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Research

Prior antimicrobial therapy in the hospital and other predisposing factors influencing the usage of antibiotics in a pediatric critical care unit

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Abstract

Background: The aim of this study was to determine whether prior antimicrobial therapy is an important risk factor for extended antimicrobial therapy among critically ill children. To evaluate other predisposing factors influencing the usage of antibiotics in a pediatric intensive care unit (PICU) setting. To examine the relationship between the extent of antimicrobial treatment and the incidence of nosocomial infections and outcome.

Methods: This prospective observational cohort study was conducted at a university-affiliated teaching hospital (760 beds) in Athens. Clinical data were collected upon admission and on each consecutive PICU day. The primary reason for PICU admission was recorded using a modified classification for mutually exclusive disease categories. All administered antibiotics to the PICU patients were recorded during a six-month period. Microbiological and pharmacological data were also collected over this period. The cumulative per patient and the maximum per day numbers of administered antibiotics, as well as the duration of administration were related to the following factors: Number of antibiotics which the patients were already receiving the day before admission, age groups, place of origin, the severity of illness, the primary disease and its complications during the course of hospitalization, the development of nosocomial infections with positive cultures, the presence of chronic disease or immunodeficiency, various interventional techniques (mechanical ventilation, central catheters), and PICU outcome.

Results: During a six-month period 174 patients were admitted to the PICU and received antibiotics for a total of 950 days (62.3% of the length of stay days). While in PICU, 34 patients did not receive antimicrobial treatment (19.5%), 69 received one antibiotic (39.7%), 42 two (24.1%), 17 three (9.8%), and 12 more than three (6.9%). The number of antibiotics prescribed in PICU or at discharge did not differ from that at admission. Indications for receiving antibiotics the day before admission and throughout during hospitalization into PICU were significantly correlated. Although the cumulative number of administered antibiotics did not correlate with mortality (9.8%), it was significantly related to the severity scoring systems PRISM ($p < .001$), TISS ($p < .002$) and was significantly related to the number of isolated microorganisms ($p < .0001$). Multiple regression analysis demonstrated that independent determinants of the cumulative number of antibiotics were: prior administration of antibiotics, presence of a bloodstream infection, positive bronchial cultures, immunodeficiency, and severity of illness.

Conclusion: Prior antimicrobial therapy should be recognized as an important risk factor for extended antimicrobial therapy among critically ill children. Severity of illness, immunodeficiency, and prolonged length of stay are additional risk factors.

Background

Judicious use of antibiotics in ambulatory practice has become increasingly important as antibiotic resistance in community bacterial pathogens continues to accelerate. It has been estimated that approximately 60% of all antibiotics prescribed in outpatients are for documented or suspected respiratory infection and that the highest rates of antibiotic use are in children [1].

The high risks associated with untreated infection in hospital patients lower the threshold for prescription of antibiotic treatment. In a twenty-year period, and despite the increasing breadth of activity of individual compounds, the percentage of patients receiving combinations of antibiotics, as opposed to single antibiotic administration, increased from 23% to 44% [2]. Extensive use of broad-spectrum antibiotics and crowding of severely ill patients in intensive care units has led worldwide to important increases in nosocomial-related infections.

Patients admitted to adult or pediatric intensive care units (PICU) are at greatest risk of acquiring nosocomial infections, partly because of their serious underlying diseases, but also because of their exposure to life-saving invasive procedures, prolonged use of in-situ invasive devices, therapy with multiple antimicrobial agents, and extended hospital stays [3-5]. Even patients and their surroundings are known reservoirs for nosocomial pathogens [6,7]. In most studies, however, antimicrobial use has been assumed to be the major factor responsible for changes in resistance [8].

In order to minimize unwarranted prescription of broad-spectrum antibiotics and to reduce the frequency of additional morbidity and mortality because of nosocomial infections, antibiotic prescription in our PICU was imposed by definite clinical indications [9], guided by microbial studies. Not unusually, however, admitted high-risk patients have already been covered with broad-spectrum antibiotics for prophylaxis or for treating documented or suspected infection in their own departments [10].

We hypothesized that prior antimicrobial therapy might be an important risk factor for extended antimicrobial therapy in PICU and that other predisposing factors such as a significant proportion of immuno-compromised or cancer patients, patients with prolonged length of stay, or increased degree of interventions might further restrict clinical efforts aimed at reducing antimicrobial treatment in critically ill patients. Subsequently, the increased usage of antibiotics in this group of patients might lead to development of nosocomial infections and increased morbidity and mortality. The objectives of this study, therefore, were a) to determine whether prior antimicrobial therapy is an important risk factor for extended antimicrobial therapy among critically ill children; b) to evaluate other predisposing factors influencing the usage of antibiotics in a PICU setting; c) to examine the relationship between the extent of antimicrobial treatment and the incidence of nosocomial infections and outcome.

Methods

Patients

This prospective observational cohort study was conducted at a university-affiliated teaching hospital: Aghia Sophia Children's Hospital (760 beds) in Athens. Subjects included all patients admitted to the PICU (10 beds) between September 2001 and March 2002. As the study did not affect patient care, the institutional review board waived the need for informed parental consent. Reasons for admission included postoperative care after pediatric surgery, severe trauma, and medical conditions requiring critical care. Antibiotic prescription in PICU was imposed by definite clinical indications, guided by microbial studies. Before microbiology was available, empiric therapy was based on: (i) proper identification of bacterial risks in each infection site; (ii) surveillance of frequent nosocomial organisms and susceptibility patterns in the PICU; (iii) identification of environmental risk factors and the patient's underlying condition. In documented infection, initial selection of antibiotics was based on patient characteristics, local drug resistance patterns, the patient's prior exposure to specific classes of antibiotics, pharmacokinetics / pharmacodynamic parameters of chosen antibiotics and concentrations at the infection site, in order to prevent selection of resistant mutants and to provide the most efficient antibiotic therapy. Our restriction program also required clinical justification for the specific antibiotic order before the drug is dispensed by the pharmacy. These regimens were administered before definitive proof of infections and until the results of microbial investigation were available (de-escalation antimicrobial chemotherapy) [11]. As culture results from respiratory specimens became available, they were used to narrow the range of pathogens targeted by the original regimen. In particular de-escalation antimicrobial chemotherapy was tailored to our critically ill patients according to their clinical status, severity of illness and suspicion of sepsis or nosocomial pneumonia. Cycling antibiotic therapy was only periodically instituted, in order to avoid the development of bacterial resistance.

