

Ecological competition and the incidence of *Acinetobacter baumannii* bloodstream infections in a teaching hospital in Southeastern Brazil

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ABSTRACT

Introduction: Recently, pathogen ecology has been recognized as an important epidemiological determinant of healthcare-associated infections (HAIs). *Acinetobacter baumannii* is one of the most important agents known to cause HAIs. It is widespread in healthcare settings and exhibits seasonal variations in incidence. Little is known about the impact of competition with other hospital pathogens on the incidence of *A. baumannii* infection. **Methods:** We conducted an ecological study, enrolling patients who presented with healthcare-associated bloodstream infections (HA-BSIs) from 2005 to 2010 at a 450-bed teaching hospital in Brazil. HA-BSIs were said to be present when bacteria or fungi were recovered from blood cultures collected at least three days after admission. Monthly incidence rates were calculated for all HA-BSIs (overall or caused by specific pathogens or groups of pathogens). Multivariate Poisson regression models were used to identify the impacts of the incidence of several pathogens on the incidence of *A. baumannii*. **Results:** The overall incidence rate of HA-BSI caused by *A. baumannii* was 2.5 per 10,000 patient-days. In the multivariate analysis, the incidence of HA-BSI caused by *A. baumannii* was negatively associated with the incidence rates of HA-BSI due to *Staphylococcus aureus* (rate ratio [RR]=0.88; 95% confidence interval [CI]=0.80-0.97), *Enterobacter* spp. (RR=0.84; 95%CI=0.74-0.94) and a pool of less common gram-negative pathogens. **Conclusions:** Our results suggest that competition between pathogens influences the etiology of HA-BSIs. It would be beneficial to take these findings into account in infection control policies.

Keywords: *Acinetobacter baumannii*. Bloodstream infections. Ecological competition.

INTRODUCTION

The burden of healthcare-associated infections (HAIs) is especially high in developing countries, most of which are in the tropics¹. Although work processes are a main cause of HAIs², ecological determinants are increasingly recognized to be relevant epidemiological factors. As an example, recent studies report the seasonality of infections caused by gram-negative bacilli in healthcare settings^{3,4}.

Acinetobacter baumannii infections are an interesting example of HAIs, with a high incidence in tropical climates⁵, seasonality⁶ and an increasing incidence of multidrug resistance⁷. *Acinetobacter baumannii* is one of the most common agents

found in HAIs in Brazilian hospitals and poses a particular threat for patients in high-risk units^{8,9}.

Several risk factors for nosocomial acquisition of *A. baumannii* (overall and multi-drug-resistant isolates) have been reported. These factors include the severity of illness and the use of invasive devices and antimicrobials¹⁰⁻¹². However, many of these risk factors are similar to those reported for other pathogens¹³. Therefore, competition among microorganisms affecting closed populations subjected to the same ecological pressures may be a possibility in this context.

Our study was designed to assess the effects of such competition. We analyzed, from an ecological perspective, the influence of several pathogens on the monthly incidence rates of healthcare-associated bloodstream infections (HA-BSIs) caused by *A. baumannii*.

METHODS

Study setting and period

The study was conducted in a teaching hospital in an interior part of the State of São Paulo. The hospital has 450 active beds and is a tertiary referral hospital for an area with 500,000

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Received 12 July 2014

Accepted 16 October 2014

inhabitants. Intensive care units comprise approximately 10% of hospital beds. The hospital has a microbiology laboratory and an infection control committee. Our study analyzed data over a time span of 72 months, from 2005 through 2010.

Study design

The study had an ecological design. We examined the monthly incidence rate data for HA-BSIs (overall or caused by specific pathogens or groups of pathogens). The total number of months for which data were analyzed was 72. The outcome of interest was the incidence rate of HA-BSIs caused by *A. baumannii*.

