

## Antibiotic prescription in intensive care units in Latin America

DANIEL J. CURCIO ON BEHALF OF THE LATIN AMERICAN ANTIBIOTIC USE IN INTENSIVE CARE UNIT GROUP<sup>1</sup>

Correspondence. E-mail: djcurcio@gmail.com

### ABSTRACT

The intensive care units (ICUs) are often considered as the epicenters of antibiotic resistance. Therefore, the total antibiotic consumption is approximately ten fold greater in ICU wards than in general hospital wards. The aim of this study was to evaluate the current use of antibiotics in Latin American ICUs. Three cross-sectional (one-day point) prevalence studies were undertaken in 43 Latin American ICUs. Of 1644 patients admitted, 688 received antibiotic treatment on the days of the study (41.8 %) and, 392 cases (57 %) were due to nosocomial-acquired infections. Of all infections, 22 % (151/688) corresponded to septic shock; and 22 % (151/688) to nosocomial pneumonia (50/151 [33 %], ventilator-associated pneumonia). In 485 patients (70.5 %), cultures were performed before starting antibiotic treatment. The most common microorganisms isolated were extended-spectrum  $\beta$ -lactamase *Enterobacteriaceae*, (30.5 %), and *Pseudomonas aeruginosa* (17 %). Carbapenems (imipenem or meropenem) were the antibiotics most frequently prescribed (151/688, 22 %), followed by vancomycin (103/688, 15 %), piperacillin- tazobactam (86/688, 12.5 %) and broad-spectrum cephalosporins (mainly cefepime) (83/688, 12 %). In summary, carbapenems were the most frequent antibiotics prescribed in Latin American ICUs. This practice seems justified for the high rates of ESBL-producing Gram-negatives found in our patients. Beyond this reason, the problem of bacterial resistance in LA requires that physicians improve the use of carbapenems. The high prevalence of carbapenem-resistant *A. baumannii* and *P. aeruginosa* in the region, along with the prevalence of carbapenem-resistant *Enterobacteriaceae*, have increased markedly. A comprehensive evidence-based stewardship program based on local antimicrobial use and resistance problems should be implemented in our clinical settings.

**Key words:** drug resistance, carbapenem,  $\beta$ -lactamases, Latin America

### RESUMEN

**Prescripción de antibióticos en unidades de cuidados intensivos de Latinoamérica.** Las unidades de cuidados intensivos (UCI) son a menudo consideradas el epicentro de la resistencia a los antibióticos. En este sentido, el consumo total de antibióticos es aproximadamente diez veces mayor en las UCI que en las salas de internación general. El objetivo de este estudio fue evaluar el hábito prescriptivo de antibióticos en las UCI de varios países de Latinoamérica. A tal fin, se realizó un estudio transversal con tres evaluaciones puntuales de un día de duración cada una, para determinar la prevalencia del uso de antibióticos en las 43 UCI ubicadas en distintos países del continente americano. De los 1644 pacientes admitidos, 688 estaban recibiendo tratamiento antibiótico en los días en que se realizó el relevamiento (41,8 %), en 392 casos (57 %), debido a infecciones nosocomiales. De todas las infecciones, 22 % (151/688) correspondieron a *shock séptico* y 22 % (151/688) a *neumonía nosocomial* (de estas últimas, el 33 % [50/151] fueron *neumonías asociadas a ventilación mecánica*). En 485 pacientes (70,5 %) se obtuvieron cultivos antes del inicio del tratamiento antibiótico. Entre los aislamientos, los microorganismos más comúnmente aislados fueron las enterobacterias productoras de  $\beta$ -lactamasas de espectro extendido (BLEE) (30,5 %) y *Pseudomonas aeruginosa* (17 %). Los carbapenems (imipenem o meropenem) fueron los antibióticos prescritos con mayor frecuencia (151/688, 22 %), seguidos por la vancomicina (103/688, 15 %), la piperacilina-tazobactama (86/688, 12,5 %) y las cefalosporinas de amplio espectro (principalmente cefepima) (83/688, 12 %). En conclusión, los carbapenems fueron los antibióticos más frecuentemente prescritos en las UCI de los países latinoamericanos evaluados. Esta práctica podría estar justificada por las altas tasas de enterobacterias productoras de BLEE halladas en los pacientes de esas regiones. Más allá de esta razón, el problema de la resistencia bacteriana en muchos países del continente requiere que los médicos optimicen el uso de los carbapenems, ya que la prevalencia de aislamientos resistentes a este grupo de antimicrobianos se ha incrementado marcadamente, tanto en *A. baumannii* y *P. aeruginosa* como en enterobacterias. Frente a este panorama, en todos estos países se torna necesario implementar programas de optimización del uso de antibióticos, basados en la epidemiología y en las tasas de resistencia locales.