In order to avoid both, inadequate antimicrobial treatment and inappropriate antibiotic over-prescription, therefore, our approach to addressing the problem of antibiotic use in our PICU was to: develop periodic guidelines for optimal use of antibiotics, including scheduled changes of antibiotic classes or single antibiotics within classes (aminoglycosides, ureidopenicillins,

cephalosporins), monitor and report broad-spectrum antibiotic use, improve antimicrobial prescribing by educational and administrative means, optimize choice and duration of empiric therapies by allowing for the selection of the most effective antimicrobial agents, and, when feasible, optimize or modify prophylaxis after operative procedures. These guidelines could not affect previous antibiotic prescription in our patients' original departments, which had their own policies and had often been the main sources of our patients. Not unusually, therefore, admitted patients had already been covered with antibiotics for prophylaxis or for treating documented or suspected infection by their own attending surgeons, oncologists, or other specialists. Accordingly, all consecutively admitted patients to our PICU during a six-month period entered the study.

Data collections and definitions

Clinical data were collected upon admission and on each consecutive PICU day. The primary reason for PICU admission was recorded using a modified classification for mutually exclusive disease categories [12]. Final diagnostic information was coded by combining appropriate for the age groups and the intensive care settings modifications of the International Classification of Diseases and the Guidelines for Developing Admission and Discharge Policies for the Pediatric Intensive Care Unit [13], and admission criteria proposed by the Guidelines for Intensive Care Unit Admission, Discharge, and Triage, following a Prioritization Model [14]. Chronic co morbidity was classified as 1) none, independent of care of others for activities of daily life, 2) chronic disease or handicapped partially or fully dependent on care of others, and 3) cancer patient. Strict guidelines and protocols for central venous catheter insertion, care, and maintenance where implemented. All blood cultures for establishing the presence of a bloodstream infection were required to be obtained from percutaneously drawn sites using sterile technique and not drawn from indwelling vascular catheters. Patients were evaluated for the development of bloodstream infections only during their stay in the PICU. Patients in whom there was a suspicion of clinical or radiologic ventilator-associated pneumonia (VAP) underwent bronchoscopy, and pneumonia was confirmed by the presence of bronchoalveolar lavage fluid culture.

Microbiological and pharmacological data

All administered antibiotics to the PICU patients were recorded during a six-month period. Microbiological and pharmacological data were also collected over this period. Bacteremia was defined as the identification of a high-grade pathogen (e.g., *Pseudomonas aeruginosa*, *Staphylococcus aureus*) in a blood culture specimen or the identification of a common skin contaminant or skin flora (e.g., coagulase-negative staphylococci) in at least two separate blood culture specimens from the same patient drawn from different sites. Bacteraemias identified from blood cultures collected within 48 hours of admission were deemed to be community-acquired. Nosocomial bloodstream infections were required to be established after 48 h of hospitalization. Similar temporal cutoffs for separating community-acquired infections from hospital-acquired infections have been proposed by other investigators [15]. Patients residing at a nursing home, skilled-care facility, or rehabilitation center who had a bloodstream infection requiring hospital admission were classified as having community-acquired infections. Nosocomial bloodstream infections, as well as other nosocomial infections (urinary tract, wound infection), were defined according to criteria established by the Centers for Disease Control and Prevention [16]. The diagnostic criteria for VAP were modified from those established by the American College of Chest Physicians, as previously described [17]. Antimicrobial resistance was determined for all clinical isolates assumed to be significant for the clinical condition of the patient. Duplicate isolates were excluded from the study and were defined as isolates of the same organism obtained from the same patient within a 7-day period.

The cumulative per patient and the maximum per day numbers of administered antibiotics, as well as the duration of administration were related to the following factors: Number of antibiotics which the patients were already receiving the day before admission, age groups, place of origin, the severity of illness, the primary disease and its complications during the course of hospitalization, the development of nosocomial infections with positive cultures, the presence of chronic disease or immunodeficiency, various interventional techniques (mechanical ventilation, central catheters), and PICU outcome. The severity of illness was assessed by the Pediatric Risk of Mortality (PRISM) Score [18], the Therapeutic Intervention Scoring System (TISS) modified for children [19], and indices of organ failure. Multiple organ system failure (MOSF) was defined using the criteria by Wilkinson et al [20].

Statistical analysis

Normally distributed data are expressed as mean ± SEM, while non-normally distributed data are given as median and range. Statistical analysis was performed with a two-tailed t-test for normally distributed paired data after Levene's correction for equality of variances or by Mann-Whitney U – Wilcoxon rank sum W test for non-normally distributed data. Probability values of $<.05$ with two-tailed tests were considered significant. When a linear regression was calculated Pearson's correlation coefficient was employed. Fisher's exact test was used for the category data. Clinical characteristics, that showed significant

Table 1: Clinical variables and antibiotic coverage of children in PICU during a six-month period (n = 174)

Variables	Mean ± SEM	Median	Minimum	Maximum
Age (years)	5 ± 0.4	3.5	0.6 -	19
Length of Stay (days)	8.8 ± 1.6	2	1 -	180
Duration of Mechanical Ventilation (days)	6.1 ± 1.4	1	0 -	180
TISS	24.6 ± 1.0	21	9 -	61
PRISM	10.8 ± 0.7	8	0 -	60
Possibility of death by PRISM (%)	11.9 ± 1.7	3	0 -	100
Number of antibiotics upon admission	1.1 ± 0.08	1	0 -	7
Maximum daily number of antibiotics given in PICU	1.2 ± 0.07	1	0 -	4
Cumulative number of antibiotics in PICU throughout during the hospitalization	1.4 ± 0.09	1	0 -	8
Cumulative number of antibiotics, including antiviral and antifungal, in PICU	1.56 ± 0.1	1	0 -	10
Number of antibiotics at discharge	1.14 ± 0.07	1	0 -	4
Duration of antibiotics in PICU (days)	6.1 ± 0.8	2	0 -	56

SEM = Standard error of mean; PRISM = Pediatric Risk of Mortality; TISS = Therapeutic Intervention Scoring System

differences in univariate analysis were subsequently examined in stepwise multiple regression analysis with the cumulative per patient number of administered antibiotics, the maximum per day number, and the duration of administration as dependent variables, using p = .05 for entry and p = .01 for removal. In this analysis, the contribution of each determinant, or resource utilization, was assessed in connection with all others. All analyses were done using the Statistical Package for the Social Sciences (SPSS) for Windows (release 10, SPSS, Chicago, IL) software package.

Results

Patients' characteristics

During the 6-month period, 174 patients, mean age 5 ± .4 (.6–19) years, 59.2% boys – 40.8% girls, were admitted to the PICU. Clinical data and data regarding antibiotic usage in PICU are shown in Table 1. Free medical history had 40.8% of the patients, cancer 23.6%, and chronic disease 35.6%. Among the patients, 91% admitted to the PICU for the first time (158/174), 13 had 2 admissions (7.5%) and 3 more than 2 admissions. The place of origin was 12.6% directly from the emergency department, 43.7% from the wards, 11.5% were transferred from other hospitals, 24.1% from the operative room (elective major surgeries), 3% from emergent operations, 3.4% were long distance air-transported, and 1.7% were chronically ill patients who were directly transferred from their homes. On the total, 54.6% were supported with mechanical ventilation (MV). The mortality rate was 9.8%, and differed significantly between those who were supported with MV (17.9%), compared to those who were not supported (0%, p < .0001). Among the patients, 6.3% had neutropenia upon admission (mortality 27.3%), while 4.6% had immunodeficiency (mortality 40%).

