ECRONICON OPEN ACCESS

EC PAEDIATRICS
Research Article

Evolution of Antibiotic Consumption in Pediatric Intensive Care Unit during a Five Year Period (2010-2015)

Héctor M Telechea[1]*, Leandro Barboza[2], Fernando Antunez[3], Adriana Varela[4], Amanda E Menchaca[5] and Gustavo A Giachetto[6]

[1]Professor Adjunct Pediatric Critical Care, Profesor Adjunct Pharmacology Department, Medicine College, Universidad de la República, Uruguay

[2]Pharmacology Department, Medicine College, Universidad de la República, Uruguay

[3]Pharmacist, Chief of Pharmacy Department,Centro Hospitalario Pereira Rossell, Uruguay

[4]Laboratory of Microbiology, Centro Hospitalario Pereira Rossell, Uruguay

[5]Professor Pediatric Critical Care, Medicine College, Universidad de la República, Uruguay

[6]Professor Pediatrics, Medicine College, Universidad de la República, Uruguay

***Corresponding Author**: Héctor M Telechea, Professor Adjunct Pediatric Critical Care, Profesor Adjunct Pharmacology Department, Medicine College, Universidad de la República, Uruguay.

Received: February 01, 2018; **Published:** February 20, 2018

Abstract

Background: Antibiotic prescription in Pediatric Intensive Care Unit (PICU) is frequent.Objective. We proposed to calculate anually antibiotic consumption in a five year period (2010 - 2015) in PICU. Also to determine the number of bacterial isolations in every year included in the study.

Methods: Antibiotics included were amikacin, cefotaxime, ceftriaxone, ceftazidime, clarithromycin, meropenem and vancomycin. Antibotic consumption was expressed by Defined Daily Dose (DDD)/every 100 hospital bed-days (DDD/100 beds). Bacterial isolations from PICU and it's antibiótic susceptibility pattern were also analized. Bacteria included were *Staphylococcus aureus*, Negative Coagulase *Staphylococcus, Klebsiella pneumoniae, Enterobacter cloacae* and *Pseudomonas aeruginosa*. Evolution of antibiotic consumption was compared with bacerial isolations.Children hospitalizaed in PICU, treated with selected antibiotics during 2010 - 2015 were included.

Results: Except amikacin, all antibiotics showed an increase in consumption. Comapring values of DDD/100 beds in year 2010 vs 2015, clarithromycin consumption growth 725% (from 0,004 DDD/100 beds to 0,034 DDD/100 besd) and cefotaxime 175% (from 0,004 DDD/100 beds to 0,011 DDD/100 beds). Vancomycin and Meropenem rised 28% and 26% respectivilly. Bacterial isolations in PICU, kept steady, during the five year period.

Conclusions: The rise in antibiotic consumption is a warning fact. We found a lack of relationship between antibiotic consumption with the number of bacterial isolations. One of the posible consequences is antimicrobial resistance. Policies for an adequate use of antibiotics in our PICU should be developed.

Keywords: *Antibiotic Consumption; Pediatric Intensive Care Unit (PICU); Nosocomial Infections*

Introduction

Infections are a common cause of admission to Pediatric Intensive Care Units (PICU). Nosocomial infections are a major health problem in critical care units and are associated with an increase of morbidity, mortality and healthhcare costs [1-3]. These infections usually are produced by multirresisitant bacteria, therefore is necessary the use of wide spectrum antibiotics for treatment [4].

Antimicrobial resistance (AR) is a major health problem worldwide. Resintance can worsen clinical outcomes and augment healthcare costs [5,6]. Massive use of antibiotics is the main risk factor for developing AR [7-11]. One of the suggested strategies for avoid continous growth of resistance, are policies of rational use of antibiotics in critical care units [12,13].