**Palabras clave:** resistencia a los antibióticos, carbapenem,  $\beta$ -lactamasas, Latinoamérica

### INTRODUCTION

Antibiotics are one of the most common therapies administered in intensive care unit (ICUs) settings (9). Hospitalized patients in these areas often suffer from a debilitated physical

condition and deficiencies of the immune system, requiring intense antibiotic therapy for longer periods and for severe infectious complications, including nosocomial infections. Therefore, the total antibiotic consumption is approximately tenfold greater in ICUs than in general hospital wards (44).

This high density of antibiotic use in the ICUs favours the development of multi-drug resistant pathogens (MDR), either by selecting a resistant mutant or allowing the emergence of MDR-bacteria in the colonisation flora (14, 21, 34, 45). Rice recently referred to these as the "ESKAPE" pathogens (42) (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) to emphasize that they currently cause the majority of worldwide hospital infections (Latin America included) (9, 50), and effectively "escape" the effects of antibacterial drugs.

Taking these data into account, the aim of this study was to evaluate the current use of antibiotics in Latin American ICUs.

## MATERIAL AND METHODS

Three cross-sectional (one-day point) prevalence studies have been performed on November 17, 2008; June 11, 2009, and September 23, 2010 in 68 LA ICUs in order to gather information about antibiotic prescription.

All participant LA ICUs completed a web-based data collection form with data from the patients receiving antibiotics, with the exception of those who received them for surgical prophylaxis. The data was collected using a unique electronic form included in the website ATB-Terapia Intensiva™ (<http://www.clinicalrec.com.ar>), designed by ClinicalREC® from Argentina.

The participating hospitals were from Argentina (n = 9), Bolivia (n = 7), Chile (n = 8), Colombia (n = 16), Costa Rica (n = 2), Ecuador (n = 16), Guatemala (n = 1), Peru (n = 5) and Venezuela (n = 4).

Each ICU had a principal investigator, who was given a personal username and password to access the electronic form. All of them received training in the method to use the website.

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

- General data of the ICU: number of beds; number of patients admitted; number of patients admitted with antibiotic treatment.
- General data of the patients: number of registry, sex, age, date of ICU admission, risk factors for infection due to MDR pathogens, 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 the antibiotic treatment (measured by the SOFA score), type of indication (i-empirical treatment –patient with signs and symptoms of infection and pending cultures-, ii-culture-directed therapy –patient with signs and symptoms of infection and positive cultures- or iii-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); and antibiotic treatment of the present infection (type and days of antibiotics used).

Established criteria were used to define clinical infection (15).

An infection was considered nosocomial when it was not present or incubating in a patient at the time of admission to a hospital, but occurred within >48 h after admission to the hospital (15, 19). 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 30 days preceding admission to the hospital (19).

Bacterial identification was performed according to the clinical microbiology procedure handbook (26). Bacterial identification was confirmed, and antibiotic susceptibility testing was performed on each of the isolates using a semi-automated system in 30 hospitals (59 %). In the remaining hospitals, bacterial susceptibility was determined by using the Kirby Bauer method (disk diffusion).

Extended-spectrum  $\beta$ -lactamase (ESBL)-producing microorganisms were detected and confirmed according to the standards of the Clinical Laboratory Standards Institute, using the double disk test for confirmation (8).

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

The study was directed in compliance with the clinical routine practices determined by the responsible physician. The study was based on a case registry methodology and did neither 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. The study was approved by the local institutional review board of each participant's hospitals and patient consent was not required because of the observational nature of the study.

Results are expressed as proportions. When applicable, two tailed hypothesis testing for difference in proportions were used (Proportion Test); a *p* value of < 0.05 was considered significant.