Classification

Among disease groups, oncology patients were more frequently hospitalized (41/23.6%, mortality 9.8%), patients with chronic disease, such as metabolic, (28/16.1%, mortality 17.9%), primary respiratory deficiency (25/14.4%, no mortality) and sepsis, not including patients from the previous groups (17/9.8%, mortality 11.8%). Classifying patients according to primary organic system according to the International Classification of Diseases and the Guidelines for Developing Admission and Discharge Policies for the Pediatric Intensive Care Unit, more often admitted in our PICU patients with cardiovascular instability, especially patients with septic shock (32.8%), postoperative patients after severe or emergent operations (24.7%), neurological problems, such as status epilepticus or coma (19.5%) and acute respiratory problems (10.3%). Regarding the admission to the PICU according to the Prioritization Model, most patients were admitted with acute manifestations of severe diseases with priority 1–2. The frequency of various interventions related to possible aggravating factors in using antibiotics in critically ill children is presented in Table 2.

Antimicrobial treatment

Frequency of coverage

The study population received antibiotics for a total of 950 days (5.6 ± .7 days, 0–56), which represented 62.3% of the cumulative 1526 length of stay days, compared with 1067 days on MV (6.1 ± 1.4 days, 0–180), which, however, represented 70% of the cumulative length of stay. While in PICU, 34 patients did not receive antimicrobial treatment (19.5%), 69 received one antibiotic (39.7%), 42 two (24.1%), 17 three (9.8%), and 12 more than three (6.9%), including agents against fungi and viruses.

Table 2: Frequency of various interventions related to possible aggravating factors predisposing to increasing administration of antibiotics in PICU (n = 174)

INTERVENTION	KINDS OF INTERVENTION	FREQUENCY
CATHETERS	Peripheral veins	17,8%
	Peripheral veins + arteries	22,4%
	Central catheter (one)	34,5%
	Central catheters 2+	25,4%
NUTRITION	Total Parenteral Nutrition	6,9%
	Enteral (nasogastric, transpyloric)	84,5%
HEMODYNAMIC	PiCCO	12,1%
	Inotropes	22,4%
BRAIN MONITORING	ICP catheters ± $SjVO_2$	5,7%
NEUROSURGICAL	External CSF drainage	8,6%
KIDNEYS' ARTIFICIAL SUPPORT	Hemofiltration continuous	3,4%
	Peritoneal dialysis	1,7%
RESPIRATORY SUPPORT	Mechanical Ventilation	54.6%
	High Frequency Ventilation	2,2%
	Tracheotomy	4,6%
	Chest drains	7,9%

PiCCO = Pulse contour cardiac output

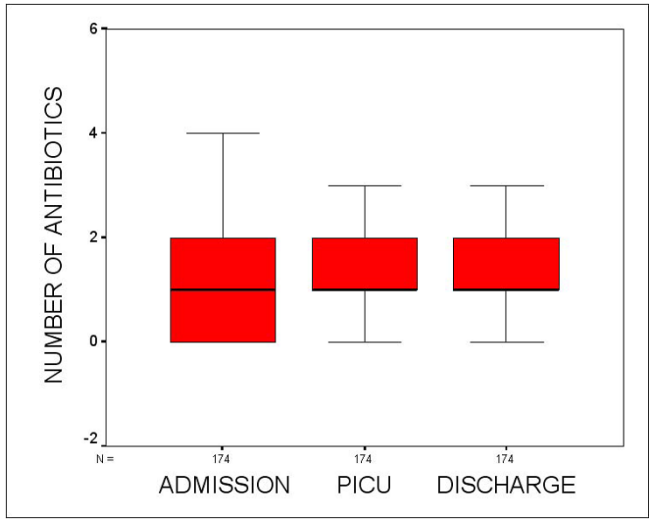

Figure 1
Antibiotics before, at, and after PICU. Box plots of the medians of antibiotics, which the patients were receiving the day before admission (one day recording), during hospitalisation in PICU (mean 9 days recording, range 1–180 days), and at discharge (one day recording).

Antibiotics upon admission, in PICU and at discharge

Not only the maximum per patient number of administered antibiotics (r^2 = .7, p < .01), but also the cumulative summary of antibiotics (r^2 = .62, p < .01) and the number of antibiotics which the patients were receiving at discharge (r^2 = .4, p < .01), were significantly correlated with the number of antibiotics which the patients were already receiving on the admission day. Antibiotics in PICU covered 79.9% of patients, compared to the 67.2% of the covered patients during admission day (p < .0001). A significant proportion of those antibiotics started only after admission to PICU represented patients with chronic diseases and long length of stay (4 patients not receiving antibiotics in PICU vs. 10 upon admission, p < .01) and patients with head injury who had always been admitted directly to the PICU without receiving antibiotics (15 patients) but received afterwards for intervening infection (5 patients without receiving antibiotics in PICU). Smaller differences were recorded among oncology patients (3 patients without receiving antibiotics in PICU vs. 5 upon admission) or patients with sepsis (no patients without receiving antibiotics in PICU vs. 1 upon admission). At discharge, 24.7% of patients did not receive any antibiotic, 43.1% one, 27% two, 3.4% three, 1.7% four. The numbers of antibiotics during hospitalisation in PICU or at discharge did not differ from those of received antibiotics the day before admission (Figure 1).

Regarding the maximum daily number of antibiotics per patient, not including agents against fungi and viruses, 21% of patients in PICU did not receive any antibiotic compared to 32.8% of the same patients who were not receiving antibiotics the day before admission. While in PICU, 46% of patients received only one antibiotic compared to 32.8% receiving one antibiotic before admission, two antibiotics 25.9% compared to 24.1%, three 5.7% versus 6.9%, and four 1.7% versus 1.8%. Oncology and

