

Antibiotic Use in Pediatric and Neonatal Intensive Care Units; Multicenter Point Prevalence Study

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Abstract

Objective: Identifying antibiotic use in pediatric and neonatal intensive care units with a point prevalence study in Adana, Turkey's sixth largest city.

Material and Methods: In this point prevalence study, demographic information and antibiotic treatment data were taken on the same day from patients in pediatric and neonatal intensive care units of 6 hospitals located in Adana's city center.

Results: Four pediatric intensive care units (two university, one research and training hospital, and one public hospital) and six neonatal intensive care units (two university, one research and training hospital, one public hospital, and two private hospital) were included in the study; 220 patients were at the intensive care units at the time of the study, 44 (20%) of the patients were in the pediatric intensive care units, and 176 (80%) of them were at the neonatal intensive care units. Also, 146 (66.4%) of the patients were using antibiotics. The frequency of antibiotic use was 72.7% in the pediatric intensive care units and 64.8% in neonatal intensive care units. There was a pediatric infectious disease physician at the university and research and training hospital. Antibiotic usage was lower ($p=0.002$) in clinics where pediatric infectious disease physician consultations could be done. Double antibiotic combination was applied most frequently. Mostly, ampicillin was preferred at neonatal intensive care units. Clarithromycin was used as a second choice because of seasonal lower respiratory tract infections. Vancomycin was the most preferred antibiotic in pediatric intensive care units, and meropenem and linezolid were the second and third choices. At both intensive care units, use of empiric antibiotic treatment was more frequent. Empiric treatment was applied in 22 (68.7%) patients in the pediatric intensive care units and 95 (83.3%) in neonatal intensive care units. Antibiotics were given to 14.3% of the patients in line with the resulting cultures.

Conclusion: Intensive care units are services where antibiotics are used most frequently both in Turkey and in the world. In our opinion, protocols need to be established in clinics, national and international guides should be followed; and pediatric infectious disease physician consultations should be increased in order to reduce the frequency of antibiotic use, inappropriate indications, and inappropriate doses.

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Introduction

Antibiotics are among the most commonly used drugs in Turkey as well as all over the world. Even though their redundant use is high, appropriate use of antibiotics saves millions of lives. However, it does not seem to be possible in this day and age for the new generation of antibiotics to go into use in the next 20 years (1, 2). Ever increasing problem of antibiotic resistance impedes the physicians to use the antibiotics of their choice at the time and place whenever they want (1). Redundant use of antibiotics not only impacts the cost of treatment, it also threatens the public health as a result of assisting the microorganisms to develop resistance against antibiotics (3, 4).

Apart from the evidence-based antibiotic use in services such as neonatal intensive care units and pediatric intensive care units where high risk patients are hospitalized, laboratory or clinic-based empiric antibiotic use or patient-specific prophylactic antibiotic use is very prevalent. Due to the fact that more serious patients are hospitalized in the neonatal and pediatric intensive care units compared to the patients in other services and their hospitalization is longer and they are open to nosocomial infections, antibiotic use is higher (2, 5). Point prevalence studies investigate the ratio of antibiotic use of clinics and take necessary precautions based on the emerging results. However, most of the studies are carried out on adult patients or all the pediatric services regardless (3, 6, 7). There are no studies involving patients hospitalized in the pediatric intensive care or neonatal intensive care units in Turkey and not very prevalent in the world either.

Adana is the sixth biggest city in Turkey with its 2.149.260 population and hosts the 5th biggest child population in Turkey with its 563 thousand children under 15 years of age. In this study, we aimed to examine the prevalence of antibiotic use with point prevalence study in 10 intensive care unit in a total of 6 hospitals, two of which were private ones in Adana city center (2 university hospitals, 1 training and research hospital, 1 maternity and pediatric hospital and 2 private hospitals with neonatal and pediatric intensive care units).