In 2014, World Health Organization (WHO) established the problem of AR arround the world by the elabortaion of a document. In this report, is standed out, the development of carbapenem-resistance in *Enterobacteriaceae*, mostly *Klebsiella pneumoniae* (*K. pneumoniae*). Carbapenems are frequentelly used in critical care unit for treatment of infections produced by Extended Spectrum Beta Lactamase

(ESBL) *Enterobacteriaceae* and multirresistant *Pseudomonas aeruginosa*. The WHO's report, states a high level of AR to third generation cephalosporins in *Escherichia coli* and *K. pneumoniae* strains [14]. These facts have been confirmed by other reports [15,16]. WHO's report also emphasizes the spread of meticillin resistant *Staphylococcus aureus* in comunity strains [14].

In Centro Hospitalario Pereira Rossell (CHPR), a tertiary level children's hospital, operates a multidisciplinary group, wich has tackled the topic of antibiotic consumption and its relationship with antimicrobial susceptibility pattern. The results of these vigilancy have been used in the update of guidelines for empirical antibiotic treatment and for antibiotic prophylaxis. Most of consumption studies have been made in ambulatory patients and in moderate care area of hospital [17-19]. Data of antibiotic consumption in PICU are lacking.

We decide to conduce an study with the goal to calculate antibiotic consumption in the period 2010 - 2015 in PICU of CHPR. Other objective was to establish relationship between antibiotic consunmption with number of bacterial isolations and it's antimicrobial susceptibilty pattern in the same period.

Methodology

An observational and retrospective study was conducted. Antibiotic consumption in PICU of CHPR was calculated in the period 2010-2015. This is a medical-surgical unit with a máximum capacity of 20 beds. In this PICU are assisted children between 1 month and 14 years.

Antibioticcs included in the analysis were those with highest level of prescription in our PICU (amikacin, cefotaxime, ceftriaxone, ceftazidime, clarithromycin, meropenem, vancomycin). Antibotic consumption was expressed by Defined Daily Dose (DDD)/every 100 hospital bed-days (DDD/100 beds). A DDD/100 beds was calculated for every year included and for each antibiotic included. The number of DDD/100 beds, is the recommended unit by WHO for measure antibiotic consumption at hospitals. DDD/100 beds was claculated by the following formula [20]:

$$\text{DDD/100 beds} = \frac{\text{consumption during a time period "a"(mg)}}{\text{DDD(mg)} \times \text{n° of days in period "a"} \times \text{n° of beds} \times \text{\% bed ocupation}}$$

Antibiotic consumption data were provided by the Unidose Unit from the Pharmacy Department. In Unidose Unit are prepared all antibiotic prescrptions from PICU and deliver to nurses for administration. For every year included in the study, the total dose (mg) of selected antibiotics was provided. So, data of antibiotic consumption proceed from those patients hospitalizaed in PICU betwen 2010 - 2015 and that were treated with antibiotics included in the study. The cause of antibiotic prescription was not analyzed.

The value of DDD for the antibiotics included was obteined from the WHO's Collaborating Centre for Drug Statistics Methodology. None of the included antibiotics has an specific DDD for children, thus the DDD for it's main indication in adults was used. These were amikacin 1g, cefotaxime, 2g, ceftriaxone 2g, ceftazidime 4g, meropenem 2g, vancomycin 2g, clarithromycin 1g [21].

The number of included days was 365, because antibiotic cansumption was calculated anually. The number of availables PICU beds and the percentage of bed ocupation were obtantined from the Statitics Department of CHPR.

Bacterial isolations from a sterile site and it's antibiótic susceptibility pattern were also analized in the period 2010 - 2015. Bacteria included were those most frequently isollated from PICU: *Staphylococcus aureus*, coagulase negative *Staphylococcus* (CNS), *Klebsiella pneumoniae (K. pneumoniae)*, *Enterobacter cloacae (E. cloacae)* and *Pseudomonas aeruginosa (P. aeruginosa)*. Data were provided by the Microbiology Laboratory of CHPR.

The protocol study was approved by Institutional Hospital Direction.

Results

Main clinical features of children hopspitalized durig the study period are shown in table 1.