Data and definitions

A search was performed using the hospital microbiology laboratory database for the period 2005 to 2010. To generate monthly data, we counted the number of patients with positive blood cultures. Patients with positive cultures (from any site) in the month previous to admission or within the first three days after admission were excluded, in accordance with the Society for Healthcare Epidemiology of America (SHEA) definitions for healthcare-associated pathogens¹⁴. We also excluded duplications, defined as the isolation of the same agent from different blood cultures obtained from the same patient within a 30-day period.

To generate a database of monthly incidence rates, we defined HA-BSIs on the basis of a single blood culture that tested positive for one or more typical pathogens. For atypical agents (e.g., coagulase-negative staphylococci [CoNS]), two positive blood cultures collected within 24h were required¹⁵. For the purpose of our study, we did not differentiate primary

(or catheter-related) bloodstream infections from those secondary to other primary sites.

Data on the durations of hospital stays (patient-days) were recovered from hospital administrative files. Monthly incidence rates were expressed as cases per 10,000 patient-days.

Statistical analysis

Analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM, Armonk, NY, USA). Briefly, we applied univariate and multivariate models of Poisson regression, selecting the monthly incidence of HA-BSIs caused by *A. baumannii* as the outcome. Infections caused by other agents or groups were included as predictive factors. A value of $p < 0.05$ was considered statistically significant. To present the data graphically, we repeated the analysis using linear regression, with similar results.

Ethical considerations

This study was approved by the local Committee for Ethics in Human Research.

RESULTS

In the study period, the overall incidence rate of HA-BSI was 15.8 per 10,000 patient-days. *Acinetobacter baumannii* ranked third in incidence among the etiologic agents, with an incidence of 2.5 per 10,000 patient-days. In the multivariate analysis (**Table 1**), the incidence rate of *A. baumannii* was

TABLE 1 - Results of Poisson regression models for the associations between the incidences of several pathogens and the incidence of *Acinetobacter baumannii*.

Pathogens	Univariate analysis			Multivariate analysis		
	Crude RR	95%CI	P	adjusted RR	95%CI	P
Fungi						
<i>Candida</i> spp.	0.90	0.81-0.99	0.04	0.94	0.84-1.04	0.23
Gram-negative bacilli						
<i>Pseudomonas aeruginosa</i>	1.06	0.97-1.17	0.21	1.05	0.94-1.15	0.38
<i>Enterobacter</i> spp.	0.84	0.74-0.94	0.003	0.84	0.74-0.94	0.004
<i>Klebsiella</i> spp.	1.07	0.99-1.16	0.08	1.09	0.99-1.18	0.053
<i>Escherichia coli</i>	1.09	0.99-1.19	0.06	1.10	0.99-1.22	0.08
Other gram-negative bacilli	0.91	0.87-0.95	0.001	0.92	0.87-0.97	0.002
Gram-positive cocci						
<i>Staphylococcus aureus</i>	0.89	0.82-0.97	0.008	0.88	0.80-0.97	0.01
Coagulase-negative staphylococci	1.10	0.98-1.24	0.11	1.19	1.03-1.37	0.02
<i>Enterococcus</i> spp.	0.92	0.81-1.05	0.32	1.01	0.87-1.17	0.88
Other gram-positive cocci	0.87	0.72-1.06	0.23	0.95	0.78-1.15	0.61

RR: rate ratio, corresponding to the proportional increase (or decrease) in the incidence rate of *Acinetobacter baumannii* for each unit increase in the incidence of other pathogens. **95%CI:** 95% confidence intervals. **Note:** Statistically significant results are presented in bold.

negatively associated with the incidence rates of *Staphylococcus aureus* (rate ratio [RR]=0.88; 95% confidence interval [CI]=0.80-0.97), *Enterobacter* spp. (RR=0.84; 95%CI=0.74-0.94), and a pool of gram-negative pathogens that individually were of low incidence (e.g., *Serratia* spp., *Citrobacter* spp., and several others). We also found a positive association between the incidence of CoNS and *A. baumannii*.