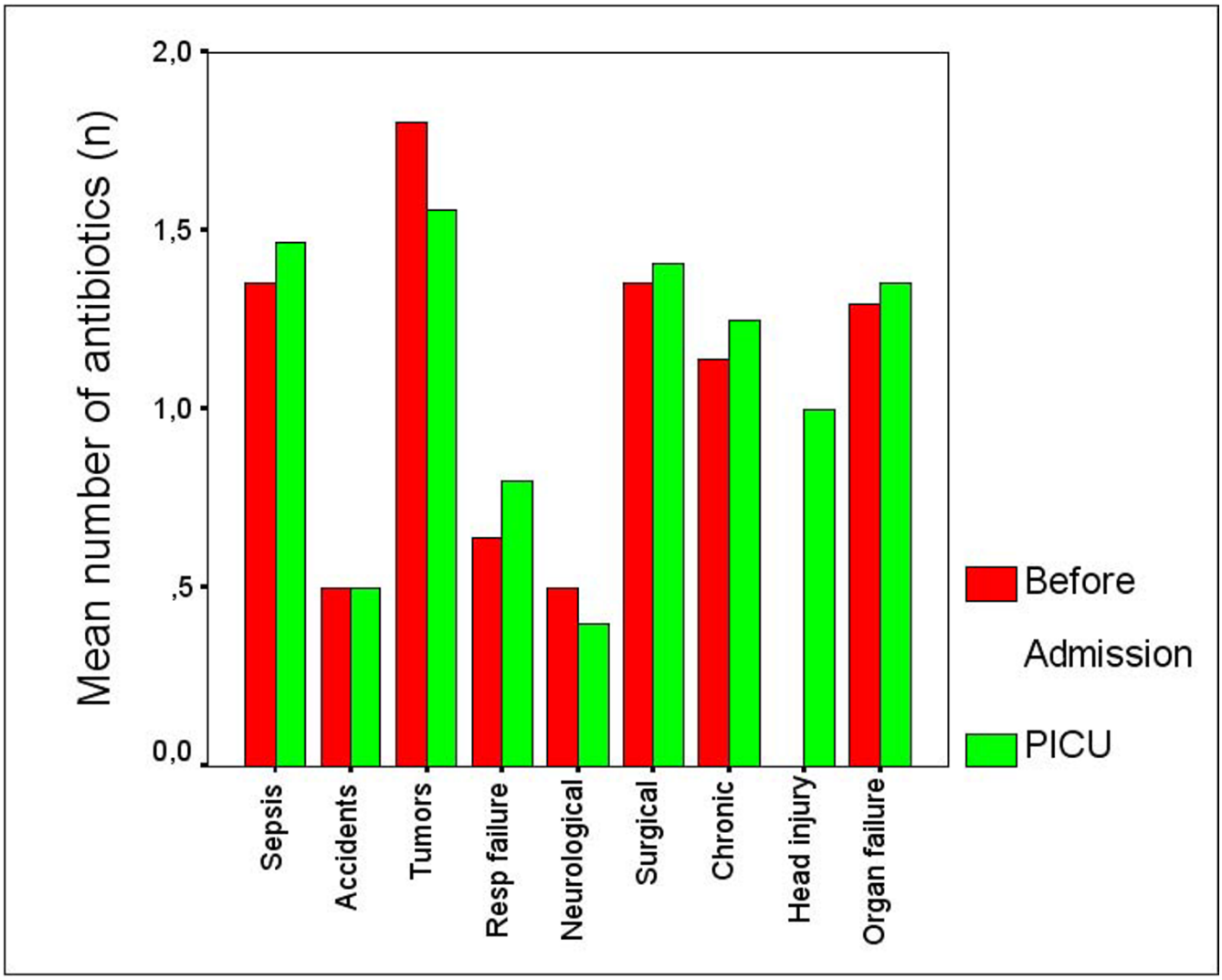

Figure 2
Antibiotics in various diagnostic groups related to PICU admission. Comparison of the mean number of antibiotics in various disease groups in PICU with the mean number of antibiotics received upon admission in the same patients.

neurosurgery patients admitted to the PICU were already receiving antibiotics at percentages as high as 90.2% and 82%, respectively. Neurosurgery patients had already being receiving two antibiotics in 44.8% (usually ceftazidime and vancomycin), whereas leukemia patients were already receiving 6 or 7 antibiotics, including carbapenems, aminoglycosides, and agents against fungi and viruses, in 40%. At admission, patients with metabolic or mitochondrial diseases were already receiving one or two antibiotics in 50%, whereas general surgery patients were receiving one antibiotic in 44% and two or more in 33.3%. In contrast, 100% of burns or head injury patients, 86% of patients with congenital heart disease, 67% of patients with non-febrile seizures, and 58.3% of patients with bronchiolitis had not received any antibiotic before admission to the PICU. At the same time 55.5% of patients with sepsis were receiving only one antibiotic while 11% had not yet received any antibiotic (most of them admitted directly through the ED). Among oncology and neurosurgery patients the mean number of antibiotics per patient in PICU was reduced (1.6 and .4, respectively), compared to the mean number of antibiotics received upon admission (1.8 and .5, respectively, $p < .0001$), while it remained unchanged in the accident group (Figure 2). Paired differences between the numbers of antibiotics given before admission or at discharge and

