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Prescription of Antibiotics in Intensive Care Units in Latin America: an Observational Study

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Summary

A one-day point prevalence study to investigate the patterns of antibiotic use was undertaken in 43 Latin American (LA) intensive care units. Of 510 patients admitted, 231 received antibiotic treatment on the day of the study (45%); in 125 cases (54%) due to nosocomial-acquired infections. The most frequent infection reported was nosocomial pneumonia (43%). Only in 122 patients (53%) were cultures performed before starting antibiotic treatment. 33% of the isolated microorganisms were Enterobacteriaceae (40% extended-spectrum b-lactamase-producing), 23% methicillin-resistant *Staphylococcus aureus* and 17% carbapenems-resistant non-fermentative Gram-negatives. The antibiotics most frequently prescribed were carbapenems (99/231, 43%); alone (60/99, 60%) or in combination with vancomycin (39/99, 40%). "Restricted" antibiotics (carbapenems, vancomycin, piperacillin-tazobactam, broad-spectrum cephalosporins, tigecycline, polymixins and linezolid) were most frequently indicated in severely ill patients (APACHE II score at admission ≥15 -p=0.0007- and, SOFA score at the beginning of the antibiotic treatment ≥3 -p=0.0000-). Only 36% of antibiotic treatments were cultured-directed.

Our findings help explain the high rates of multidrug-resistant pathogens in LA settings (i.e. ESBL-producing Gram-negatives) and the severity of the registered patients´ illnesses.

Key words: intensive care unit, antibiotics, carbapenems, resistance.

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INTRODUCTION

Critically ill patients treated in intensive care units (ICUs) frequently have an infection or are prone to developing new infections. Therefore, total antibiotic consumption is approximately ten times greater in ICU wards than in general hospital wards [1]. This high density of antibiotic use favors the development of multidrug resistant pathogens (MDR) either by selecting a resistant mutant or allowing the emergence of an MDR bacteria in colonized flora [2-5]. Rice recently reported these as the "ESKAPE" pathogens [6] (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa,* and *Enterobacter* species) to emphasize that they currently cause the majority of worldwide hospital infections (Latin America included [7]) and effectively "escape" the effects of antibacterial drugs.

There are several reasons for ICU specialists to choose the "best" antibiotic treatment for seriously ill patients; these include the well-known relationship between inappropriate or delayed antibiotic treatment and an increase in mortality [8-10], as well as specialists´ fear of encountering lawsuits. However, after these treatments are initiated, discontinuation or streamlining of the antibiotic empirical therapy based on culture results and/or clinical parameters is not the most widely practiced strategy [11,12]. In this scenario, infectious diseases (ID) specialists may help to improve adherence to local antibiotic therapy guidelines, and to achieve a correct balance between the risk of an inappropriate initial therapy and the indiscriminate use of broad-spectrum antibiotics [13-15].

The purpose of this study was to investigate the patterns of antibiotic use in ICUs in Latin America, as well as the influence of the ID physician on prescription habits in critically ill patients.

PATIENTS AND METHODS

This was an observational, cross-sectional study in which 43 Latin America (LA) ICUs completed a web-based data collection form with data about patients who received antibiotics (a one-day point prevalence done on November 17, 2008). The participating hospitals were in Argentina (n=8), Bolivia (n=8), Chile (n=1), Colombia (n=13) and Ecuador (n=13). Data were collected using a unique electronic form included in the website ATB-Terapia Intensiva™ (http://www.atb-uci.com.ar), designed by Infectología Institucional SRL and Tida SRL from Argentina. Each ICU had a principal investigator, all of whom had a personal username and password to access the electronic form.

The following data were recorded only for patients treated with antibiotic in the ICU (prophylaxis was not included):

General data of the ICU: number of ICU beds; number of patients admitted; number of patients admitted with antibiotic treatment.

General data of the patients: number of registry, sex, age, date of admission in ICU, and severity of illness at admission (measured by the APACHE II score).

Infection data: date of diagnosis of infection, source of infection (community or nosocomial-acquired); diagnosis when the antibiotic treatment was started; and microbiological documentation.

Antibiotic use data: severity of the disease at the beginning of antibiotic treatment (measured by SOFA score), type of indication (empirical treatment: patient with signs and symptoms of infection and cultures pending, culture-directed prescription: patient with signs and symptoms of infection and positive cultures, or clinically-documented infection: patient with signs and symptoms of infection without cultures or with negative cultures); previous antibiotic therapy during the present hospitalization (type and days of antibiotics used); antibiotic treatment of the present infection (type and days of antibiotics used); and physician who prescribed the present antibiotic treatment (ICU or ID specialist).