## RESULTS

### Patients' general data

On the three days of the prevalence study, there were 1644 patients in the participating ICUs (1927 total beds), 688 of whom (41.8 %, range between ICUs 0-100 %) were receiving antibiotics.

Median age of patient was 60.3 years (range 14-93); 471 were male (63 %).

Median of APACHE II score at admission was 18 (SD  $\pm$  5) ( $\geq$  15 in 482/688 patients –70 %–, and < 15 in 206/688 patients –30 %–) (Table 1).

The prevalence of risk factors for infections due to MDR pathogens was 100 % in this patient population. Hospitalization in an acute care hospital for 2 or more days within the past 90 days, recipients of recent intravenous antibiotic therapy, and immunosuppressive illness or therapy were the risk factors more frequently observed (69 %, 51 % and 30 %, respectively) (Table 2).

### Infection data

The mean of length of stay (LOS) in an ICU from admission date to infection diagnosis was 7.3 days (range 2-13 days).

The indication for antibiotic treatment corresponded to community-acquired infections in 43 % (n = 296) and to nosocomial-acquired infections in 57 % (n = 392) of cases.

The most frequent infections were: septic shock (22 % [151/688]), nosocomial pneumonia (22 % [151/688]), complicated skin and skin structure infections (7.8 % [53/688]), sepsis of unknown origin (5.8 % [40/688]), and complicated intrabdominal infections (5.6 % [39/688])

**Table 1.** General and infection data of patients

Characteristics	Value
Number of patients admitted, n	1644
Number of patients receiving antibiotics, n/total (%)	688/1644 (41.8)
Age; mean years (range)	60.3 (14-93)
Male; n (%)	471 (63)
APACHE II, median	18 (SD ± 5)
• ≥ 15, n (%)	482 (70)
• < 15, n (%)	206 (30)
LOS <sup>(1)</sup> between date of admission to the diagnostic of infection, median (range)	7.3 (2-13)
Origin of the infection, n (%)	
• Nosocomial acquired	392 (57)
• Community acquired	296 (43)
Type of infection, n (%)	
• Septic shock	151 (22)
• Nosocomial pneumonia	151 (22)
• Skin and skin structure infection	53 (7.8)
• Sepsis of unknown origin	40 (5.8)
• Complicated intra abdominal infection	39 (5.6)
• Community-acquired pneumonia	35 (5)
• Genitourinary infection	13 (1.8)
• Endovascular infection	7 (1)
• Others	199 (29)
Culture sites, n patients/total (%)	485/688 (70.5)
Culture sites, n samples/n per patient	500/1.03
• Blood cultures, n/total (%)	160/500 (32)
• Respiratory samples <sup>(2)</sup> , n/total (%)	126/500 (25)
• Peritoneal fluid, n/total (%)	42/500 (8.5)
• Skin and soft tissue	35/500 (7)
• Others	137/500 (27.5)
Positive cultures	
• n positive cultures/ n total cultures (%)	310/500 (62)
• Blood cultures, n positive cultures/ n total cultures (%)	68/160 (42.5)
• Respiratory samples, n positive cultures/ n total cultures (%)	91/126 (72)
• Peritoneal fluid, n positive cultures/ n total cultures (%)	38/42 (90)
• Skin and soft tissue, n positive cultures/ n total cultures (%)	6/35 (17)
• Others; n positive cultures/ n total cultures (%)	107/137 (78)
Clinical Isolates,	
• n isolates/ n total positive cultures	341/310
ESBL <sup>(3)</sup> -producing <i>Enterobacteriaceae</i> , n/total (%)	104/341 (30.5)
<i>P. aeruginosa</i> , n/total (%)	58/341 (17)
• carb-R <sup>(4)</sup> - <i>P. aeruginosa</i> , n/total (%)	19/58 (33)
• carb-S <sup>(5)</sup> - <i>P. aeruginosa</i> , n/total (%)	39/58 (67)
MRSA <sup>(6)</sup>	48/341 (14)
<i>Acinetobacter</i> spp.	44/341 (13)
• carb-R(4)- <i>Acinetobacter</i> spp.	29/44 (66)
• carb-S(5)- <i>Acinetobacter</i> spp.	15/44 (35)
• Others	87/341 (25.5)