Year	Incomes (n)	PIM2 (%)	Mortality (%)	LOS (days)	IMV (%)	Length IMV (days)
2010	556	14.7	3.2	8.91	30.4	9.57
2011	511	10.05	6,7	8.33	30.3	9.48
2012	644	5.68	4.5	6.82	28,9	7.51
2013	609	5.56	3.9	6.76	28,1	7.26
2014	587	4.31	2.6	6.11	24,5	5.92
2015	761	3.73	3.2	4.52	23,2	4.35

Table 1: *Clinical features of children hospitalized between 2010 - 2015.*
PIM2: Pediatric Index Mortality 2; LOS: Length of Stay; IMV: Invasive Mechanical Ventilation

Antibiotics with the highest value of DDD/100 beds in the period 2010-2015 were ceftriaxone, vancomycin and meropenem. Except amikacin, all antibiotics included showed an increase in consumption. Amikacin consumption kept steady, with little variations between the years included. Clarithromycin consumption rised 750% comparing value of DDD/100 beds in 2010 and in 2015. Cefotaxime consumption was 175% higher in 2015 than in 2010. Vancomycin and meropenem consumption also increased in the period 2010 - 2015, with the highest value of DDD/100 bed in 2013 for both antibiotics. Cetriaxone and ceftazidime also showed a higher consumption in 2015 than in 2010. Data of antibiotic consumption, expresed as DDD/100 beds are shown in table 2 and figure 1. The percent change in comsumptiom compared the year 2010 with 2015 is also shown in table 2.

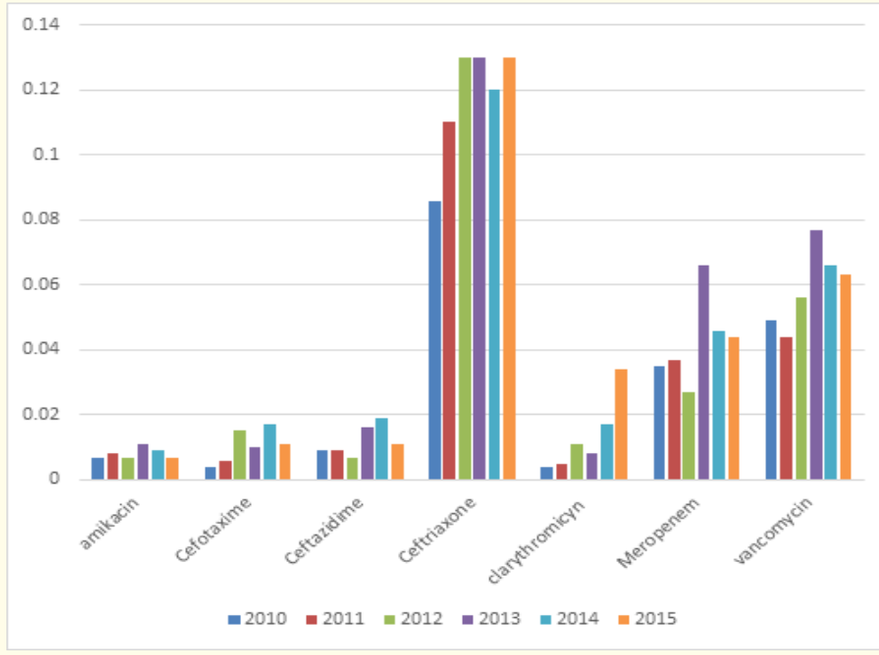

Figure 1: *Evolution of antibiotic consumption. PICU- CHPR, 2010-2015 (DDD/100 beds).*

Year	DDD/100 beds						
	Amikacin	**Cefotaxime**	**Ceftazidime**	**Ceftriaxone**	**Clarithromycin**	**Meropenem**	**Vancomycin**
2010	0,007	0,004	0,009	0,086	0,004	0,035	0,049
2011	0,008	0,006	0,009	0,11	0,005	0,037	0,044
2012	0,007	0,015	0,007	0,13	0,011	0,027	0,056
2013	0,011	0,01	0,016	0,13	0,008	0,066	0,077
2014	0,009	0,017	0,019	0,12	0,017	0,046	0,066
2015	0,007	0,011	0,011	0,13	0,034	0,044	0,063
% change 2010 vs 2015	0%	175%	22%	51%	750%	26%	28%

