Research Article

ANTIBIOTIC UTILIZATION STUDY IN PATIENTS WITH NOSOCOMIAL PNEUMONIA IN A PEDIATRIC HOSPITAL IN PACHUCA, HIDALGO

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ABSTRACT

Objective of the study was to identify the antibiotics most frequently used for treatment of nosocomial pneumonia in the DIF Pediatric Hospital of Hidalgo and evaluate the rationality of their prescription by determining the intrinsic value of each antibiotic. This was a descriptive, cross-sectional, indication-prescription study that included patients hospitalized with nosocomial pneumonia from January to December 2014. Data were obtained using the electronic medical record program Histoclin® and were analyzed with SPSS v18. Seventy-six patients stratified by age group were studied with infants predominating in 47.4% of cases. The most frequently used antibiotics were beta-lactams 98.7%, glycopeptides 71%, aminoglycosides 35.5%, imidazole derivatives 32.9% and lincosamides 22.4%. Antibiotic treatment interruption at 48–72 hours was 12% (meropenem, cefepime and vancomycin). Intrinsic value according to blood cultures was correct in 100% of cases. Total consumption of antibiotics expressed as DDD/100 bed-days was for imipenem 9.23 DDD/100 bed-days, amphotericin B 9 DDD/100 bed-days, cefepime 8.27 DDD/100 bed-days, and vancomycin 8.11 DDD/100 bed-days. Total consumption of antibiotics during this period was 2,740,019.85 mg with a total investment of \$2,724, 224.30 pesos. The intrinsic value of the evaluated drugs was correct. We recommend a standardized antibiotic administration guideline that favors their rational use.

Keywords: Drug utilization study, pharmacoepidemiology, rational antibiotic use, nosocomial pneumonia, antibiotic, defined daily dose.

INTRODUCTION

Nosocomial infections (NI) represent an important clinical and epidemiological problem that causes greater morbidity and mortality with a subsequent social and economic cost. One example of these is nosocomial pneumonia¹. Nosocomial pneumonia (NP) is a pulmonary parenchyma infection developing after ≥ 3 days of hospitalization or occurring less than 7 days after hospital discharge^{2,3}. A prevalence study of NI performed in 61 intensive care units in the United States found that NP was the most frequent type of infection in 21% of cases⁴. Another European study, carried out in 20 pediatric units estimated the incidence of NI as 23.6% and positioned pneumonia as the most frequent cause in 53%⁵. In Mexico, Ávila-Figueroa et al.⁶ determined the prevalence of NI in pediatric patients in 21 Mexican hospitals. They found that 9.8% (95% CI, 8.1–11.6) of all patients seen had a nosocomial infection with pneumonia being the most frequent cause (25%).

Beta-lactams and aminoglycosides are antibiotics prescribed for NI in Mexico and more than 60% of the patients with these diseases receive two or more antibiotics⁷. Indiscriminate use of antibiotics has caused an increase in multiresistant microorganisms. There is a direct relationship between antibiotic use and the increase in resistance of enterobacteria such as *P. aeruginosa*, vancomycin-resistant enterococcus, *Klebsiella*, and methicillin-resistant *S. aureus*, among others^{8,9}. According to a study by Luna et al., inadequate treatment in the first 48 hours is associated with greater mortality (91%), while with appropriate treatment, mortality decreases to 38%¹⁰.

According to the World Health Organization (WHO), infections caused by resistant microorganisms do not respond to common treatment¹¹. This causes prolonged illness and a greater risk of death. Mortality rates in hospitalized patients with severe infections are twice that of patients with infections caused by non-resistant bacteria. Irrational use of antibiotics contributes to this problem. This is why Drug Utilization Studies (DUS) have been implemented as a valuable tool for evaluating if antibiotic use in a hospital is rational. This allows hospitals to continue with their policies or implement interventions to correct the problem¹².

According to the WHO, DUS evaluate the commercialization, distribution, prescription and drug use in a society, and the resulting medical, social and economic consequences. This includes prescription, dispensing, and whether patients take the drug, and it is the main tool for detecting deficient use, identifying causal factors, designing effective improvement interventions, and evaluating intervention achievements¹². It is a multidisciplinary effort with specific tasks for physicians, pharmacists, health professionals, economists, information technologists, and other professionals^{13,14}.