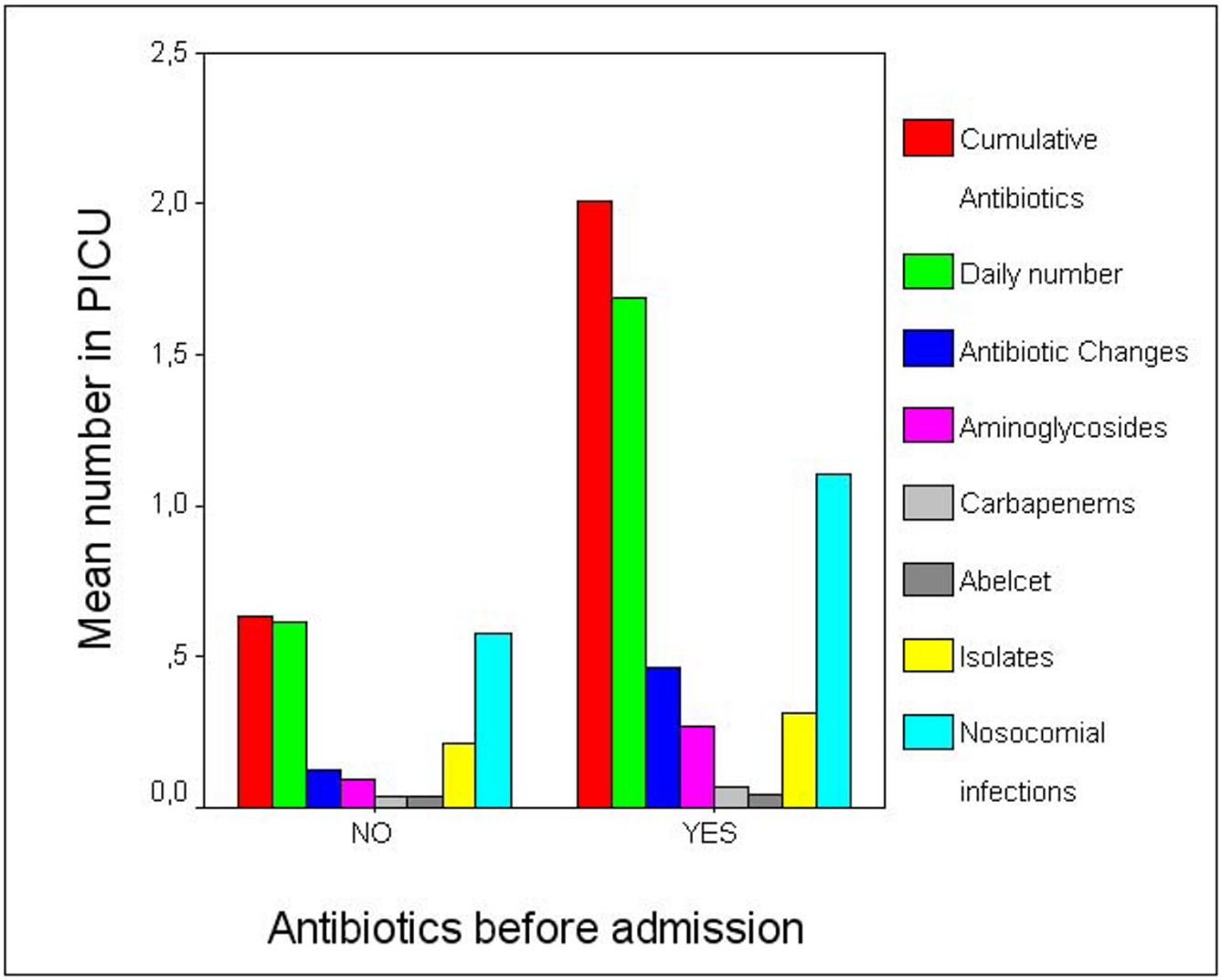

Figure 3
Antibiotics usage, changes, isolates and nosocomial infections. Differences in mean numbers of antibiotics usage, changes, isolates and nosocomial infections in PICU (after admission) between patients who were receiving or not receiving antibiotics the day before admission to the PICU.

the maximum (but not the cumulative: $p < .001$) number of antibiotics in PICU were not significant.

Prior use of antibiotics

Patients already receiving antibiotics were at higher risk of been infected with nosocomial microorganisms isolated in blood (15.4% vs. 8%), bronchial (21.4% vs. 15.8%), and cumulative cultures from different sites (31% vs. 21%, $p < .002$). These patients were also at higher risk of developing various nosocomial infections (Figure 3) and septic shock (9% vs. 2%, $p < .002$), but not nosocomial pneumonia (10.2%), despite the fact that more patients who had received antibiotics were supported with mechanical ventilation (57%) compared to patients who had not received antibiotics previously (49%). Regarding antibiotics, patients who were already receiving antibiotics were at significantly higher risk of receiving higher percentages of antibiotics in PICU in (98% vs. 44%, $p < .02$) and of receiving significantly higher daily and cumulative number of antibiotics ($p < .0001$), especially aminoglycosides (25% vs. 9%, $p = .003$), agents against fungi (9.4% vs. 3.5%, $p = .05$), ureidopenicillins with β-lactamase inhibitors (29% vs. 8.8%, $p < .03$), and ceftazidime (14.5% vs. 3.5%, $p < .03$), but not carbapenems ($p = .3$),

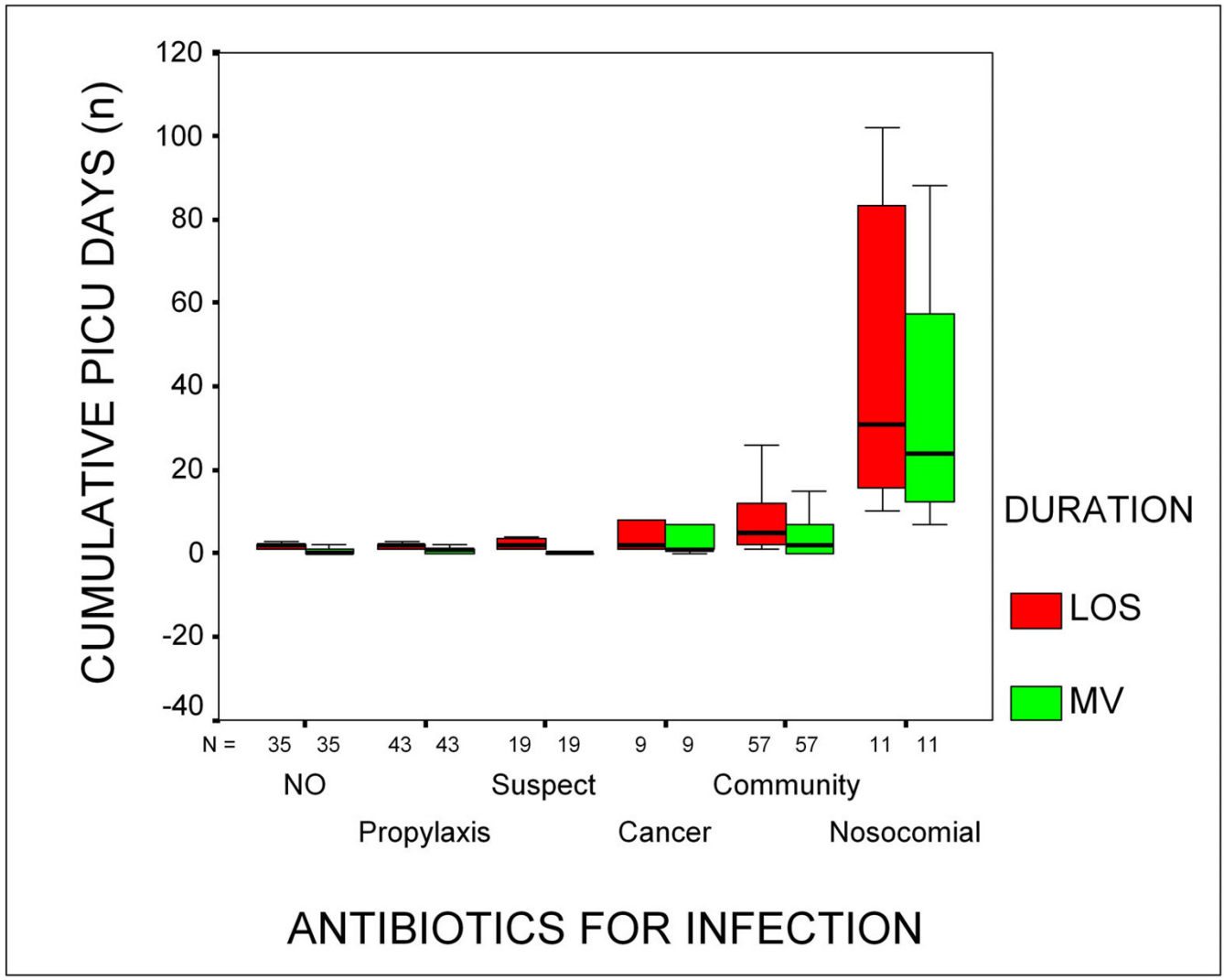

Figure 4
Resource utilisation in various indications for antibiotics usage. Relation of the length of stay and mechanical ventilation duration to various indications for prescribing antibiotics in PICU.