Established criteria were used to define clinical infection [16]. Infections were classified as nosocomial-acquired when onset occurred >48 h after admission to the hospital [16,17]. Infections occurring within 48 h of admission to the hospital were considered community-acquired, unless the patients had been transferred directly from another hospital or nursing home or discharged from a hospital within the 30 days preceding admission to the hospital [17].

Bacterial identification was performed according to the clinical microbiology procedures handbook [18]. Bacterial identification was confirmed and antibiotic susceptibility testing was performed on each of the isolates using a semi-automated system in 23 hospitals (53%). In the remaining hospitals bacterial susceptibility was determined with the Kirby Bauer method (disc diffusion).

Extended-spectrum b-lactamase (ESBL)-producing microorganisms were detected and confirmed according to the Clinical Laboratory Standards Institute, using the double disc test for confirmation [19].

For the analysis, carbapenems, vancomycin, piperacillin-tazobactam, broad-spectrum cephalosporins, tigecycline, polymixins and linezolid were considered as "restricted antibiotics" based on their epidemiological and economical implications in the hospitals.

The study focused on compliance with the clinical routine practices determined by the responsible physician. The study was based on a case registry methodology and did not require the prescription of specific drugs or other treatments, nor the performance of procedures or diagnostic tests other than those prescribed by the responsible physician.

Statistical methods: Results are expressed as proportions. When applicable, two-tailed hypothesis testing for difference in proportions was used (Proportion Test); a $p < 0.05$ was considered significant.

RESULTS

Forty-three general ICUs in Latin America (614 total beds) participated and recruited 231 patients who had received antibiotic treatment on the day the of study of 510 patients hospitalized (45%, range between ICUs 34-56%) (*Table 1*). Patients' median age was 54 years (range 18-92); 153 were male (66%). Their median APACHE II score at admission was 21 (≥15 in 172/231 patients 74%, and <15 in 59/231 patients 26%) (*Table 1*).

The mean of length of stay (LOS) since the date of admission to the diagnosis of infection was 4.5 days (range 0-10).

Nosocomial-acquired infections (NAI) were observed in 125 patients (54%). Of all infections, 43% (99/231) were nosocomial pneumonia; 13% (30/231) sepsis of unknown origin and 12% (28/231) central nervous system infections (*Table 1*).

Only in 122 patients (53%) were cultures performed before starting antibiotic treatment. In 68% of them (83/122) a microorganism considered as the causative agent of the infection was isolated (*Table 1*).

We found that blood cultures (60%, 74/122) were the samples processed most frequently, in combination with cultures of respiratory secretions (tracheal aspirate and brochoalveolar lavage) in 50% of the patients (61/122) (*Table 1*).

The most common isolates were Enterobacteriaceae, mainly *Klebsiella pneumoniae* and *Escherichia coli* (33%), and methicillin-resistant *Staphylococcus aureus* (MRSA) (23%), followed by *Acinetobacter* spp. (18%), and *Pseudomonas aeruginosa* (10%). Of the Gram-negative bacteria, 40% of the Enterobacteriaceae were ESBL-producing, whereas 50% of the *Acinetobacter* spp. and 25% of the *Pseudomonas aeruginosa*, were carbapenem-resistant respectively (*Table 1*).

The median SOFA score at the beginning of antibiotic treatment was 13 (≥3 in 183/231 patients 79%, and <3 in 48/231 patients 21%) (*Table 2*).

We found that antimicrobial therapy was prescribed on the study day as empirical treatment, culture-directed prescription and clinically documented infection in 8.5%, 36%, and 55.5% respectively. At no point were antibiotic courses discontinued, not in cases where cultures were not done nor in cases where culture results were negative (*Table 2*).

Fifty percent of the patients (116/231) had received previous antibiotic therapy during their current hospitalization, (≥3 days of treatment in 80/116 patients (69%), and <3 days of treatment in 26/116 patients (31%). Piperacillin-tazobactam and ampicillin-sulbactam (in both cases alone or in combination with other antibiotics) were the most frequent antibiotics previously used (45% and 12% respectively) (*Table 2*).