Table 2: *Evolution of antibiotic consumption. PICU CHPR, 2010-2015 (DDD/100 beds-day).*

Number of bacterial isolations showed scarce variations during the study period (Table 3-5). The only exception was CNS, that in 2010 and 2013 showed an increase (Table 3). The pattern of antibiotic susceptibility of *Staphylococcus aureus* and coagulase negative are shown table 2. Staphylococcal isolations were 100% susceptible to vancomycin. CNS had a multiresistant pattern to others antibiotics. *S. aureus* isolations presented high level of resistance to oxacillin, without resistance to Trimethoprim Sulphamethoxazole (Table 3).

Coagulase negative Staphylococcus						
Antibiotic	2010 n = 37 (%)	2011 n = 27 (%)	2012 n = 28 (%)	2013 n = 40 (%)	2014 n = 22 (%)	2015 n = 27 (%)
Oxacillin	89,2	88,5	92,9	89,7	81,8	85,2
Gentamicin	43,2	51,9	39,3	52,5	45,5	25,9
TMP-SMX	32,4	37	25	32,5	36,4	25,9
Clindamycin	59,5	51,9	71,4	65,0	45,5	48,1
Erythromycin	94,6	74,1	89,3	90,0	72,7	81,5
Vancomycin	0	0	0	0	0	0
Staphylococcus aureus						
	n = 5 (%)	n = 5 (%)	n = 9 (%)	n = 4 (%)	n = 5 (%)	n = 1 (%)
Oxacillin	60,0	60,0	22,0	50,0	80,0	100
Gentamicin	0	40,0	11,0	25,0	60,0	0
TMP-SMX	0	0	0	0	0	0
Clindamycin	40,0	60,0	0	0	0	100
Erythromycin	60,0	60,0	0	0	20,0	100
Vancomycin	0	0	0	0	0	0

Table 3: *Isolations and antibiotic resistance pattern of Staphylococcus. 2010 - 2015.*
TMP-SMX: Trimethoprim Sulphamethoxazole

At the end of the study period, *P. aeruginosa* isolations recovered antimicrobial susceptibility to ceftazidime and ciprofloxacin. Isolations resistant to aminoglycosides were not identyfied and resistance to carbapenems was low (Table 4).

Antibiotic	**2010 n = 4 (%)**	**2011 n = 4 (%)**	**2012 n = 4 (%)**	**2013 n = 6 (%)**	**2014 n = 5 (%)**	**2015 n = 3 (%)**
Ceftazidime	0	25	50,0	16,7	20	0
Imipenem	25,0	50	0	16,7	0	0
Meropenem	0	25	0	0	0	0
Amikacin	0	0	0	0	0	0
Gentamicin	0	0	0	0	0	0
Ciprofloxacin	25,0	50	0	0	0	0

Table 4: *Isolations and antibiotic resistance pattern of Pseudomonas aeruginosa. 2010 - 2015.*

The evolution of antimicrobial susceptibility of *K. pneumoniae* and *E. cloacae* are shown in table 4. Frequency of isolations with ESBL was high till 2014. After this year, the number of isolations ESBL producing *Enterobacteriaceae* was low. All isolations were susceptible to carbapenems. Amikacin resistance was infrequent, but gentamicin resistance was common (Table 5).