which most of these patients had already been started on before admission (Figure 3). Finally, patients with prior administration of antibiotics needed significantly more changes in antibiotic regimens during their hospitalization in PICU (.46 ± .09 vs. .12 ± .06, p < 003). Of those receiving antibiotics before admission, 70 were post-surgical patients and/or patients with cancer (83% receiving antibiotics), whereas of the remaining 104, only 34% were receiving antibiotics for suspected infection or infection of community (p < .0001). While in PICU, these percentages did not change significantly and their differences remained unchanged (92% for the post-surgical and cancer patients receiving antibiotics vs. 48% for the rest patients with acute or chronic diseases, p < .0001).

Indications for prescribing antibiotics

Indications for prescribing antibiotics the days before admission and during hospitalization in the PICU were significantly correlated and recorded as follows: No indication – no antibiotics 32.8% before vs. 20.1% after admission, antibiotics for prophylaxis 22.4% vs. 24.7%, suspected infection not proved 10.9% vs. 10.9%, immuno-compromised cancer patients with fever or other clinical signs of infection 6.3% vs. 5.2%, infection of community (sepsis, pneumonia, meningitis, etc) 27.6% vs.

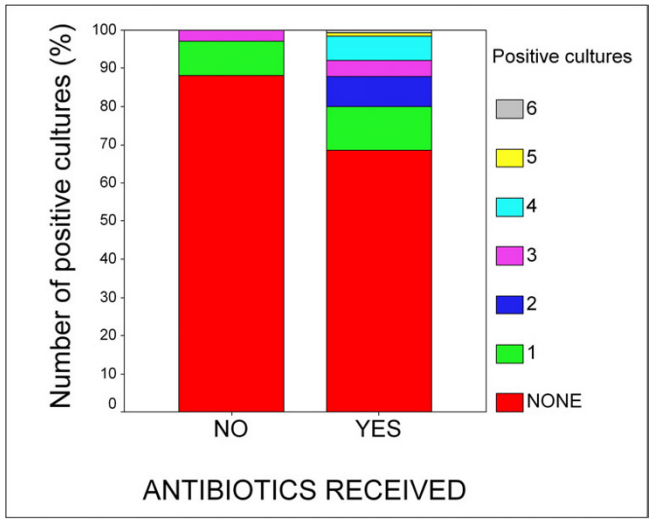

Figure 5
Isolated microorganisms and antibiotics in PICU. Distribution of groups of numbers of positive cultures with isolated pathogenic microorganisms in PICU patients receiving or not antibiotics (percentage scale 100%).

32.8%, p < .0001, and nosocomial infection while in PICU 6.3%. Although some of the last group patients who suffered of chronic metabolic or mitochondrial diseases or brain hemorrhages did not initially receive antibiotics, they subsequently developed VAP, probably because of the prolonged length of stay and mechanical ventilation duration, and finally received various combinations of antibiotics (Figure 4). Patients who had received antibiotics only for prophylaxis before admission, finally received more antibiotics in PICU than patients who had not received antibiotics previously (1.7 ± .2 vs. .6 ± .1, p < .0001).

Length of stay and antibiotics

Patients who stayed more than one week (40 patients) in the PICU received significantly higher number of antibiotics than the 134 patients hospitalised less than 8 days (2.5 ± .28 vs. 1.1 ± .02, p < .0001). Similarly, the antibiotics prescribed differed significantly between the 65 who were hospitalised more than 3 days and the109 patients who were hospitalised less than 3 days (2.1 ± .2 vs. 1.0 ± .8, p < .0001).

Microbial studies

Positive cultures during hospitalization were isolated in 60 bronchial secretions (26 during the 1st week, 21 the 2nd week, 13 the 3rd week) of 34 patients (19.5%), 28 blood cultures (18 during the 1st week, 10 beyond the 2nd week) in 23 patients (13.2%), 16 urine cultures (9%), 16 pleuritic or other body fluids and in 16 CSF (9%, including admission CSF of patients with meningitis), all of which were significantly related to the cumulative longitudinal number of received antibiotics (p < .0001) and were also significantly more frequently isolated in the group receiving antibiotics (Figure 5). Most of these isolates were sensitive to either ureidopenicillins and aminoglycosides (gram negative) or teicoplanin and vancomycin (gram positive strains). Cumulative sum of received antibiotics during hospitalization in PICU was significantly related to the number of isolated microorganisms (26% of patients, p < .0001). This significant correlation was retained when antiviral and antifungal agents were also taken into account (r^2 = .6, p < .0001), while borderline was the correlation of administered antibiotics at admission or discharge to the positive culture results (p = .05).

Correlation to clinical factors

A higher percentage of patients admitted from the OR (85.7%) or the wards (84.2%) had still been receiving antibiotics compared to those admitted from the ED (72.7%), home (66.7%) or other hospitals (65%), although this difference did not reach statistical significance. Similarly, significant was the burden of 51 patients with chronic disease (90.2% received antibiotics) or 37 patients with tumors (82.3%) in relation to 39 medical and 12 surgical patients with free previous medical history (73.2%, p < .03). Differences were also recorded among disease groups regarding the number of administered antibiotics (septic shock 100%, tumors 92.7%, surgical 88.2 compared to only 40% for neurological, 50% accidents and 60% respiratory diseases, p < .0001), predominant organic systems affected (respiratory 75.4%, septic shock 94.4%, p < .02), priority admission model (77.2% priority I vs. 92.6% priority III, p < .05). Finally, significantly larger number of antibiotics has been given to patients supported with mechanical ventilation (89.5%) compared to that administered to patients who were not mechanically supported (68.4%, p = .003) and had also received a smaller mean number of daily antibiotics. In the whole study population (including patients with cancer or major surgery), VAP had developed 11 patients (10.4%), nosocomial sepsis 23 patients (13.2%), urine infections 3 patients (1.7%), and CNS or other infections 3 patients (1.7%), including diagnoses made in other departments (oncology, surgical). Multiple regression analyses showed various clinical factors to be independently related to the range of antibiotic coverage in PICU (Table 3). Especially patients who needed various interventions during their hospitalisation, tended to receive larger number of antibiotics.

