LETTERS TO THE EDITOR

Is the Polymyxin B Resistance Among Multidrug-Resistant Enterobacteriaceae (Except for the Carbapenemase-producing Ones) a Myth or a Matter?

To the Editor—In recent years, polymyxins have been reintroduced into the arsenal of antimicrobial therapy because they are one of the few agents clinically available to treat infections caused by carbapenem-resistant gram-negative bacteria.[1] Although their clinical usefulness has been put into practice in most treatment approaches, including many empirical therapies, ever-greater resistance has been observed in regions where polymyxins have become more heavily prescribed.[2]

Polymyxins have been widely applied to treat infections related to non-fermentative gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter* spp., and the rapid emergence of resistance to this class of drug among carbapenem-resistant Enterobacteriaceae (CRE), mostly those *Klebsiella pneumoniae* carbapenemase (KPC) producers, is notable.[3,4]

While attention is focused on the widespread resistance to polymyxins among KPC producers, with important repercussions for their usefulness, little is known about the polymyxin resistance rates among multidrug resistant (MDR) Enterobacteriaceae with *in vitro* carbapenem susceptibility. Would selective pressure via the use of polymyxins also act on this type of threat as much as it has on the KPC-producing ones?

To answer this question, a retrospective survey was conducted to assess the prevalence of polymyxin B (PMB) resistance among MDR Enterobacteriaceae. MDR was defined as nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories, including isolates not susceptible to at least 1 carbapenem agent (eg, ertapenem, meropenem, or imipenem), except KPC-producers and those intrinsically resistant to polymyxins. These isolates were recovered from inpatients between January 1 and September 10, 2016, at a tertiary hospital in Porto Alegre, Southern Brazil.

Identification of bacterial species as well as antimicrobial susceptibility testing were initially performed using an automated broth microdilution system (MicroScan; Beckman Coulter, Brea, CA, USA). Polymyxin B minimum inhibitory concentration (MIC) was confirmed using Etest (AB Biodisk, Solna, Sweden). To attribute the resistance mechanism for the enterobacterial species, a synergistic test was applied using phenyl-boronic acid to detect KPC (isolates not included in the study). Enzymatic inhibition testing with clavulanic acid and cloxacillin was used to detect extended spectrum β-lactamases (ESBLs) and *Amp*C enzymes, in that order, as previously described.[5]

During the study period, 67 enterobacterial isolates presenting a multidrug-resistance phenotype were recovered from 45 patients. These isolates were found in blood (26.9%; 18 of 67), in respiratory secretions (14.9%; 10 of 67), in urine (55.2%; 37 of 67), and at other sites (3%; 2 of 67). According to the phenotypic testing, 47 isolates were ESBL producers, including 42 *Klebsiella pneumoniae*, 4 *Escherichia coli*, and 1 *Enterobacter aerogenes*. The remaining 20 isolates (15 *Enterobacter cloacae*, 4 *E. aerogenes*, and 1 *E. coli*) were categorized as CRE because they were able to hydrolyze at least 1 carbapenem agent (ie, a single *E. aerogenes* was resistant to meropenem and ertapenem while others were only resistant to ertapenem). Notably, decreased susceptibility to any carbapenem agent among many (if not all) CRE isolates is related to the production of an ESBL and/or *Amp*C enzymes associated with membrane impermeability. In this study, the "majority mechanism" regarding the spectrum of antimicrobial hydrolysis detected by the phenotypic tests was considered.