<sup>(1)</sup>length of stay; <sup>(2)</sup>traqueal aspirate (25%), bronchoalveolar lavage -BAL-(1.5%), and mini-BAL (2%); <sup>(3)</sup>extended-spectrum  $\beta$ -lactamases (*K. pneumoniae* and *Escherichia coli*); <sup>(4)</sup>carbapenem-resistant; <sup>(5)</sup>carbapenem-susceptible; <sup>(6)</sup>methicillin-resistant *S. aureus*

**Table 2.** Risk factors for infections due to multidrug-resistant pathogens

Risk factor	n (%)
Hospitalization for 2 or more days within the past 90 days	475 (69)
Previous antibiotic treatment within the past 90 days	351 (51)
Immunosuppressive illness or therapy	206 (30)
Wound care at home	41 (6)
Hemodialysis within the past 90 days	20 (3)
Residents of a nursing home or long-term care facility	20 (3)
Intravenous antibiotic therapy/chemotherapy at home	7 (1)

(Table 1). Thirty-three percent of nosocomial pneumonia were ventilator-associated (VAP) (50/151).

Five hundred samples for bacterial culture were obtained before starting antibiotic therapy in 485 patients (70.5 %). Thirty-two percent of the samples were from blood (160/485), whereas 25 % (126/500) were from the respiratory tract (tracheal aspirate -23 %-, bronchoalveolar lavage [BAL] -1 %-, and mini-BAL 1 %).

In 62 % of the cultures performed (310/500), a microorganism considered as the causative agent of the infection was isolated (72 % in respiratory tract samples and in 42.5 % of blood cultures) (Table 1).

Among isolates, extended-spectrum  $\beta$ -lactamase *Enterobacteriaceae*, -mainly *K. pneumoniae* and *E. coli*- (30.5 %), and *P. aeruginosa* (17 %) were the most common microorganisms, followed by methicillin-resistant *S. aureus*-MRSA- (14 %), and *Acinetobacter* spp. (13 %), 66 % of *Acinetobacter* spp. and 33 % of *P. aeruginosa*, were carbapenem-resistant -imipenem and meropenem-respectively (Table 1).

#### Antibiotic use data

Median of SOFA score at the beginning of the antibiotic treatment was 7 (SD  $\pm$  4.2) ( $\geq$  6 in 564/688 patients -82 %-, and  $<$  6 in 124/688 patients -18 %-) (Table 3).

We found that antimicrobial therapy was prescribed on the study day as empirical treatment, culture-directed prescription and clinically documented infection in 52 %, 32 %, and 12 %, respectively. At no point were antibiotics discontinued, not even in cases in which cultures were not done or yielded negative results (Table 3).

Fifty-eight percent of the patients (399/688) had received previous antibiotic therapy during current hospitalization, ( $\geq$  3 days of treatment in 320/399 patients [80.2 %], and  $<$  3 days of treatment in 79/399 patients [19.8 %]). Third generation cephalosporins, fluoroquinolones, carbapenems and vancomycin (in all cases alone or in combination with other antibiotics) were the most frequent antibiotics previously used (42 %, 24 %, 24 % and 23 %, respectively) (Table 3).

On the days of the study, carbapenems (imipenem or meropenem) were the most frequently prescribed antibiotics (151/688, 22 %), followed by vancomycin (103/688,

15 %) and piperacillin-tazobactam (86/688, 12.5 %) and broad-spectrum cephalosporins (mainly cefepime) (83/688, 12 %) (Table 3). Carbapenems were prescribed in combination with vancomycin in 67 % (101/151) of the cases.

There were no significant differences in "restricted" antibiotic prescriptions (carbapenems, vancomycin, piperacillin-tazobactam, broad-spectrum cephalosporins, tigecycline, polymyxins and linezolid) among the four groups of APACHE II and SOFA score at the beginning of the antibiotic treatment ( $<$  15 and  $\geq$  15 and  $<$  6 and  $\geq$  6, respectively) (Table 4).