Although Poisson regression did not presuppose a linear correlation between the incidence rates, linear regression analysis showed a negative impact of *Staphylococcus aureus* (Figure 1), *Enterobacter* spp. (Figure 2) and several minor enterobacteria on the incidence *A. baumannii*. To illustrate these relationships, Figure 3 presents the time-series of the monthly incidence rates for *S. aureus*, *Enterobacter* spp. and *A. baumannii*.

DISCUSSION

Infection control practitioners are faced with several challenges in the control of multi-drug-resistant organisms (MDROs). Guidelines emphasize active surveillance and prompt institution of isolation precautions to contain the

spread of MDROs throughout healthcare settings^{16,17}. Nevertheless, most current evidence comes from studies focusing on gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci^{16,18}. However, a systematic review found insufficient evidence that these recommendations are effective¹⁹.

The debate becomes more complex when *A. baumannii*²⁰ is considered. There are still gaps in our knowledge of the role of antimicrobial use, inanimate reservoirs, asymptomatic colonization and even continuous introduction from environmental sources outside healthcare settings^{21,22}. In addition, the risk factors for the acquisition of drug-resistant *A. baumannii* isolates may vary with the extent of colonization pressure (i.e., the intensity of exposure to other patients harboring this agent) experienced by patients¹². It is difficult to choose separate, appropriate strategies for fighting *A. baumannii* for each specific setting and period of time.

An ecological approach may help in delineating optimal strategies. We hypothesize that healthcare-associated pathogens compete for reservoirs, both animate and inanimate. Competition between microorganisms has been widely documented in nature²³ and in the human microbiota²⁴. It is plausible that the same phenomenon occurs within hospitals. If so,