Material and Methods

A total of 6 hospitals, 2 university hospitals, 1 training and research hospital, 1 maternity and pediatric hospital and 2 private hospitals with neonatal and pediatric intensive care units in Adana city center were included in the study. All the patients hospitalized in the pediatric intensive care and neonatal intensive care units were included in this study. The study was designed in such a way to

be started and completed on the same day as a prevalence study.

The demographic information, diagnosis of the patients, whether they were on the ventilator, the existence of central venous catheter, use of antibiotics, the active ingredient of that antibiotic, the culture test results, if they are available, patient capacity of the clinic, number of physicians on duty and their fields of expertise, the presence of night-shift physicians and their field of expertise were all investigated. All this information was obtained through the monitoring of the patients by nurses, physician's demand and consultation to the physician.

It was recorded whether antibiotic use was prophylactic, empiric or evidence-based. The diagnoses leading to the use of antibiotics were defined as lower respiratory tract infections, sepsis and others (post-op prophylaxis, an underlying primer disease, urinary system infection, wound site infection etc.).

Approval was obtained on the 25th of February, 2014 from the Ethical Committee of Noninvasive Clinical Studies of Adana Numune Education and Research Hospital. Permission was also obtained from all the centers involved in the study.

Statistical analysis

The statistical analysis was carried out by using the "Statistical Package for Social Sciences" version 15 (SPSS Inc., Chicago, IL, USA). Firstly, the descriptive statistics (number, ratio, average and standard deviation) of the variables in the study group were calculated. Secondly, comparative analyses were carried out through the chi-square test. The limit of significance was considered as $p < 0.05$ and their real values were defined.

Results

The clinical features, diagnoses, whether they used antibiotics, the active ingredient of the antibiotic if they used one, culture test results, ventilator therapy, central venous catheter presence of the patients hospitalized in the pediatric intensive care and neonatal intensive care units in the city center of Adana on 14/03/2014 were evaluated. A total of 220 patients from 2 university hospitals, 1 training and research hospital, 1 maternity and pediatric hospital and 2 private hospitals were included in the study.

The patient capacity of neonatal intensive and pediatric intensive care units of the concerned hospitals was 257. While the pediatric intensive care unit capacity was 49, neonatal intensive care unit capacity was 208. In general, these units had the occupancy capacity of 85.6% (220/257), during the period of the study, the occupancy

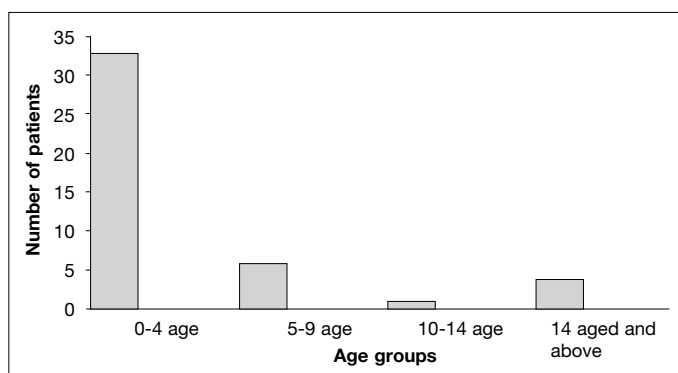


Figure 1. Age groups of patients in the pediatric intensive care unit capacity of neonatal intensive units was 84.6% (176/208) and in pediatric intensive care unit, it was 89.8% (44/49) (Table 1).

There was a consultant physician in all clinics during the day and night shifts. While there was an intensive care consultant during the day shift at the State University hospital, a subspecialist assistant was on duty during the night shift.