#### DISCUSSION

The results of this observational, cross-sectional study shows that 41.8 % of patients hospitalized in a general LA ICU were receiving at least one antibiotic, in 57 % of the cases to treat nosocomial infections. Previously published studies show a wide range of prevalence of antibiotic use in the ICU setting (between 45-85 %) (5, 16, 40, 54). There are several reasons for the high consumption of antibiotics in the ICU (5, 16, 36, 40, 54): i-patients admitted with serious community-acquired infections (ie. community-acquired pneumonia and complicated intra abdominal infection), and ii-the acquisition of the infection during the nosocomial stay, favored by the presence of multiple comorbidities, the high rates of invasive device use and the presence of risk factors for infections due to MDR pathogens (17, 36, 37). In that sense, all our patients presented at least one risk factor for infections due to MDR bacteria, mainly hospitalization for 2 or more days and previous antibiotic treatment within the past 90 days in both cases.

In order to improve these antibiotic prescription patterns, it is well-established that the precise knowledge of the pathogens associated with the disease allows a rational antibiotic selection. In clinical practice, however, antibiotics are often used even when culture results are not available (10). It is the rational of the de-escalation strategy which proposes to reassess the patient on day 3 to define the initial antibiotic treatment based on culture results and the clinical response (23, 24). In our patients, cultures were obtained before beginning the antibiotic

**Table 3.** Patient antimicrobial prescription data (n = 688)

Characteristics	Value
SOFA score at the beginning of the antibiotic treatment, median	7
• $\geq 6$ , n (%)	564 (82)
• $< 6$ , n (%)	124 (18)
Type of indication, n (%)	
• Empirical treatment	358 (52)
• Cultured-directed therapy	248 (36)
• Clinical documented treatment	82 (12)
Previous antibiotic therapy; n (%)	399 (58)
Days	
• $\geq 3$ days, n (%)	320 (80.2)
• $< 3$ days, n (%)	79 (19.8)
Type <sup>1</sup>	
• Broad-spectrum cephalosporins	167 (42)
• Fluoroquinolones	96 (24)
• Carbapenems (imipenem or meropenem)	96 (24)
• Vancomycin	92 (23)
• Ampicillin-sulbactam	85 (21)
• Piperacillin-tazobactam	80 (20)
• Others	45 (11)
Patients with antibiotic on prevalence day; n/total (%)	688/1644 (41.8)
• Carbapenems (imipenem or meropenem) <sup>(1)</sup>	151/688 (22)
• Vancomycin <sup>(1)</sup>	103/688 (15)
• Piperacillin-tazobactam <sup>(1)</sup>	86/688 (12.5)
• Broad-spectrum cephalosporins <sup>(1)</sup>	83/688 (12)
• Fluoroquinolones	52/688 (7.5)
• Ampicillin-sulbactam	41/688 (6)
• Aminoglycosides <sup>(1)</sup>	34/688 (5)
• Others	93/688 (13.5)

<sup>(1)</sup>alone or in combination with other antibiotics

**Table 4.** Prescription of "restricted" antibiotics in patients with different severity scores values

Antibiotic prescriptions	SOFA		p	APACHE II		p
	$< 6$ n <sup>(1)</sup>	$\geq 6$ n <sup>(1)</sup>		$< 15$ n <sup>(1)</sup>	$\geq 15$ n <sup>(1)</sup>	
Total	124	564		206	482	
"Restricted" antibiotics <sup>(2)</sup>	84 (68%)	406 (72%)	0.4034	132 (64%)	306 (63.5)	0.8550

<sup>(1)</sup>number of prescriptions, <sup>(2)</sup>carbapenems, vancomycin, piperacillin-tazobactam, broad-spectrum cephalosporins, tigecycline, polymyxins and linezolid

treatment in 70.5 % of the cases. In more than 60 % of these patients, a microorganism considered as the causative agent of the infection was isolated; nevertheless, only 32 % of patients received a culture-directed antibiotic prescription. In a large European study which included 20 hospitals, Ansari *et al.* (2) have recently published that

samples for bacterial culture were obtained before therapy only in 43 % of cases (1822 of 4242 adult patients).

