# Will There Ever Be Cure for Chronic, Life-Changing Colistin-Resistant *Klebsiella pneumoniae* in Urinary Tract Infection?

Aye Mya Sithu Shein[1,2,3†], Parichart Hongsing[4,5†], Shuichi Abe[6], Sirirat Luk-in[7], Naveen Kumar Devanga Ragupathi[8,9,10], Dhammika Leshan Wannigama[1,2,8,11*] and Tanittha Chatsuwan[1,2*]

[1] Department of Microbiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand, [2] Antimicrobial Resistance and Stewardship Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, [3] Interdisciplinary Program of Medical Microbiology, Graduate School, Chulalongkorn University, Bangkok, Thailand, [4] Mae Fah Luang University Hospital, Chiang Rai, Thailand, [5] School of Integrative Medicine, Mae Fah Luang University, Chiang Rai, Thailand, [6] Department of Infectious Diseases and Infection Control, Yamagata Prefectural Central Hospital, Yamagata, Japan, [7] Department of Clinical Microbiology and Applied Technology, Faculty of Medical Technology, Mahidol University, Bangkok, Thailand, [8] Biofilms and Antimicrobial Resistance Consortium of ODA Receiving Countries, The University of Sheffield, Sheffield, United Kingdom, [9] Department of Chemical and Biological Engineering, The University of Sheffield, Sheffield, United Kingdom, [10] Department of Clinical Microbiology, Christian Medical College, Vellore, India, [11] School of Medicine, Faculty of Health and Medical Sciences, The University of Western Australia, Nedlands, WA, Australia

## INTRODUCTION

Urinary tract infection (UTI) is a considerable public health issue that threatens 150 million individuals globally each year, exhibiting a significant impact on the economy and quality of life in affected individuals (1, 2). UTI is especially prevalent among females, both in terms of occurrence and recurrence (2). Bacterial colonization and subsequent invasion in various parts of the urinary tract, combined with biofilm formation, induce uncomplicated mild UTI, chronic recurrent UTI, and complicated severe UTI which can lead to septicemia and renal failure, resulting in mortality rates of 20–40% among patients with underlying immunocompromised conditions, long-term urinary catheterization, and chronic kidney diseases (2–6).

*Klebsiella pneumoniae* is one of the most common causal microorganisms that causes UTI in clinical settings (7). Their abilities to construct biofilms in medical devices, including urinary catheters, as their critical step in their disease pathogenesis can result in biofilm-mediated antibiotic tolerance in these pathogens (7, 8). Moreover, worldwide emerging trends of multidrug-resistant (MDR) and pandrug-resistant (PDR) strains in *K. pneumoniae* make it challenging for clinicians to provide prompt and efficient therapy, imposing a considerable negative burden on patient's morbidity and mortality (9, 10). The growing incidences of antimicrobial resistance and biofilm-mediated antimicrobial tolerance in *K. pneumoniae* with limited treatment alternatives,

combined with the failure to discover new antibiotics have triggered the reappraisal of colistin as a valid therapeutic option (11).

Colistin is a bactericidal cationic antibiotic that triggers increased membrane permeabilities and cell death via electrostatic interactions with lipid A of lipopolysaccharide (LPS) (11, 12). However, colistin-resistant *K. pneumoniae* has been continuously raised from <2 to 9% worldwide as a result of the current surge in colistin treatment administration (13, 14). Infections with colistin-resistant *K. pneumoniae* were also revealed to be independently associated with the excess of mortality in healthcare settings (15).

The intrinsic chromosome-mediated and acquired plasmid-mediated alteration of lipid A phosphate moieties in LPS with amino-4-deoxy-L-arabinose (L-Ara4N) and phosphoethanolamine (pEtN) weakens the electrostatic affinity of colistin to LPS, causing colistin resistance in *K. pneumoniae* (**Figure 1**) (10). The therapeutic efficacy of colistin become compromised as a consequence of increased genetic mutation and the dissemination of plasmid-mediated *mcr* genes, emphasizing the importance of exploring innovative alternative treatment strategies to address untreatable colistin-resistant *K. pneumoniae* related with UTI (**Table 1**). There for in this opinion we discuss potential effective treatment options for patients who suffer from chronic colistin-resistant *Klebsiella pneumoniae* urinary tract infection.

## NOVEL ANTIBIOTIC THERAPIES TO OVERCOME COLISTIN-RESISTANT *K. PNEUMONIAE* ASSOCIATED WITH UTI

Plazomicin, FDA approved new semisynthetic aminoglycoside for UTI, was reported to be efficacious against colistin-resistant *Enterobacteriaceae* with both plasmid-mediated *mcr1* and chromosomal mutation of *pmrAB* or *phoPQ* or *mgrB*, although 10% of tested *K. pneumoniae* isolates demonstrated resistance to this novel medication (16).

Meropenem-vaborbactam, an innovative carbapenem-β lactamase inhibitor and FDA-approved medication for severe UTIs, has been reported to be effective against drug-resistant *Enterobacteriaceae* from all over the world (18, 19). However, the efficacy of this new antibiotic was reported to be decreased among KPC-producing *K. pneumoniae* strains lacking outer membrane porins and overexpressing AcrAB efflux pump (48).

Cefiderocol is another promising novel siderophore cephalosporin against drug-resistant *K. pneumoniae* due to its enhanced outer membrane penetration ability using iron transport system and intrinsic effective antimicrobial activities (21). Nevertheless, resistance issues were recorded following 21 days of initiating cefiderocol therapy (49).