The day of the study, carbapenems (imipenem or meropenem) were the antibiotics most frequently prescribed (99/231, 43%), followed by piperacillin-

TABLE 1 - *Patients' characteristics and infection data.*

Characteristics	Value
Number of patients admitted, n	510
Number of patients receiving antibiotics, n/total (%)	231/510 (*45*)
Age; mean years (range)	54 (18-92)
Male; n *(%)*	153 (*66*)
APACHE II, median	21
• ≥15, n *(%)*	172 (*74*)
• < 15, n *(%)*	59 (*26*)
LOS[1] between date of admission to the diagnostic of infection, median (range)	4.5 (0-10)
Origin of the infection, n *(%)*	
• Nosocomial acquired	125 (*54*)
• Community acquired	106 (*46*)
Type of infection, n *(%)*	
• Nosocomial pneumonia	99 (*43*)
• Sepsis of unknown origin	30 (*13*)
• Central nervous system infection	28 (*12*)
• Gastrointestinal infection	23 (*10*)
• Skin and skin structures infection	14 (*6*)
• Genitourinary infection	9 (*4*)
• Endovascular infections	5 (*2*)
• Others	23 (*10*)
Cultures sites, n/total *(%)*	122 (53)
• Blood plus respiratory secretions[2]	61/122 (*50*)
• Urine only	22/122 (*18,5*)
• Stool	20/122 (*16*)
• Blood plus urine	8/122 (*6,5*)
• Blood only	5/122 (*4*)
• Others	6/122 (*5*)
Clinical Isolates,	
• n/total patients *(%)*	83/231 (*36*)
• n/total cultures *(%)*	83/122 (*68*)
-*Enterobacteriaceae*	27/83 (*33*)
• ESBL[3]-producing	11/27 (*40*)
• non- ESBL-producing	16/27 (*60*)
-MRSA[4]	19/83 (*23*)
-*Acinetobacter* spp.	16/83 (*19*)
• carb-R-*Acinetobacter* spp.[5]	8/16 (*50*)
• carb-S-*Acinetobacter* spp.[6]	8/16 (*50*)
-*Pseudomonas aeruginosa*	8/83 (*10*)
• carb-R-*P.aeruginosa*[7]	2/8 (*25*)
• carb-S-*P.aeruginosa*[8]	6/8 (*75*)
-Others	13 (*15*)

[1]length of stay
[2]tracheal aspirate and bronchoalveolar lavage
[3]extended-spectrum -lactamases
[4]methicillin-resistant *S.aureus*
[5]carbapenem-resistant *Acinetobacter* spp.
[6]carbapenem-susceptible *Acinetobacter* spp.
[7]carbapenem-resistant *P.aeruginosa.*
[8]carbapenem-susceptible *P.aeruginosa.*

TABLE 2 - *Patients' antimicrobial prescription data (n=231).*

Characteristics	Value
SOFA score at the beginning of the antibiotic treatment, median	13
• ≥3, n *(%)*	183 *(79)*
• 3, n *(%)*	48 *(21)*
Type of indication, n *(%)*	
• Empirical treatment	20 *(8.5)*
• Microbiological documented treatment	83 *(36)*
• Clinical documented treatment	128 *(55.5)*
Previous antibiotic therapy; n *(%)*	116 *(50)*
-Days	
• ≥3 days, n *(%)*	80 *(69)*
• <3 days, n *(%)*	26 *(31)*
-Type	
• Piperacillin-tazobactam[1]	52 *(45)*
• Ampicillin-sulbactam[1]	14 *(12)*
• Broad-spectrum cephalosporins	11 *(10)*
• Carbapenems (imipenem or meropenem)	11 *(10)*
• Others	28 *(21)*
Patients with antibiotic in the prevalence day; n/total *(%)*	231/510 *(45)*
• Carbapenems (imipenem or meropenem)	60/231 *(26)*
• Carbapenems + vancomycin	39/231 *(17)*
• Piperacillin-tazobactam	39/231 *(17)*
• Piperacillin-tazobactam + amikacin	37/231 *(16)*
• Ampicillin-sulbactam[1]	30/231 *(13)*
• Broad-spectrum cephalosporins[1]	14/231 *(6)*
• Others	12/231 *(5)*
Type of indication of carbapenems, n/total *(%)*	99/231 *(43)*
• Empirical treatment	18/99 *(18)*
• Culture-directed precription	58/99 *(58)*
• Clinical documented treatment	23/99 *(24)*

[1]alone or in combination with other antibiotic
[2]with or without vancomycin

tazobactam (76/231, 33%) and ampicillin-sulbactam (13%). Broad-spectrum cephalosporins were prescribed in 6% of the patients (alone or in combination). In 40% of the cases carbapenems were prescribed in combination with vancomycin and in 49% of the cases piperacillin-tazobactam was prescribed in combination with amikacin (*Table 2*).

