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Treatment of infections caused by critically resistant *Klebsiella pneumoniae* strains: Current challenges and future prospectives. Minireview

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ABSTRACT

Klebsiella is a Gram-negative bacterium that belongs to the family *Enterobacteriaceae*. *Klebsiella pneumoniae* is the most pathogenic species of this genus that causes a number of nosocomial and community-acquired infections. Due to the misuse of antibiotics, *K. pneumoniae* acquires different genetic elements leading to the development of multidrug resistance (MDR) and extremely drug-resistant (XDR) strains. Among the emerging resistant strains, carbapenem-resistant *K. pneumoniae* (CRKP), extended-spectrum beta-lactamases (ESBL) producing *K. pneumoniae*, as well as MDR hypervirulent (Hv)-*K. pneumoniae* strains represent a global threat. These *K. pneumoniae* strains cause severe infections which lack effective therapy. CRKP is on the top of the priority pathogens list published by the world health organization (WHO) in 2024, for which the development of new therapeutic options is critical. This mini-review discusses the evolution of the critically resistant *K. pneumoniae* strains and highlights the available treatment options for these strains. In addition, the novel therapeutic strategies that are still in research stages or under clinical trials will be reported herein.

1. Introduction

Klebsiella is a Gram-negative bacterium that is considered clinically as the most important member of the family *Enterobacteriaceae* **[1].** *Klebsiella* is a ubiquitous organism that is present abundantly in various environments including soil and water**.** In addition, *Klebsiella* spp. can colonize skin, nose, throat and the intestinal tract of healthy individuals in addition to its ability to reside temporary on the hands of health-care workers **[2].** On the other hand, *Klebsiella* spp. can cause several infections in susceptible people, most commonly pneumonia, wound, soft tissue and bloodstream infections, in addition to urinary tract infections. *Klebsiella pneumoniae* is one of the main causes of nosocomial infections where about 10% of nosocomial infections are caused by *K. pneumoniae* [3]. K. pneumoniae infections are considered as a nightmare within the hospitals especially for neonates, elderly, and immunocompromised patients due to their higher resistance to the available therapeutic agents [4]. The spread of antimicrobial resistance (AMR) represents a global public health crisis. It is estimated that more than 700,000 patients die annually due to AMR. The elevated AMR not only increases the mortality rates, but also prolongs the hospital stays and increases the treatment costs [5]. The World Health Organization (WHO) published in 2017, a list of critical pathogens for which the development of new antibiotic treatments is of high priority [6]. Six of these pathogens designated the acronym ESKAPE standing

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for the Gram-positive pathogens *Enterococcus faecium*, *Staphylococcus aureus*, and the Gram-negative pathogens *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp*. ESKAPE pathogens have acquired resistance against most antibiotic treatments including the last resort antibiotics including carbapenem class [7]. In 2024, the WHO updated the list of antibiotic-resistant bacterial pathogens (Figure 1) to address the growing challenges of antibiotic resistance and to guide the development of strategies to control this alarming antimicrobial resistance. The carbapenem resistant *K. pneumoniae* (CRKP) jumped to be on the top of this list (WHO, 2024). Once infection with *K. pneumoniae* is suspected, antibiotics should be prescribed immediately according to the general hospital guidelines of antibiotic prescription until the antibiotic susceptibility testing is performed. The delay in initiation of an effective therapy has been associated with a 5-fold increase in mortality rate [8]. Empiric therapy for nosocomial infections needs to consider the local susceptibility data in order to prevent the selection of resistant strains [9]. It is reported that administration of antibiotics without susceptibility tests is connected to the development of high rates of AMR [10]. For hospital-acquired infections (HAIs), carbapenem is usually used alone until sensitivities are reported. In case of community-acquired infections (CAIs) with *K. pneumoniae*, therapeutic options include a 14-day therapy with either cephalosporin as monotherapy (third or fourth-generation) or a respiratory quinolone as monotherapy or either of them in combination with aminoglycoside. If the patient is penicillin-allergic, then respiratory quinolone or aztreonam should be prescribed [11,12].