Correlation to outcome

When restricted to the patients with free history, PICU-related nosocomial infections were diagnosed in 13

Table 3: Multiple regression analyses of the range of antibiotic coverage related to various independent clinical determinants

Dependent variable	Independent determinant	p value
Cumulative number of antibiotics	Prior administration of antibiotics	.0001
	Presence of a bloodstream infection	.0001
	Positive bronchial cultures	.0001
	Negative outcome	.0001
	Severity of illness (PRISM)	.03
	Development of MOSF	.002
	Immunodeficiency	.001
	Number of central catheters	.03
Maximum daily number of antibiotics	Interventional TISS	.007
Duration of antibiotic coverage	Length of stay	.0001

patients (7.5%), with mortality rate 18% for the sepsis group, but none for VAP group. When expanding to the whole group (including cancer and chronic disease patients with nosocomial infection developed before admission to the PICU) nosocomial sepsis mortality increased to 23% and differed significantly from the null mortality associated with VAP ($p < .03$). Mortality rate (30.8%) in the PICU-related sepsis group (13/8.3%) was significantly higher compared to the 7.6% of the non-septic patients in PICU or the 11.8% of the admitted septic patients ($p < .02$). All 13 patients of the PICU-related sepsis group who died were high-risk patients with cancer (6/46.2%), chronic illnesses (5/38.5%), and end-stage organ failure (2/15.4%).

The percent antibiotic coverage of patients did not differ between survivors and non-survivors (81.5% vs. 70.6%) although the total administered number of antibiotics was different between the two groups. Higher percentage of non-survivors was supported by mechanical ventilation compared to survivors ($97 \pm 2.9\%$ vs. $35 \pm 3.1\%$, $p < .0001$). In relation to the maximum daily number of antibiotics, however, there were no significant differences between non-survivors and survivors, although they differed significantly regarding the PRISM (26.9 vs. 8.9, $p < .0001$), the possibility of death by PRISM (48.5 vs. 7.7, $p < .0001$), the TISS (44.7 vs. 22.4, $p < .0001$), and the age (9,3 ναντι 4,6, $p < .0001$). Although the cumulative number of administered antibiotics did not correlate with mortality (9.8%), it was significantly related to the severity scoring systems PRISM ($p < .001$), TISS ($p < .002$) and the probability of death by PRISM ($p < .002$).

Discussion

We demonstrated in this study that although a high percentage of critically ill children were receiving antibiotics in PICU (79%), most of them had already been receiving antibiotics before admission (68%). We also identified potential risk factors for increasing use of antibiotics in an intensive care setting. We further showed that the maximum and the cumulative per patient number of administered antibiotics, which the patients were receiving in PICU or at discharge, were significantly correlated with the number of antibiotics that the patients were already receiving on the admission day. Additionally, our study demonstrated three important results as consequences of following a strict approach to addressing the problem of antibiotic use in PICU. The first is that the mean number of antibiotics per patient in PICU was reduced compared to the mean number of antibiotics received upon admission, especially among oncology and neurosurgery patients. Use of monotherapy was more often in PICU (46% vs. 33%) whereas use of three antibiotics was less often (5.7% vs. 6.9%) than the day before admission. The second is that the duration of antibiotic usage was shortened, since the antibiotic days in PICU represented only 62.3% of the cumulative length of stay days compared to the 67.2% coverage at admission day. The third is that the cumulative sum of received antibiotics during hospitalization in PICU was significantly related to the number of isolated microorganisms, whereas this correlation was only borderline for the admission antibiotics.

A substantial proportion of PICU patients consists of oncology patients or patients with chronic diseases or sepsis (48% in our unit, 32.8% presented with septic shock). Other patients, presented with either severe community infections (meningococcus-induced purpura fulminans) or nosocomial infections from multi-resistant strains, might eventually need initiation or modification of preexisted antibiotic regimens or initiation of combined antibiotic treatment with broad-spectrum antibiotics. In this study the increased probability of covering severely ill children with antibiotics was shown by the significant correlation between the cumulative number of administered antibiotics and the severity scoring systems PRISM, TISS or the probability of death by PRISM. We further showed that prior administration of antibiotics, presence of a

bloodstream infection, positive bronchial cultures, mechanical ventilation, immunodeficiency, number of central catheters, a negative outcome, a high PRISM or interventional TISS, development of MOSF, and length of stay were all independently related to increased possibility of critically ill children receiving antibiotics in PICU. A previous study also showed that a PRISM score greater than 10 on PICU admission characterizes a population within the PICU at increased risk of infection [21]. Other researchers also showed that duration of MV and duration of stay in the PICU increase the risk of developing nosocomial infection [22], or that increasing severity of illness, compromise of the immune system, invasive interventions, and admission of patients from other health care facilities increase antibiotic resistance and, accordingly, antibiotic usage [23,24].

Several sources of inappropriate antibiotic utilization were identified in various studies. In our study, failure to discontinue treatment in the wards after starting empiric therapy and prolonged or excessive prophylaxis were the main reasons for inappropriate antibiotic utilization of admitted patients. Especially more than 80% of the oncology patients and more than 90% of the neurosurgical patients, or patients suffering from chronic illnesses, or priority III patients were covered with antibiotics for treatment or prophylaxis of their illnesses. Almost half of patients of these groups had been receiving prophylactic or empiric antibiotic regimens with 2 or more antibiotics. Another significant proportion of admitted patients had also been receiving antibiotics for non-proven suspected-infection or as a prophylaxis for community infection, despite the fact that many infectious disease societies published clinical guidelines to control administration of antibiotics [25] and to ensure optimal therapy while minimizing drug costs [26]. Such over-prescription might relate to misinformation on the part of physicians, pharmacists, and patients. Diagnostic uncertainty might also contribute to physicians prescribing the drugs for primarily viral infections to cover the "chance" of bacterial infection. Community wide consumption of antibiotics, however, has been strongly associated with infection or colonization with resistant organisms [27]. Similarly, prior antimicrobial therapy has been recognized as an important risk factor for the administration of inadequate antimicrobial treatment among ICU patients with clinically suspected infections [10]. These reports are in accordance with our findings, which showed that more isolates, nosocomial infections and cumulative antibiotics were prescribed in the group covered with antibiotics before admission to the PICU. Fortunately, most of our patients with head injuries were admitted to the PICU directly and did not receive prophylactic antibiotic therapy. This policy has been verified by a recent study which showed that the prophylactic administration of more than 1 antibiotic for more than 24 hours following severe trauma did not offer additional protection against sepsis, organ failure, and death, but increased the probability of antibiotic-resistant infections [28]. Resistance has been shown to be proportional to the volume of antimicrobial consumption, and reduction in resistance may require a similar reduction in the consumption [29]. Similarly, recent work has shown that isolates obtained from patients in the hematology ward were more often resistant to antimicrobial agents than isolates obtained from patients in the intensive care unit, and the agents against which the highest rates of resistance were found were also used more frequently in the hematology ward than in the intensive care unit [30]. Therefore, hospitals, and not only intensive care units, are common sites for breeding resistant bacteria, which require more expensive antibiotics, lead to prolonged hospitalization, and increase morbidity, mortality, and the cost of care [31,32]. In our study, nosocomial infections doubled the mortality of PICU patients and increased significantly the length of stay, the antibiotic usage and, presumably, their accompanying cost.