Although these newly discovered medications proved useful as rescue therapy at different stages of clinical trial, one of the most efficacious approaches for limiting the evolution of resistance to newer medications and tackling colistin-resistant
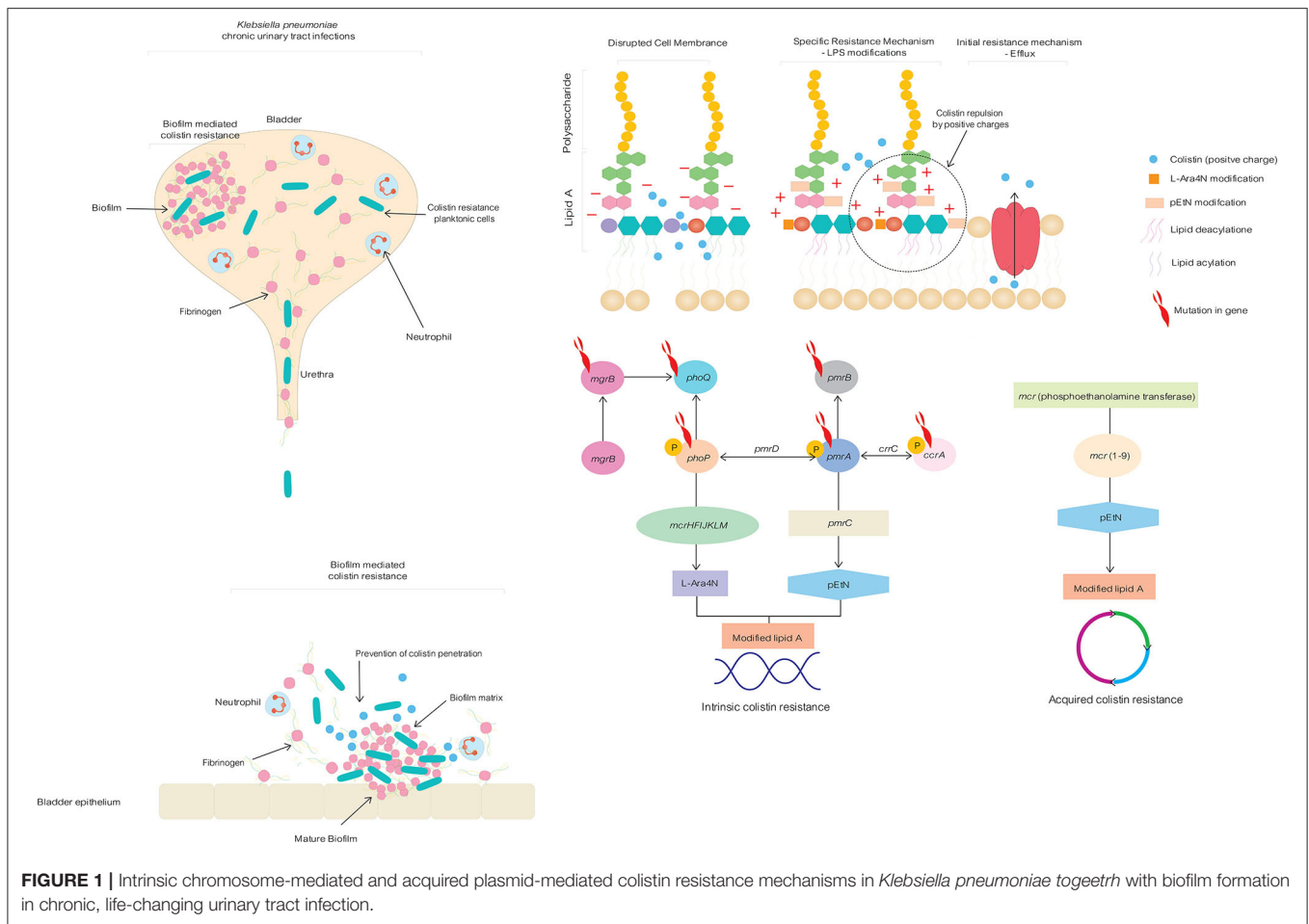
*K. pneumoniae* is utilizing the combination therapy which combines two or more antimicrobial throughout a treatment course (50).

## COMBINATION ANTIBIOTIC THERAPIES TO OVERCOME COLISTIN-RESISTANT *K. PNEUMONIAE* ASSOCIATED WITH UTI

Colistin in combination with different classes of antibiotics displayed substantial synergistic effects in suppressing the growth of colistin-resistant *K. pneumoniae* isolates *in vitro* (23). Sulfadiazine in combination with colistin had a remarkable *in vitro* synergy against colistin-resistant *K. pneumoniae*, independent of underlying colistin resistance mechanisms (24). According to previous study, colistin permeabilization on Gram-negative outer membrane allowed minocycline, linezolid, fusidic acid, and levofloxacin to generate significant *in vitro* synergistic interactions in the treatment of colistin-resistant *Enterobacteriaceae* (25). Recent study reported that combination therapy comprising double carbapenems and colistin displayed significant synergistic bactericidal effects against colistin-resistant *K. pneumoniae in vitro* (26). Ceftazidime-avibactam, recently approved for treating UTI can also be explored as a potential combination treatment with avibactam to overcome colistin-resistance in *K. pneumoniae in vitro* (27). Synergistic combinations that have been discovered to be effective *in vitro* are needed to investigate further for *in vivo* efficacies, pharmacokinetic/ pharmacodynamic characteristics, and subsequent clinical trials to evaluate their therapeutic usefulness.

According to retrospective cohort evaluation, combined gentamicin and tigecycline was significantly correlated with higher treatment success rates and survival in patients with colistin-resistant *K. pneumoniae* (28). A multicenter prospective study revealed that addressing extensively and pandrug-resistant *K. pneumoniae* with colistin-fosfomycin combination was significantly related with favorable clinical outcomes in critically ill patients (29). In septic shock patients with colistin-resistant *K. pneumoniae*, recent prospective cohort study found that targeted combination therapy with gentamicin. fosfomycin and tigecycline was significantly related with lower mortalities (30). According to a prior case study, administration of double carbapenem treatment was proven to be beneficial in eliciting an effective therapeutic response with no recurrence in patients with pandrug-resistant *K. pneumoniae* bacteremia and UTI (31).