Forty four (20%) patients were hospitalized in the pediatric intensive care unit, 176 (80%) in the neonatal intensive care unit. While 105 (47.7%) patients were female, 115 (52.3%) were male patients (Table 1). The average age of the patients hospitalized in the pediatric intensive care unit was 3.74 ± 4.94 years. The average age of the patients hospitalized in the pediatric intensive care unit was 35.7 ± 46 day (Table 1). Thirty three (75%) patients hospitalized in the pediatric intensive care units were aged between 0-4, six patients were aged between 5-9 (13.7%), one patient was aged between 10-14 (2.3%) and 4 patients were aged 14 and older (9%) (Figure 1). In general The hospitalization period of the patients was 26.3 ± 51.8 day, in the pediatric intensive care units 39.5 ± 88.5 day and in the neonatal intensive care units, 23 ± 37 day (Table 1).

One hundred and forty six (66.4%) patients were given an antimicrobial treatment. Thirty two (22%) of the patients given antimicrobial treatment were hospitalized in the pediatric intensive care unit, 114 (78%) in the neonatal intensive care unit (Table 2). While 72.7% (32/44) of the patients in the pediatric intensive care unit were given an antimicrobial treatment, 64.8% (114/176) of the patients in the neonatal intensive care unit were given the same treatment (Table 2). The general period of antibiotic use was 5.66 ± 4.32 days. While this period in the pediatric intensive care units was 5.47 ± 3.67 day, and 5.71 ± 4.5 days in the neonatal intensive care units.

Of the six centers, only two had a pediatric infection diseases specialist. In these two centers, totally seventy six patients (76/220, 34.5%) were hospitalized, 24 (24/44, 54.5%) in the pediatric intensive care units, and 52 (52/176, 29.5%) in the neonatal intensive care units

Table 1. Assessment of clinic and patient characteristics

	Pediatric Intensive Care	Neonatal Intensive Care	Total
Capacity	49	208	257
Patients number	44 (%20)	176 (%80)	220
Ratio of occupancy	%89.8	%84.6	%85.6
Gender			
Female	22 (%50)	83 (%47.2)	105 (47.7)
Male	22 (%50)	93 (%52.8)	115 (%52.3)
Age*	3.74 year	35.7 day	
Hospitalization length**	39.5 ± 88.5 day	23 ± 37 day	26.3 ± 51.8 gün (general)
*average, **average and standard deviation			

(Table 2). 54% (41/76) of the patients hospitalized in those institutions were given antibiotics; this ratio was 70,8% (17/24) in the neonatal intensive care units and 46.2% (24/52) in the pediatric intensive care units (Table 2). The use of antibiotics was lower in the hospitals with no pediatric infection diseases specialist in comparison to those with a specialist ($p=0.007$). Of all these patients, a total of 56 (56/220, 25.4%) patients, 24 patients (24/44, 54.5%) in the pediatric intensive care units, 32 patients (32/176, 18.1%) in the neonatal intensive care units were examined by a pediatric infectious diseases specialist (Table 3). While 18.5% of the patients using antimicrobial drugs were consulted by a pediatric infectious diseases specialist, 81.5% of them were not consulted and/or could not be consulted by a pediatric infectious diseases specialist. While the use of antibiotic in children consulted by a pediatric infectious diseases specialist was 48.2%, the ratio in those without consultation was 72.6% ($p=0.002$). Antibiotic use in patients not consulted by a specialist despite the presence of one in the hospital, rose from 48.2% to 53.9%.

The antibiotics used in the patients hospitalized in the neonatal intensive care units were; the most prevalent one, ampicillin (38/114 patients, 33%), the second most prevalent, clarithromycin (31/114 patient, 27%), followed by gentamycin (26/114 patients, 22.8%), and cefotaxime (19/114 patients, 16.6%) (Figure 2). The antibiotics used in the patients hospitalized in the pediatric intensive care units were; the most prevalent, vancomycin (8/32 patients, 25%), the second most prevalent ones, meropenem and linezolid (7/32 patients, 21,8%) (Figure 3).