2. Evolution of critically resistant *K. pneumonia* strains and their treatment options

K. pneumoniae is frequently associated with HAIs. Owing to the prevalence of *K. pneumoniae* in hospital settings, it is constantly exposed to antibiotics. Therefore, *K. pneumoniae* is continuously subjected to selective pressure which leads to the occurrence of multiple genetic mutations or transfer and the evolution of either multidrug resistance (MDR) or extremely drug-resistant (XDR) strains [13]. In addition, global climate changes have a significant effect on the evolution of resistance in environmental *Klebsiella* strains. Climatic changes subject bacteria to a new selective pressure. This pressure drives the evolution of environmental isolates of *Klebsiella* spp. which are resistant to antibiotics, these strains can disseminate into communities causing CAIs that are difficult to treat [14]. The most dominant resistant strains in nosocomial infections include CRKP, as well as ESBL-producing *K. pneumoniae* [15]. The ESBL-KP and CRKP contributed to the emergence of MDR strains, thus diminishing the available treatment options [16]. Hypervirulent (Hv) *K. pneumoniae* is an evolving global pathotype that is more virulent than classical K. pneumoniae; these strains have a strong ability of infecting healthy individuals from the community. Hv-

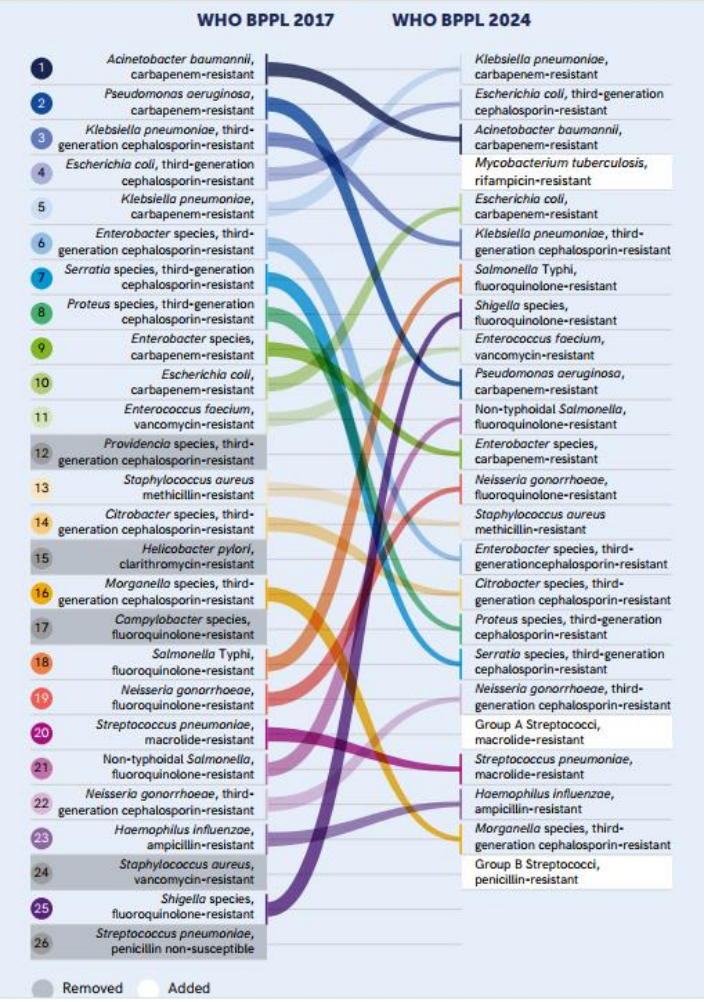

Figure 1: WHO bacterial priority Pathogens list updated in 2024 as compared with the 2017 list (adopted from WHO, 2024).

K. pneumoniae can infect nearly every site of the body, few examples of these infections include non-hepatic abscesses, pneumonia, endophthalmitis, and meningitis [17]. In the past, MDR and hypervirulence (hv) phenotypes were regarded as well segregated pathotypes. Recently, *K. pneumoniae* has established the ability to acquire genetic changes that confer both resistance and virulence, leading to the critical emergence of a novel clone, termed MDR-Hv *K. pneumoniae* [18]. It was proposed that three main patterns can lead to emergence of MDR-Hv *K. pneumoniae* i) Hv-Kp isolates acquire genetic elements carrying MDR genes, ii) MDR-Kp isolates gain hyper-virulence plasmids, or iii) *K. pneumonia* strains gain plasmids carrying both virulence and resistance genes [19]. The MDR-Hv *K. pneumoniae* superbugs represent a major public health threat causing severe infections that lack effective therapy [20].