However, previous single-center retrospective study revealed that using different combination therapies for colistin- and carbapenem-resistant *K. pneumoniae* did not contribute to a substantial improvement in patients survival (51). Moreover, combination therapy involving multiple antibiotics has been attributed to the risks of drug resistance, toxicities, bacterial superinfections, higher costs, and probable antagonism (52). Reutilizing the currently prescribed non-antibiotic drugs in combination therapy is another plausible repurposing

**FIGURE 1** | Intrinsic chromosome-mediated and acquired plasmid-mediated colistin resistance mechanisms in *Klebsiella pneumoniae togeetrh* with biofilm formation in chronic, life-changing urinary tract infection.

approach for managing colistin resistance in *K. pneumoniae* uropathogens (53).

## NON-ANTIBIOTIC DRUGS IN COMBINATION THERAPIES TO OVERCOME COLISTIN-RESISTANT *K. PNEUMONIAE* ASSOCIATED WITH UTI

FDA-approved Metal ions chelator - EDTA was demonstrated to perform as an efficacious adjuvant for colistin to reverse colistin resistance both in *in vitro* and *in vivo* catheter-related biofilm infections of colistin-resistant *K. pneumoniae* (36).

Azidothymidine is an approved antiretroviral drug, and it also exhibits antibacterial activities against *Enterobacteriaceae* by acting on bacterial DNA synthesis (32). Previous studies demonstrated significant synergistic activities of azidothymidine for retaining therapeutic efficacies of colistin in colistin-resistant *K. pneumoniae* that express *mcr-1*, both *in vitro* and *in vivo* (33, 34).

Antiprotozoal pentamidine has been demonstrated to have antibacterial activity against carbapenem and colistin-resistant *Enterobacteriaceae* isolates both individually and in combination with other antibiotics including aminoglycosides, tigecycline,

doripenem, and rifampicin (37). Their effective perturbant actions on bacterial outer membrane help the combined antibiotics to produce significant synergistic activities for increasing bacterial clearance in internal organs and enhancing survival in a systemic mouse infection model of colistin resistant *Acinetobacter baumannii* with pEtn-mediated LPS modification similar to that conferred by *mcr-1* (38).

Mitotane is currently used chemotherapeutic agent for adrenocortical carcinoma. Whereas, mitotane monotherapy had limited antimicrobial activities, polymyxin B combined with mitotane therapy displayed substantial synergistic antibacterial effects for bacterial killing and impeding regrowth of polymyxin-resistant *K. pneumoniae* pathogens both *in vitro* and *in vivo* murine burn models due to permeabilization effects of polymyxin, which allows migration of mitotane into bacterial cells for its antibacterial effects (39).

Veterinary antihelminth closantel was observed to be ineffective when it was given as monotherapy in treating *A. baumanii* (40). However, with uncoupling oxidative phosphorylation activities of closantel, polymyxin was proved to recover its antimicrobial properties against polymyxin-resistant *A. baumannii* isolates and this combination drastically prevented the establishment of resistance in polymyxin-susceptible isolates (40).

**TABLE 1** | Different therapeutic strategies to confront colistin resistance in chronic, life-changing colistin-resistant *Klebsiella pneumoniae* urinary tract infection.

| Drugs | Single therapy/combination therapy | Mechanism of action | Antibacterial spectrum | Dosage | Pharmacokinetic properties | Advantage and efficacy | Trial stage | References |
|---|---|---|---|---|---|---|---|---|
| **Novel antibiotic therapies** | | | | | | | | |
| Plazomicin (Aminoglycoside) | Single therapy | Bactericidal drug that inhibit bacterial protein synthesis | Multidrug-resistant Gram-negative ESBL-producing, carbapenem-resistant and colistin-resistant *Enterobacteriaceae* with *mcr1* and *pmrAB* or *phoPQ* or *mgrB* mutations | Intravenous 30-min infusion of single dose plazomicin (15 mg/kg) but modification of dosage to 10 mg/kg is needed in patients with lower creatinine clearance. | • Plazomicin is entirely eliminated by renal tubular excretion.<br>• Compared to patients with normal renal function, reduced Volume of distribution at steady state (Vss) and Total clearance (CLT) were observed in patients with impaired renal function. | Excellent treatment response rates with favorable safety and tolerability profiles | Phase III | (16, 17) |
| Meropenem-vaborbactam (Carbapenem-β lactamase inhibitor) | Single therapy | Bactericidal drug that targets to bind directly catalytic serine residues to inhibit β-lactamases activities | Multidrug-resistant Gram-negative ESBL-producing, carbapenem-resistant *Enterobacteriaceae* | Intravenous 3-h infusion of 4 g (2 g meropenem/2 g vaborbactam) every 8 h, but modification of dose is needed in patients with lower creatinine clearance. | • Similar linear pharmacokinetic profiles of both meropenem and vaborbactam<br>• Both drugs are entirely eliminated by renal tubular excretion.<br>• Compared to patients with normal renal function, reduced Volume of distribution at steady state (Vss) and Total clearance (CLT) were observed in patients with impaired renal function. | Excellent treatment response rates with favorable safety and tolerability profiles | Phase III | (18–20) |

