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Polymyxin B Consumption and Incidence of Gram-Negative Bacteria Intrinsically Resistant to Polymyxins

To the Editor—The increase in antimicrobial resistance in gram-negative bacilli (GNB), especially driven by the widespread use of carbapenemase-producing isolates, and the lack of new drugs in the pipeline have determined the reemergence of polymyxins into clinical practice.[1] Polymyxin B and colistin have been increasingly prescribed worldwide as the unique therapeutic option for many infections by these organisms.[1,2] Both polymyxins exhibit potent in vitro antibacterial activity against many GNB, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and many species of Enterobacteriaceae, such as *Klebsiella pneumoniae*, *Enterobacter* spp., and *Escherichia coli*.[1] Nonetheless, some species of the Enterobacteriaceae family present intrinsic resistance against these agents, such as *Proteus* spp., *Serratia marcescens*, and *Providencia* spp.[1] Although these agents are involved in the etiology of some nosocomial infections, the prevalence of these agents is lower when compared to other GNB.[3]

As could be expected, a recent study showed that colistin exposure was associated with increased colonization or infection rates by colistin-resistant *K. pneumoniae* but also with GNB intrinsically resistant (GNB-RP) to polymyxins in individual patients.[4] However, an evaluation of a possible correlation between increasing polymyxin B use and an increase in GNB-RP isolates in nosocomial settings has not been performed so far. The aim of this study was to assess the impact of polymyxin B consumption in the epidemiology of GNB-RP recovered from hospitalized patients.

The study was performed from January 2005 to December 2010 at Hospital Nossa Senhora da Conceição, a 950-bed tertiary general hospital, located in Porto Alegre, Brazil. Data on the utilization of polymyxin B in the hospital were obtained from the computerized database and expressed in defined daily doses (DDD) per 100,000 bed-days. The DDD of polymyxin B was 150 mg according to the Anatomical Therapeutic Chemical classification/DDD system.[5]

Bacterial isolates recovered during the period were also obtained from the Infection Control Service database. All isolates were identified at the microbiology laboratory of our institution. They were routinely identified by the Vitek 2 system (bioMérieux). We measured individually the overall incidence rate of GNB-RP and *Proteus* spp., *S. marcescens*, and *Providencia* spp. per 100,000 bed-days.

Statistical analyses were made with SPSS 16.0. The Pearson correlation coefficient was utilized to compare DDD of polymyxin B and incidence rate of all GNB-RP and each one separately. The tests were 2-tailed and a P value less than or equal to .05 was considered significant.

A total of 1,726,716 admissions occurred during the study period, and a total of 2,650 GNB-RP were recovered, resulting in a total incidence rate of 153.47 GNB-RP per 100,000 bed-days. *Proteus* spp. were the most common GNB-RP (n = 1,655, 62.45%), followed by *S. marcescens* (n = 715, 26.98%) and *Providencia* spp. (n = 280, 10.57%).

A significant increase in polymyxin B usage was noted from 12.7 DDD/100,000 bed-days in 2005 to 872.3 in 2010 (r = 0.86, $P < .05$). The occurrence of GNB-RP isolates ranged from 145 isolates/100,000 bed-days in 2005 to 168 in 2010 (r = 0.49, P = .32; Figure 1). No significant correlation was found between incidence rates and polymyxin B use with any group of organisms separately: *Proteus* spp. (r = 0.695, P = .125), *S. marcescens* (r = 0.212, P = .68), and *Providencia* spp. (r = −0.166, P = .75).

Our data showed that despite a remarkable increase in polymyxin B use during the study period, the overall incidence of GNB-RP remained stable, although there was a trend toward increasing incidence rates of *Proteus* spp. A possible explanation for this finding may be the fact that such organisms might have no fitness advantage other than resistance to polymyxins, such as virulence factors or ability to survive in adverse-environment conditions, when compared to *P. aeruginosa*, *A. baumannii*, and other Enterobacteriaceae, which may impair the widespread occurrence of GNB-RP isolates. However, the trend of increasing rates of *Proteus* spp. might be driven by the increasing use of polymyxin B.

A limitation of our study was that we did not perform

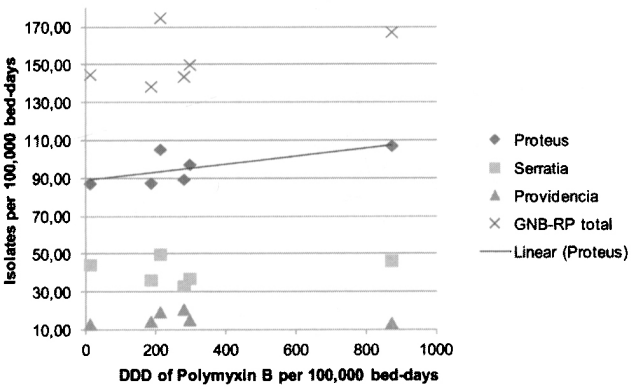

FIGURE 1. Scatterplot of the relationship between incidence rate of intrinsically resistant gram-negative bacilli (GNB-RP) and defined daily doses (DDD) of polymyxin B. A trend line was observed for *Proteus* spp. ($r = 0.69$, $P = .125$). Other organisms: *Serratia marcescens* ($r = 0.21$, $P = .68$), *Providencia* spp. ($r = -0.16$, $P = .75$), all GNB-RP ($r = 0.49$, $P = .32$).

molecular typing to better understand the dynamics of GNB-RP epidemiology in our institution. However, it might be expected a priori that the increased use of polymyxins would facilitate the dissemination of both clonal and nonclonal strains. Additionally, we could not analyze each unit of our institution separately, such as critical care units, for example; thus, we cannot ensure that a change in the epidemiology of GNB-RP may have occurred in some specific ward. Finally, a larger period of observation might be necessary to find a modification in the epidemiology of GNB infections, especially because the major increase in polymyxin B occurred in the latter year of the study (data not shown).

In summary, increasing incidence rates of GNB-RP were not observed in our study along with increasing polymyxin B consumption, although a trend toward increasing incidence rates of *Proteus* spp. was observed. However, the epidemiology of GNB in institutions with high polymyxin consumption should be closely observed, since the emergence of any carbepenem-resistant GNB-RP would critically impair antimicrobial therapy.

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Diego R. Falci, MD, MSc;[1] Liliane S. Pacheco, MD;[1] Luciana S. Puga, PharmD;[1] Renato C. F. da Silva, MD;[1] Anelise P. Alves, MD;[1] Paulo R. P. Behar, MD, PhD;[1] Alexandre P. Zavascki, MD, PhD[2]

Affiliations: 1. Infection Control Service, Hospital Nossa Senhora da Conceição, Porto Alegre, RS, Brazil; 2. Infectious Diseases Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

Address correspondence to Diego R. Falci, MD, MSc, Infection Control Service, Hospital Nossa Senhora da Conceição, 596 Francisco Trein Street, Porto Alegre, RS, Brazil (diego.falci@gmail.com).

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