As demonstrated by Erlandsson *et al.* (11), septic shock and nosocomial pneumonia account for nearly one half of all antibiotics prescribed to our patients. In these particular indications, it is well-established that the appropriate



empirical antimicrobial treatment is associated with better survival, therefore several authors recommend the use of broad spectrum antibiotics (alone or in combination) for the empirical treatment of these serious infections (20, 31, 41). However, not to consider the tailored therapy in these cases could lead to the possibility of "collateral damage", where overuse/misuse of antibiotics is associated with MDR-pathogen infections (43). The low level of intent to document the microbiology of the infections (especially in severely ill patients) increases this possibility. The challenge for ICU physicians is to understand that obtaining microbiological cultures before initiating empirical antimicrobial therapy is part of the diagnostic work-up of ICU patients (49).

"ESKAPE pathogens" (with the exception of *E. faecium*) were the most common microorganisms isolated from our patients (74.5 %), with a similar MDR-profile to those described by several microbiological surveillance systems in the region (47, 50). The TEST 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 Latin America than in North America and Europe (37.9 %; 37.6 %; 35.8 % vs. 9.7 %; 13.1 %, 15.1 % and 15.3 %; 14.8 %; 17.4 %, respectively). In contrast, rates of methicillin resistance among *S. aureus* were higher in North America (53.7 %) than in Latin America (46.6 %) and Europe (25.1 %) (50).

We found that the prevalence of MRSA and *Acinetobacter* spp. were lower than other series published by LA authors (1, 3, 4). The low frequency of VAP described in our patients (7.2 %, 50/688), where these microorganisms are the most frequent etiologic agents in our region, could be the reason of this finding.

Prior antibiotic usage is one factor that predisposes to infections with MDR-bacteria (6, 7, 12). In 58 % (80.2 %  $\geq$  3 days) of the cases in our study, the evaluated patients had received previous antibiotic treatment, most of them broad-spectrum agents). In one third of the patients, broad-spectrum cephalosporins or fluoroquinolones were used, both of which are in close relationship with the selection of MDR microorganisms, mainly ESBL-producing gram-negatives, the microorganisms most frequently isolated in our study (27, 32, 48).

In terms of antibiotic prescription on the day of the study, we observed that carbapenems (imipenem or meropenem, alone or in combination with vancomycin), were the most frequently prescribed antibiotics in Latin American ICUs, followed by vancomycin, piperacillin-tazobactam and broad-spectrum cephalosporins.

This pattern of prescription habits seems justified for several reasons: i- sixty-four percent of the registered infections were nosocomial, where MDR-microorganisms are frequently involved (13); ii- fifty-eight percent of patients had received previous antibiotic therapy other than carbapenems during the present hospitalization in more than 70 % of cases to extend the spectrum of the previously

prescribed antibiotic which is a very common concept between ICU-physicians; iii- high rates of ESBL-producing gram-negatives were found in our patients. Carbapenems are stable against hydrolyzing activity of ESBLs and are regarded as the drugs of choice for the treatment of infections caused by ESBL-producing *Enterobacteriaceae*. The combination with vancomycin extends the spectrum towards MRSA; iv- the early effective therapy for infections in critically ill patients (defined as antimicrobial treatment against pathogens associated with infection) is associated with low mortality rates (20, 22, 25); therefore, a fresh approach to the effective treatment of septic shock and nosocomial pneumonia (the most frequent pathologies in our study), is to use a broad-spectrum antibacterial treatment followed by precision therapy based on susceptibility results (41), and v- physicians believe in carbapenems because it is a potent antibiotic having an ultra-broad spectrum of activity that encompasses MDR and difficult-to-treat gram-negative bacteria with several clinical trial data that support its clinical effectiveness. In fact, we have found that there is a trend to use carbapenems in severely ill patients (alone or in combination with vancomycin), regardless of the microbiological documentation.

Beyond these reasons, there are several issues related with the antibiotics most frequently used in Latin American ICUs (carbapenems and vancomycin), which physicians must take into account.

The high prevalence of carbapenem-resistant *A. baumannii* in the region has increased markedly (51), along with the prevalence of carbapenem-resistant strains of *P. aeruginosa* (47). Another concern 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 (52, 53), Brazil (35, 39), and Argentina (38)]. In fact, the increased use of carbapenems to combat the growing prevalence of MRB, particularly ESBL-producing strains, shows early signs of eroding carbapenem effectiveness. 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 reach this objective; for example, the use of tigecycline instead of carbapenems in intra abdominal infections where ESBL-producing gram-negatives are suspected.

