

# The Multidrug-Resistant Gram-negative Superbug Threat Requires Intelligent Use of the Last Weapon

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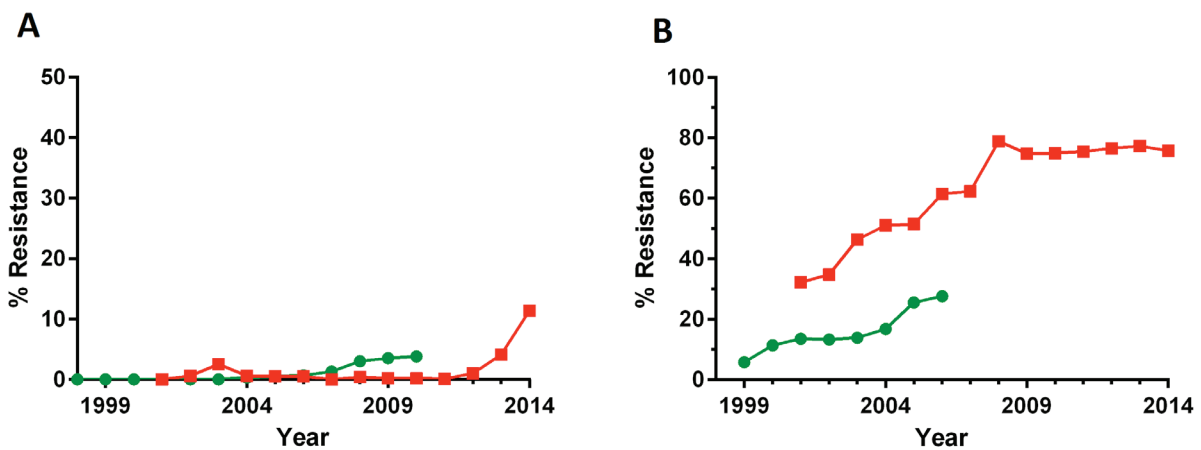
## Abstract

The global emergence and dissemination of multidrug-resistant Gram-negative superbugs, particularly carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae*, lead to the limited effectiveness of antibiotics for treating nosocomial infections. In most cases, polymyxins are the last resort therapy, and these antibiotics must be used intelligently to prolong their efficacy in clinical practice. Polymyxin B and colistin (polymyxin E) were introduced prior to modern drug regulation, and the majority of the 'old' drug information is unreliable. Recent pharmacokinetic data do not support the renal dose adjustment of intravenous (IV) polymyxin B as suggested by the manufacturer, and this drug must be scaled by the total body weight. Whereas IV colistin is formulated as an inactive prodrug, colistin methanesulfonate (CMS) has different pharmacokinetic profiles than polymyxin B. To achieve maximum efficacy, CMS should be administered as a loading dose scaled to body weight and a maintenance dose according to the renal profiles. Polymyxin combination therapy is suggested due to a sub-therapeutic plasma concentration in a significant proportion of patients and a high incidence of polymyxin hetero-resistance among Gram-negative superbugs. In conclusion, polymyxins must be reserved as a last resort and should be wisely used when truly indicated