	Klebsiella pneumoniae					
Antibiotic	2010 n = 4 (%)	2011 n = 8 (%)	2012 n = 4 (%)	2013 n = 2 (%)	2014 n = 3 (%)	2015 n = 4 (%)
Ampicillin/sulbactam	50,0	62,5	50,0	100	66,7	0
Ceftazidime	75,0	62,5	50,0	50,0	66,7	0
Cefotaxime	75,0	62,5	50,0	50,0	66,7	0
Imipenem	0	0	0	0	0	0
Meropenem	0	0	0	0	0	0
Amikacin	50,0	0	0	0	0	0
Gentamicin	50,0	50,0	50,0	0	33,3	0
TMP-SMX	25,0	50,0	50,0	0	33,3	25,0
Enterobacter cloacae						
Antibiotic	n = 2 (%)	n = 2 (%)	n = 4 (%)	n = 3 (%)	n = 3 (%)	n = 1 (%)
Ampicillin/sulbactam	100	100	100	100	66,7	0
Ceftazidime	100	0	50	33,3	0	0
Cefotaxime	100	0	50	33,3	0	0
Imipenem	0	0	0	0	0	0
Meropenem	0	0	0	0	0	0
Amikacin	0	0	0	0	0	0
Gentamicin	50	0	0	0	0	0
TMP-SMX	50	0	0	0	0	0

Table 5: *Isolations and antibiotic resistance pattern in Klebsiella pneumoniae and Enterobacter cloacae. 2010-2015.*
TMP-SMX: Trimethoprim Sulphamethoxazole

Discussion and Conclusion

Our study is the first report that quantify evolution of antibiotic consumption in a PICU during a 5 year period in Uruguay and also internationally. Antibiotic consumption was shown together with the evolution of bacterial isolations and its susceptibility pattern in the same period. One of the most important findings was that antibiotic consumption and the number of bacterial isolations were not related. Rise in consumption was not matched with a growth in the number of bacterial isolations. Clarhytromicin was the one with highest rise in consumption. Neither *Bordetella* sp. nor *Mycoplasma* sp. were included in the study. Any way this high consumption is a warning fact. This rise in clarhytromicin consumption may be seccondary to its use in severe bronchyolitis, wich is a common practice in our PICU.

Between 2001 and 2006, antibiotic consumption was quantified for ambulatory assitance and for moderate care sectors in the same Hospital. PICU was excluded from this study. During this peroid, methicilin resistant *Staphylococcus aureus* adquired in community emerged, and there was a signifficant rise in antibiotic consumption, specially for clindamycin, Trimethoprim Sulphamethoxazole, ceftriaxone and vancomycin [19]. Similar experiencies, calculating antibiotic consumption have been made in other countries [22].

In our study antibiotic consumption was calculated in an accurate way. This was secondary to precise data of consumption provided by the Unidose Unit from Pharmacy Department. This Unit records all antibiotic prescriptions from PICU and the quantity of prepared antibiotic for each patient during PICU stay. Thus we knew with accuracy the amount of each antibiotic included in the study that was preapered by the Unit and subsequently administered to hospitalized patients in PICU from 2010 to 2015.

Antibiotic consumption was expressed as DDD/100 beds. This is an international unit that allows to compare consumption between countries and in different periods. The DDD/100 beds detects changes in prescription patterns, but not causes of these changes [20]. The main limitant of our study is the use of DDD from adults. It has been stated that pediatrics DDD are very difficult to assign due to body weigth variation. Thus stablishing antibiotic consumption in pediatric populations is dificult. The problem of DDDs value is the main weakness of our study, because results of antibiotic consumption are less fiable. Liem., *et al.* have developed neonatal DDDs to quantify antibiotic consumption in neonates, but in children have not been stablished [23]. It has been sugested the use of Days of Therapy (DOT) in children, but has not been validted for hospitalized children [24]. Despite that DDD/100 beds shows limitatios in children, we could obtain an approach to antibiotics consumption in the period 2010 - 2015.

A trend toward a higher consumption for all antibiotics was found with exception of amikacin. This trend was not associated with an increase in number of bacterial isolations. According to the nature of the study, we cannot conclude that antibiotic use was inappropriate. Nevertheless some findings of our experience should be analized.

Neither antibiotic consumption showed a clear relation with the number of isolations nor with the incidene of nosocomial infections in PICU. The incidence of bacteriemia associated to central venous catheter (BCVC) diminished form 5.06/1000 days in 2010 to 2.38/1000 days in 2013. In 2016 incidence was less than 1.0/1000 days of catheterization [25,26].

