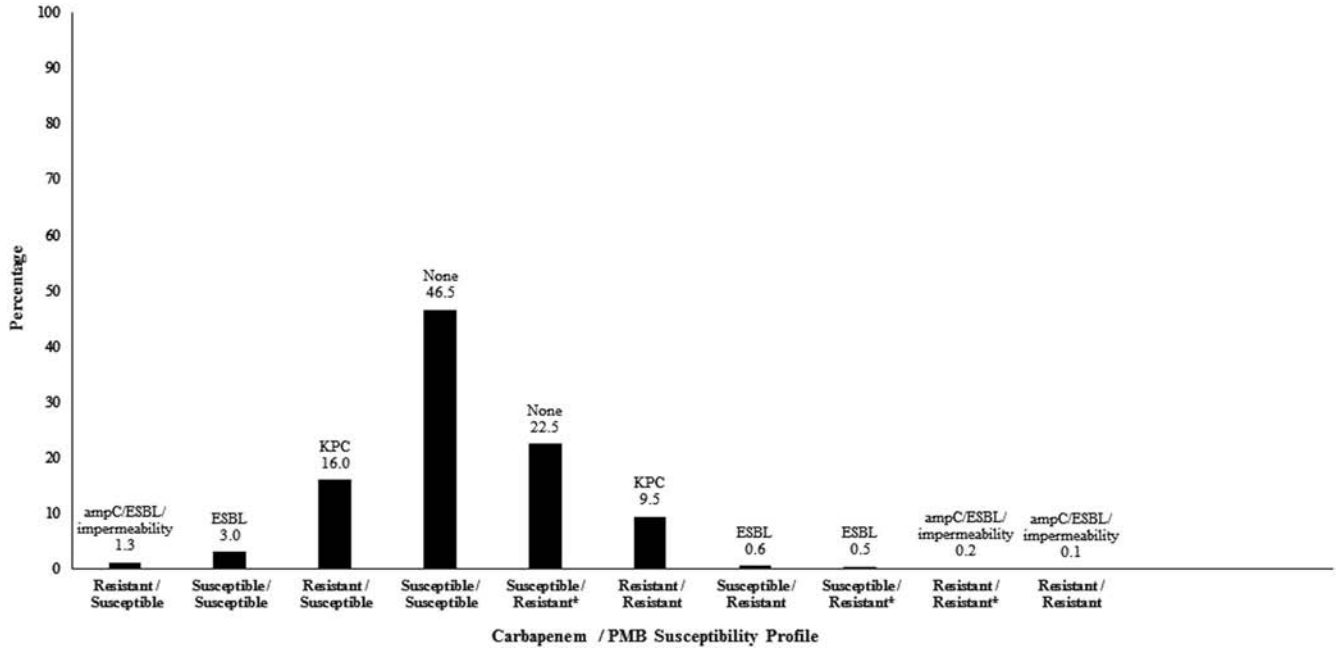

FIGURE 1. Crude prevalence of PMB susceptibility pattern of all enterobacterial species, distributed by the presence (or not) of any resistance mechanism to carbapenem and PMB agents, enrolled during the study period. Resistant with asterisk indicates intrinsic resistance to the antimicrobial agent.

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Epidemiology of Adaptive and Intrinsic Polymyxin Resistance Mechanisms by Comparing Polymyxin-Resistant Pathogen Prevalence in a One-Year Follow-Up Survey

To the Editor—The alarming increase in antibiotic resistance among enterobacterial species (ie, carbapenem-resistant Enterobacteriaceae [CRE]), mostly driven by the massive use of

carbapenem agents, in addition to the lack of new drugs in the armamentarium, has increased the use of drugs, especially polymyxins, in clinical practice.[1] Polymyxins (ie, polymyxin B [PMB] and colistin) have been prescribed in many nosocomial protocols because they show the most active therapeutic value in treating CRE-related infections as well as nonfermenter species such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[2]