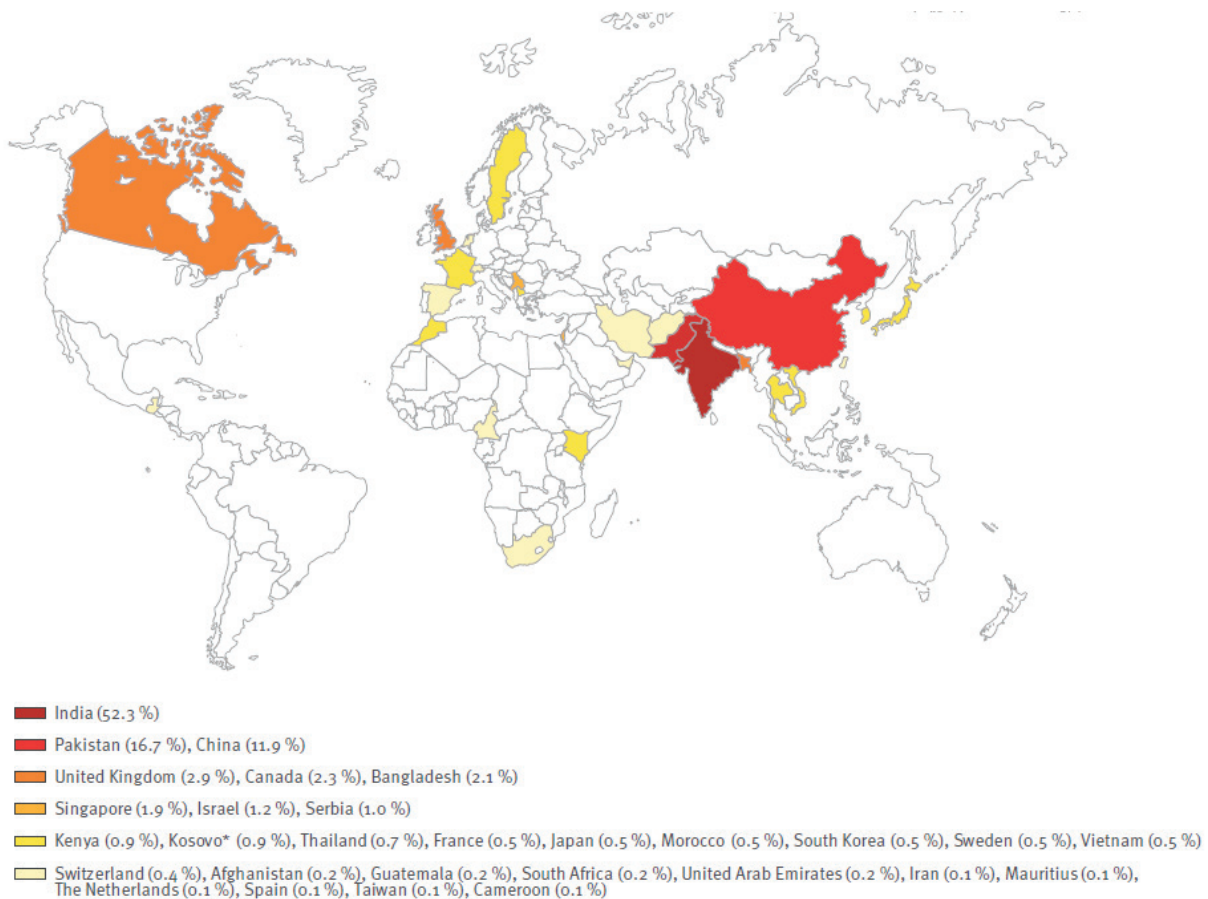
**Keywords:** Gram-negative, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, polymyxin B, colistin

Before the 1960s, Gram-negative bacteria uncommonly caused bacteraemia and received less attention compared to Gram-positive bacteria (1). The incidence of Gram-negative bacteraemia increased significantly after the 1960s, and by end of the 1980s, the Centers for Disease Control estimated that the annual incidence in the United States was approximately 176 per 100 000 people (or 425 000 cases) (2). By the 2000s, Gram-negative bacteria were a major threat in critically ill patients, and rapid antimicrobial resistance occurred, particularly for microorganisms that cause nosocomial infections, such *Acinetobacter baumannii* and *Klebsiella pneumoniae* (3,4). Figure 1 shows an increase in carbapenem-resistant *A. baumannii* and *K. pneumoniae* in both the United States of America (US) and our locale, Hospital Universiti Sains Malaysia (HUSM), over the past decade. *Acinetobacter* sp. were among

the most common organisms isolated from blood cultures at HUSM, with a prevalence of 6.11% and an attack rate of 2.77 episodes per 1000 hospital admissions (5). The proportion of carbapenem-resistant *A. baumannii* approached 80% (Figure 1), indicating a small range of antibiotic choices to treat nosocomial infections at the local hospital. The global spread of these resistant superbugs is unprecedented and likely inevitable (6). For example, a worldwide bacterial threat is carbapenem-resistant New Delhi  $\beta$ -lactamase (NDM)-1-producing *K. pneumoniae*, and the first documented case of infection with this bacterium occurred in 2008 and spread to over 40 countries within five years (7,8) (Figure 2). From Enterobacteriaceae, the genetically encoded NDM-1 (*bla*<sub>NDM-1</sub>) was found in a wide variety of non-fermenting Gram-negative species (7). The therapeutic options for these NDM-1 producers



