The role of Colistin against Multidrug Resistant Gram-Negative Bacteria in the Current Era

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Colistin (polymyxin E), along with polymyxin B, were discovered back in the 1940s. Both were initially withdrawn due to neurotoxicity and nephrotoxicity but were reintroduced in the 1990s to treat multidrug-resistant gram-negative bacilli (MDR-GNR), including carbapenem-resistant *Enterobacteriales* (CRE), *Pseudomonas aeruginosa* (CRPA), and *Acinetobacter baumannii* (CRAB), when no other effective options were available [1].

Colistin kills bacteria primarily by disrupting the bacterial membrane through electrostatic and hydrophobic interactions with lipopolysaccharide (LPS). It has a narrow spectrum, mainly targeting gram-negative bacteria. It is effective against Enterobacteriaceae (e.g., *Citrobacter*, *E. coli*, *Salmonella*, *Shigella*, *Klebsiella*) and non-fermenters like *Acinetobacter*, *Pseudomonas aeruginosa*, and most *Stenotrophomonas maltophilia* strains. However, most anaerobes, gram-positive bacteria, gram-negative cocci (e.g., *Neisseria*), and pathogens such as *Moraxella catarrhalis*, *Helicobacter pylori*, *Proteus mirabilis*, *Pseudomonas mallei*, *Serratia marcescens*, and *Burkholderia cepacia* are intrinsically resistant to colistin.

Although polymyxins exhibit potent bactericidal activity against many gram-negative (GNR) bacteria, their extensive use has led to the emergence of resistant strains through different pathways, mainly driven by structural modifications of LPS in the bacterial cell. The mcr gene on bacterial plasmids facilitates this primary resistance mechanism. Studies conducted in two Greek hospitals reported a significant increase in colistin resistance, from <3.5% before 2010 to >20% after 2010 [2]. Interestingly, an increase in colistin use by one Defined Daily Dose (DDD) per 100 patient-days was associated with a 0.05 increase in the incidence rate of colistin resistance [3].

Colistin demonstrates rapid bactericidal activity against susceptible strains, with concentrations above the MIC leading to rapid killing even within five minutes following exposure, exhibiting a modest post-antibiotic effect. The free-drug area under the concentration-time curve to MIC ratio (fAUC: MIC) is considered the best PK/PD index for the efficacy and antibacterial activity of colistin. Commonly recommended doses, expressed in terms of colistin base (CBA) are 2.5-5 mg/kg/day divided q6-12hr IV/IM; not to exceed 5 mg/kg/day (milligrams of CBA) with a conversion factor of 1 million IU ~33 mgCB [1,2,4,5]. Therapeutic drug monitoring (TDM) is recommended for colistin, whenever possible, since doses cannot be safely optimized using clinical observation and dosing algorithms alone. Plasma concentrations required for antibacterial effect overlap with those associated with acute kidney injury, making the therapeutic window extremely narrow [5]. The most common side effects include nephrotoxicity (6-55%) and neurotoxity (7%), with both being dose-dependent and reversible on discontinuation of treatment [1,3,5].

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According to CLSI, the MIC break points for colistin are defined as ≤2 μg/ml for susceptibility and ≥4 μg/ml for resistance in *Pseudomonas aeruginosa* and *Acinetobacter* spp; no breakpoints are set for Enterobacteriaceae. EUCAST defines susceptibility as ≤2 μg/ml and resistance as >2 μg/ml for *P. aeruginosa*, *Acinetobacter* spp., and Enterobacteriaceae [2,5].

In the presence of new β-lactam/β-lactamase inhibitors (BL/BLIs), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Infectious Diseases Society of America (IDSA) guidelines on the management of MDR -GNR pathogens give a conditional recommendation for the use of colistin against CRAB, CRE or CRPA, following available clinical evidence [6,7].