To simplify measurement of drug consumption according to expense or number of units, the WHO proposed an international technical unit that measures drug consumption, the defined daily dose (DDD), which is used by the European Research Group^{15,16}.

The DDD, which is different for each drug, is the average maintenance dose per day of a drug when it is used for its main indication. The DDD is nothing more than a technical unit of measure of drug consumption that is arbitrarily established by recommendations from scientific publications, the drug manufacturer, and experience with each product. In general, the DDD of a country, region or center is expressed per 1,000 inhabitants per day. To calculate consumption in hospitals, the same rules apply but the number is expressed as DDD/100 bed-days. The resulting figure is a raw estimation of the probability that a patient is being treated with a certain drug during his/her hospital stay or the percentage of patients treated with a certain drug during a period of time^{12,16}.

In general, classifications do not group DUS based on the methodology used for the study (epidemiological design). Thus, a specific DUS within one classification can belong to more than one type of study by analyzing several types of variables without specific classification criteria¹⁷. The main types of DUS according to their objective are: quantitative studies that analyze numerical aspects (purchase, dispensing) with regard to drug use, and qualitative studies that analyze aspects related to the quality of drug use/prescription, i.e., rationality. Among the latter studies are prescription-indication studies that assess the degree of adequacy of the indication, and indication-prescription studies that analyze the reasons for prescribing the drug.

For qualitative analysis of drug use, the WHO proposes using the intrinsic value (IV) of the drug, which is used to evaluate the quality of the prescription or the drug's therapeutic quality. For this, it is necessary to review each drug to know its dose, formulation, and the suitability of the prescription^{15,18}.

The purpose of this study was to evaluate antibiotic use in the DIF Pediatric Hospital of Hidalgo, Mexico for the treatment of pediatric NP based on the antibiotics' intrinsic value.

MATERIALS AND METHODS

This was a cross-sectional, descriptive indication-prescription study carried out in the DIF Pediatric Hospital in Pachuca, Mexico. A nonprobabilistic sample of 76 hospitalized patients of both sexes with nosocomial pneumonia was selected during the period of January–December 2014 with an age range of 1 day to 18 years from any of the hospitalization services (Infants, Internal Medicine, Neonatal Intensive Care Unit [NICU], Pediatric Intensive Care Unit [PICU] Oncology, Isolation, Surgery and the Emergency Room) The data collected were age, sex, weight, service, days of hospital stay since diagnosis, antibiotic prescribed (generic), weight-based dose, dose administered, interval, day of administration (starting from day 0), start and end date. Data were collected from the HistoClin® electronic record program, a database was created with Excel 2013, and the information exported into SPSS version 18 for statistical analysis. Descriptive statistics were used. In the case of quantitative variables, measures of central tendency and dispersion were applied. In the case of qualitative variables ratios and proportions were obtained.

Using a specialized search engine from the CCDEM (MHO Collaborating Centre for Drug Statistics Methodology), the annual occupation index, the total number of beds and the annual quantity of drug (antibiotic) consumed were used to assign the DDD to each antibiotic using the following formula:

$$\text{DDD}/100 \text{ bed-days} = \text{Drug consumption in mg during a period of time "a"} / \text{DDD in mg} \times \text{no. of days included in the period "a"} \times \text{no. of beds} \times \% \text{ of occupation.}$$

The protocol was approved by the Ethics and Research Committees of the Hidalgo Health Services, the Administration of the Health Research Coordination, and the DIF Pediatric Hospital of Hidalgo

RESULTS

Seventy-six cases of NP were identified in patients hospitalized during January - December 2014. Of these, 55.3% were girls with a predominance of 2:1. Distribution by age groups was adolescents 12 – 18 years 9 (11.8%); school children 5 - 12 years, 15 (19.7%); infants 1 month to 2 years, 57 (48.7%), neonates 0 – 28 days, 6 (7.9%), and preschoolers, 2 - 5 years, 9 (11.8%). The service with the greatest number of cases of NP was the PICU with 27.6%, followed by the Infants Service with 23.7% and Oncology with 18.4%. Isolation with 7.9%, Surgery with 5.3%, Internal Medicine with 5.3%, the Emergency Room with 1.3% and NICU with 10.5%.