*(Continued)*

**TABLE 1 |** Continued

| Drugs | Single therapy/combination therapy | Mechanism of action | Antibacterial spectrum | Dosage | Pharmacokinetic properties | Advantage and efficacy | Trial stage | References |
|---|---|---|---|---|---|---|---|---|
| Cefiderocol (Siderophore cephalosporin) | Single therapy | Bactericidal drug with enhanced outer membrane penetration ability using iron transport system and inhibit bacterial cell wall synthesis | Gram-negative ESBL-producing, carbapenem-resistant *Enterobacteriaceae* | Intravenous infusion of single or multiple doses (2 g) every 8 h, but modification of dose is needed in patients with lower creatinine clearance. | • Cefiderocol is entirely eliminated by renal tubular excretion.<br>• Compared to patients with normal renal function, reduced Volume of distribution at steady state (Vss) and Total clearance (CLT) were observed in patients with impaired renal function. | Excellent treatment response rates with favorable safety and tolerability profiles | Phase III | (21, 22) |
| **Combination antibiotic therapies** | | | | | | | | |
| Colistin | + Aminoglycosides (Amikacin, Gentamicin, and Tobramycin)<br>+ Carbapenems (Imipenem and Meropenem)<br>+ Cephalosporins (Cefoperazone, Cefotaxime, Ceftazidime and Ceftolozane and Tazobactam)<br>+ Fluoroquinolones (Ciprofloxacin, Moxifloxacin)<br>+ Fosfomycin<br>+ Tetracyclines (Minocycline)<br>+ Penicillin (Piperacillin) | Bactericidal | Colistin-resistant *K. pneumoniae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (23) |
| Colistin | + Sulfadiazine | Bactericidal | Colistin-resistant *K. pneumoniae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (24) |
| Colistin | + Minocycline<br>+ Linezolid<br>+ Fusidic acid<br>+ Levofloxacin | Bactericidal | Colistin-resistant *Enterobacteriaceae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (25) |

*(Continued)*

**TABLE 1 |** Continued

| Drugs | Single therapy/combination therapy | Mechanism of action | Antibacterial spectrum | Dosage | Pharmacokinetic properties | Advantage and efficacy | Trial stage | References |
|---|---|---|---|---|---|---|---|---|
| Colistin | + Ertapenem + Meropenem | Bactericidal | Colistin-resistant *K. pneumoniae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (26) |
| Ceftazidime-avibactam | + Avibactam | Bactericidal | Colistin-resistant and carbapenemase-producing *K. pneumoniae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (27) |
| Gentamicin | + Tigecycline | Bactericidal | Carbapenem-resistant and colistin-resistant *K. pneumoniae* | Combined gentamicin and tigecycline therapy during the first 5 days after diagnosis and maintained for at least 5 days. | Not applicable | Improve treatment success rates and clinical outcomes of patients | Retrospective cohort study | (28) |
| Colistin | + Fosfomycin | Bactericidal | Extensively and pandrug-resistant *K. pneumoniae* | Intravenous Fosfomycin with 24 g/day median dose for a median of 14 days, in combination with colistin | Not applicable | Better bacterial eradication with improved clinical outcomes in critically ill patients | Multicenter prospective study | (29) |
| Gentamicin | + Fosfomycin and Tigecycline | Bactericidal | Colistin-resistant *K. pneumoniae* | Intravenous single daily dose of Gentamicin 5 mg/kg combined with intravenous Tigecycline at loading dose of 100–200 mg followed by 50–100 mg every 12 h and Fosfomycin 4 g every 6 h for 10–14 days | Not applicable | Improve survival of patients | Prospective cohort study | (30) |
| Ertapenem | + Doripenem or Meropenem | Bactericidal | Pandrug-resistant *K. pneumoniae* | Ertapenem 1 g every 24 h + Doripenem 2 g every 8 h or Meropenem 1 g every 8 h for a total of 10–20 days | Not applicable | Effective therapeutic response with no recurrence | Case study | (31) |
| **Non-antibiotic drugs in combination therapies** | | | | | | | | |
| Azidothymidine (Antiretroviral drug) | + Colistin | Bactericidal | Gram-negative colistin-resistant *Enterobacteriaceae* including colistin-resistant *K. pneumoniae* and *Escherichia coli* with *mcr1* | Intravenous infusion of colistin 4,2 and 2 MIU together with 200, 100, and 100 mg of Azidothymidine | Low dose regimen (Azidothymidine with Colistin 2 MIU) with no observed renal toxicities. | Favorable therapeutic combination for overcoming colistin resistance in *Enterobacteriaceae* | Phase I | (32–35) |
| EDTA (Metal ions chelator) | + Colistin | Bactericidal | Colistin-resistant *K. pneumoniae* | EDTA 12 mg/ml with Colistin 1 µg/ml | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (36) |

*(Continued)*

**TABLE 1 |** Continued

| Drugs | Single therapy/combination therapy | Mechanism of action | Antibacterial spectrum | Dosage | Pharmacokinetic properties | Advantage and efficacy | Trial stage | References |
|---|---|---|---|---|---|---|---|---|
| Pentamidine (Antiprotozoal drug) | + Aminoglycosides + Tigecycline + Doripenem, + Rifampicin | Bactericidal | Colistin-resistant *Enterobacteriaceae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (37, 38) |
| Mitotane (Chemotherapeutic drug) | + Polymyxin B | Bactericidal | Polymyxin-resistant *K. pneumoniae* | Mitotane (4 mg/L) with Polymyxin B (2 mg/L) | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (39) |
| Closantel (Antihelminth drug) | + Polymyxin | Bactericidal | Polymyxin-resistant *A. baumannii* | Closantel (4–16 mg/L) with polymyxin B (2 mg/L) | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (40) |
| Niclosamide (Parasiticidal drug) | + Colistin | Bactericidal | Colistin-resistant *K. pneumoniae* with *mgrB* & *pmrB* mutation | Niclosamide (2 μM) with Colistin (sub-MIC) | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (41) |
| Tamoxifen, Raloxifen, and Toremifen (Selective estrogen receptor modulators) | + Colistin | Bactericidal | Polymyxin-resistant *K. pneumoniae* | Tamoxifen (8 mg/L) with Polymyxin B (0.5 mg/L) | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (42) |
| **Natural compounds in combination therapies** | | | | | | | | |
| Pterostilbene (Potent *mcr1* inhibitor) | + Polymyxin | Bactericidal | *mcr* variants-positive *Enterobacteriaceae* | Pterostilbene (80 mg/kg) with Polymyxin B (5 mg/kg) | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (43) |
| Resveratrol (Natural chemical of many plants) | + Colistin | Bactericidal | Colistin-resistant *K. pneumoniae* with *mgrB* & *pmrB* mutation | Resveratrol (128 mg/L) with Colistin (2 mg/L) | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (44) |
| Eugenol (Natural chemical of plants that bind Mcr1) | + Colistin | Bactericidal | Colistin-resistant *E. coli* with *mcr1* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (45) |
| **Additional therapies** | | | | | | | | |
| Bacteriophage therapy | Single therapy | Bactericidal | Colistin-resistant *K. pneumoniae* with *mcr1* and *mgrB* mutations | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (46) |
| Nanoparticle encapsulation of colistin for targeted delievery | Single therapy | Bactericidal | Drug-resistant *K. pneumoniae* | Not applicable | Not applicable | Not applicable | Pre-clinical (*in vitro*) | (47) |