Carbapenem-resistant Enterobacterales (CRE)

In a retrospective clinical trial including 109 patients with carbapenem-resistant *Klebsiella pneumoniae* bacteraemia, 50% of whom in the intensive care unit (ICU), ceftazidime-avibactam (CAZ-AVI) treatment was associated with higher rates of clinical success while aminoglycoside and colistin-containing regimens were associated with increased rates of nephrotoxicity [8]. Similarly, monotherapy with meropenem–vaborbactam for CRE infection was associated with increased clinical cure, decreased mortality, and reduced nephrotoxicity compared with best available therapy (BAT) including polymyxin alone or in combination (47%) [9]. In the case of imipenem/relebactam, a 28-day favourable clinical response and mortality was noted in 71% versus 10% and 40% versus 30%, among 47 patients who received imipenem/relebactam versus 16 colistin+imipenem, respectively [10]. According to the ESCMID guidelines, the use of meropenem-vaborbactam or CAZ-AVI for severe infections due to CRE, and the use of cefiderocol in case of CRE carrying metallo-b-lactamases and/or resistant to all other antibiotics are suggested. For non-severe infections caused by CRE, and in alignment with antibiotic stewardship principles, the use of an older antibiotic, that shows *in vitro* activity may be considered on a case-by-case basis, taking into account the site of infection [6].

Whether polymyxins should be used as monotherapy or in combination therapy for CRE infections remains controversial. Combination therapy appears to be beneficial, as polymyxins alone have notable limitations, including unpredictable plasma concentrations at the infection site, restricted dose escalation due to a narrow therapeutic window, and the risk of resistance development with monotherapy. Mechanistically, polymyxins can enhance synergy by increasing membrane permeability, thereby boosting intracellular concentrations of co-administered antibiotics [5].

A 2010 study by Michalopoulos et al. involving 11 ICU patients with CRE infections reported an 18.2% mortality rate using fosfomycin combined with colistin, gentamicin, or piperacillin/tazobactam, highlighting the potential of fosfomycin–colistin therapy despite the small sample size [11]. For invasive CRE infections, colistin is strongly recommended in combination with at least one agent with a susceptible MIC; if none are available, combine with one or more agents showing the lowest MICs, even if non susceptible [5]. In severe CRE infections susceptible only to polymyxins, aminoglycosides, tigecycline, or fosfomycin, or when new BL/BLIs are unavailable, combination therapy with two or more active agents, including meropenem (if MIC ≤8 mg/L and no BL/BLI is used), is recommended [6].

Pseudomonas aeruginosa

In the case of *P. aeruginosa*, a multicenter retrospective study on the use of ceftolozan/tazobactam (C-T) in 35 patients infected with CRPA showed a clinical success rate of 74%, mainly as monotherapy or in combination with agents such as colistin [12].

When combined with amikacin or colistin, greater overall reductions in MDR *P. Aeruginosa* bacterial burden are noted, particularly against those strains that were intermediate or resistant to C-T [13]. This aligns with *in vivo* studies highlighting the potent synergy of colistin with other drugs against *P. aeruginosa* [14].

In a multicentre, observational, prospective study in 11 ICUs including patients with bacteraemia and VAP by carbapenemase-associated *K. pneumoniae* and CRPA, treatment with fosfomycin plus mainly colistin or tigecycline reached a 54.2% clinical success by day 14 [14]. Nonetheless, a randomized controlled trial of 406 adults with severe carbapenemase resistant GNR infections (MIC >2 mg/L) susceptible to colistin (MIC ≤2 mg/L for *A. baumannii* and Enterobacteriaceae, ≤4 mg/L for *P. aeruginosa*) found no significant difference between colistin monotherapy and colistin–carbapenem combination therapy [15]. Given the limited and mostly observational data, the International Consensus Guidelines recommend combination therapy for invasive CRPA infections, using polymyxins with at least one agent showing a susceptible MIC. If no such agent is available, colistin should be combined with

one or more non susceptible agents, preferably those with the lowest MICs relative to breakpoints (e.g., a carbapenem) [5,7].

