A Potential Cellular Explanation for the Increased Risk of *Clostridium difficile* Infection Due to Hypoalbuminemia: Reply Di Bella et al

To the Editor—In their intriguing investigation, reported in "The protective role of albumin in *Clostridium difficile* infection: A step toward solving the puzzle," Di Bella et al[1] explored the cellular mechanism of the potential protective effect of albumin in *C. difficile* infection (CDI). Their findings deepen our understanding of the association between low albumin levels and increased risks for CDI.[2] We applaud their effort.

Previous epidemiological work has revealed that hypoalbuminemia is a robust independent risk factor for mortality for hospitalized patients across a spectrum of clinical categories.[3–5] Our most recent CDI predictive model demonstrated that hypoalbuminemia is one of the independent risk factors that are associated with, or predictive of, hospital-onset CDI.[1] The study by Di Bella et al demonstrates that at the cellular level hypoalbuminemia plays a role in the predisposition to CDI, due to compromising the protective properties of albumin. Future studies may further explore the mechanism of low albumin levels and other pathological manifestations.

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Carbapenem-Resistant Enterobacteriaceae: A Major Prevalence Difference due to the High Performance of Carbapenemase Producers when compared to the Nonproducers

To the Editor—Carbapenem resistance among enterobacterial species has increased alarmingly and is a major worldwide threat. Two distinct paths evidence this phenotype: (1) resistance to carbapenems by any mechanism, including the production of an acquired carbapenemase or the production of extended spectrum β-lactamase (ESBL) or AmpC combined with porin-loss (carbapenem-resistant Enterobacteriaceae [CRE]) and (2) resistance to carbapenems by means of an acquired carbapenemase (carbapenemase-producing Enterobacteriaceae—CPE).[1]

A prevalence survey monitoring carbapenem resistance among Enterobacteriaceae, including rectal screens and clinical specimens, was performed in a tertiary hospital in southern Brazil between April 2013 and May 2015. Rectal swabs were collected at admission and weekly from all patients in an intensive care unit (ICU) as described previously.[2]

Identification and prior carbapenem susceptibility were performed using a MicroScan Walkaway system (Siemens). Minimum inhibitory concentration (MIC) for ertapenem and meropenem were assessed by Etest. A synergistic test was applied using phenyl-boronic acid and ethylenediaminetetraacetic acid for detecting *Klebsiella pneumoniae* carbapenemase (KPC) and New Delhi metallobetalactamase, respectively. Enzymatic inhibition using clavulanic acid and cloxacillin was used to detect ESBLs and AmpC enzymes, in that order. All isolates were submitted to polymerase chain reaction (PCR) for carbapenemase gene detection.[3]

Statistical analyses were conducted using SPSS version 13.0 (IBM, Inc., Chicago, IL, USA). Prevalence ratio (PR), odds ratio (OR), and 95% confidence intervals (CIs) were calculated. *P* value was calculated using χ^2 or Fisher's exact test.

In total, 3,975 rectal swabs were obtained from 1,334 distinct patients, of whom 294 patients (PR, 22%; 95% CI, 19.9–24.3) had a rectal swab with CPE and the remaining 21 patients (PR, 1.6%; 95% CI, 1.0–2.4) had rectal swabs with non-carbapenemase producers. The prevalence of CPE was significantly higher than non-carbapenemase producers (OR, 5.7%; 95% CI, 3.6–8.9; $P < .001$).

TABLE 1. Distribution and Identification of Enterobacterial Species Characterized as Carbapenem-Resistant Enterobacteriaceae among the 497 Samples (Rectal Screen and Clinical Specimens)

	Distribution (%; No./Total No.)		Enterobacteriaceae species (%; No./Total No.)	
Carbapenemase	Rectal screen	Clinical	Rectal screen	Clinical
Producers[a]	95.6 (475/497)	87.2 (184/211)	***Klebsiella pneumoniae***[b] (**93.4**; 464/497)	***K. pneumoniae***[b] (**94.6**; 174/184)
			K. oxytoca (0.6; 3/497)	*E. cloacae* (2.2; 4/184)
			Citrobacter freundii (0.6; 3/497)	*E. coli* (1.6; 3/184)
			Escherichia coli (0.6; 3/497)	*S. marcescens* (1.6; 3/184)
			Serratia marcescens (0.4; 2/497)	
Nonproducers	4.4 (22/497)	12.8 (27/211)	***K. pneumoniae*** (**90.9**; 20/22)	***E. cloacae*** (**66.7**; 18/27)
			Enterobacter cloacae (9.1; 2/22)	*K. pneumoniae* (29.6; 8/27)
				Providencia stuartii (3.7; 1/27)

[a]bla_{KPC-2} was the sole carbapenemase gene detected;
[b]A randomly selected sample of isolates (rectal swab, n = 10 and clinical specimen, n = 13) was typed by pulsed-field gel electrophoresis and showed the same macrorestriction profile of DNA.

Distribution and identification of species are shown in Table 1. Among the 497 enterobacteriaceae isolates with reduced susceptibility to any carbapenem detected in rectal swabs, 475 (95.6%; 95% CI, 93.4–97.1) were KPC-2 producers, as identified by polymerase chain reaction (PCR) assay (3 isolates with a negative phenotypic test). Another 22 isolates (4.4%; 95% CI, 2.9–6.6) were negative for carbapenemase production (phenotypic and PCR).

In total, 211 isolates from 145 distinct patients presenting reduced susceptibility to carbapenems were found in blood (93.9%), respiratory secretions (91.3%), urine (84.5%), and other sites (75%). Of these 211 isolates, in 184 (87.2%; 95% CI, 82–91) the bla_{KPC-2} gene was detected (although 3 would not have been detected using only phenotypic testing). The remaining 27 isolates (12.8%; 95% CI, 8.9–18) from urine (15.5%), respiratory secretions (8.7%), blood (6.1%), and others (25%), were negative for carbapenemase production. For all isolates in which a carbapenemase gene was not detected, AmpC and/or ESBL production by phenotypic tests were positive.