2.1. Extended spectrum beta lactamase (ESBL)-producing *K. pneumoniae*

β–lactam is a large class of antibiotics that are widely used in the treatment of *K. pneumonia* infections. Resistance to β–lactams has increased dramatically with the production of β-lactamases enzymes [21]. ESBLs are plasmid-mediated enzymes produced by several bacteria. In 1983, ESBLs were first detected in Germany in clinical isolates of *K. pneumoniae* [22]. More than 100 different ESBLs have been identified. ESBLs belong to three main types TEM, SHV, and CTX-M. TEM and SHV types are mostly connected to HAIs caused by *Klebsiella* spp. [23]. Worldwide, there is a dramatic increase in the production of ESBLs. For example, in a South African hospital, 83% of bloodstream infections were attributed to ESBL-producing *K. pneumoniae* (ESBL-KP) strains [24]. The mortality rates ranged from 14% to 43 % in patients with bloodstream infections caused by ESBL-KP [25]. ESBL-KP isolates pose resistance to almost all β-lactam antibiotics, except for cephamycins and carbapenems. When ESBL production is confirmed, carbapenem therapy should be started. Carbapenems alone or in combination with other antibiotics have been recommended as the first-line therapy in critically ill patients infected with ESBL-producing Gram-negative bacteria [9]. ESBL-KP can develop co-resistance to other antimicrobial agents including antibiotics belonging to fluoroquinolones and aminoglycosides [26]. Tigecycline was reported to have a broad-spectrum activity against ESBL-producing strains. However, tigecycline has significantly higher rates of adverse effects and therefore its usage is reserved for cases when other treatments are not effective [27].

2.2. Carbapenem-resistant *K. pneumoniae* (CRKP)

Carbapenems are among the last-resort antibiotics that are used against *K. pneumonia*. The rapid spread of carbapenem-resistant *Enterobacteriaceae* (CRE) including carbapenem resistant-*K. pneumoniae* (CRKP) represents a global public health problem [28]. In the past decade, CRKP has emerged in several countries including Egypt reaching rates of 40%–60% and this prevalence is on the rise [15,29]. It is stated that CRKP strains have a strong ability to cause severe infections in human. The mortality rates due to CRKP infections ranged from 37 % to 65% [30, 31,32]

Carbapenem resistance in *K. pneumoniae* is mainly attributed to the production of carbapenemases, these enzymes have the ability to hydrolyze carbapenems and other β-lactams. Carbapenemases are classified into 3 classes: class A and D enzymes that depend on serine for β-lactams hydrolysis and class B metalloenzymes which require zinc ions for drug hydrolysis. The most important class A carbapenemase is *K. pneumoniae* carbapenemase (KPC). New Delhi metallo-beta-lactamase (NDM) and Verona Integron-encoded MBL(VIM) are important examples of class B enzymes, while class D represented by OXA-48-like carbapenemases [33]. KPC-type enzymes are the most prevalent carbapenemases identified globally in *K. pneumoniae* and are associated with high mortality rates. In the era between 2013 to 2018, treatment of infections caused by KPC-producing *K. pneumoniae* mostly depended on combined therapies, including polymyxin, tigecycline, fosfomycin, or aminoglycoside. Importantly, the combined therapy has the potential to decrease mortality as compared to monotherapy [34]. Starting from 2019, novel carbapenemase inhibitors have been approved for medical use; these include avibactam, relebactam, and