The most frequent comorbidities were epilepsy and acute lymphoblastic leukemia in 18.45% and 15.8%, respectively (Table 1). Associated mortality was 23.7% (18 of 76 patients with NP). The infant group had the greatest number of deaths (14.5%) (Table 2); the service with the highest mortality rate was the PICU.

Of the 26 antibiotics administered, the most frequently prescribed were beta-lactams (98.7%), followed by glycopeptides (71%), aminoglycosides (35.5%), imidazole derivatives (32.9%) and lincosamides (22.4%) (Table 3). The beta-lactams most frequently prescribed were cefepime (51%), cefotaxime (27.6%), imipenem (48.7%), and meropenem (32.9%). Vancomycin was the most frequent glycopeptide (77.6%); of the aminoglycosides, amikacin (34.21%); of the imidazole derivatives, fluconazole (22.4%) and of the lincosamides, clindamycin (25%). The remaining antibiotics less frequently used were classified as "others" (Table 4). Of the 76 cases included in the study, blood cultures were done in 62, and in 21, there were positive results with the presence of *Streptococcus imitis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecium*, *Pseudomonas stutzeri*, *Staphylococcus epidermidis* and *Candida tropicalis*, and with asensitivity to carbapenems and aminoglycosides. Treatment was interrupted in the first 48 to 72 hours in 26.3%. The most frequently used antibiotics in this period were 3rd and 4th generation cephalosporins, carbapenems, and glycopeptides (Figure 1).

Of the cases with a positive blood culture, in 100% the antibiotic indicated was correct according to the causal agent.

Total consumption of antibiotics was 2,740,019.85 mg with an economic impact of \$2,724,224.3 MXP (Tables 5 and 6). Regarding total consumption in milligrams of the antibiotics most used during the year, piperacillin/tazobactam had a consumption of 572,672 mg at a cost of \$ 927,728.64 MXP; imipenem was 433, 739.5 mg at a cost of \$ 754,706.74 MXP; cefepime 388,425.5 mg at a cost of \$ 140,610.031 MXP and vancomycin 380,911 mg at a cost of \$ 418,621.20 MXP. Monthly antibiotic consumption is shown in Figure 2. Beta-lactams reached maximum consumption during the month of July, as did glycopeptides, aminoglycosides and imidazole derivatives, while lincosamides had a maximum peak during February, and the group classified as "others," the month of May. This allowed us to estimate the historical consumption of

drugs with the goal of predicting necessary acquisitions and avoiding a lack of drugs by adapting to available financial resources.

Table 1: Comorbidities associated to NP

Pathology	Frequency (%)
Epilepsy	14 (18.4)
ALL	12 (15.8)
Septic shock	4 (5.4)
Cholestatic syndrome	3 (3.9)
AML	3 (3.9)
Other diagnoses	40 (52.6)
Total	76 (100)

NP, nosocomial pneumonia; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia

Table 2: Mortality associated with NP based on age group

Age group	Frequency (%)	Accumulated prevalence (%)
Adolescents 12 – 18 years	9 (11.84)	3.95
Preschool children 2 - 5 years	9 (11.84)	2.63
Infants 1 month to 2 years	37 (48.68)	14.5
Neonates 0 – 28 days	6 (7.9)	2.63
Schoolchildren 5 – 12 years	15 (19.7)	0
Total	76 (100)	23.7

NP, nosocomial pneumonia

Table 3: Frequency of antibiotic prescription by age group

Antibiotic group	Age group					Total %
	Neonates	Infants	Preschoolers	Schoolchildren	Adolescents	
Aminoglycosides	4	8	4	7	4	35.5 (n=27)
Beta-lactams	6	37	9	14	9	98.7 (n=75)
Glycopeptides	5	27	4	13	5	71 (n=54)
Lincosamides	1	9	3	3	1	22.4 (n=17)
Quinolones	2	4	0	1	1	10.5 (n=8)
Macrolides	1	3	1	2	3	13.16 (n=10)
Imidazole derivatives	3	12	2	4	4	32.9 (n=25)
Polyenes	2	2	1	1	1	9.2 (n=7)
TMP/SMX	0	2	1	1	0	5.3 (n=4)
Total % (n=76)	7.9 (n=6)	48.7 (n=37)	11.8 (n=9)	19.7 (n=15)	11.8 (n=9)	

TMP/SMX, Trimethoprim/Sulfamethoxazole; neonates 0 – 28 days; infants 1 month to 2 years; preschoolers 2 - 5 years; schoolchildren 5 – 12 years; adolescents 12 – 18 years.