Among KPC producers, MIC_{50} and MIC_{90} were >32 mg/L for meropenem and ertapenem. Among the nonproducers, MIC_{50} and MIC_{90} were 8 μg/mL and 16 mg/L for meropenem and 32 mg/L and >32 mg/L for ertapenem, respectively.

Carbapenem resistance due to the production of an ESBL or AmpC associated with impermeability may be related to further reductions in carbapenem susceptibility during therapeutic treatment. On the other hand, carbapenem resistance is often unstable as it uses up a lot of energy, meaning that these strains rarely spread.[4]

In contrast with the findings of Drew et al,[1] in which the carbapenem resistance for most isolates was due to AmpC or ESBL combined with impermeability in a UK pediatric population, an acquired carbapenemase gene seems to be the issue in our institution. Undoubtedly, high prevalence of CRE is due to the rapid spread of a specific carbapenemase (KPC-2 in this study) and a bacterial species with a high capacity to adapt and survive (*Klebsiella pneumoniae* in this study).

A potential limitation of this study is that a denominator for clinical specimens was not given; therefore, the prevalence in these sites cannot be expressed. However, the fact that ~20% of ICU patients were colonized with CRE is a concern, as >93% were due to KPC-2-producing *K. pneumoniae*, subsequently reflecting on the development of infections (Table 1).

Although *K. pneumoniae* was the main species recovered in rectal swabs in both carbapenemase producers and nonproducers, it is noteworthy that *Enterobacter cloacae* appears to be the protagonist (66.7%) among the nonproducers in clinical specimens. However, these latter isolates were successfully treated with meropenem, as AmpC plus impermeability conferred only a low-level of carbapenem resistance, often with ertapenem MICs just above the cutoff; while for the KPC-2 producers only polymyxin B exhibited a good *in vitro* activity.[5]

Because KPC producers show a higher prevalence than nonproducers, early appropriate therapy is necessary, mainly in bloodstream infections for which high mortality rates have been attributed.[6] In addition, control measures should be implemented to avoid further spread of this resistance mechanism.

In conclusion, this study demonstrates a major prevalence of carbapenemase producers compared with nonproducers as a CRE etiological agent in our institution. This finding is based on the high performance of a dominant clone identified as KPC-2-producing *K. pneumoniae* being the prevalent agent and being responsible for the current endemic level. Nevertheless, the prevalence of CRE, no matter the mechanism, must be further evaluated, since its occurrence may greatly impact infection control practices.

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CPE Colonization - Once A Carrier Always A Carrier? Response to Lewis and Bart

To the Editor—We read with interest the studies by Lewis et al[1] and Bart et al[2] on efforts to predict clearance of gastrointestinal colonization with carbapenemase-producing *Enterobacteriaceae* (CPE) based on follow-up rectal screens. The authors are to be congratulated for trying to address an important infection prevention issue, ie, whether there is a time when contact precautions, specifically isolation, can be discontinued. Both studies report that a significant proportion of patients who had negative CPE surveillance cultures following their initial positive screen remained colonized with CPE at follow-up screening: 13% (36 of 276) and 33% (7 of 31) in the studies by in the study by Bart et al and Lewis et al, respectively. Indeed, even after further screening, CPE was detected in 2 patients who had been found to be negative on 3 occasions following their initial positive screen.[1] It is also important to note that no single culture-based screening method routinely employed has the high level of sensitivity required to detect all genotypes of CPE, particularly those displaying low-level resistance.[3] Therefore, the rates of recurrent carriage may, in fact, be underestimated. Bart et al attempt to identify those risk factors that correlate with CPE recurrence. However, given the relatively small numbers of patients identified and the limitations of this study, further work is certainly needed in this area.

Recent guidelines on infection prevention and control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients highlight the dearth of good evidence and confirm that no consensus exists on when contact precautions may be discontinued.[4] Furthermore, it is mistaken to make assumptions based upon other multidrug-resistant organisms, specifically methicillin-resistant *Staphylococcus aureus* (MRSA), where recognized decolonization regimens are commonly used because such treatment often assists in shortening the duration of carriage. In addition, for MRSA, the major reservoir of colonization is the skin and nasal mucosa, whereas for CPE and vancomycin-resistant enterococci (VRE), the gastrointestinal tract is the important reservoir. Although guidelines suggest that 3 consecutive negative swabs may allow for discontinuation of contact precautions in patients with VRE, this may be difficult to achieve in practice given the gastrointestinal reservoir.[5] In a study on a renal unit, 64% of patients remained positive for VRE when 3 or more follow-up rectal screening specimens were taken.[6] However, many of these were patients with chronic renal failure, which, in addition to other factors, may help explain this statistic. It is possible that, for groups with similar risk factors, the same difficulties arise with regard to persistent CPE carriage.

Much remains unknown about the natural epidemiology of patients with CPE and specifically when, and if, some patients ever lose the organism. Factors governing this condition are likely to be complex and include the underlying condition of the patient; the setting in which the patient is being cared for; recent, current, and the future administration of antibiotics and other drugs; and the complex milieu of the intestinal microbiome, which is dynamic and is likely to have an important impact on colonization. To date, we have largely relied on cultures to determine changes in the epidemiology of colonized patients with CPE, but the relationship between CPE and the remainder of the intestinal flora is likely to be complex. We need to apply meta-genomic approaches to explore that relationship and how it might affect the dynamic of CPE colonization.[7] As our knowledge regarding possible exploitation and restoration of the intestinal microbiome develops, so