In the 28 (18%) of 146 patients given antimicrobial treatment, monotherapy was used, in 79 (54.1%) patients double, in 33 (22.6%) patients triple and in 6 patients quadruple drug combinations were used. In both inten-

Table 2. Assessment of patients' hospitalization services, antibiotic use, presence of infectious diseases specialist and appropriate dose of antibiotic

	Pediatric Intensive Care	Neonatal Intensive Care	Total
Hospitalized patients	44 patients (%20)	176 patients (%80)	220 patients
Pediatric infectious diseases specialist present	24 patients	52 patients	76 patients
	%54.5	%29.5	%34.5
Patients given antibiotics	32 patients	114 patients	146 patients
	%72.7	%64.8	%66.4
*Pediatric infectious diseases specialist present	17 patients	24 patients	41 patients
	%53	%21	%28
*Pediatric infectious diseases specialist not present	15 patients	90 patients	105 patients
	%47	%79	%72
Patients given inappropriate dose antibiotics	3 patients	5 patients	8 patients
	%9.5	%4.5	%5.6
*Pediatric infectious diseases specialist present	1 patients	2 patients	3 patients
	%5.8	%1.8	%2
*Pediatric infectious diseases specialist not present	2 patients	3 patients	5 patients
	%13.3	%2.6	%3.4

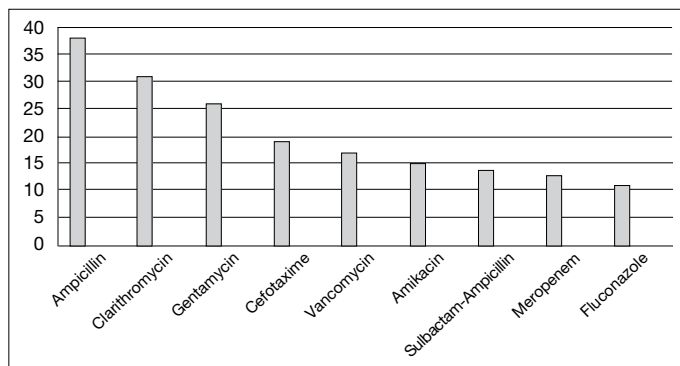


Figure 2. Antibiotics used in neonatal intensive care units

sive care units, double antibiotic combination was used the most prevalently.

In pediatric intensive care units, 22 (68.7%) patients were given empiric treatment (lower respiratory tract infection, sepsis and other); 8 (25%) patients were given antibiotic based on the culture test results; and 2 (6.3%) patients were given prophylactic antibiotic treatment. While 21 (65.6%) patients in the pediatric intensive care units were given antibiotics for the treatment of lower respiratory tract infection, 7 (21.9%) patients were given antibiotic for sepsis and 4 (12.5%) for other reasons. While the most prevalent antibiotics used for lower respiratory tract infections in pediatric intensive care units were vancomycin, ceftriaxone and clarithromycin, there was no specific unity in antibiotic combinations. While the most prevalently used antibiotics for sepsis were vancomycin, meropenem, linezolid and colistin, the most prevalent one of the antibiotic combinations was meropenem-linezolid.

