Agents of Last Resort
Polymyxin Resistance

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KEYWORDS

• Colistin • Polymyxin *B* • Polymyxins • Resistance • Gram-negative

KEY POINTS

- Polymyxin resistance is a major public health threat, as the polymyxins represent "last-line" therapeutics for Gram-negative pathogens resistant to essentially all other antibiotics.
- Improved understanding of mechanisms of, and risk factors for, polymyxin resistance, as well as infection prevention and stewardship strategies, together with optimization of dosing of polymyxins including in combination regimens, can help to limit the emergence and dissemination of polymyxin resistance.

INTRODUCTION

The polymyxins, colistin (also known as polymyxin E) and polymyxin B, have a unique and interesting history. Originally introduced in the 1950s for the treatment of infections due to Gram-negative organisms, the polymyxins fell out of favor by the mid-1970s because of high rates of nephrotoxicity (approaching 50%) and neurotoxicity and the advent of less toxic alternatives, notably the antipseudomonal aminoglycosides. By the mid-1990s the polymyxins were reintroduced into clinical practice, not because of an enhanced safety profile, but rather due to the development of extensively drug-resistant (XDR) Gram-negative bacilli resistant to all other treatment options.[1,2] The polymyxins now serve a critical role in the antimicrobial armamentarium, as they are one of few, and sometimes the only, antimicrobial agent retaining activity against carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae (CRE), organisms that frequently cause life-threatening infections in the most vulnerable of patient populations. These pathogens have been recognized by the Centers for Disease Control and Prevention as serious or

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urgent threats to human health and mortality rates in invasive infections due to these pathogens can exceed 50%.[2,3] The relatively dry antimicrobial pipeline for the treatment of infections caused by these organisms magnifies the importance of the polymyxins. Given the critical role of the polymyxins in the care of hospitalized patients, an understanding of both the epidemiology of polymyxin resistance as well as strategies to prevent resistance are paramount. Therefore, this article introduces similarities and differences between the two clinically available polymyxins, discusses the mechanism of action and resistance to these agents, describes the clinical epidemiology of polymyxin-resistant organisms, and finally suggests strategies to minimize the development and spread of polymyxin resistance.

Colistin (also known as polymyxin E) and polymyxin B are nearly structurally identical, differing by only one amino acid at position 6 (Fig. 1). They are considered to be very similar microbiologically and cross-resistance exists. Both polymyxins are products of fermentation and therefore are multicomponent mixtures. Colistin and polymyxin B have two major components (colistin A and B; polymyxin B1 and B2) that slightly differ at the site of the *N*-terminal fatty acyl tail.[4] The polymyxins are

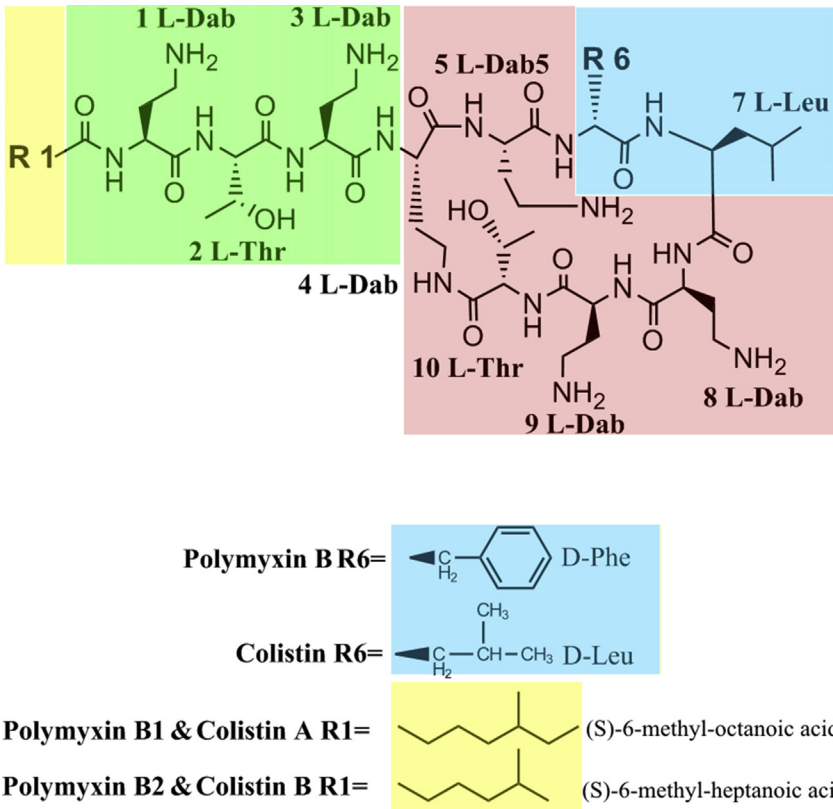

Fig. 1. Chemical structures of polymyxin B and colistin. The functional segments of polymyxins are colored as follows: yellow, fatty acyl chain; green, linear tripeptide segment; red, the polar residues of the heptapeptide; blue, the hydrophobic motif within the heptapeptide ring. (*Reprinted* with permission from Velkov T, Thompson PE, Nation RL, et al. Structure–activity relationships of polymyxin antibiotics. J Med Chem 2010;53(5):1898. Copyright © 2010 American Chemical Society.)