The year with highest value of consumption for most antibiotics was 2013. Nevertheless, in this year, only CNS showed an increase in the number of isolations. Also in this year the incidence of BCVC was lower than in 2010. The lack of asociattion between antibiótic consumption with the number of isolations and with the incidence of BCVC in PICU, is a significant fact.

One of the posible causes of rise in antibiotic consumption is illness severity of children admitted to PICU. To predict mortality risk at admission, Pediatric Index of Mortality 2 (PIM2) is used in our PICU. As shown in table 1, mean value of PIM2 diminished from 2010 to 2015. In 2010, mean value of PIM2 was 14.9% and subsequently falled progressivilly to a zenit value of 3.71% in 2015. This fall of PIM2, was not related with a minor antibiotic consumption. Length of stay in PICU and duration of invasive mechanical ventilation also diminished and mortality kept steady (Table 1). Based on these data, illness severity is not a plausible explanation for the observed rise in consumption.

In Intensive Critical Care Units and in PICU, antibiotic consumption use to be 10 times higher than in moderate care area [27]. This elevated consumption may be related to different causes. One of them is the unjustified use of antibiotic for prophylaxis and in viral infections [28,29]. This inappropiate use may be related to illness seveirty. In severe bronchiolitis produced by Synsitial Respiratory Virus (SRV), when mechanical ventilation is required, bacterial co-infection may be present in 20% - 40% of cases [30,31]. This fact, may contribute to the frequent use of antibiotics in severe SRV bronchiolitis, specially ceftriaxone and cefotaxime. Both of them presented high consumption and use to be prescribed in children with SRV bronchiolitis in our PICU.

Data of evolution of antimicrobial susceptibility of isolations should be highlighted. First of all, Staphylococcal isolations showed a multiresisntant pattern and were 100% susceptible to vancomycin. Thus vancomycin is an reasonable option for Staphycoccal infections treatment in our PICU. Although vancomycin susceptibility was universal, minimal inhibitory concentration (MIC) value to vancomycin was not informed. MIC's value of vancomycin is one of the main predictors of success treatment and a major determinant in the dosage and should be informed for guide treatment [32,33].

P. aeruginosa isolations showed variability in carbapenems susceptibility in different years of study, but all isolations were susceptible to aminoglycosides (gentamicin and amikacin). Based on these results, amynoglycosides could be considered as treatment option for *P. aeruginosa* infections in our PICU.

Although there was a rise in meropenem consumption during the study, Carbapenemase producer *Enterobacteriacea* were not isollated. The presence of ESBL was frequent in isolations of *Enterobacteriaceae*, so third generation cephalosporins are not recommended for infections produced by *Enterobacteriaceae* in our PICU. Isolations of *Enterobacteriaceae* were globally susceptible to amikacin. Based on the obtained resuts of the susceptibility pattern of gram negative bacteria, amikacin may constitute an option in management of nosocomial infections produced by *P. aeruginosa* and *Enterobacteriaceae*. Despite widespread use of amikacin, pediatric clinical trials wich evaluate comprative efficacy of amikacin in tretament of nosocomial infections are lacking. Most of clinical studies focus on antimicrobial susceptibility pattern with limited data to clinical evolution and comparative efficacy with other antibiotics [34,35].

Although one of the inclusion criteria of the study was that bacterial isolation should be obtained from a sterile site, the presence of contaminant cannot be rejected, specially for CNS. This is other weakness of our study.

From the obtained results we cannot affirm that antibiotics use was inappropiate, although a lack of association between antibiotic consumption and the number of bacterial isolations was a warning fact. Antibiotic use is frequent in critically ill children, even when a viral infection has been confirmed or when the risk of invasive bacterial infection is low. This practice is dificult to change, because is based on different beliefs about antibiotics benefits and risks in critically ill chidren. The excesive and unjustified use of antibiotics increases the risk of developing AR [7-11,36,37].