Acinetobacter baumannii

For CRAB infections, a recent meta-analysis of RCTs and observational studies in critically ill adults showed cefiderocol treatment was linked to lower 30-day mortality compared to other therapies, including colistin [16]. According to the 2024 IDSA guidelines, the preferred regimen against CRAB infections is sulbactam-durlobactam in combination with acarbapenem (ie, imipenem-cilastatin or meropenem). However, polymyxins (or minocycline, tigecycline, or cefiderocol) remain a reasonable choice, as an alternative regimen with high-dose ampicillin-sulbactam (total daily dose of 9 grams of the sulbactam component) when sulbactam-durlobactam is not available [17].

When considering combination regimens, recommendations for invasive infections caused by CRAB support the use of polymyxins with one or more additional agents to which the pathogen displays a susceptible MIC. Contrary to *P. aeruginosa* and CRE infections, polymyxin monotherapy is preferred to combination therapy for *A. baumannii,* when no susceptibility is displayed to a second agent [5]. Interestingly, colistin-glycopeptide combination (CGC) has been previously shown to be a protective factor against mortality when administered for more than five days and not associated with increased nephrotoxicity. This is likely due to its action on the outer membrane, enabling glycopeptides access to cell wall targets from which they are usually excluded, while it also led to colistin being active against other MDR GNB that were heteroresistant [18].

Intrathecal / intraventricular or inhaled administration has also been utilized in clinical practice in cases of MDR pathogens, where permeability and levels are poor. Local administration can lead to much higher concentrations in cerebrospinal and pulmonary fluid, respectively, compared to systemic administration, resulting in lower plasma exposure and reduced toxicity.

Inhaled Colistin

The use of nebulized colistin to reduce side effects and enhance treatment of MDR GNR respiratory infections, especially VAP, remains controversial. A meta-analysis of 373 patients showed inhaled colistin was well tolerated and achieved 71.3% microbiologic success, with a 33.8% mortality rate. However, most studies were retrospective with varied endpoints, confounding factors, and often lacked control groups. Its role as adjunctive or substitute therapy remains unclear, particularly as an adjunct to standard treatment [19]. Two recent meta-analyses found that adding inhaled colistin to intravenous therapy for nosocomial pneumonia or VAP significantly improved clinical outcomes, microbiological eradication, and reduced infection-related mortality, though overall mortality remained similar between groups [20]. The International Consensus Guidelines for the optimal use of the polymyxins, support that IV polymyxin therapy for suspected or documented XDR gram-negative HAP or VAP should be combined with adjunctive polymyxin aerosol therapy [5], even though, recent ESMID and IDSA guidelines do not support its use [6,17].

Intrathecal (ITH) and intraventricular (IVT) polymyxin

Colistin penetrates cerebrospinal fluid (CSF) poorly, reaching only about 5% of serum levels, but achieves 34–67% during meningitis. ITH and IVT colistin infusions are effective alternatives.

A systematic review of 234 cases of healthcare-associated ventriculitis or meningitis caused by GNR-pathogens and treated with once-daily ITH or IVT colistin showed an 85% success rate. Toxicity, including chemical ventriculitis or meningitis, occurred in 7% of cases. Guidelines recommend IVT or ITH polymyxins at 125,000 IU CMS (~4.1 mg CBA) daily, combined with IV polymyxin, for MDR and XDR gram-negative infections [5].

CONCLUSION

Overall, colistin is a narrow-spectrum antibiotic effective against several MDR and XDR GNR bacteria. It demonstrates synergy with rifampicin, carbapenems, and less commonly, vancomycin.

Despite the emergence of resistance to new BL/BLIs, colistin remains a valuable option against CRE and CRPA infections and should be considered for CRAB when sulbactam/durlobactam is unavailable. Evidence on alternative administration routes, such as inhalation or intrathecal/intraventricular, is limited. However, inhalation appears promising for step-down therapy or prophylaxis. Colistin must be used carefully, at the correct dosage, duration, and in combination with other agents, to minimize toxicity, curb resistance, and optimize clinical outcomes against MDR gram-negative infections.

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