.3389/FMICB.2019.00539/FULL
6. Sikarwar AS, Batra HV (2011) Prevalence of antimicrobial drug resistance of Klebsiella pneumoniae in India. Int J Biosci Biochem Bioinform 1(3):211. https://doi.org/10.7763/IJBBB.2011.V1.38
7. Pulzova L, Navratilova L, Comor L (2017) Alterations in outer membrane permeability favor drug-resistant phenotype of Klebsiella pneumoniae. Microb Drug Resist 23(4):413–420
8. Chung PY (2016) The emerging problems of Klebsiella pneumoniae infections: carbapenem resistance and biofilm formation. FEMS Microbiol Lett. https://doi.org/10.1093/FEMSLE/FNW219
9. Bush K, Bradford PA (2016) β-Lactams and β-lactamase inhibitors: an overview. Cold Spring Harb Perspect Med 6:a025247
10. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, Walsh TR (2009) Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob Agents Chemother 53:5046–5054
11. Tooke CL, Hinchliffe P, Krajnc A, Mulholland AJ, Brem J, Schofield CJ, Spencer J (2020) Cyclic boronates as versatile scaffolds for KPC-2 β-lactamase inhibition. RSC Med Chem 11:491–496
12. Theuretzbacher U, Carrara E, Conti M, Tacconelli E (2021) Role of new antibiotics for KPC-producing Klebsiella pneumoniae. J Antimicrob Chemother 76:I47–I54
13. Liu Y, Wan LG, Deng Q, Cao XW, Yu Y, Xu QF (2015) First description of NDM-1-, KPC-2-, VIM-2- and IMP-4-producing Klebsiella pneumoniae strains in a single Chinese teaching hospital. Epidemiol Infect 143:376–384
14. Li Y, Kumar S, Zhang L, Wu H, Wu H (2023) Characteristics of antibiotic resistance mechanisms and genes of Klebsiella pneumoniae. Open Med. https://doi.org/10.1515/MED-2023-0707
15. Sirot D, Sirot J, Labia R, Morand A, Courvalin P, Darfeuille-michaud A, Perroux R, Cluzel R (1987) Transferable resistance to third-generation cephalosporins in clinical isolates of Klebsiella pneumoniae: identification of CTX-1, a novel beta-lactamase. J Antimicrob Chemother 20:323–334
16. Li CF, Tang HL, Chiou CS, Tung KC, Lu MC, Lai YC (2018) Draft genome sequence of CTX-M-type β-lactamase-producing Klebsiella quasipneumoniae subsp. similipneumoniae isolated from a Box turtle. J Glob Antimicrob Resist 12:235–236
17. Achouak W, Heulin T, PagÃ¨s J-M, (2001) Multiple facets of bacterial porins. FEMS Microbiol Lett 199:1–7
18. Buchanan SK (1999) β-Barrel proteins from bacterial outer membranes: structure, function and refolding. Curr Opin Struct Biol 9:455–461
19. Doménech-Sánchez A, Martínez-Martínez L, Hernández-Allés S, del Carmen Conejo M, Pascual A, Tomás JM, Benedí VJ (2003) Role of Klebsiella pneumoniae OmpK35 Porin in antimicrobial resistance. Antimicrob Agents Chemotherapy 47(10):3332–3335
20. Pilonieta MC, Erickson KD, Ernst RK, Detweiler CS (2009) A protein important for antimicrobial peptide resistance, YdeI/OmdA, is in the periplasm and interacts with OmpD/NmpC. J Bacteriol 191:7243–7252
21. Desai S, Sanghrajka K, Gajjar D (2019) High adhesion and increased cell death contribute to strong biofilm formation in Klebsiella pneumoniae. Pathog (Basel, Switzerland). https://doi.org/10.3390/PATHOGENS8040277
22. Ong C-LY, Ulett GC, Mabbett AN, Beatson SA, Webb RI, Monaghan W, Nimmo GR, Looke DF, Mcewan AG, Schembri MA (2008) Identification of Type 3 fimbriae in uropathogenic escherichia coli reveals a role in biofilm formation. Am Soc Microbiol 190:1054–1063