Developing antimicrobial rational use policies is necessary for minimizing the impact of AR. For the succes of this intervention is crucial the involvment of all PICU staff. For this policy, also is essential the knowledge of antimicrobial susceptibility pattern of PICU bacterial microbiome and apply a de-escalating therapy in antibiotic treatment for avoid the use of wide-spread antibiotics for prolonged periods [38].

Financial Support

No financial support was received for the study.

Conflict of Interest

None of the authors presented conflict of interest and none to declare.

Bibliography

1. Slonim AD., *et al*. "The costs associated with nosocomial bloodstream infections in the pediatriv intensive care unit". *Pediatric Critical Care Medicine* 2.2 (2001): 170-174.

2. Mermel LA., *et al*. "Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection". *Clinical Infectious Diseases* 49.1 (2009): 1-45.

3. Randolph AG., *et al*. "Identification of central venous catheter-related infections in infants and children". *Pediatric Critical Care Medicine* 6.3 (2005): S19-S24.

4. Brusselaers N., *et al*. "The rising problem of antimicrobial resistance in the intensive care unit". *Annals of Intensive Care* 1 (2011): 47.

5. "National Nosocomial Infections Surveillance System Report, Data Summary from January 1992 to June 2002, Issued August 2002". *American Journal of Infection Control* 30.8 (2002): 458-475.

6. Guven G. "Principles of good use of antimicrobial in hospitals". *Journal of Hospital Infection* 53.2 (2003): 91-96.

7. Hillier S., *et al*. "Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case-control study". *Journal of Antimicrobial Chemotherapy* 60.1 (2007): 92-99.

8. Paschke A., *et al*. "Previous antimicrobial exposure is associated with drug-resistant urinary tract infections in children". *Pediatrics* 125.4 (2010): 664-672.

9. Huang Y., *et al*. "Risk factors of nosocomial infection with extended-spectrum beta-lactamase-producing bacteria in a neonatal intensive care unit in China". *Infection* 35.5 (2007): 339-345.

10. Chow JW., *et al*. "Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy". *Annals of Internal Medicine* 115.8 (1991): 585-590.

11. Gentry C., *et al*. "Analysis of antimicrobial resistance among gram-negative bacilli and antimicrobial use in intensive care unit patients for 5 years in a Veterans Affairs medical center". *American Journal of Infection Control* 30.7 (2002): 411-416.

12. Kollef M. "Is antibiotic cycling the answer to preventing the emergence of bacterial resistance in the Intensive Care Unit?" *Clinical Infectious Diseases* 43.2 (2006): S82-S88.

13. Bantar C. "A hospital wide intervention program to optimize the quality of antibiotic use: impact on prescribing practice, antibiotic consumption, cost savings and bacterial resistance". *Clinical Infectious Diseases* 37.2 (2003): 180-186.

14. World Health Organization. Antimicrobial resistance: global report on surveillance. Geneva: Switzerland (2014).

15. European Centre for Disease Prevention and Control. Annual Epidemiological Report 2013. Reporting on 2011surveillance data and 2012 epidemic intelligence data. Stockholm: ECDC (2013).

16. English surveillance programme for antimicrobial utilisation and resistence (ESPAUR). Report (2014).

17. Speranza N., *et al*. "Profilaxis antibiótica en la cesárea. Centro Hospitalario Pereira Rossell: necesidad de protocolización". *Revista Médica del Uruguay* 19 (2003): 66-70.

18. Giachetto G., *et al*. "Uso de Vancomicina en Servicios de Internación Pediátrica". *Archivos de Pediatria del Uruguay* 77.2 (2006): 118-124.

19. Telechea H., *et al*. "Evolución del consumo de antibióticos y de la susceptibilidad antimicrobiana en el Centro Hospitalario Pereira Rossell en la era de Staphylococcus aureus resistente a meticilina". *Revista Chilena de infectología* 26.5 (2009): 413-419.