**Figure 1:** The increasing trend of imipenem-resistance among *Klebsiella pneumoniae* (A) and *Acinetobacter baumannii* (B) isolates from clinical specimens in the US (●) and Hospital USM (■). The US data were plotted based on data of *K. pneumoniae* (3) and *A. baumannii* (4), whereas the Hospital USM were data from Infection Control and Hospital Epidemiology Unit.

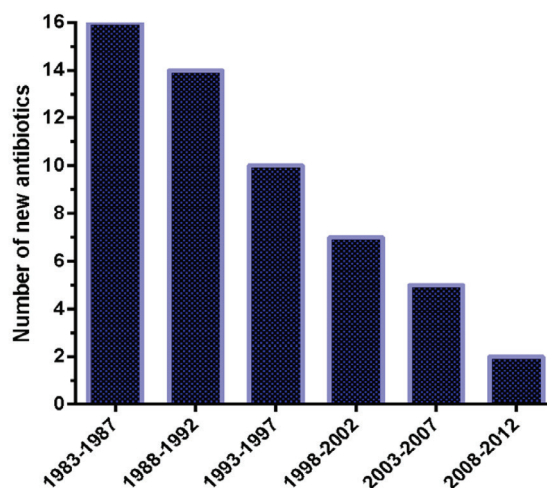


**Figure 2:** Global spread of bla<sub>NDM-1</sub> from 1 December 2009–31 December 2012. The figure is reproduced from (7).

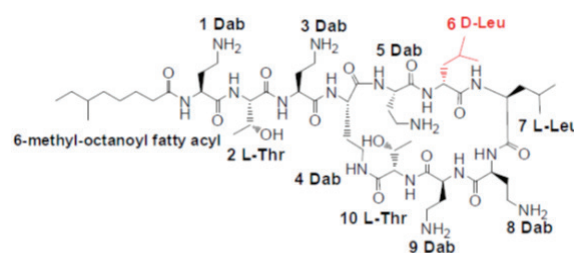
are limited because the organisms are resistant to virtually all available antibiotics except polymyxins and occasionally tigecycline (9).

Reduced antibiotic efficacy because of increased bacterial resistance can lead to problems in the clinical setting. We reported that inappropriate antibiotic therapy was associated with mortality attributed to infection (10). The incidence of multidrug-resistant (MDR) pathogens continue to rise despite many different efforts to combat antibiotic resistance (11), leading to increased inappropriate antibiotic treatment. By contrast, new antibiotics in development pipelines for Gram-negative superbugs have decreased (12). Only two new chemical classes of antibiotics were approved for clinical use during the last few decades, the oxazolidinone group (linezolid) and the lipopeptide groups (daptomycin) (13). Both target Gram-positive bacteria. Several analogues of cephalosporin, fluoroquinolone, and carbapenem antibiotics have been launched against Gram-negative pathogens since 2000 (13), but they are not typically designed for MDR and NDM-producing superbugs. Figure 3 shows a reduction in newly approved antibiotics in the US for the past three decades. As a result, clinicians treat resistant bugs with whatever resources available. In many cases, old polymyxins are the only available option because they generally retain excellent activity against many MDR Gram-negative pathogens (14). This last line of defence must be used intelligently in truly indicated cases to reduce the emergence of resistance and consequently prolong their potency in the clinic.

Understanding the pharmacology of polymyxins will help us reduce adverse effects and optimize the dosing regimens to maximise efficacy and minimise the development of resistance. Polymyxins were discovered in the 1950s, before modern regulatory requirements, but their use waned in the 1970s mainly due to nephrotoxicity concerns following parenteral administration (15). A resurgence in the use of polymyxins in the clinics occurred in the 2000s for the treatment of MDR Gram-negative superbugs. Two polymyxins are available for clinical use, polymyxin B and polymyxin E (colistin) (Figure 4). Polymyxin B and colistin have similar pharmacodynamics (PD) activity *in vitro*, but they differ in the parenteral formulation for administration to patients (16). The parenteral polymyxin B preparation is in the active form, polymyxin B sulfate, but colistin is formulated as an inactive prodrug form, colistin methanesulfonate (CMS) (16). It is estimated that only ~20% of CMS is converted into active colistin (16).