Several groups of clinical investigators have demonstrated a strong association between prior antibiotic administration and the emergence of VAP (as well as other nosocomial infections) caused by antibiotic-resistant bacteria [33,34]. Interestingly, infection with antibiotic-resistant bacteria has been associated with an increased risk of hospital mortality [35-38]. It was suggested therefore that scheduled changes of antibiotic classes for the empirical treatment of gram-negative bacterial infections could reduce the occurrence of inadequate antibiotic treatment for nosocomial infections and improve, therefore, the outcomes of critically ill patients [39]. This is further supported from our results that: a) mortality of the community and hospital-related sepsis (11.8%) did not differ compared to the non-sepsis PICU-mortality (7.6%); b) the PICU-related sepsis mortality was restricted to the high-risk patients with cancer or chronic illnesses; c) all the VAP patients survived.

There is reason to believe that the epidemiology of antibiotic usage in PICU settings may be different from that in other hospital settings because the patients' preadmission health status, the compromise of their immune systems, and their outpatient exposure to antibiotics are different from those seen in adults [40,41]. Despite all these difficulties, by following a strict protocol including surveillance cultures, we managed to have many antibiotics readily available for use in our unit (data not shown), according to culture results. Accordingly, not only the mean number of antibiotics per patient in PICU was reduced among oncology and neurosurgery patients, but also at discharge one fourth of our patients did not receive

any antibiotic. This is in accordance to a recent report suggesting that among febrile patients in PICU, applying common-use standards could have reduced approximately 15% of total antibiotic-days [42]. We believe that an even higher reduction of antibiotic prescription in our PICU could have been feasible, if we had attempted to restrict previously prescribed broad-spectrum empiric antibiotic regimens more rigorously or discontinue them, when appropriate.

The high rates of antibiotic misuse in specific departments of hospitals highlight the need for a thorough revision of strategies that deal with the proper use of antibiotics. The so-called 'optimal use of all antibiotics', restriction guidelines and use of a combination of antibiotics are well-established strategies but ignored in most non-PICU departments [43]. In a recent study surveillance cultures allowed that two thirds of the resistant isolates were imported and that the introduction of newer potent systemic antibiotic combinations failed to control the endemic reservoir of these multidrug-resistant bacteria [44]. We now showed that not only increasing rates of resistant isolates but also increasing numbers of wide-range antibiotics are also imported into PICU. Interestingly, we showed that patients already receiving antibiotics were at higher risk of been infected with nosocomial microorganisms, mainly isolated in blood and bronchial cultures, and of developing various nosocomial infections. Accordingly, these patients needed significantly more changes of antibiotic regimens during their hospitalization in PICU and received significantly higher daily and cumulative number of broad-spectrum antibiotics and agents against fungi. Supporting this view is the observation that most patients colonized or infected with ceftazidime – resistant gram-negative bacilli had positive surveillance cultures at the time of admission to the intensive care, suggesting that acquisition frequently occurred in other wards and institutions [8]. Although we restricted the use broad-spectrum cephalosporins as empirical treatment of nosocomial infections in our unit, a high percentage of admitted post surgical patients had been already exposed to cephalosporins, which they were still receiving upon admission.

These observations require that strategies to control infections in PICUs be reassessed and expanded to the wards. Published guidelines are available from several societies for providing optimal therapy and curtailing resistance in hospitals [25]. However, they are based primarily on expert opinion and what is needed is point-of-care delivery of clinical guidelines and evidence-based recommendations [45]. It has been shown that peer education improves quality of care and reduces cost of antibiotic prescribing in office practices [46]. The use of computerized antiinfectives-management programs might lead to significant reductions in excess drug dosages and antibiotic-susceptibility mismatches, in the mean number of days of excessive drug dosage and in the cost of antiinfective agents [47]. Furthermore, new potential strategies, such as combination of dosage optimization and antibiotic cycling, require further study and evaluation. We propose that additional long-term studies are required to better track the impact of liberal use of antibiotics in wards and to determine the optimal modalities of programmed changes of antibiotic prescribing as an antibiotic resistance prevention or control strategy of prolonged prophylaxis or empiric antibiotic misuse. Such modalities should also include institution of an effective infection control committee and a strict hospital antibiotic policy creating barriers to inappropriate practices and limiting prescribers' autonomy.

Several limitations of this study should be noted. First, it was conducted at a single unit. Therefore, these results may not be applicable to other PICUs with lower or higher rates of patients with cancer or chronic diseases. Second, we examined a mixed group of medical and surgical patients requiring intensive care. It is possible that other types of critically ill patients (neonates, cardiothoracic patients) may have different rates of pre-admission antimicrobial treatment and different risk factors predisposing to increasing administration of antibiotics. Finally, the observational nature of this investigation does not allow us to draw an absolute causal relationship between the administration of antimicrobial treatment and specific risk factors. Simultaneously, these limitations themselves constitute a unique advantage of this study, the results of which could be fully explored, based on homogeneous data and strategies. It is for this reason that the range of antibiotic coverage before and after PICU admission could be clearly shown and compared. Furthermore, predisposing factors influencing the use of antibiotics in critically ill children could be probably better established in an homogenous intensive care setting population than in multicenter studies with various policies, multiple interventions, different methods and mixed populations.

Conclusions

Prior antimicrobial therapy should be recognized as an important risk factor for extended antimicrobial therapy among critically ill children. The significant proportion of immuno-compromised or cancer patients, patients with prolonged length of stay, the increased degree of interventions and development of nosocomial infections restrict clinical efforts aimed at reducing antimicrobial treatment in critically ill patients. Despite these limitations, however, the antibiotic usage before and at PICU admission for prophylaxis and suspected infections might be reduced at about entry levels (community, nosocomial

infections) by imposing definite clinical indications, guided by microbial studies. Although such strategies might well be implemented and tightly controlled in closed health care systems such as intensive care units, the challenge now is to maintain their efficacy in a less restrictive system and for a wider array of prescribers.

List of abbreviations

Pediatric intensive care units (PICU); ventilator-associated pneumonia (VAP); Pediatric Risk of Mortality (PRISM); Therapeutic Intervention Scoring System (TISS); Multiple organ system failure (MOSF); mechanical ventilation (MV)

Authors' contributions

GB had primary responsibility for study design and writing the manuscript, LN had responsibility for collection of data, AT performed the final data analyses as well as the writing of manuscript. TH had intellectual contribution.

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