Of the 67 isolates, 11 (16.4%) were recovered from 9 distinct patients and were resistant to PMB: 8 ESBL-producing *K. pneumoniae*, 1 ESBL-producing *E. coli*, 1 ESBL-producing

TABLE 1. Microbiological Features of the PMB-R MDR Noncarbapenemase-Producing Enterobacteriaceae Evaluated in This Study

Organism (No. of Isolates)	Clinical Specimens	Resistance to Carbapenems[a]	Attributable Resistance Mechanism[b]	Polymyxin B Etest MIC (mg/L)[c]
Klebsiella pneumoniae (6)	Urine	None	ESBL	Range, 3.0–32.0
K. pneumoniae (2)	Tracheal secretion	None	ESBL	8.0 and 16.0
Escherichia coli (1)	Blood	None	ESBL	8.0
Enterobacter aerogenes (1)	Blood	None	ESBL/*Amp*C	4.0
E. aerogenes (1)	Tracheal secretion	Meropenem/Ertapenem	ESBL/*Amp*C/impermeability	12.0

NOTE. PMB-R MDR, polymyxin B-resistant multidrug resistant; MIC, minimum inhibitory concentration; ESBL, extended spectrum β-lactamase.

[a]According to results obtained using a MicroScan automated system.

[b]Attributable resistance mechanism for a MDR phenotype inferred by phenotypic tests.

[c]Considering ≤2 mg/L and >2 mg/L as susceptible and resistant, respectively.

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E. aerogenes, and 1 carbapenem-resistant *E. aerogenes*. The microbiological data regarding the PMB-resistant enterobacterial species found in this study are shown in Table 1.

Resistance to carbapenems (formerly cephalosporins) among Enterobacteriaceae does matter, which could be interpreted as strong justification to be more liberal with polymyxins (formerly carbapenems) in empirical therapies.[6] However, the degree to which this can be reflected among MDR organisms other than carbapenem-resistant ones, equally recovered from a setting with a high-level selection pressure, has not been evaluated properly.

Although the resistance rate was lower among MDR Enterobacteriaceae than among KPC producers (16.4% vs 34.8%, respectively) during the same period of evaluation, the outcome reported here is an important matter (and not a myth) because it illustrates a possible influence of PMB use on other bacteria whose infectious processes need not be treated with it.

Additionally, some important observations in this study follow: First, *K. pneumoniae* seems to be a specie with fitness for resistance acquisition. Second, although not as notable as the bloodstream, for example, the urinary site appears to be a reservoir for MDR organisms. Third, PMB resistance does occur without carbapenem resistance: among the 11 PMB-resistant isolates found in this study, only one *E. aerogenes* was a CRE (Table 1).

In conclusion, in this study, an important PMB resistance rate was detected among MDR Enterobacteriaceae isolates with the exception of the carbapenemase-producing ones. This finding emphasizes the need for a constant monitoring program to prevent the emergence of PMB resistance, not only among carbapenemase producers but especially among organisms that have a fitness to develop it.

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Fear of Failure: Engaging Patients in Antimicrobial Stewardship after Fecal Transplantation for Recurrent *Clostridium difficile* Infection

To the Editor—Patients and family members are often perceived as part of the problem driving inappropriate use of antibiotics. Patients may request antibiotics due to factors such as the fear of adverse consequences if an infection is not treated or the belief that antibiotics will help them get better faster.[1] In our practices, patients commonly request antibiotics for vague complaints such as fatigue that they believe must be due to a urinary tract infection (UTI) despite the absence of urinary symptoms. Prior experiences in the healthcare system usually underlie such requests: inappropriate prescription of antibiotics for self-limited conditions such as viral upper respiratory infections (URTI) or asymptomatic bacteriuria leads to the belief that antibiotics may be beneficial despite controlled trials demonstrating no benefit.[2,3]

The request for an antibiotic is further strengthened by a belief that antibiotics are relatively harmless; thus, the possible benefit outweighs any risk.[3,4] In contrast to most patients, fecal microbiota transplantation (FMT) recipients for recurrent *Clostridium difficile* infection (CDI) have personal knowledge of the adverse consequences of antibiotics and are highly motivated to avoid antibiotics to prevent failure of the transplant. In our FMT practices, FMT recipients are encouraged to contact their FMT providers and/or have their physicians contact the FMT providers for consultation regarding antibiotic prescriptions after the transplant. Here, we report our experience with this antimicrobial stewardship intervention.