Eighteen patients received carbapenems as empirical treatment (18%), 58 patients as cultured-directed prescription (58%), and 23 patients for clinically documented infections (24%) (*Table 2*).

We divided the patients into two groups according to whether they had received (Group 1) or not (Group 2) antibiotics considered as "restricted" on the day of the study.

Restricted antibiotics (Group 1) were most frequently used in patients with APACHE II score at admission ≥15 (p=0.0007); the SOFA score at the beginning of the antibiotic treatment ≥3 (p=0.0000); microbiological documentation (p=0.0130), and previous antibiotic treatment (p=0.0862). Group 2 antibiotics were most frequently used in patients with community-acquired infections (p=0.0019) (*Table 3*).

We observed that the percentage of non-culture-directed prescriptions of carbapenems were correlated with high APACHE II at admission, even though this trend was not statistically significant (p=0.1934) (*Figure 1*).

Other analysis was performed by dividing the total prescriptions of "restricted" antibiotics (Group 1) in those institutions in which these are prescribed by the ICU specialist (Institutions 1: 18/43, 42%) and those in which these antibiotics are prescribed or recommended by the ID physician (Institutions 2: 25/43, 58%). There was no significant difference between Institutions 1 and 2 regarding the APACHE II score at admission ≥15 (p=0.1302); SOFA score at the beginning of the antibiotic treatment ≥3 (p=0.4390); nosocomial origin of the infections (p= 0.6363); and prescription of Group 1 antibiotics (p= 0.2176). On the other hand, microbiological documentation rates of the infection were better when the ID physician was involved in the prescription process (*Table 4*).

TABLE 3 - *"Restricted" antibiotic* use according to patients' and infection characteristics.*

	APACHE II[c]		SOFA[d]		Previous antibiotics	Community infection	Nosocomial infection	CDP[e]
	≥ 15	< 15	≥ 3	< 3				
Group 1[a] n (%)	137 (78)	33 (56)	134 (73)	16 (33)	65 (56)	52 (40)	46 (45)	53 (64)
Group 2[b] n (%)	35 (22)	26 (44)	49 (27)	32 (67)	51 (44)	78 (60)	55 (55)	30 (34)
	p=0.0007		*p*=0.0000		*p*=0.0862	*p*=0.0019	*p*=0.2603	*p*=0.0130

*carbapenems, vancomycin, piperacillin-tazobactam, broad-spectrum cephalosporins
[a]patients whom received "restricted" antibiotics
[b]patients whom did not received "restricted" antibiotics
[c]at admission
[d]at the beginning of the antibiotic treatment
[e]culture-directed prescription

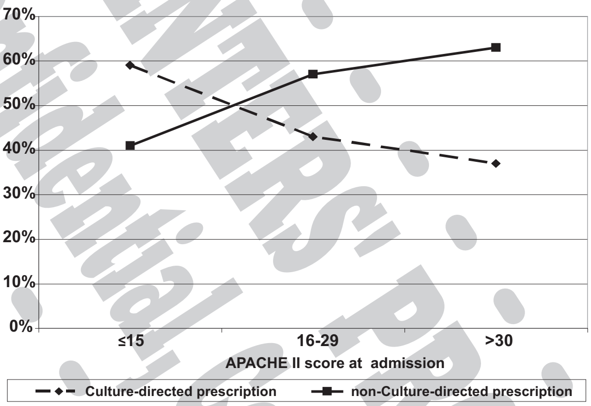

FIGURE 1 - Culture and non-culture directed carbapenem prescriptions in relation to patient's APACHE II score at admission.

DISCUSSION

The results of this observational, cross-sectional study show that 45% of patients admitted to a general ICU in Latin America were receiving at least one antibiotic and in 54% of the cases, to treat nosocomial infections. The antibiotic consumption rate found in this study was similar to that published by other authors such as Bergmans in a 1997 study (59%) [20]. In patients admitted with serious community-acquired infections, the acquisition of the infection during hospital stay, the presence of multiple co-morbidities and high rates of invasive device use were the main reasons for high consumption of antibiotics in the ICU [21].