Niclosamide, parasiticidal drugs for tapeworm infection, has previously been shown to increase negative surface charges of colistin-resistant *K. pneumoniae* with mutated *mgrB* and *pmrB* genes, allowing colistin to reactive against these clinical strains (41).

Additionally, colistin was reported to regain effectiveness against polymyxin-resistant *K. pneumoniae* when given in combination with membrane-active selective estrogen receptor modulators (SERM) such as tamoxifen, raloxifen, and toremifene by their combined synergistic effects in disrupting the outer membrane (42).

Antidepressants (amitriptyline, citalapram, and sertraline), antipsychotics (chlorpromazine and levopromazine), and statins (simvastatin) were discovered to possess synergistic activities with polymyxin in treatment of *K. pneumoniae*. Among these, citalopram, sertraline, and spironolactone were demonstrated to exert consistent synergistic effects in augmenting polymyxin activities (54).

## NATURAL COMPOUNDS IN COMBINATION THERAPIES TO OVERCOME COLISTIN-RESISTANT *K. PNEUMONIAE* ASSOCIATED WITH UTI

Natural compounds used for other treatment purposes have also demonstrated promising outcomes as a prospective combination therapy for overcoming colistin resistance. Potent *mcr1* inhibitory activities of natural compound - pterostilbene in combination with polymyxin as inhibitor-antibiotic combination significantly improved antimicrobial activities of polymyxin against different *mcr* variants-positive *Enterobacteriaceae*, resulting in lower bacterial-induced pathological damage in internal organs and better lifespan in treated mice (43).

Resveratrol, a natural chemical found in many plants, was discovered to augment colistin efficacy against a diverse panel of colistin-resistant *K. pneumoniae* strains with various resistance mechanisms involving the *mgrB* and *pmrB* mutations (44).

Previous research has also demonstrated combining eugenol and colistin showed a remarkable synergistic impact in lowering the colistin dose required to elicit antibacterial effects on colistin-resistant *E. coli* due to activities of eugenol in binding Mcr1 and suppressing *mcr1* expression (45, 55).

## ADDITIONAL THERAPIES TO OVERCOME COLISTIN-RESISTANT *K. PNEUMONIAE* ASSOCIATED WITH UTI

Bacteriophage therapy is an additional therapeutic modality with favorable clinical outcomes that exploits the bacteriolytic activities of phage to target a variety of drug-resistant pathogens in infected individuals (10). In biofilm-producing colistin-resistant *K. pneumoniae* with *mcr1* and *mgrB* mutations, higher sensitivities to phage were also reported both *in vitro* and *in vivo*, owing to better adherence of negative-charge phage to altered LPS of this pathogen (46).

Nanocarrier strategies are revolutionary therapies for combating drug-resistant pathogens by increasing penetration and concentration of drug at the infection site through targeted delivery approaches (56). Nanoparticle encapsulation of colistin has also shown to have stronger colistin counteracting activities against planktonic and biofilms of drug-resistant *K. pneumoniae* as compared to providing free colistin (47).

Another feasible alternative is to modify urinary catheters with antifouling coatings including hydrogels, polytetrafluoroethylene, polyzwitterions, and polyethylene glycol which limit bacterial colonization and subsequent biofilm formation in catheter-associated UTI by their repulsive properties (57). Moreover, silver nanoparticles in hydrogel composite were efficient antimicrobial coating in providing significant inhibitory effects against *K. pneumoniae* uropathogens (58). Various research on biocidal catheters, such as gentamicin-coated, nitric oxide-coated, nitrofurazone-impregnated, antimicrobial peptide-coated, and phage-impregnated catheters, have shown promising results in minimizing the growth and biofilm development of UTI-causing *K. pneumoniae* pathogens (59).

## CONCLUSION

Increasing resistance to colistin in *K. pneumoniae* uropathogens due to chromosomal mutations and plasmid-mediated *mcr* genes result in chronic severe and recurrent UTI in clinical settings. Furthermore, they could serve as a source for pathogen dissemination in the healthcare environment, emphasizing the significance of discovering alternative therapeutic strategies to effectively combat colistin-resistant *K. pneumoniae* uropathogens. Although novel antibiotics including plazomicin, meropenem/vaborbactam, and cefiderocol have been demonstrated to be successful as rescue therapy for colistin-resistant *K. pneumoniae*, reports of emerging resistance to these newer antibiotics render them concerning for use as monotherapy. Instead of utilizing antibiotic monotherapy, combining two or more antibiotics or repurposing non-antibiotic medications or natural compounds in combination therapy is another promising approach for tackling colistin resistance in *K. pneumoniae*. Bacteriophage therapy, nanocarrier strategies and modification of urinary catheters are also designated to be used as future innovative treatment modalities for successful control of colistin-resistant *K. pneumoniae* uropathogens. While several *in vitro* and *in vivo* studies have revealed the potent therapeutic effects of various alternative strategies for addressing colistin-resistant *K. pneumoniae*, further clinical trial studies are required to investigate their therapeutic efficacies and safety in human patients.