Kontopidou et al[3] reported an association between increased infection rates by polymyxin-resistant *Klebsiella pneumoniae* and enterobacterial species intrinsically resistant to polymyxins (ie, PMB-IR: *Proteus* spp, *Providencia* spp, *Serratia* spp, and *Morganella morgannii*), while some studies have reported an independent emergence of colistin-resistant bacteria in humans (including *K. pneumoniae* carbapenemase [KPC]-producing Enterobacteriaceae isolates) without colistin use.[4,5] Thus, the influence of polymyxin use on the prevalence rates of the different resistance mechanisms to this class of drug (adaptive or intrinsic) is still controversial and poorly understood.

The aim of this study was to assess the impact of PMB use on the cumulative epidemiological prevalence of the different PMB resistance mechanisms inferred by the prevalence rates of enterobacterial isolates presenting these resistance characteristics.

The study was performed from January 1 to December 26, 2016, in a cohort of critically ill patients from an adult intensive care unit of a tertiary hospital in Porto Alegre, southern Brazil.

The carbapenemase-producing Enterobacteriaceae (CPEs) and the multidrug-resistant Enterobacteriaceae but not the CPE (MDRs) were selected as representatives of the adaptive PMB resistance mechanism and were compared with those of PMB-IRs. Samples from both groups were recovered from clinical specimens from the intensive care patients.

The identification of bacterial species as well as antimicrobial susceptibility testing were initially performed using an automated broth microdilution system (MicroScan; Beckman Coulter, Brea, CA). To attribute the resistance mechanism for the enterobacterial species, a synergistic test was applied using phenyl-boronic acid to detect KPC. 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.[6] An MDR was defined as nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories, including nonsusceptibility to at least 1 carbapenem agent (a CRE but not a CPE).

During the study period, a total of 552 enterobacterial isolates were recovered from different clinical specimens. Of these, 212 were characterized as KPC-producing organisms (the solely carbapenemase detected in this study) being 210 *K. pneumoniae* (99%), 1 *Escherichia coli* (0.5%), and 1 *Citrobacter freundii* (0.5%). According to the phenotypic testing, 21 isolates were ESBL producers, including 18 *K. pneumoniae*, 2 *E. coli*, and 1 *Enterobacter aerogenes*. The remaining 10 isolates (6 *Enterobacter cloacae* and 4 *E. aerogenes*) were categorized as CRE because they were able to hydrolyze at least 1 carbapenem agent.

A stable cumulative prevalence (media ± standard deviation; 22.5% ± 2.2%) was observed among those PMB-IR organisms. However, an increase in the resistance rate (33.2% ± 9.6%) was observed for KPC producers, but it was