vaborbactam. The new carbapenemase inhibitors used in combinations with β-lactam (BL) antibiotics for treatment of severe infections caused by KPC-producing *K. pneumoniae.* The approved novel combinations for human use are ceftazidime-avibactam, meropenem-vaborbactam, and imipenem/cilastatin-relebactam. These combinations are active against class A carbapenemases (including KPC) in addition to class C [35,36]. It was reported that administration of imipenem/cilastatin-relebactam by nosocomial-acquired pneumonia patients reduced percentage of death in comparison to piperacillin–tazobactam-treated patients [37]. In addition, novel BL/β-lactamase inhibitors in clinical development such as aztreonam-avibactam, cefepime-zidebactam, and meropenem-nacubactam have proved a promising efficacy against class A and C, as well as class B carbapenemases [38]. Cefiderocol, a recently approved siderophore cephalosporin that named as 'Trojan horse' antimicrobial agent, has shown exceptional activity against critically resistant Gram-negative bacteria including CRKP [39]. Cefiderocol is potent against all β-lactamases, including metallo-β-lactamases and has been indicated for both complicated urinary tract infections and ventilator-associated pneumonia [40]. Apramycin is an aminoglycoside that has been traditionally used in veterinary medicine since 1980s. Recently, apramycin is under development for human use under the drug name EBL-1003 [41]. Apramycin showed a promising in vivo activity against MDR carbapenemase producing K. pneumoniae strains [42].

2.3. The MDR-hypervirulent (Hv) *K. pneumoniae* (MDR-Hv-KP) superbug

Hypervirulent *K. pneumoniae* (Hv-Kp) is a variant of *K. pneumoniae* that exhibits hyper-mucoviscocity and possesses multiple siderophores as virulence factors. Unlike infections caused by the classical *K. pneumoniae*, Hv-Kp strains are characterized by high infectivity in healthy people in the community and usually affect multiple sites [43]. The mortality rate in Hv-Kp associated infections was reported to be very high reaching 87.5% [44]. Previously, it was reported that antimicrobial resistance is low in Hv-Kp ([45].

However, recent studies reported an elevated incidence of MDR-Hv-Kp [17]. MDR-HvKP strains are highly pathogenic and resistant to most of the available antimicrobials. MDR-HvKP strains appeared first in 2014 in China, after this they have been reported in Asia, Europe, North, and South America [46]. These strains have been reported to pose resistance to β-lactams mediated by production of ESBLs and carbapenemases [47]. Additionally, recent studies reported the increasing emergence of polymyxin - resistant Hv-KP strains in China [48, 49]. Currently, there are no effective methods for therapy and control of this superbug [47]. For MDR-KP, the optimal treatment option has not been well established yet. Combination therapies including high-doses of meropenem, colistin, fosfomycin, tigecycline, and aminoglycosides are widely used, with sub-optimal results [50]. Other combinations that prove success are the use of polymyxin plus a high dose of a carbapenem or dual carbapenem therapy. These regimes were effective in case of patients with K. pneumoniae isolates that have low-level of carbapenem resistance [51]. Recently, some older antibiotics such as tetracyclines and chloramphenicol showed efficacy in treatment of MDR-*K. pneumoniae* isolates [52,53].

New antimicrobials targeting MDR-KP have been developed during the last decades. Efforts in infection control and stewardship programs remain the cornerstone for limiting the spread of MDR-KP [54]. The management of MDR-hv Kp infections requires both proper antibiotic therapy and adequate infection control. The antibiotic treatment options to consider include eravacycline, plazomicin, colistin, tigecycline, cefiderocol, meropenem/vaborbactam and imipenem/relebactam. These antibiotics have not been systematically evaluated for their efficacy against MDR-hv Kp strains [46]. However, a lower activity of cefiderocol was observed in these emerging MDR-hv-Kp strains because of the decreased drug uptake as a result of the accumulation of multiple siderophore in these strains [55].

3.New therapeutic strategies to combat critically resistant *K. pneumoniae* strains

As requested by the WHO, identifying new medicines or novel combinations to combat fatal *K. pneumoniae* isolates is urgently needed. For a while, the pipeline of

new drugs for the treatment of MDR Gram-negative pathogens had been described to be dry. However, the development of new therapies in the near future seems to be promising [56]. To combat this escalating threat, a number of non-traditional antibacterial agents targeting *K. pneumoniae* resistant isolates have been explored in the recent years. These include phage therapy, nano-medicine, the use of natural products such as plant phytochemicals and microbial metabolites, in additions to the development of antibodies-based therapy including the monoclonal antibodies [57,13].