In order to improve these antibiotic prescription patterns, it is well established that precise knowledge of the pathogens associated with the disease allows rational antibiotic selection. In clinical practice, however, antibiotics are often employed even when culture results are not available [22]. The number of cultures obtained in our study is very low (53%), reflecting that only 36% of patients received a culture-directed antibiotic prescription. It is important that ICU physicians understand that obtaining microbiological cultures before initiating antimicrobial therapy is part of the diagnostic work-up of ICU patients [23].

As demonstrated in the Epidemiology of Infection in Intensive Care study [24], nosocomial pneumonia accounts for nearly one-half of all antibiotic prescriptions used in our patients. In the particular case of nosocomial pneumonia, it is well established that, even when microbiological cultures are taken, and regardless of the pathogen isolated pathogen and its sensitivity pattern, empirical antibiotic therapy is invariably continued [23]. Not considering de-escalation strategy (tailored therapy) in nosocomial pneumonia, can lead to the possibility of "collateral damage", where overuse/misuse of antibiotics is associated with MDR-pathogen infections [25].

"ESKAPE pathogens" (with the exception of *Enterococcus faecium*) were the most common microorganisms isolated in our patients (84%), with an MDR-profile similar to those described by several microbiological surveillance systems of the region [7-26]. The T.E.S.T. program (Tigecycline Evaluation and Surveillance Trial), has found that rates of ESBL-*K. pneumoniae,* and carbapenem-resistant *A. baumannii* and *P. aeruginosa* were higher in LA than in North America and Europe (respectively 37.9%, 37.6%, 35.8% LA) vs (9.7%, 13.1%, 15.1% North America) and (15.3%, 14.8%, 17.4% Europe). In contrast, rates of methicillin resistance among *S. aureus* were higher in North America (53.7%) than in LA (46.6%) and Europe (25.1%)[7].

Prior antibiotic usage is one factor that predisposes to infections with MDR-bacteria [27-29]. In our study, the evaluated patients received previous antibiotic treatment in 50% of the cases (69% ≥3 days); most of them broad spectrum agents. Although the majority of patients received piperacillin-tazobactam, in 20% imipenem and broad-spectrum cephalosporins were used, both of which are closely related to the selection of MDR microorganisms [30-32].

TABLE 4 - *Role of the infectious diseases consultant in the prescription of "restricted" antibiotics* in the ICU.*

	APACHE II[c]		SOFA[d]		Previous antibiotics	Nosocomial infection	CDP[e]	Group 1 antibiotics prescribed
	≥15	<15	≥3	<3				
Institutions 1[a] n, (%)	48 (69)	22 (31)	57 (82)	13 (18)	29 (42)	33 (48)	42 (60)	60 (86)
Institutions 2[b] n, (%)	127 (79)	34 (21)	122 (76)	39 (24)	93 (58)	83 (52)	122 (76)	125 (78)
	p=0.1302		p=0.4390		p=0.0322	p=0.6363	p=0.0232	p=0.2176

*carbapenems, vancomycin, piperacillin-tazobactam, broad-spectrum cephalosporins
[a]institutions with "restricted" antibiotics indicated by the infectious diseases physicians
[b]institutions with "restricted" antibiotics indicated by the intensive care unit physicians
[c]at admission
[d]at the beginning of the antibiotic treatment
[e]culture-directed prescription

In terms of antibiotic prescriptions on the day of the study, we observed that the "restricted" antibiotics (piperacillin-tazobactam, broad-spectrum cephalosporins, vancomycin and carbapenems) were prescribed more frequently in high-risk infected patients with APACHE II at admission ≥15 and SOFA at the start of antibiotic treatment ≥3. The rationale of these prescription habits among ICU physicians could be based on studies suggesting the advantages of starting with "the best and most powerful" antibiotic treatment in terms of favorable clinical outcome [33-35].

Available studies demonstrate that interaction between the ID specialist and attending physician may improve diagnosis and the appropriateness of antibiotic treatment of severe infections [36-38]. Two of us (DC and RB) have found that the close interaction between the ID consultant and ICU physician has reduced use of broad-spectrum cephalosporins and vancomycin consumption significantly in the ICU, using a prospective audit of antimicrobial use strategy [39]. Several authors have demonstrated that ID consultation is significantly associated with an increased proportion of appropriate first-line treatments, as well as of an increase in correction of first-line inappropriate treatments, when the microbiologic results become available [40-42].