## AUTHOR CONTRIBUTIONS

AS: conception and writing the original draft of the manuscript. PH: conception, supervision, and writing the original draft of the manuscript. SA, SL-i, and NR: supervision, critical review, and editing of the manuscript. DW and TC: conception, supervision,

## REFERENCES

1. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. *J Infect Dis.* (2001) 183:S1–4. doi: 10.1086/318850

2. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, economic costs. *Am J Med.* (2002) 113:5–13. doi: 10.1016/S0002-9343(02)01054-9

3. Wagenlehner FM, Lichtenstern C, Rolfes C, Mayer K, Uhle F, Weidner W, et al. Diagnosis and management for urosepsis. *Int J Urol.* (2013) 20:963–70. doi: 10.1111/iju.12200

4. Wannigama DL, Hurst C, Pearson L, Saethang T, Singkham-In U, Luk-In S, et al. Simple fluorometric-based assay of antibiotic effectiveness for *Acinetobacter baumannii* biofilms. *Sci Rep.* (2019) 9:6300. doi: 10.1038/s41598-019-42353-0

5. Phuengmaung P, Somparn P, Panpetch W, Singkham-In U, Wannigama DL, Chatsuwan T, et al. Coexistence of *Pseudomonas aeruginosa* with *Candida albicans* enhances biofilm thickness through alginate-related extracellular matrix but is attenuated by N-acetyl-l-cysteine. *Front Cell Infect Microbiol.* (2020) 10:594336. doi: 10.3389/fcimb.2020.594336

6. Wannigama DL, Hurst C, Hongsing P, Pearson L, Saethang T, Chantaravisoot N, et al. A rapid and simple method for routine determination of antibiotic sensitivity to biofilm populations of *Pseudomonas aeruginosa*. *Ann Clin Microbiol Antimicrob.* (2020) 19:8. doi: 10.1186/s12941-020-00350-6

7. Amalaradjou MAR, Venkitanarayanan K. Role of bacterial biofilms in catheter-associated urinary tract infections (CAUTI) and strategies for their control. *Recent Adv Field Urin Tract Infect.* (2013) 10:1–32. doi: 10.5772/55200

8. Salzo A, Ripabelli G, Sammarco ML, Mariano A, Niro C, Tamburro M. Healthcare-associated infections and antibiotics consumption: a comparison of point prevalence studies and intervention strategies. *Hosp Top.* (2021) 99:140–50. doi: 10.1080/00185868.2021.1902758

9. Navon-Venezia S, Kondratyeva K, Carattoli A. Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance. *FEMS Microbiol Rev.* (2017) 41:252–75. doi: 10.1093/femsre/fux013

10. Di Tella D, Tamburro M, Guerrizio G, Fanelli I, Sammarco ML, Ripabelli G. Molecular epidemiological insights into colistin-resistant and carbapenemases-producing clinical *Klebsiella pneumoniae* isolates. *Infect Drug Resist.* (2019) 12:3783–95. doi: 10.2147/IDR.S226416

11. Biswas S, Brunel J-M, Dubus J-C, Reynaud-Gaubert M, Rolain J-M. Colistin: an update on the antibiotic of the 21st century. *Exp Rev Anti Infect Ther.* (2012) 10:917–34. doi: 10.1586/eri.12.78

12. Luk-In S, Chatsuwan T, Kueakulpattana N, Rirerm U, Wannigama DL, Plongla R, et al. Occurrence of mcr-mediated colistin resistance in Salmonella clinical isolates in Thailand. *Sci Rep.* (2021) 11:14170. doi: 10.1038/s41598-021-93529-6

13. Gales AC, Jones RN, Sader HS. Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). *J Antimicrob Chemother.* (2011) 66:2070–4. doi: 10.1093/jac/dkr239

14. Marchaim D, Chopra T, Pogue JM, Perez F, Hujer AM, Rudin S, et al. Outbreak of colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae* in metropolitan Detroit, Michigan. *Antimicrob Agents Chemother.* (2011) 55:593–9. doi: 10.1128/AAC.01020-10

15. Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, et al. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. *Clin Microbiol Infect.* (2013) 19:E23–30. doi: 10.1111/1469-0691.12070

16. Denervaud-Tendon V, Poirel L, Connolly LE, Krause KM, Nordmann P. Plazomicin activity against polymyxin-resistant Enterobacteriaceae, including MCR-1-producing isolates. *J Antimicrob Chemother.* (2017) 72:2787–91. doi: 10.1093/jac/dkx239

17. Clark JA, Burgess DS. Plazomicin: a new aminoglycoside in the fight against antimicrobial resistance. *Ther Adv Infect Dis.* (2020) 7:2049936120952604. doi: 10.1177/2049936120952604

18. Castanheira M, Huband MD, Mendes RE, Flamm RK. Meropenem-vaborbactam tested against contemporary Gram-negative isolates collected worldwide during 2014, including carbapenem-resistant, KPC-producing, multidrug-resistant, and extensively drug-resistant Enterobacteriaceae. *Antimicrob Agents Chemother.* (2017) 61:e00567–17. doi: 10.1128/AAC.00567-17

19. Andrei S, Valeanu L, Chirvasuta R, Stefan M-G. New FDA approved antibacterial drugs: 2015-2017. *Discoveries.* (2018) 6. doi: 10.15190/d.2018.1

20. Burgos RM, Biagi MJ, Rodvold KA, Danziger LH. Pharmacokinetic evaluation of meropenem and vaborbactam for the treatment of urinary tract infection. *Expert Opin Drug Metab Toxicol.* (2018). 14:1007–21.

21. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and *in vivo* profiles of a novel siderophore cephalosporin. *Clin Infect Dis.* (2019) 69:S538–43. doi: 10.1093/cid/ciz826

22. Katsube T, Echols R, Arjona Ferreira JC, Krenz HK, Berg JK, Galloway C. Cefiderocol, a siderophore cephalosporin for Gram-negative bacterial infections: pharmacokinetics and safety in subjects with renal impairment. *J Clin Pharmacol.* (2017) 57:584–91. doi: 10.1002/jcph.841

23. Ontong JC, Ozioma NF, Voravuthikunchai SP, Chusri S. Synergistic antibacterial effects of colistin in combination with aminoglycoside, carbapenems, cephalosporins, fluoroquinolones, tetracyclines, fosfomycin, and piperacillin on multidrug resistant *Klebsiella pneumoniae* isolates. *PLoS ONE.* (2021) 16:e0244673. doi: 10.1371/journal.pone.0244673

24. Okdah L, Le Page S, Olaitan AO, Dubourg G, Hadjadj L, Rolain JM. New therapy from old drugs: synergistic bactericidal activity of sulfadiazine with colistin against colistin-resistant bacteria, including plasmid-mediated colistin-resistant mcr-1 isolates. *Int J Antimicrob Agents.* (2018) 51:775–83. doi: 10.1016/j.ijantimicag.2018.01.027

25. Brennan-Krohn T, Pironti A, Kirby JE. Synergistic activity of colistin-containing combinations against colistin-resistant Enterobacteriaceae. *Antimicrob Agents Chemother.* (2018) 62:e00873–18. doi: 10.1128/AAC.00873-18

26. Erdem F, Abulaila A, Aktas Z, Oncul O. *In vitro* evaluation of double carbapenem and colistin combinations against OXA-48, NDM carbapenemase-producing colistin-resistant *Klebsiella pneumoniae* strains. *Antimicrob Resist Infect Control.* (2020) 9:70. doi: 10.1186/s13756-020-00727-4

27. Jayol A, Nordmann P, Poirel L, Dubois V. Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing *Klebsiella pneumoniae*. *J Antimicrob Chemother.* (2018) 73:542–4. doi: 10.1093/jac/dkx393

28. Gonzalez-Padilla M, Torre-Cisneros J, Rivera-Espinar F, Pontes-Moreno A, López-Cerero L, Pascual A, et al. Gentamicin therapy for sepsis due to carbapenem-resistant and colistin-resistant *Klebsiella pneumoniae*. *J Antimicrob Chemother*. (2015) 70:905–13. doi: 10.1093/jac/dku432

29. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. *Int J Antimicrob Agents*. (2014) 43:52–9. doi: 10.1016/j.ijantimicag.2013.09.010

30. Machuca I, Gutiérrez-Gutiérrez B, Gracia-Ahufinger I, Rivera Espinar F, Cano Á, Guzmán-Puche J, et al. Mortality associated with bacteremia due to colistin-resistant *Klebsiella pneumoniae* with high-level meropenem resistance: importance of combination therapy without colistin and carbapenems. *Antimicrob Agents Chemother*. (2017) 61:e00406–17. doi: 10.1128/AAC.00406-17

31. Giamarellou H, Galani L, Baziaka F, Karaiskos I. Effectiveness of a double-carbapenem regimen for infections in humans due to carbapenemase-producing pandrug-resistant. *Klebsiella pneumoniae*. *Antimicrob Agents Chemother*. (2013) 57:2388–90. doi: 10.1128/AAC.02399-12

32. Hu Y, Liu Y, Coates A. Azidothymidine produces synergistic activity in combination with colistin against antibiotic-resistant enterobacteriaceae. *Antimicrob Agents Chemother*. (2019) 63. doi: 10.1128/AAC.01630-18

33. Loose M, Naber KG, Hu Y, Coates A, Wagenlehner FME. Serum bactericidal activity of colistin and azidothymidine combinations against mcr-1-positive colistin-resistant *Escherichia coli*. *Int J Antimicrob Agents*. (2018) 52:783–9. doi: 10.1016/j.ijantimicag.2018.08.010

34. Chang YT, Yang TY, Lu PL, Lin SY, Wang LC, Wang SF, et al. Combination of colistin and azidothymidine demonstrates synergistic activity against colistin-resistant, carbapenem-resistant *Klebsiella pneumoniae*. *Microorganisms*. (2020) 8. doi: 10.3390/microorganisms8121964

35. Naber K, Walker H, Mair S, McKenzie L, Upton C, Whitaker G. Safety and Pharmacokinetics of IV Azidothymidine alone and combined with Colistin Being Developed for Treatment of Carbapenem-and Colistin-Resistant Enterbacteriaceae (Phase 1-Study). Poster# 3265 In: *European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Madrid, Spain)*, (2018), 21–4.

36. Shein AMS, Wannigama DL, Higgins PG, Hurst C, Abe S, Hongsing P, et al. Novel colistin-EDTA combination for successful eradication of colistin-resistant *Klebsiella pneumoniae* catheter-related biofilm infections. *Sci Rep*. (2021) 11:1–13. doi: 10.1038/s41598-021-01052-5

37. Cebrero-Cangueiro T, Álvarez-Marín R, Labrador-Herrera G, Smani Y, Cordero-Matía E, Pachón J, et al. *In vitro* activity of pentamidine alone and in combination with aminoglycosides, tigecycline, rifampicin, and doripenem against clinical strains of carbapenemase-producing and/or colistin-resistant enterobacteriaceae. *Front Cell Infect Microbiol*. (2018) 8:363. doi: 10.3389/fcimb.2018.00363

38. Stokes JM, Macnair CR, Ilyas B, French S, Côt,é JP, Bouwman C, et al. Pentamidine sensitizes Gram-negative pathogens to antibiotics and overcomes acquired colistin resistance. *Nat Microbiol*. (2017) 2:17028. doi: 10.1038/nmicrobiol.2017.28

39. Tran TB, Wang J, Doi Y, Velkov T, Bergen PJ, Li J. Novel polymyxin combination with antineoplastic mitotane improved the bacterial killing against polymyxin-resistant multidrug-resistant gram-negative pathogens. *Front Microbiol*. (2018) 9:721. doi: 10.3389/fmicb.2018.00721