3.1. The use of natural products

Plants have been extensively explored as sources for identification of effective therapies including antimicrobials. Many phytochemicals have shown antibacterial activity against K. pneumoniae including: alkaloids, flavonoids, glycosides, tannins, and phenolic acids [13]. The essential oils (EOs) are plant products with a lipophilic nature that showed several biological activities. For example, a recent study has reported that EO of Zingiber officinale has a significant antibacterial activity against Gram-negative MDR pathogens, including carbapenem- and polymyxin-resistant *K. pneumoniae*. In CRKP-mice sepsis model, this EO exhibited a reduction of bacterial load and an increase in the survival of animals without causing any toxicity to the host [58]. Moreover, EO from the seeds of *Camellia japonica*, curcumin and chitosan combination showed significant antibacterial and anti-biofilm activities against CRE isolates [59]. Many other plant-based products have demonstrated anti-biofilm activity against *K. pneumoniae* such as *Pulicaria crispa* phenolic extract and *Vaccinium corymbosum* aqueous extract. It is well known that biofilm-based infections represent a major challenge in therapy, since biofilm structure restricts antibiotic penetration [60].

Regarding other plant metabolites, the methanolic and aqueous extract of *Plumbago indica* roots proved antibacterial activity against drug-resistant *K. pneumoniae* isolates [61]. The flavonoids and polyphenol from aerial parts of *Vernonia auriculifera* had a strong activity against Gram-negative pathogens such as *K. pneumoniae* [62]. Additionally, flavone and coumarin semi-synthetic derivatives have the potential to be used as inhibitors of both serine β-lactamases and metallo β-lactamases [63]. In a recent study, coumarin showed synergy when combined with meropenem against CRKP due to its inhibitory activity against carbapenemases hydrolytic activity [64].

On the other hand, antimicrobial peptides (AMPs) which pose a broad spectrum antimicrobial activity, represent a family of small proteins (10–50 amino acids) that are produced in nature by different organisms. The first AMP was discovered in the silkworm chrysalis, large numbers of AMPs have been widely identified in various living organisms, including microorganisms, plants and animals [65]. Currently, the AMP database [http://dramp.cpu-bioinfor.org/] contains 30260 entries; most of them are from the animal kingdom. The mechanisms of action of AMPs include reducing membrane permeability in addition to inhibition of protein, DNA and RNA synthesis [66]. AMPs represent a promising source of developing new drugs for treatment of infections caused by MDR K. pneumoniae [67]. In addition, AMPs have a potent anti-biofilm activity. For example, osmin is a well-known bee venom peptide which exhibits a significant anti-biofilm activity against CRKP strains [68].

Due to their action as permeability modifiers, AMPs can act synergistically when combined with several antibiotics. For example, AMPs were reported to induce synergistic effect with colistin, rifampicin and azithromycin against resistant Gram-negative pathogens including *K. pneumoniae* [69,70]. In addition, human cathelicidin-derived peptide D-11 had synergy with 13 antibiotics using *in vitro, ex vivo* and *in vivo* models of *K. pneumoniae infections* [71].

K11 is a novel synthetic AMP derived from natural AMPs that had a strong anti-biofilm activity against MDR and XDR *K. pneumoniae* and showed synergy when combined with chloramphenicol, meropenem, rifampicin, and ceftazidime [72]. Although AMPs revealed a promising in vitro activity, their application is still having several challenges, including the lack of stability, possible cytotoxicity, and high production cost. There are many trials to improve the antimicrobial activity of AMPs through chemical modifications or the use of new formulations [67]. About 50 AMPs have been registered in clinical trials worldwide. For example, some nano-formulations containing

antibiotics and antimicrobial peptides are currently in clinical trials [73]. Regarding the bacterial secondary metabolites, bacteriocins are a heterogeneous group of antimicrobial compounds that are secreted by many bacterial species to kill competitors. In general, bacteriocins have a narrow spectrum, targeting closely related bacteria without disrupting human microbiome [74]. Klebicin E; a novel bacteriocin derived from K. pneumoniae; exhibited a strong efficacy against MDR *K. pneumoniae* strains by acting as a pore-forming toxin [75]. On the other hand, biosurfactants are compounds with both hydrophobic and hydrophilic nature that are naturally produced by certain microorganisms. It was reported that biosurfactants produced by human microbiota play a role in the maintenance of microbial homeostasis, especially in the gastrointestinal tract, respiratory tract, skin in addition to urinary tract and vagina [76].