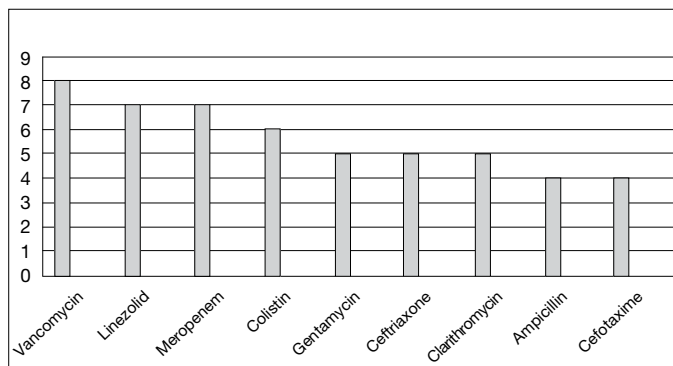


Figure 3. Antibiotics used in the pediatric intensive care units

In neonatal intensive care units, the empiric treatment was on the top of the list (lower respiratory tract infections, sepsis and other). 95 (83.3%) patients in the neonatal intensive care units were given empiric treatment, 13 (11.4%) antibiotic treatment based on the culture test results and 6 (5.3%) patients prophylactic antibiotic treatment. 11 (9.6%) patients in the neonatal intensive care unit who were given antibiotics based on the ampicil or culture test results were simultaneously given prophylactic fluconazole treatment as well. While 51 (44.7%) patients in the neonatal intensive care units were given antibiotic due to sepsis, other antibiotics were given to 49 (43%) patients for lower respiratory tract infections and 14 (12.2%) patients for other reasons. While the most prevalently used antibiotics used for lower respiratory tract infections in the neonatal intensive care units were clarithromycin, ampicillin and cefotaxime, the most prevalent antibiotic combinations were ampicil-

Table 3. Assessment of pediatric infectious diseases specialist consultation, antibiotic use and appropriate antibiotic dose

	Pediatric Intensive Care	Neonatal Intensive Care	Total
Antibiotic use in patients consulted by a pediatric infectious diseases specialist	24 (%42.8)	32 (%57.2)	56 hasta
Available	17 (%63)	10 (%37)	27 (%48.2)
Not available	7 (%24.1)	22 (%75.9)	29 (%51.8)
Antibiotic use in patients not consulted by a pediatric infectious diseases specialist	20 (%12.2)	144 (87.8)	164 hasta
Available	15 (%12.6)	104 (%87.4)	119 (%72.6)
Not available	5 (%14.2)	30 (%85.8)	35 (%28.4)
Appropriate antibiotic dose in patients consulted by a pediatric infectious diseases specialist	17 (%63)	10 (%37)	27 hasta
Appropriate	16 (%61.5)	10 (%38.5)	26 (%96.3)
Not appropriate	1	0	1 (%3.7)
Appropriate antibiotic dose in patients not consulted by a pediatric infectious diseases specialist	15(%12.6)	104 (%87.4)	119 hasta
Appropriate	13 (%11.6)	99 (%88.4)	112 (%94.1)
Not appropriate	2 (%28.5)	5 (%71.5)	7 (%5.9)

Table 4. Microorganisms reproducing in cultures

	Pediatric intensive care	Neonatal intensive care	Total
<i>Pseudomonas aeruginosa</i>	4 patients	6 patients	10 patients
<i>Klebsiella pneumoniae</i>	4 patients	5 patients	9 patients
Candida	1 patients	2 patients	3 patients
Acinetobacter	1 patients	-----	1 patients
Serratia	1 patients	-----	1 patients
<i>Stenotrophomonas maltophilia</i>	-----	1 patients	1 patients
*Microorganism grown in all the four patients			

lin-clarithromycin and cefotaxime-clarithromycin. While the most prevalently used antibiotics used for sepsis in the neonatal intensive care units were ampicillin, gentamycin and vancomycin, the most prevalent antibiotic combinations were ampicillin-gentamycin and vancomycin-meropenem.

Inappropriate dose of antibiotic use was in general 5.6%; it was 9.5% in pediatric intensive care units and 4.5% in neonatal intensive care units. Inappropriate dose of antibiotic use in centers with a pediatric infectious diseases specialist was in general 2.1%; it was 5.8% in pediatric intensive care units and 1.8% in neonatal intensive care units (Table 2).

There was growth in the cultures (blood, tracheal aspirate and urine) of 21 (14.3%) out of 146 patients given antimicrobial treatment. The most common micro-

organisms in the cultures were *Pseudomonas aeruginosa* (10 patients, 47.6%), *Klebsiella pneumoniae* (9 patients, 42.8%), *Candida albicans* (3 patients, 14.2%). The antibiotics and their doses used in patients with culture growth were correct. While growth was found in the cultures of 8 (8/32, 25%) patients hospitalized in the pediatric intensive care units, it was found in 13 (13/114, 11.4%) patients in the neonatal intensive care units (Table 4). Microorganism growth in cultures in the pediatric intensive care units was higher; however, the ratio was not statistically significant ($p=0.086$).