Although our study did not specifically address this point, considering only the prescription habit of "restricted" antibiotics, we did not find significant differences between the indications of the ID physicians and those given by the ICU specialist. Furthermore, the percentage of microbiologically proven infections was greater in those institutions where the antibiotic was indicated by the ICU specialist. Our thought, based on personal experience, is that ID physicians in LA probably have the same limitations in prescribing antibiotics for an ICU patient as the ICU specialist (i.e. patient´s high severity score, low percentage of microbiological documentation, misdiagnosis, "just in case" prescriptions, and legal imperatives).

Carbapenems (alone or in combination with vancomycin), were the most frequently prescribed antibiotics in LA ICUs. This practice seems justified for several reasons: (a) 54% of the registered infections were **NAI (AUTHORS, IDENTIFY)**, in which MDR microorganisms are frequently involved [42]; (b) 50% of patients had received previous antibiotic therapy other than carbapenems in 90% of the cases during their hospitalization (extending the spectrum of the previously prescribed antibiotic is a very common concept for ICU physicians); (c) high rates of ESBL-producing Gram-negatives and MRSA were found in our patients. Carbapenems are stable against hydrolyzing activity of ESBLs and are regarded as the drug of choice for treatment of infections caused by ESBL-producing Enterobacteriaceae. The combination with vancomycin extends the spectrum towards MRSA; (d) The severity scores of more than 70% of the registered patients were high at admission (APACHE II) and at the beginning of the antibiotic treatment (SOFA). Early effective therapy for infections in critically ill patients (defined as antimicrobial treatment that covers the infecting pathogens) is associated with lower mortality rates [33-35]. Therefore, a fresh approach to the effective treatment of nosocomial pneumonia (the most frequent pathology in our study), is to use a broad-spectrum antibacterial treatment followed by precision therapy based on susceptibility results [9]. (e) Physicians believe in carbapenems because they are potent antibiotics, with an ultra-broad spectrum of activity that encompasses MDR and difficult-to-treat Gram-negative bacteria (several clinical trials support their clinical effectiveness). In fact, we have found that there is a trend to use carbapenems in severely ill patients regardless of the microbiological documentation.

Beyond these reasons, the problem of bacterial resistance in LA requires that physicians improve their use of carbapenems. The high prevalence of carbapenem-resistant *A. baumannii* in the region has increased markedly [43], along with the prevalence of carbapenem-resistant strains of *P. aeruginosa* [26]. Another problem to be concerned about is the description in LA of Enterobacteriaceae isolates (particularly *K. pneumoniae*) that possess carbapenem-hydrolyzing enzymes belonging to the KPC family of beta-lactamases (Colombia [44,45], Brazil [46,47] and Argentina [48]). This increasing medical issue calls for a more effective solution by means of new antimicrobial agents. However, at present, not one of the 16 antimicrobial compounds in late-stage clinical development is specifically directed against carbapenem-resistant pathogens [49]. In fact, the increased use of carbapenems to combat the growing prevalence of MDR bacteria, particularly ESBL-producing strains, shows early signs of eroding the effectiveness of the carbapenems. A more highly targeted and restrained use of these drugs, aimed at preserving their antimicrobial activity, is probably warranted. Their therapeutic substitution in specific pathologies is one of the strategies to achieve this objective; for example, the use of tigecycline instead of carbapenems in intra-abdominal infections where ESBL-producing Gram-negatives are suspected. In that sense, Lucía *et al* have demonstrated that it is possible to reduce the selection pressure of group 2 carbapenems (imipenem, meropenem) by using ertapenem in patients with infections due to ESBL-producing microorganisms [50].

In summary, our survey was limited in scope and simply sought to analyze patterns of antibiotic prescription; however, these data show that "restricted" antibiotics (mainly carbapenems) are heavily used and that infections in LA ICUs have low microbiological testing. We hope that the limitations of our current study may generate enthusiasm for prospective studies, with more robust designs, in order to improve our knowledge of antibiotic prescription habits in Latin American ICUs.

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TRANSPARENCY DECLARATION: Daniel Curcio is speaker for Wyeth SA (Argentina) and Abraham Ali is speaker for Wyeth (Colombia).

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