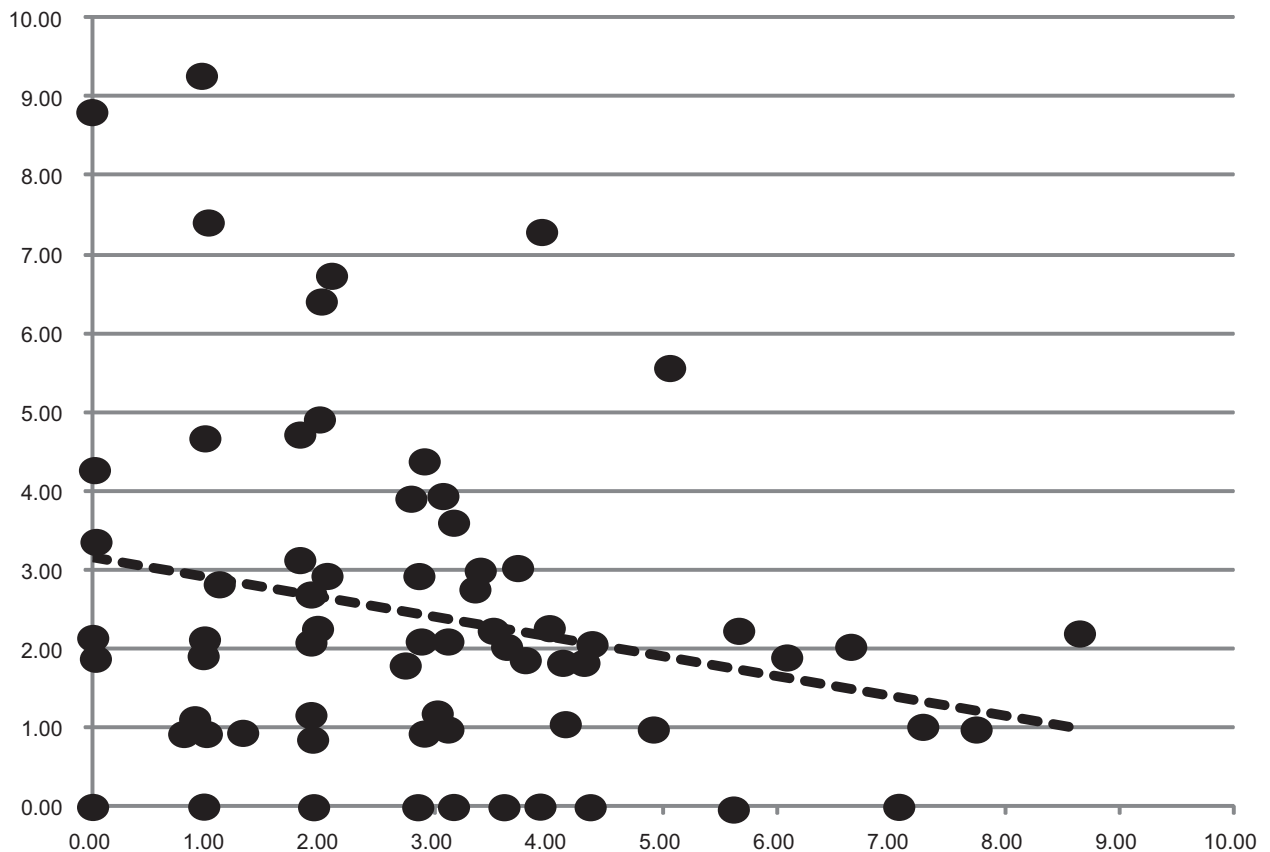


FIGURE 1 - Univariate correlation between the incidences of healthcare-associated bloodstream infections caused by *Staphylococcus aureus* (x-axis) and *Acinetobacter baumannii* (y-axis; Pearson's correlation coefficient = -0,23). Note: Incidences are shown as infections per 10,000 patient-days.