Glycolipid biosurfactants were reported to have antibacterial activity against several Gram-negative microorganisms including *E. coli* and *K. pneumoniae* by targeting microbial cell membrance [77]. Other studies have proved the antimicrobial activity of biosurfactants against clinical isolates of family of Enterobacteriaceae including *K. pneumoniae* strains [78,79]. In addition, biosurfactants are proved to have potent anti-adhesive and anti-biofilm activities against bacterial pathogens [80]. The anti-biofilm activity of biosurfactants may be attributed to their effect on the quorum sensing (QS) system in addition to their ability to reduce surface tension and prevent bacterial attachment [81]. However, large-scale production and wide application of biosurfactants are limited by their low yields and high costs of biosurfactants production in a pure form [82].

3.2. Nanotechnology approaches

Nanotechnology has emerged as a promising strategy for fighting MDR bacteria. Antibiotics carried on nanoparticles (NPs) have the potential to facilitate successful drug delivery to the desirable site [83]. Many types of nanoparticles, such as graphene, polymers, vesicles, and green synthesized NPs, have been developed as drug delivery systems for infectious diseases caused by MDR strains [84, 85]. For example, a study has explored the effect of zinc ferrate (ZnFeO) NPs on *K. pneumoniae* strains. ZnFeO-NPs exhibited both a promising antimicrobial efficiency and anti-biofilm activity [86]. Another recent study showed that bismuth NPs have a high potential to control the expression of NDM-β-lactamase gene in MDR *K. pneumoniae* clinical isolates [87].

Nano-antibiotics represent a promising therapeutic strategy. The transformation of therapeutic agents into nanoscale can modify their physiochemical properties, increase drug bioavailability, reduce toxicity, and improve its interaction and penetration into resistant strains [88]. Meropenem-loaded silica-NPs had much lower inhibitory concentration than meropenem drug against CRE [89]. In addition, recent studies explored plant-derived ZnO-NPs and plant-base Ag-NPs and reported their strong antibacterial activity against MDR-bacteria including *K. pneumoniae* [90, 91].

Importantly, liposomes have emerged as an innovative nanotechnology-based approach for drug delivery. Additionally, liposomes can be engineered for controlled release of drugs including antibiotics [92]. Several liposomal formulations have been approved for clinical use such as AmBisome® (amphotericin B) which is uded for the treatment of fungal infections [93]. A recent *in vitro* study designed PEGylated liposomal formulation loaded with different antibiotics which showed a 9- to 18-fold reduction in the MIC of tested antibiotic against both MDR *E. coli* and *K. pneumoniae* isolates. In addition, this liposomal formulation promoted wound healing in an in vitro scratch assay model [94].

3.3. Phage therapy

One of the recent approaches that that have been explored for the treatment of infections caused by critically resistant strains is the bacteriophage therapy. Bacteriophages are viruses that can infect and kill bacterial cell, hence they are considered as natural predators of bacteria [95]. Exploring and enhancing phage technology is crucial for fighting the critically resistant *K. pneumoniae* strains [96]. Certain phages are reported to have efficacy against CR-*K. pneumoniae* infections *in vitro* and *in vivo* [97]. Other in vivo studies had shown that bacteriophages provide potential protection against pneumonia caused by MDR *K. pneumoniae* strains [98,99]. Moreover, a recent study