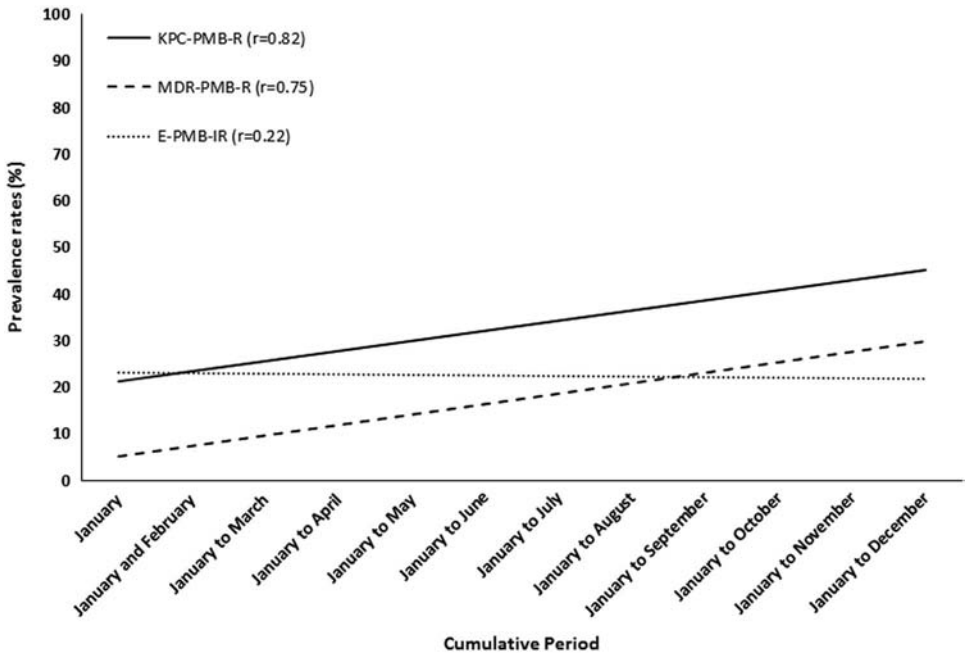

FIGURE 1. Trendlines of the prevalence rate for the adaptive resistance (*Klebsiella pneumoniae* carbapenem-polymyxin B–resistant [KPC-PMB-R] and multidrug-resistant polymyxin B–resistant [MDR-PMB-R] groups) and for the polymyxin B intrinsically resistant group (ie, PMB-IR organisms).

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more noticeable for MDR (17.6% ± 10.8%). The cumulative prevalence of these enterobacterial isolates regarding the PMB resistance mechanisms are shown in Figure 1.

The development of PMB resistance is of utmost concern. Although the resistance rate was lower among MDRs than among KPC producers (17.6% vs 33.2%, respectively) during the same period of evaluation, the microbiological outcome reported here may illustrate a crucial impact of PMB use on the resistance development in bacteria whose infectious processes need not be treated with it (eg, ESBLs).[7]

Notably, a remarkable increase in adaptive PMB resistance rates was observed during the study period despite a stable cumulative prevalence of PMB-IR organisms. This fact may suggest a major predilection for the development of resistance among bacteria previously susceptible to this class of drug. Also, it is reasonable to speculate that such organisms might not have any fitness advantage (eg, virulence factors) other than resistance to PMB when compared to organisms more able to adapt and survive, such as *K. pneumoniae* and *Enterobacter* spp.[8]

A limitation of this study was that no evaluation of the genetic background of the isolates was performed. Thus, an increased PMB resistance, especially among KPC producers, where *K. pneumoniae* emerges from other species, may be due to the selection of a PMB-resistant clone. However, increased resistance was also observed in the MDR group, where *Enterobacter* spp were expressive. This finding indicates a trend of PMB resistance development among other enterobacterial species.[7]

In conclusion, an increase in the prevalence of an adaptive resistance mechanism, inferred by the increased prevalence of PMB resistance rates in KPC and MDR groups, was identified. In addition, the prevalence rate of those PMB-IR organisms remained stable over the same survey period. Exposure to PMB does not seem to protect against an increase in adaptive resistance, and this finding emphasizes the need for a constant monitoring program to prevent the emergence of PMB resistance and for a better therapeutic approach ensuring its safe use.

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Characteristics of *Enterobacteriaceae* Isolates Coharboring Distinct Carbapenemase Genes

To the Editor—The emergence of carbapenemase-producing *Enterobacteriaceae* (CPE) isolates is an important public health problem; the treatment of carbapenem-resistant isolates is extremely difficult because few options remain available for clinical use.[1] Usually, CPE harbors only 1 carbapenemase gene, although other resistance mechanisms (ESBL, porin loss, eflux pumps) may also be present. However, relatively few studies have reported *Enterobacteriaceae* isolates producing more than 1 carbapenemase.[2] In the present study, we describe the characteristics of 10 *Enterobacteriaceae* coharboring carbapenemase genes.

The isolates were selected from an epidemiologic study evaluating *Enterobacteriaceae* with reduced susceptibility to carbapenems in several hospitals in the southernmost state of Brazil. The methods of this epidemiologic study are detailed