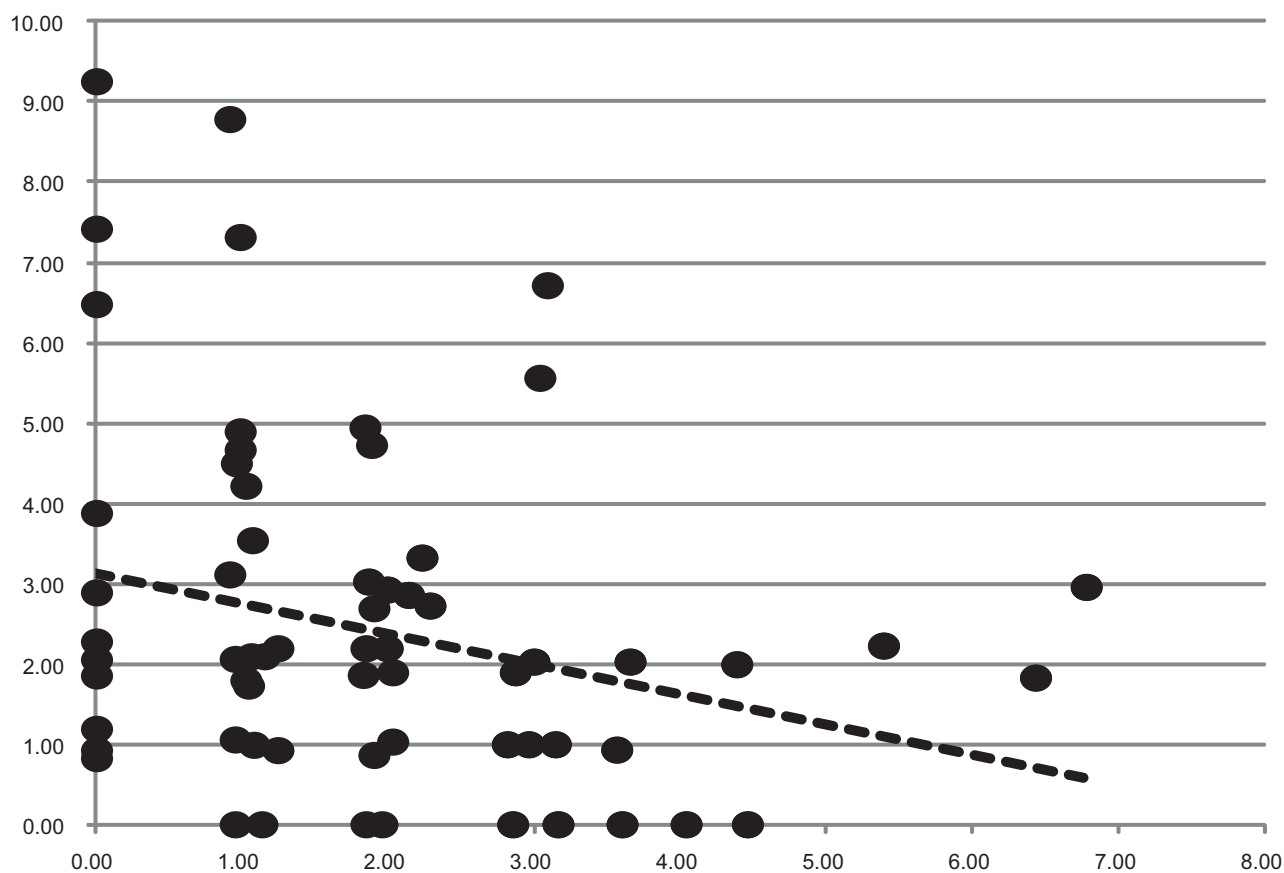


FIGURE 2 - Univariate correlation between the incidences of healthcare-associated bloodstream infections caused by *Enterobacter* spp. (x-axis) and *Acinetobacter baumannii* (y-axis; Pearson's correlation coefficient=-0,26). Note: Incidences are shown as infections per 10,000 patient-days.