40. Tran TB, Cheah SE, Yu HH, Bergen PJ, Nation RL, Creek DJ, et al. Anthelmintic closantel enhances bacterial killing of polymyxin B against multidrug-resistant *Acinetobacter baumannii*. *J Antibiot*. (2016) 69:415–21. doi: 10.1038/ja.2015.127

41. Ayerbe-Algaba R, Gil-Marqués ML, Jiménez-Mejías ME, Sánchez-Encinales V, Parra-Millán R, Pachón-Ibáñez ME, et al. Synergistic activity of niclosamide in combination with colistin against colistin-susceptible and colistin-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*. *Front Cell Infect Microbiol*. (2018) 8:348. doi: 10.3389/fcimb.2018.00348

42. Hussein MH, Schneider EK, Elliott AG, Han M, Reyes-Ortega F, Morris F, et al. From breast cancer to antimicrobial: combating extremely resistant gram-negative "superbugs" using novel combinations of polymyxin B with selective estrogen receptor modulators. *Microb Drug Resist*. (2017) 23:640–50. doi: 10.1089/mdr.2016.0196

43. Zhou Y, Liu S, Wang T, Li H, Tang S, Wang J, et al. Pterostilbene, a potential MCR-1 inhibitor that enhances the efficacy of polymyxin B. *Antimicrob Agents Chemother*. (2018) 62. doi: 10.1128/AAC.02146-17

44. Cannatelli A, Principato S, Colavecchio OL, Pallecchi L, Rossolini GM. Synergistic activity of colistin in combination with resveratrol against colistin-resistant gram-negative pathogens. *Front Microbiol*. (2018) 9:1808. doi: 10.3389/fmicb.2018.01808

45. Wang YM, Kong LC, Liu J, Ma HX. Synergistic effect of eugenol with colistin against clinical isolated colistin-resistant *Escherichia coli* strains. *Antimicrob Resist Infect Control*. (2018) 7:17. doi: 10.1186/s13756-018-0303-7

46. Hao M, Chen AI, Liu M, Zhou H, Egan M, Yang X, et al. Colistin-resistance-mediated bacterial surface modification sensitizes phage infection. *Antimicrob Agents Chemother*. (2019) 63. doi: 10.1128/AAC.01609-19

47. Scutera S, Argenziano M, Sparti R, Bessone F, Bianco G, Bastiancich C, et al. Enhanced antimicrobial and antibiofilm effect of new colistin-loaded human albumin nanoparticles. *Antibiotics*. (2021) 10. doi: 10.3390/antibiotics10010057

48. Lomovskaya O, Sun D, Rubio-Aparicio D, Nelson K, Tsivkovski R, Griffith DC, et al. Vaborbactam: spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in Enterobacteriaceae. *Antimicrob Agents Chemother*. (2017) 61:e01443–17. doi: 10.1128/AAC.01443-17

49. Klein S, Boutin S, Kocer K, Fiedler MO, Störzinger D, Weigand MA, et al. Rapid development of cefiderocol resistance in carbapenem-resistant enterobacter cloacae during therapy is associated with heterogeneous mutations in the catecholate siderophore receptor cirA. *Clin Infect Dis*. (2021). doi: 10.1093/cid/ciab511

50. Worthington RJ, Melander C. Combination approaches to combat multidrug-resistant bacteria. *Trends Biotechnol*. (2013) 31:177–84. doi: 10.1016/j.tibtech.2012.12.006

51. Kaur A, Gandra S, Gupta P, Mehta Y, Laxminarayan R, Sengupta S. Clinical outcome of dual colistin-and carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections: a single-center retrospective study of 75 cases in India. *Am J Infect Control*. (2017) 45:1289–91. doi: 10.1016/j.ajic.2017.06.028

52. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. *Clin Microbiol Rev*. (2012) 25:450–70. doi: 10.1128/CMR.05041-11

53. Farha MA, Brown ED. Drug repurposing for antimicrobial discovery. *Nat Microbiol*. (2019) 4:565–77. doi: 10.1038/s41564-019-0357-1

54. Otto RG, Van Gorp E, Kloezen W, Meletiadis J, Van Den Berg S, Mouton JW. An alternative strategy for combination therapy: interactions between polymyxin B and non-antibiotics. *Int J Antimicrob Agents*. (2019) 53:34–9. doi: 10.1016/j.ijantimicag.2018.09.003

55. Singkham-In U, Higgins PG, Wannigama DL, Hongsing P, Chatsuwan T. Rescued chlorhexidine activity by resveratrol against carbapenem-resistant *Acinetobacter baumannii* via down-regulation of AdeB efflux pump. *PLoS ONE*. (2020) 15:e0243082. doi: 10.1371/journal.pone.0243082

56. Yeh Y-C, Huang T-H, Yang S-C, Chen C-C, Fang J-Y. Nano-based drug delivery or targeting to eradicate bacteria for infection mitigation: a review of recent advances. *Front Chem*. (2020) 8:286. doi: 10.3389/fchem.2020.00286

57. Andersen MJ, Flores-Mireles AL. Urinary catheter coating modifications: the race against catheter-associated infections. *Coatings*. (2020) 10:23. doi: 10.3390/coatings10010023

58. Alshehri SM, Aldalbahi A, Al-Hajji AB, Chaudhary AA, In Het Panhuis M, Alhokbany N, et al. Development of carboxymethyl cellulose-based hydrogel and nanosilver composite as antimicrobial agents for UTI pathogens. *Carbohydr Polym*. (2016) 138:229–36. doi: 10.1016/j.carbpol.2015.11.004

59. Singha P, Locklin J, Handa H. A review of the recent advances in antimicrobial coatings for urinary catheters. *Acta Biomater*. (2017) 50:20–40. doi: 10.1016/j.actbio.2016.11.070