demonstrated the efficacy of phage therapy in the treatment of mice wounds infected with *K. pneumoniae* [100]. As it is well known that biofilm-based infections are very hard to treat, phages therapy provide a targeted approach to eradicate *K. pneumoniae* virulence factors including biofilms [101 102]. One of the drawbacks of phage therapy is the ability of bacteria to develop resistance to bacteriophages. This problem can be solved by the use of phage cocktails. A study conducted in the National Institutes of Health (NIH) suggested that using lytic phage cocktail successfully lowered the level of MDR-*K. pneumoniae* in the gut of infected mice without off-target dysbiosis [103]. In addition, a new study designed phage cocktails to combat the emergence of bacteriophage-resistant mutants in MDR *K. pneumoniae* isolates [104]. On the other hand, phage enzymes such as depolymerases could target and degrade bacterial surface polysaccharides, and effectively reduce bacterial virulence factors including biofilm formation [97]. Lysins of bacteriophages showed bactericidal activity both against Gram negative and Gram positive bacteria [105]. Phage depolymerases showed a potential activity in treatment of CRKP infections [106]. Additionally, phage depolymerase gp531 was found to bind and cleave the capsule of *K. pneumoniae* [107]. A new study suggested that mini phage depolymerases can be combined in recombinant enzymes to provide extend activity, enabling the use of these enzymes against multiple *K. pneumoniae* strains [108].

In addition, phage-antibiotic synergy represents a promising treatment strategy for *K. pneumoniae* infections. The combination of a novel hypervirulent *K. pneumoniae* phage and ceftazidime showed a synergistic effect in suppressing the emergence of resistance [109]. The limitations of phage therapy include the high production costs and the possibility of microbiome dysbiosis, in addition to that other safety implications in humans are still under investigation [110].

3.4. Monoclonal antibodies-based approaches

Although the field of antibodies-based therapies has many advances in recent years, the development of antibacterial monoclonal antibodies (mAbs) has progressed relatively slower. Since the first mAb was approved in USA by Food and Drug Administration (FDA) in 1986, around 80 therapeutic mAbs have been approved and marketed, most of them for cancer therapy and immunotherapy. The main targets for the developed antibacterial mAbs are neutralizing toxins/virulence factors. The mAbs-based approaches can be used for therapy or prophylaxis especially in case of immunocompromised or elderly patients who will not respond efficiently to vaccination [111,112]

There are several forms of mAbs, for example, a nucleic acid-encoded mAb was developed; in which DNA version of chimeric mAb 2C7 was generated against Neisseria gonorrhoeae infection [113]. Bispecific mAb is a form that combines two distinct mAbs to concurrently target two different proteins. Antibody–drug conjugate is another form in which drugs or antibiotics are covalently attached to the immunoglobulin. The combined use of mAbs and antibiotic therapy is a multi-attack approach that would provide a promising strategy for tackling bacterial resistance [114]. Only 26 anti-bacterial mAbs are in the clinical trial stages, most of them are designed against *S. aureus* and *P. aeruginosa*, none of them is targeting *K. pneumoniae* [115]. *In vivo* study reported the efficacy of anti-capsular mAb against infections caused by Hv-Kp strains [116]. In another study, the authors isolated two mAbs and claimed that these mAbs can be considered promising candidates for the treatment of CRKP infections [117]. A recent study reported the discovery of mAbs binding to type 3 fimbrial proteins in *K. pneumoniae* including MrkA. The anti-MrkA mAbs were cross-reactive to a diverse panel of *K. pneumoniae* clinical isolates and provide a modest protection *in vivo* in lung infection model [118].

Conclusions

K. pneumoniae represents a worldwide public health threat, as it is one of the most frequent pathogens associated with nosocomial infections. Antimicrobial resistance to bacterial pathogens including *K. pneumoniae* has been dramatically increasing in the past few years. MDR-*K. pneumonia*e was listed as a priority pathogen for which new antibiotics are urgently needed by WHO. Although some novel antibiotics and antibiotic combinations have been approved recently

for the treatment of critically resistant *K. pneumoniae* strains, more therapeutic options are still needed. Several researchers are exploring new therapeutic options including phage therapy, antibodies-based therapy, the use of nano-formulations, natural products such as plant phytochemicals and microbial secondary metabolites. Beside these new therapies, strict implementation of infection control measures and following treatment guidelines in health-care settings could help in prevention of the spread of critically resistant K. pneumoniae strains.

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