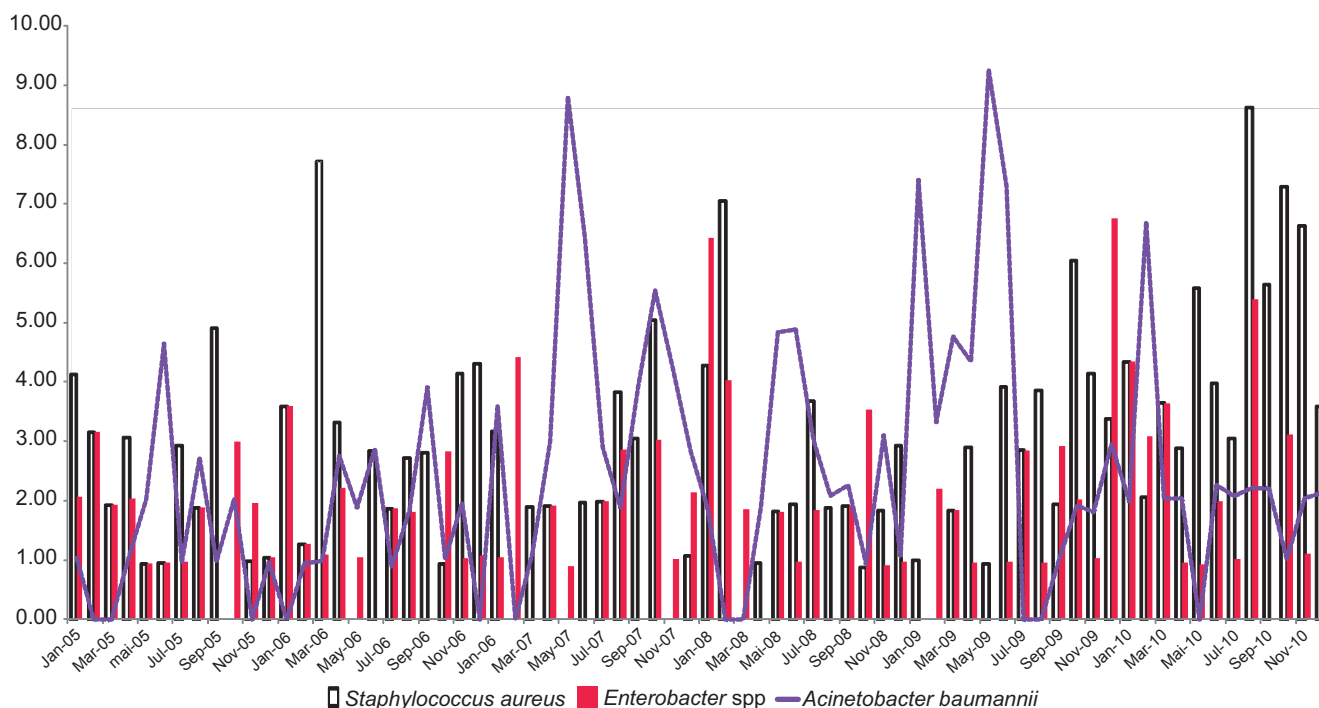


FIGURE 3 - Time series of the incidence (per 10,000 patient-days) of bloodstream infections caused by *Staphylococcus aureus*, *Enterobacter* spp. (bars) and *Acinetobacter baumannii* (line).

we can estimate trends in the incidence of *A. baumannii* (or any pathogen of interest) in relation to the epidemiology of other microorganisms. An understanding of these relationships may guide the choice of which microorganisms are priority targets for infection control efforts during specific periods. Such an understanding of these relationships may also further our understanding of the behavior of endemic pathogens (e.g., *A. baumannii*) when challenged with the introduction of emerging agents (e.g., carbapenem-resistant enterobacteria)^{25,26}.

Our study found a negative association between the incidence of *A. baumannii* and the incidences of both *S. aureus* and *Enterobacter* spp. These findings are noteworthy because they are consistent with our impression, based on experience, that waves of MRSA and multi-drug-resistant *A. baumannii* infections alternate over time. The finding that competition exists between *Acinetobacter baumannii* and *Enterobacter* was unexpected, however, because a previous study in our hospital found that the incidences of both agents (*A. baumannii* and *Enterobacter* spp.) are seasonal, with peaks during the warmer months of the year⁷. The negative association between *A. baumannii* and other, low-incidence gram-negative pathogens was only perceptible when the latter were grouped together, due to a lack of statistical power when they were considered individually. Nevertheless, this finding suggests the possibility that other associations could have been identified if more cases occurred or if the sampling period had been longer. Our study also found a positive association between the incidence rates of CoNS and *A. baumannii*. While the reasons for this finding are unclear, it suggests that future studies should focus on the competition between staphylococcal species (both coagulase-positive and negative) and *A. baumannii*.

Our study was limited by the retrospective design and relatively short time span considered. We used a retrospective ecological design, and aggregate data may not be indicative of risks related to individuals (an ecological fallacy). However, ecological analysis is warranted when the implications of interventions are essentially collective, as is the case for many infection control policies²⁷. Another limitation of our analysis is that the direction of causality could not be determined in this study. While we found negative correlations between the incidences of pathogens, we cannot be sure whether, for instance, the incidence of *S. aureus* (or *Enterobacter* spp.) affects that of *A. baumannii* or whether the opposite occurs. Thus, we must interpret the results in terms of their predictive capability, not in terms of causality. Finally, our study focused only on blood cultures. While this strategy may have lowered the statistical power of our study, we believe that blood cultures are more robust markers of infection than are other microbiological samples.

In conclusion, we found that the incidence of HA-BSIs caused by *A. baumannii* was negatively associated with the incidence of *S. aureus*, *Enterobacter* spp., and other gram-negative pathogens. Our findings suggest that competition between pathogens occurs in hospital settings and that the effects of this competition should be considered when developing infection control policies.

ACKNOWLEDGMENTS

RGM and RTA received university student research grants from the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) of the Ministry of Science and Technology in Brazil. JCM received a high school scientific grant (PIBIC Junior) from the same agency.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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