The vancomycin MIC creep in MRSA is a worldwide problem which limits the use of this antibiotic in severely ill patients. In respiratory infections, such as VAP or bacteremia due to MRSA, the clinical success using vancomycin was associated with the possibility of reaching a pharmacodynamic target of  $> 350$  of AUC/MIC (18). When the MRSA has a vancomycin MIC  $\geq 1$  mg/ml (more than 70 % of the LA isolates) (18), the probability of achieving this AUC/MIC target with the standard dose is between 40 % and 60 %, and when the MRSA vancomycin MIC is 2 mg/ml, the probability is 0 % (33, 46). Therefore, in

these cases we need higher doses of vancomycin, with the consequent risk of nephrotoxicity (28, 30). Therapeutic options other than vancomycin should be considered in patients with risk factors for infection due to MRSA with high vancomycin MIC (*ie.* patients' recent exposure to vancomycin) (29).

We did not find significant differences between antibiotic prescription (global and "restricted" antibiotics), in different groups of patients based on the mean of the APACHE II score at admission ( $< 15$  and  $\geq 15$ ) and the SOFA score at the beginning of the antibiotic treatment ( $< 6$  and  $\geq 6$ ). Our observation revealed that the main condition to select the antibiotic treatment in our hospitals was the fact of "being a patient in ICU" rather than the severity of illness. Whether this is due to a low potential of our observational methodology or the small number of cases analyzed needs further evaluation.

Our findings show that our web-based method for collection of one-day point prevalence was implemented successfully. However, based on the limitations of the model used, the results of this study must be taken with caution.

We hope that the limitations of our current study may generate enthusiasm for prospective studies having more robust designs, in order to improve our knowledge on antibiotic prescription habits in Latin American ICUs.

#### **<sup>1</sup>Latin American Antibiotic Use in Intensive Care Unit**

**Group:** Daniel Curcio, Instituto Sacre Coeur, Argentina; Abraham Alí, Fundación Cardioinfantil, Colombia; Alejandro Duarte, Hospital Regional Río Grande, Argentina; Alfredo Defilippi Pauta, Hospital Luis Vernaza, Ecuador; Alvaro Fernando Erazo Guerrón, Hospital Quito Nro 1 Policía Nacional, Ecuador; Ana Bañales Churrut, Hospital San José, Chile; Blanca Salcedo, Hospital Oncológico Solón Espinosa Ayala, Ecuador; Carlos Humberto Paz Chávez, Hospital Central de la Fuerza Aérea y Clínica San Gabriel, Perú; Carlos Ibáñez-Guzmán, Hospital Obrero N° 1, Bolivia; Carlos Rebolledo Maldonado, Clínicas SaludCoop, Colombia; Daniel Alvarado Cueto, Clínica Madre Bernarda, Colombia; David López García, Hospital Universitario San Vicente de Paúl, Colombia; David Yepes, Clínica CES, Colombia; Eduardo Labarca, Hospital Naval Almte Nef, Chile; Electra Moreno Veloz, Hospital de Infectología Dr. Daniel Rodríguez Maridueña, Ecuador; Erick Valencia, Clínicas Saludcoop, Colombia; Fabian Plano, Hospital Privado Modelo, Argentina; Fabio Varón, Fundación Cardioinfantil, Colombia; Fausto Guerrero Toapanta, Hospital Carlos Andrade Marín, Ecuador; Fernando Paredes Oña, Hospital de Clínicas Pichincha, Ecuador; Francisco Arancibia, Instituto Nacional del Tórax, Chile; Francisco Molina Saldarriaga, Clínica Universitaria Bolivariana, Colombia; Franco Montufar Andrade, Hospital Pablo Tobón Uribe, Colombia; Freddy Morales Alava, Hospital Oncológico Dr. Julio Villacreses Colmont, Ecuador; Gleinner Cañarte Bermudez, Hospital IEES de Portoviejo, Ecuador; Gustavo La Fuente Zerain, Hospital Universitario Japonés, Bolivia; Henry Caballero Narváez, Hospital Enrique Garcés, Ecuador; Iván Ramos Palomino, Clínica San Gabriel, Perú; Juan Salas Villasante, Hospital Regional Docente de Trujillo, Perú; Juan Villalobos Vindas, Hospital México, Costa Rica; Jorge Castagnino, Sanatorio de La Providencia, Argentina; Jorge Espitaleta Gómez, Hospital San Rafael de Alajuela, Costa Rica; Jorge Ranero Meneses, Instituto Guatemalteco de Seguridad Social, Guatemala; José Rojas Suarez, Gestión Salud SA and Grupo de Investigación en Cuidados Intensivos y Obstetricia, Colombia; Juan Carlos Fernández Mercado, Gestión Salud SA and Grupo de Investigación