There was no statistically significant correlation between the frequency of antibiotic use of the patients and the presence of ventilator therapy ($p=0.268$). 41 (18.6%) patients had central venous catheter. The ratio of central venous catheter usage was 52.3% (23/44) in the pediatric intensive care units and 10.2% (18/176) in the neonatal intensive care units. The most frequent central venous catheter site in the pediatric intensive care units was femoral venous (12/23), followed by subclavian vein (11/23). The most frequent central venous catheter in the neonatal intensive care units was umbilical vein (9/18), followed by subclavian vein (8/18). 92.7% of the patients with central catheter received an antibiotic ($p=0.000$).

Regarding the institution where the patients were hospitalized, antibiotic use and correctness of antibiotic dose; with regards to the differentiation between public* and public sectors (*public state hospitals and foundation (private) hospital), antibiotic use in the public sector was 61% and 80% in the private sector; inappropriate dose of antibiotics was 7.3% in the public sector and 2% in the private sector. With regards to the grouping of

Table 5. Assessment of the institution where the patients are hospitalized, antibiotic use and appropriate dose of antibiotic

	Antibiotic was used	Antibiotic was not used	Antibiotic dose was appropriate	Antibiotic dose was not appropriate
University hospitals	40 patients 66.6%	20 patients 33.4%	38 patients 95%	2 patients 5%
Other hospitals	106 patients 71%	43 patients 29%	100 patients 94.3%	6 patients 5.7%
Public institutions*	96 patients 61%	62 patients 39%	89 patients 92.7%	7 patients 7.3%
Private sector	50 patients 80%	12 patients 20%	49 patients 98%	1 patients 2%
Training hospitals**	60 patients 58%	43 patients 42%	56 patients 93.3%	4 patients 6.7%
Other hospitals	86 patients 74%	31 patients 26%	82 patients 95.3%	4 patients 4.7%

*Public (state) hospitals and foundation (private) university
**University hospitals and training research hospitals

hospitals as university hospitals and others, antibiotic use in the university hospitals was 66.6% and 71% in others; while inappropriate antibiotic use in the university hospitals was 5%, it was 5.7% in others. Regarding the grouping as training hospitals** and other (**universities and training-research hospitals); antibiotic use in training hospitals was 58% and 74% in other; inappropriate antibiotic use was 6.7% in training hospitals and 4.7% in others (Table 5).

Discussion

For the rational use of the drugs and clinical needs of the patients, the World Health Organization describes the right drug as correct dose, for right duration and for the most affordable prices for the patients and their country of residence (8). The targets are failed in antibiotic use and the growing resistance to antibiotics cannot be stopped.

Antibiotics are on the top of the list of drugs most prevalently used in our country, constitute the 20% of all the drugs used and create the 30% of hospital treatment costs (4, 9).

In studies carried out in order to establish the prevalence of antibiotic use, different results such as 30.6%, 54.6%, 65% and 75.8% were obtained (3, 7, 10, 11). The previous studies were usually done on adult patients; in the pediatric studies, all the pediatric services and intensive care units were not included in the study. The previous studies demonstrated that pediatric antibiotic use in hospitalized cases was higher than adult use (3, 7).

While the antibiotic use in our study in general was 66.4%, 72.7% in the pediatric intensive care units and 64.8% in neonatal units, in a 2008-study in a pediatric hospital in Turkey, it was in general 50.4%, in the pedi-

atric intensive care unit 41.2% and in the neonatal intensive care unit 20%; in a 2009-multi-centered study in pediatric services, it was in general 54.6%, in the pediatric intensive care unit 75.7% and in the neonatal intensive care units 73.3% (3, 6). Since our study coincided with a period during which there was seasonal increase in the lower respiratory tract infections in infants under 2 months, clarithromycin, which was not initially used in the care of neonatal intensive patients, came to be used in a ratio as high as 27% (31/114 patients). The difference between antibiotic uses may be down to seasonal infections and ever-growing antibiotic resistance. The fact that Adana is a reference center for the whole region and the resulting abundance of complicated patients may be another reason for the increase in the use of antibiotics.