23. Cepas V, López Y, Muñoz E, Rolo D, Ardanuy C, Martí S, Xercavins M, Horcajada JP, Bosch J, Soto SM (2019) Relationship between biofilm formation and antimicrobial resistance in gram-negative bacteria. Microb Drug Resist 25:72–79
24. Samuelsen Ø, Naseer U, Tofteland S, Skutlaberg DH, Onken A, Hjetland R, Sundsfjord A, Giske CG (2009) Emergence of clonally related Klebsiella pneumoniae isolates of sequence type 258 producing plasmid-mediated KPC carbapenemase in Norway and Sweden. J Antimicrob Chemother 63:654–658
25. Breurec S, Guessennd N, Timinouni M et al (2013) Klebsiella pneumoniae resistant to third-generation cephalosporins in five African and two Vietnamese major towns: multiclonal population structure with two major international clonal groups, CG15 and CG258. Clin Microbiol Infect 19:349–355
26. Liu P, Li P, Jiang X, Bi D, Xie Y, Tai C, Deng Z, Rajakumar K, Ou HY (2012) Complete genome sequence of Klebsiella pneumoniae subsp. pneumoniae HS11286, a multidrug-resistant strain isolated from human sputum. J Bacteriol 194:1841–1842
27. Kitchel B, Rasheed JK, Patel JB, Srinivasan A, Navon-Venezia S, Carmeli Y, Brolund A, Giske CG (2009) Molecular epidemiology of KPC-producing Klebsiella pneumoniae isolates in the United States: clonal expansion of multilocus sequence type 258. Antimicrob Agents Chemother 53:3365–3370
28. Baraniak A, Izdebski R, Herda M, Fiett J, Hryniewicz W, Gniadkowski M, Kern-Zdanowicz I, Filczak K, Łopaciuk U (2009) Emergence of Klebsiella pneumoniae ST258 with KPC-2 in Poland. Antimicrob Agents Chemother 53:4565–4567
29. Nicoletti AG, Fehlberg LCC, Picão RC, Machado ADO, Gales AC (2012) Clonal complex 258, the most frequently found multilocus sequence type complex in KPC-2-producing Klebsiella pneumoniae isolated in Brazilian hospitals. Antimicrob Agents Chemother 56:4563–4564
30. Naas T, Cuzon G, Truong HV, Nordmann P (2012) Role of ISKpn7 and deletions in blaKPC gene expression. Antimicrob Agents Chemother 56:4753–4759
31. Chmelnitsky I, Shklyar M, Leavitt A, Sadovsky E, Navon-Venezia S, Ben Dalak M, Edgar R, Carmeli Y (2014) Mix and match of KPC-2 encoding plasmids in Enterobacteriaceae-comparative genomics. Diagn Microbiol Infect Dis 79:255–260
32. Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, Lee SH (2016) Global dissemination of carbapenemase-producing Klebsiella pneumoniae: epidemiology, genetic context, treatment options, and detection methods. Front Microbiol 7:184902
33. Jacoby GA (2009) AmpC beta-lactamases. Clin Microbiol Rev 22:161–182
34. Bush K (2010) Bench-to-bedside review: the role of beta-lactamases in antibiotic-resistant Gram-negative infections. Crit Care. https://doi.org/10.1186/CC8892
35. Poulikakos P, Falagas ME (2013) Aminoglycoside therapy in infectious diseases. Expert Opin Pharmacother 14:1585–1597
36. Srinivasan VB, Venkataramaiah M, Mondal A, Vaidyanathan V, Govil T, Rajamohan G (2012) Functional characterization of a novel outer membrane porin KpnO, regulated by PhoBR two-component system in Klebsiella pneumoniae NTUH-K2044. PLoS ONE. https://doi.org/10.1371/JOURNAL.PONE.0041505