20. Capella D and Laporte J. "Métodos aplicados en estudios descriptivos de utilización de medicamentos". En: Laporte J, Tognoni G. Principios de epidemiología del medicamento. 2nd edition. Barcelona: Masson-Salvat (2003): 67-93.

21. Who Collaborating Centre for Drugs Statics Methodology (2017).

22. Muller-Pebody B., *et al*. "Increase and change of Hospital antimicrobial use, Denmark 1997-2001". *Journal of Antimicrobial Chemotherapy* 54.6 (2004): 1122-1126.

23. Liem T., *et al*. "Quantifying antibiotic use in paediatrics: a proposal for neonatal DDDs". *European Journal of Clinical Microbiology and Infectious Diseases* 29.10 (2010): 1301-1303.

24. Guillot J., *et al*. "Usefulness of Defined Daily Dose and Days of Therapy in Pediatrics and Obstetrics-Gynecology: A Comparative Analysis of Antifungal Drugs (2000-2001, 2005-2006, and 2010-2011)". *Journal of Pediatric Pharmacology and Therapeutics* 19.3 (2014): 196-201.

25. Telechea H., *et al*. "Incidencia y etiología de la bacteriemia asociada al uso de catéteres venosos centrales en una unidad de cuidados intensivos pediátricos". *Archivos de Pediatria del Uruguay* 84.3 (2013): 181-186.

26. Iroa A., *et al*. "Prevención de bacteriemia asociada a catéteres intravenosos en UCIN mediante la implementación de un protocolo de trabajo". *Archivos de Pediatria del Uruguay* 86.2 (2015): 106-112.

27. Bergmans DC., *et al*. "Indications for antibiotic use in ICU patients: a one year prospective surveliance". *Journal of Antimicrobial Chemotherapy* 39.4 (1997): 527-535.

28. Erbay A., *et al*. "Evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey". *Journal of Hospital Infection* 59.1 (2005): 53-61.

29. Levin D., *et al*. "Empiric antibiotics are justified for infants with respiratory syncytial virus lower respiratory tract infection presenting with respiratory failure: A prospective study and evidence review". *Pediatric Critical Care Medicine* 11.3 (2010): 390-395.

30. Thorburn K., *et al*. "High incidence of pulmonary bacterial co-infection in children ventilated for severe respiratory syncytial virus (RSV) bronchiolitis". *Thorax* 61.7 (2006): 611-615.

31. Randolph AG., *et al*. "Risk of bacterial infection in previously healthy respiratory syncytial virus-infected young children admitted to the intensive care unit". *Pediatric Infectious Disease Journal* 23.11 (2004): 990-994.

32. Frymoyer A., *et al*. "Current recommended dosing of vancomycin for children with invasive methicillin-resistant Staphylococcus aureus infections is inadequate". *Pediatric Infectious Disease Journal* 28.5 (2009): 398-402.

33. Moise-Border PA., *et al*. "Pharmacodynamics of vancomycin and others antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections". *Clinical Pharmacokinetics* 43.13 (2004): 925-942.

34. Salazar H and Cisneros M. "Antibiotic Resistance by nosocomial infections causal agents". *Revista Médica del Instituto Mexicano del Seguro Social* 54.4 (2016): 462-471.

35. Rosenthal V., *et al*. "International Nosocomial Infection Control Consortium report, data summary of 50 countriesfor 2010-2015: Device-associated module". *American Journal of Infection Control* 44.12 (2016): 1495-1504.

36. Gasink L., *et al*. "Risk factors and Clinical impact of Klebsiella pneumoniae Carbapenemase-producing K. pneumoniae". *Infection Control and Hospital Epidemiology* 30.12 (2009): 1180-1185.

37. Robino L., *et al*. "Risk factors for the acquisition of extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospitalized children". *Journal of Infection in Developing Countries* 7.4 (2013): 361-364.

38. Bassetti M., *et al*. "Focus on antimicrobial resistance in the era of increasing antimicrobial resistance in ICU". *Intensive Care Medicine* 42.6 (2016): 955-958.

Volume 7 Issue 3 March 2018