Antibiotics are on the top of the list of drugs most prevalently used in our country (12). The ratio of antibiotic use out of all drugs in 2002 was in the region of 24%. For the use of broad spectrum antibiotics in 2003 in our country, approval obligation by an infectious diseases specialist was brought in and limitation on its use was introduced; in the studies ensuing this limitation, 26.4% decrease was found in antibiotic use (12, 13). There was an infection control committee in all the hospitals involved in our study; however, only 2 of them had an infectious diseases specialist. While the ratio of antibiotic use in pediatric infectious diseases-consulted patients was 48.2%, it was 72.6% in those not consulted ($p=0.001$). It was reported in a 2006 study in Turkey that in 57.4% of the treatments, a change was observed after the consultation of an infectious diseases specialist; similarly, in a 2013 study in Germany that in as high as 66% of the patients, a change was reported in the treatment of those patients after the consultation of an infectious diseases specialist (14, 15). In our study, antibiotic use in the clin-

ics where there was a pediatric infectious diseases specialist was lower than those without one and it was statistically significant ($p=0.007$). Less antibiotics were used in patients who were consulted by a pediatric infectious diseases specialist and this was statistically significant ($p=0.002$).

In various studies done in our country regarding the inappropriate dose of antibiotic use, it was found as 10,5% in general pediatric services in one study, and 10,9% in another one (2, 16). Inappropriate dose of antibiotic use in neonatal intensive care units in our study was established as 4.5% and 9.5% in the pediatric intensive care units. The fact that inappropriate dose of antibiotic use in neonatal intensive care units was lower than pediatric intensive care units was acknowledged in general and this can be justified by the commonly used antibiotic guidelines and resource books (17). We are of the opinion that there is a need for similar guidelines for pediatric intensive care units that have not completed their development or establishment like neonatal intensive care units.

Antibiotic use in our study increased in the following ascending order of university hospitals, training and research hospitals, public (state) hospitals and private (sector) hospitals. For various reasons, antibiotic use in training and research hospitals in comparison to other hospitals in Turkey as well as all over the world is less, a study done in 2010 in Brazil revealed that when private sector and public (state) hospitals were compared, antibiotic use in the private sector higher (18, 19). In our study, inappropriate dose of antibiotic use, choice of antibiotic and their combinations amongst the hospitals were similar.

In an attempt to reduce inappropriate antibiotic use, local-national-international guidelines are prepared by the institutions, antibiotic restriction practices, organized changes in antibiotic use, antibiotic combination practices, antibiotic rotation, clinic-region specific antibiotic usage is implemented, infection control committees are set up, periodical training is provided (1, 2). However, inappropriate antibiotic use continues and as a result, resistance develops.

Conclusion

In conclusion, speed of resistance development against antibiotics is faster than antibiotic surveys. It is impossible to totally stop resistance development against antibiotics in the real world. However, it is up to us to slow down resistance development (1). Even if efforts are made to stop inappropriate use of antibiotic and resistance development through methods such as introducing

restrictions for the use of broad spectrum antibiotics, pediatric infectious diseases specialist consultations and publishing guidelines, patients' unique clinical features, physicians' decisions and experiences have an impact over the final decisions (2). We are of the opinion that periodical studies regarding antibiotic use should be implemented and training efforts in the regions where inappropriate and prevalent antibiotic use is high should be expedited.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Noninvasive Clinical Investigations of Adana Numune Training and Research Hospital (25.02.2014/ANEAH.EK.201/1).

Informed Consent: Written informed consent was not obtained due to the retrospective nature of this study.

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