37. Guillard T, de Jong A, Limelette A, Lebreil AL, Madoux J, de Champs C (2016) Characterization of quinolone resistance mechanisms in Enterobacteriaceae recovered from diseased companion animals in Europe. Vet Microbiol 194:23–29
38. Villa L, Feudi C, Fortini D, Garciá-Fernández A, Carattoli A (2014) Genomics of KPC-producing Klebsiella pneumoniae sequence type 512 clone highlights the role of RamR and ribosomal S10 protein mutations in conferring tigecycline resistance. Antimicrob Agents Chemother 58:1707–1712
39. Lupien A, Gingras H, Leprohon P, Ouellette M (2015) Induced tigecycline resistance in Streptococcus pneumoniae mutants reveals mutations in ribosomal proteins and rRNA. J Antimicrob Chemother 70:2973–2980
40. Redgrave LS, Sutton SB, Webber MA, Piddock LJV (2014) Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. Trends Microbiol 22:438–445
41. Wong MHY, Chan EWC, Chen S (2015) Evolution and dissemination of OqxAB-like efflux pumps, an emerging quinolone resistance determinant among members of Enterobacteriaceae. Antimicrob Agents Chemother 59:3290–3297
42. Ruiz E, Sáenz Y, Zarazaga M, Rocha-Gracia R, Martínez-Martínez L, Arlet G, Torres C (2012) qnr, aac(6')-Ib-cr and qepA genes in Escherichia coli and Klebsiella spp.: genetic environments and plasmid and chromosomal location. J Antimicrob Chemother 67:886–897
43. da Silva DM, Faria-Junior C, Nery DR, de Oliveira PM, de Silva L, OR, Alves EG, Lima GR de C e. C, Pereira AL, (2021) Insertion sequences disrupting mgrB in carbapenem-resistant Klebsiella pneumoniae strains in Brazil. J Glob Antimicrob Resist 24:53–57

44. Poirel L, Jayol A, Bontron S, Villegas MV, Ozdamar M, Türkoglu S, Nordmann P (2015) The mgrB gene as a key target for acquired resistance to colistin in Klebsiella pneumoniae. J Antimicrob Chemother 70:75–80
45. Cannatelli A, Santos-Lopez A, Giani T, Gonzalez-Zorn B, Rossolini GM (2015) Polymyxin resistance caused by mgrB inactivation is not associated with significant biological cost in Klebsiella pneumoniae. Antimicrob Agents Chemother 59:2898–2900
46. Li R, Xie M, Lv J, Wai-Chi Chan E, Chen S (2017) Complete genetic analysis of plasmids carrying mcr-1 and other resistance genes in an Escherichia coli isolate of animal origin. J Antimicrob Chemother 72:696–699
47. Kurabayashi K, Tanimoto K, Fueki S, Tomita H, Hirakawa H (2015) Elevated expression of GlpT and UhpT via FNR activation contributes to increased Fosfomycin susceptibility in Escherichia coli under anaerobic conditions. Antimicrob Agents Chemother 59:6352–6360
48. Falagas ME, Athanasaki F, Voulgaris GL, Triarides NA, Vardakas KZ (2019) Resistance to fosfomycin: mechanisms, frequency and clinical consequences. Int J Antimicrob Agents 53:22–28
49. Liu P, Chen S, Wu Z, ying, Qi M, Li X yang, Liu C xia, (2020) Mechanisms of fosfomycin resistance in clinical isolates of carbapenem-resistant Klebsiella pneumoniae. J Glob Antimicrob Resist 22:238–243
50. Doorduijn DJ, Rooijakkers SHM, van Schaik W, Bardoel BW (2016) Complement resistance mechanisms of Klebsiella pneumoniae. Immunobiology 221:1102–1109
51. Mondal SI, Ferdous S, Jewel NA, Akter A, Mahmud Z, Islam MM, Afrin T, Karim N (2015) Identification of potential drug targets by subtractive genome analysis of Escherichia coli O157:H7: an in silico approach. Adv Appl Bioinform Chem 8:49–63