Table 4: Frequency of antibiotic prescription

Pharmacologic group	Active substance	Frequency (%)
Betactams, penicillins, cefalosporins	Cefepime (4th generación)	39 (51.3)
	Ceftazidime	21 (27.6)
	Cefotaxime	9 (11.8)
	Ceftriaxone (3rd generation)	4 (5.3)
	Cefuroxime (2nd generation)	1 (1.3)
Carbapenems	Imipenem	37 (48.7)
	Meropenem	25 (32.9)
	Ertapenem	1 (1.3)
Penicillins resistant to beta-lactams	Dicloxacillin	12 (15.8)
Betactam inhibitors	piperacillin/tazobactam	8 (10.5)
broad-spectrum penicillins	Ampicillina	4 (5.3)
Penicillins sensitive to betalactamase	PGSC	1 (1.3)
Glycopeptides	Vancomycin	59 (77.6)
	Teicoplanin	1 (1.3)
Aminoglycosides	Amikacin	26 (34.2)
	Gentamicin	1 (1.3)
Imidazole derivatives	Fluconazole	17 (22.4)
	metronidazole	13 (17.1)
Lincosamides	Clindamycin	19 (25)
Others	Linezolid	12 (15.8)
	Clarithromycin	10 (13.1)
	Amphotericin B	7 (9.2)
	TMX/SMZ	4 (5.3)
	Levofloxacin	4 (5.3)
	Ciprofloxacin	7 (9.2)
	Azithromycin	2 (2.6)

PGSC, penicillin g sodium crystalline; TMX/SMZ, trimethoprim/sulfamethoxazole

Table 5: Total consumption and cost of antibiotics from January–December 2014

Antibiotic	Total dose consumed (mg)	Total cost MXP	DDD/100 bed-days
Amikacin	78,338	4,935.29	3.3
Ampicillina	160,635	2,891.43	3.42
Amphotericin B	739.85	887.82	9
Azithromycin	7,040	5,800.96	5.99
Cefepime	388,425.5	140,610.03	8.27
Cefotaxime	45,590	26,214.25	4.64
Cefuroxime	19,560	14,709.12	1.67
Ceftazidime	157,979	55,608.61	1.68
Ceftriaxone	61,270	1,684.92	1.30
Ciprofloxacin	1,244	1,355.96	5.30
Clarithromycin	17,598	27,452.88	1.5
Clindamycin	69,606	35,847.09	2.47
Dicloxacillin	73,427	17,916.19	1.56
Ertapenem	180	257.4	7.66
Gentamicin	928	127.14	1.65
Fluconazole	9,619	68,073.66	2.05
Imipenem	433,739.5	754,706.74	9.23
Levofloxacin	8,747	7,898.54	7.45
Linezolid	42,900	85,800	1.52
Meropenem	155,322	120,063.90	3.31
Metronidazole	49,235	2,207.92	1.40
Piperacillin/tazobactam	572,672	927,728.64	1.74
Teicoplanin	500	906	5.32
TMP/SMX	5,814	1918.62	6.19
Vancomycin	380,911	418,621.19	8.11
Total	2,740,019.85	2,724,224.3	

MXP, Mexican pesos; TMX/SMZ, trimethoprim/sulfamethoxazole

Table 6: Cost of antibiotic prescribed by formulation and milligram

Antibiotic Group	Active substance	Cost by formulation MXP	Cost per mg
Beta-lactams, penicillins			
Cefalosporins	4th generation		
	Cefepime	181.00	0.362
	3rd generation		
	Ceftazidime	352.50	0.352
	Cefotaxime	287.50	0.575
	Ceftriaxone	27.50	0.0275
	2nd generation		
	Cefuroxime	564	0.752
Carbapenemes	Imipenem	872.50	1.74
	Meropenem	773.00	0.773
	Ertapenem	1,435.50	1.43
Penicillins resistant to beta-lactams	Dicloxacillin	11.00	0.244
Betalactam inhibitors	Piperacillin/tazobactam	810.20	1.62
Broad-spectrum penicillins	Ampicillin	9.00	0.018
Penicillins sensitive to betalactamase	PGSC	11.00	0.011 / IU
Glycopeptides	Vancomycin	549.70	1.099
	Teicoplanin	906.30	1.812
Aminoglycosides	Amikacin	6.31	0.063
	Gentamicin	11.00	0.137
Imidazole derivatives	Fluconazole	1,415.50	7.077
	Metronidazole	27.50	0.055
Lincosamides	Clindamycin	154.50	0.515
Others	Linezolid	1,200	2
	Clarithromycin	782.56	1.56
	Amphotericin B	600	1.2
	TMX/SMZ	135	0.33
	Levofloxacin	451.60	0.903
	Ciprofloxacin	218.50	1.09
	Azithromycin	412.00	0.824