en Cuidados Intensivos y Obstetricia, Colombia; José Guzmán Torrico, Centro Médico Quirúrgico Boliviano Belga, Bolivia; José Vergara Centeno, Hospital Luis Vernaza, Ecuador; Juan Carlos Medina, Sanatorio Itoiz, Argentina; Julio Durán Pérez, Hospital Uninorte, Colombia; Karina Marín, Hospital Oncológico Solón Espinosa Ayala, Ecuador; Lenny Alba Caero, Hospital Clínico Viedma, Bolivia; Leonardo Durán Crespo, Hospital Universitario Univalle, Bolivia; Leonina Ferreira Cabrera, Hospital Guillermo Grant Benavente, Chile; Luis Castillo Bravo, Instituto Enfermedades Neoplásicas, Perú; Luis Soto Germani, Hospital San Pablo De Coquimbo, Chile; Martín Carvajal Herrera, Clínica Medihelp Services, Colombia; Martín Oyanguren, Hospital Nacional Edgardo Rebagliati, Perú; Miguel Chung Sang, Clínica Guayaquil and Hospital Militar de Guayaquil, Ecuador; Miguel Llano, Hospital General de las Fuerzas Armadas, Ecuador; Mijail Játiva, Hospital Eugenio Espejo, Ecuador; Norma Ruiz Oliveros, Hospital Militar de Caracas, Venezuela; Oscar López Acosta, Clínica Martha, Colombia; Rafael Cotes, Clínica Sur, Colombia; Rafael Thomen, Clínica La Asunción, Colombia; Ray Mendoza Franco, Hospital Consorcio Gestión UCI, Colombia; Ramón Belloni, Sanatorio Güemes, Argentina; Ricardo Morales, Clínica Las Lilas, Chile; Ricardo Romero, Clínica Sagrada Familia and Clínica Adventista Belgrano, Argentina; Rolando Aguilera Perrogón, Hospital Obrero Nro 3, Bolivia; Ruben Camacho Alarcón, Clínica San Gregorio and Hospital IESS-Manta, Ecuador; Ruben Camargo, Clínica General del Norte, Colombia; Stenio Cevallos, Hospital Alcivar, Ecuador; Stevens Salva Sutherland, Hospital de Clínicas Caracas, Venezuela; Victor Alanis Mirones, Hospital Universitario San Juan de Dios, Bolivia; Víctor Figueroa, Hospital Oncológico Solón Espinosa Ayala, Ecuador; Virginia Intriago Cedeño, Hospital Verdi Cevallos Balda, Ecuador; Viviana Romero, Hospital Padre Pedro Tardivo, Argentina; Werner Jensen, Hospital Dr. Gustavo Fricke, Chile; Zulma Urbina Contreras, Clínica Universitaria del Norte de Santander, Colombia; Alfonso Socorro Morales, Hospital Dr. Manuel Noriega Trigo, Venezuela; Arnoldo Rivero Mendoza, Hospital Dr. Miguel Orea, Venezuela; Vinko Tomcic Flores, Clínica Alemana, Chile.

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(Hospital Oncológico Solón Espinosa Ayala); Alvaro Villacrés, Juan Carlos Carrión and Emérita Basantes (Hospital Oncológico Solón Espinosa Ayala); Enrique Boloña (Clínica Guayaquil); Killen Briones Claudett (Hospital Militar de Guayaquil); Gustavo Granda (Hospital Eugenio Espejo); Jorge Vera (Hospital Verdi Cevallos Balda); El Salvador: Gerardo Campos Mezquita and Corina Esmeralda Arevalo Huerdo (Hospital General. ISSS); Guatemala: Rudy López (Instituto Guatemalteco de Seguridad Social); Perú: Deysi Diaz Seijas (Clínica San Gabriel).

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