52. Kumar V, Sun P, Vamathevan J, Li Y, Ingraham K, Palmer L, Huang J, Brown JR (2011) Comparative genomics of Klebsiella pneumoniae strains with different antibiotic resistance profiles. Antimicrob Agents Chemother 55:4267–4276
53. Moriya Y, Itoh M, Okuda S, Yoshizawa AC, Kanehisa M (2007) KAAS: an automatic genome annotation and pathway reconstruction server. Nucleic Acids Res. https://doi.org/10.1093/NAR/GKM321
54. Lu H, Tonge PJ (2008) Inhibitors of FabI, an enzyme drug target in the bacterial fatty acid biosynthesis pathway. Acc Chem Res 41:11–20
55. Edwards P, Nelsen JS, Metz JG, Dehesh K (1997) Cloning of the fabF gene in an expression vector and in vitro characterization of recombinant fabF and fabB encoded enzymes from Escherichia coli. FEBS Lett 402:62–66
56. Heath RJ, Rock CO (1996) Roles of the FabA and FabZ beta-hydroxyacyl-acyl carrier protein dehydratases in Escherichia coli fatty acid biosynthesis. J Biol Chem 271:27795–27801
57. Heath RJ, Rock CO (1996) Inhibition of beta-ketoacyl-acyl carrier protein synthase III (FabH) by acyl-acyl carrier protein in Escherichia coli. J Biol Chem 271:10996–11000
58. Metzger LE, Lee JK, Finer-Moore JS, Raetz CRH, Stroud RM (2012) LpxI structures reveal how a lipid A precursor is synthesized. Nat Struct Mol Biol 19:1132–1138
59. Zhou P, Zhao J (2017) Structure, inhibition, and regulation of essential lipid A enzymes. Biochim Biophys acta Mol cell Biol lipids 1862:1424–1438
60. Mohammadi T, Karczmarek A, Crouvoisier M, Bouhss A, Mengin-Lecreulx D, Den Blaauwen T (2007) The essential peptidoglycan glycosyltransferase MurG forms a complex with proteins involved in lateral envelope growth as well as with proteins involved in cell division in Escherichia coli. Mol Microbiol 65:1106–1121
61. Hrast M, Anderluh M, Knez D, Randall CP, Barreteau H, O'Neill AJ, Blanot D, Gobec S (2014) Design, synthesis and evaluation of second generation MurF inhibitors based on a cyanothiophene scaffold. Eur J Med Chem 73:83–96
62. Jin J, Hsieh Y, Chaudhary A, JC-F microbiology, 2018 undefined SecA inhibitors as potential antimicrobial agents: differential actions on SecA-only and SecA-SecYEG protein-conducting channels. Acad. Jin, YH Hsieh, AS Chaudhary, J Cui, JE Houghton, S Sui, B Wang, PC TaiFEMS Microbiol. Lett. 2018•academic.oup.com
63. Chaudhary AS, Chen W, Jin J, Tai PC, Wang B (2015) SecA: a potential antimicrobial target. Fut Med Chem 7:989–1007
64. Masuda N, Church GM (2002) Escherichia coli gene expression responsive to levels of the response regulator EvgA. J Bacteriol 184:6225–6234
65. Perraud AL, Kimmel B, Weiss V, Gross R (1998) Specificity of the BvgAS and EvgAS phosphorelay is mediated by the C-terminal HPt domains of the sensor proteins. Mol Microbiol 27:875–887
66. Piddock LJV (2006) Clinically relevant chromosomally encoded multidrug resistance efflux pumps in bacteria. Clin Microbiol Rev 19:382–402
67. Kostakioti M, Hadjifrangiskou M, Pinkner JS, Hultgren SJ (2009) QseC-mediated dephosphorylation of QseB is required for expression of genes associated with virulence in uropathogenic Escherichia coli. Mol Microbiol 73:1020–1031

Publisher's Note