MXP, Mexican pesos; PGSC, penicillin g sodium crystalline; TMX/SMZ, trimethoprim/sulfamethoxazole

Figure 1: Percent of antibiotic treatments interrupted in the first 24 to 48 years.

Figure 2: Monthly antibiotic consumption during the study.

Regarding DDD/100 bed-days, we found the following: imipenem, 9.23 DD/100 bed-days, amphotericin B, 9 DDD/100 bed-days, cefepime, 8.27 DDD/100 bed-days, and vancomycin 8.11 DDD/100 bed-days. It is important to mention that DDD was calculated based on the average dose in adults recommended by the WHO since pediatric doses published by this organization do not exist.

DISCUSSION

DUS are basic tools that permit correct institutional use of drugs. Furthermore, they can be useful to adopt adequate measures for the rational use of drugs. This is why, in this study, we considered two indicators to evaluate rational drug use: rationality of the drug prescription using the intrinsic value of each antibiotic and drug consumption based on DDD to obtain the economic impact considering the cost.

Regarding rational prescription, it is understood that drug prescription is an individualized and dynamic clinical process, including absorption of drugs from the gastrointestinal tract because is a complex process in the variability of which is influenced by many physicochemical and physiologic factors. The two most important physicochemical factors that affect both the extent and the rate of absorption are lipophilicity and solubility.^{17, 18, 19} Antibiotic consumption is an indicator of the prescription that can be modified based on disease variation and prescription habits. The spread of bacterial resistance due to changes in hospital epidemiology forces the need for new antibiotic treatment strategies. The establishment of clinical guidelines by consensus is usually very effective as is the case in Latin America⁸.

The proposed antimicrobial treatment guideline for Latin America is based on empirical therapy. It considers the patient's clinical data, previous antibiotic therapy, time of hospital stay, the prevalence of pathogens and their natural and hospital resistance patterns with the aim of providing timely and appropriate treatment, in addition to establishing rational antibiotic use to prevent the development of bacterial resistance⁸⁻¹⁰.

Even though treatment in the DIF Pediatric Hospital Hidalgo has been prescribed considering previous antibiotic therapy, time of hospital stay, and underlying diseases, it is essential to consider the hospital's epidemiology and apply it in a clinical guideline that supports current empirical treatment and its duration (treatment interruption and changes in treatment schemes) taking into consideration the recommendations for the aforementioned guide as in the case of changes in treatment schemes before 72 hours.⁸

Identifying the causal agent favors focused antimicrobial therapy. With this we can reevaluate the use and dose of broad-spectrum antibiotics making it possible to reduce the spectrum with a subsequent reduction in cost.

The WHO states that providing information and policies on antimicrobial consumption monitoring to both the physician who prescribes and health authorities, may be the first step to create awareness in careful prescription of these drugs. This combined with monitoring antibiotic resistance can help establish policies for antibiotic use and local guidelines for empirical treatment (without cultures) in addition to explaining the cases presented, making predictions or generating a working hypotheses, and providing significant savings for institutions and patients¹⁸.

CONCLUSIONS

The intrinsic value of the evaluated drugs was correct. Antibiotic consumption in the DIF Pediatric Hospital Hidalgo is based on epidemiological data of the institution to provide adequate and timely treatment; however, it is necessary to consider the application of a guideline that supports pharmacotherapy. We recommend periodically performing drug utilization studies as the main tool for detecting consumption patterns, identifying responsible factors, designing effective interventions to improve and assess the achievements of these interventions to be able to promote the rational use of these drugs, and to optimally use financial resources for the purchase of antibiotics.

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