**Figure 3:** New antibiotics approved in the United States, 1983–2012. The two last antibiotics from new classes were linezolid and daptomycin; both of them targeted against Gram-positive bacteria. The figure is reproduced from Infectious Diseases Society of America report (21).



**Figure 4:** Chemical structure of polymyxin B and colistin. In polymyxin B, D-Phe (phenylalanine) replaces the D-Leu (leucine) marked (red words). Colistin methanesulfonate (CMS) is produced by the reaction of colistin with formaldehyde and sodium bisulphite, which leads to the addition of a sulphomethyl group ( $\text{SO}_3\text{CH}_2$ ) to the primary amines ( $\text{NH}_2$ ) of colistin. Dab,  $\alpha,\gamma$ -diaminobutyric acid, Thr, threonine. Modified from (22).

The pharmacokinetic (PK) profiles of IV polymyxin B indicated remarkably low inter-individual variability of polymyxin B concentrations after scaling to body weight without significant effects on renal functions (17). Therefore, IV polymyxin B doses are best scaled by the total body weight. The renal dose adjustment advised by the manufacturer is not recommended (16). In fact, we found that inappropriate doses after adjustments based on the creatinine clearance led to treatment failures in critically ill patients (manuscript in preparation). The current recommended doses of polymyxin B (up to 2.5 mg/kg/day, 25000 units/kg/day) are appropriate for a pathogen with minimal inhibitory concentrations (MIC)  $\leq 1$  mg/L or less severe infections with superbugs with MICs of  $\leq 2$  mg/L (17).

The dose of IV CMS is controversial, and there is a significant difference in the suggested doses for the US and European products. The recommended upper limit dosage for adults heavier than 60 kg is 480 mg/day of CMS (6 million units/day,  $\sim 180$  mg/day colistin based activity (CBA)) for the European product and approximately 800 mg/day of CMS (10 million units/day, 300 mg/day CBA) for the U.S. product (18). This difference creates problems in Malaysia, particularly because CMS is not a standard pharmacy item and hospitals must import from either Europe or the US. The dose recommended for European product is very low and causes treatment failure, whereas when the US recommendation is wrongly calculated as 800 mg/day CBA, fatal drug overdose can occur. With either dose, the formed colistin after IV CMS dosing is greatly influenced by creatinine clearance and renal replacement therapy. It is recommended that a new loading dose for IV CMS is used according to the body weight followed by a maintenance dose based on the patient's renal conditions (19). The serum concentrations of formed colistin with the current recommendation are not reliable as monotherapy against isolates with MICs  $> 0.5$  mg/L (19).

The PD data of polymyxins revealed important information. Polymyxin hetero-resistance among virtually susceptible strains were identified in greater than 90% of certain Gram-negative species (20), and regrowth of these resistant subpopulations with monotherapy are documented in in vitro studies even when concentrations exceed those achieved clinically (15). In these situations, polymyxin combination therapies significantly eliminated the development of resistance and increased antimicrobial activity (15). In addition, polymyxin monotherapy is

attenuated at a high inoculum that can be, to a certain extent, overcome by combination regimens (20). Synergy was observed in many in vitro time-kill studies of polymyxin-carbapenem combinations against MDR *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* (15). However, our clinical data suggest that a combination of polymyxin B and cefoperazone-sulbactam against MDR *A. baumannii* bacteraemia and/or pneumonia has similar effects that lead to clinical success of the therapy (manuscript in preparation).

In summary, the spread of Gram-negative superbugs that are resistant to nearly all antibiotics available on the market need special attention from all stakeholders. This condition is worsened by the limited availability of active agents and antibiotic candidates against Gram-negative bacteria. In the inevitable circumstances in which polymyxins are the only active antibiotics against pathogens, these antibiotics must be used appropriately based on the PK/PD data to prolong their effectiveness in the clinic.

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