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Inappropriate antimicrobial use in Turkish pediatric hospitals: A multicenter point prevalence survey

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Summary
Objectives: Although well-defined principles of rational antimicrobial use are available, inappropriate prescribing patterns are reported worldwide. Accurate information on the usage of antimicrobials, including factors associated with and influencing their use, is valuable for improving the quality of prescription practices.
Methods: In this cross-sectional point prevalence survey, data on patients hospitalized in 12 different children's hospitals were collected on a single day. Appropriateness of prescription was compared between the types of antimicrobials prescribed, indications, wards, and presence of/consultation with an infectious disease physician (IDP).

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Results: A total 711 of 1302 (54.6%) patients evaluated were receiving one or more antimicrobial drugs. The antimicrobial prescription rate was highest in pediatric intensive care (75.7%) and lowest in the surgery wards (37.0%). Of the 711 patients receiving antimicrobials, 332 patients (46.7%) were found to be receiving at least one inappropriately prescribed drug. Inappropriate use was most frequent in surgery wards (80.2%), while it was less common in oncology wards (31.8%; $p < 0.001$). Respiratory tract infection was the most common indication for antimicrobial use (29.4%). Inappropriate use was more common in deep-seated infections (54.7%) and respiratory infections (56.5%). Fluoroquinolones were used inappropriately more than any other drugs (81.8%, $p = 0.021$). Consultation with an IDP appears to increase appropriate antimicrobial use ($p = 0.008$).

Conclusions: Inappropriate antimicrobial use remains a common problem in Turkish pediatric hospitals. Consultation with an IDP and prescribing antimicrobial drugs according to microbiological test results could decrease the inappropriate use of antimicrobials.

Introduction

While antimicrobial drugs are responsible for some of the most dramatic improvements in medical therapy in history, these medicines are also the only class of drug whose efficacy diminishes with their wide-scale use in hospital-based and outpatient settings. The increased use of antimicrobial drugs has coincided with the emergence of antimicrobial resistance, which constitutes an important clinical, economic, and public health problem.[1–3] Resistant pathogens increase healthcare associated expense, complicate therapy, and make treatment failure more likely. Therefore, there has been a growing attentiveness to the rational use of antimicrobials since the 1990s.[4]

Although the number of prescriptions for antibiotics for children decreased during the 1990s, the use of broad-spectrum antibiotics increased at the same time.[5,6] The overuse of expensive broad-spectrum intravenous (IV) agents and the ecological impact of prescribed drugs on the hospital microflora have contributed to high levels of expenditure in healthcare management.[7–9] The indirect costs of IV therapy include preparation, administration, and monitoring of injections or infusions, which also affect nursing, medical, and/or pharmacy time. Surveying antibiotic prescribing in hospitals is important to detect the current situation and for policy-making to change incorrect practices. Continuous surveillance may be time-consuming and expensive. However, point prevalence studies of antibiotic prescribing provide a useful insight into patterns of prescribing, potentially reporting a more focused audit on specific agents or specialties.[10] Such surveys may point to changes in prescribing practices within the same hospital over time or indeed highlight differences between hospitals.

Point prevalence studies have been increasingly undertaken in adult hospitals in many countries including Turkey.[11,12] However, there is no information on the use of antimicrobials for children in our country, and data are very limited worldwide. Therefore, we performed this cross-sectional national point prevalence survey in patients hospitalized in children's hospitals to determine the prevalence of inappropriate antimicrobial use and factors associated with and influencing this.

Materials and methods

After obtaining ethical approval from the local ethics boards of all the participating centers and the Central Ethical Committee of the Ministry of Health, a questionnaire was developed by the Turkish Collaborative Study Group on Hospital Infections and sent to the study centers. Twelve pediatric hospitals in nine cities located in all of the seven geographic regions of Turkey were selected to represent the population characteristics of the country. Two centers from each of the three largest cities and one center from each of the other cities were included. Each health center serves as a referral center for its region in the field of pediatric diseases. The centers serve approximately 32% of the entire pediatric population of Turkey.

Data on diagnosis, demographics, antimicrobials given to the patients, dosage, indications, microbiological test results, existence of pediatric infectious disease specialist in the center, and presence of pediatric infectious disease physician consultation for all pediatric patients (aged 0—16 years) hospitalized in intensive care units, neonatal intensive care units, pediatric wards (including special infectious diseases and oncology wards) or surgical wards were collected by pediatricians and infection control nurses on October 3, 2007. All patients who were receiving antimicrobials for any reason were included in the study. Lists of patients were obtained between 8:00 a.m. and 9:00 a.m. on the day that the surveillance was conducted. Wards were surveyed over a 10-hour period starting at 9:00 a.m. and finishing at 9:00 p.m. on the same day. Children admitted or prescribed new antibiotics after 9:00 p.m. were not included. Data were collected from chart review, discussions with nursing staff, and laboratory records. Data were collected on manually completed forms and forwarded to the Department of Pediatric Infectious Diseases, Medical School, Hacettepe University for data entry and analysis. The records were evaluated by the principal investigator together with two other pediatric infectious disease specialists from the study group.

Antimicrobial drug use was considered inappropriate if indication and choice of the drug(s) or dose of the antimicrobials were wrong. Information in the guidelines of the American Academy of Pediatrics and classical textbooks was used in this evaluation.[13,14] Indication and dosage errors

Table 1 Rate of antibiotic use in different pediatric wards

Ward	Number of patients ordered antibiotics	Total hospitalized patients	Percentage antibiotic prescription	*p*-Value
Intensive care	89	119	74.8	0.033
PICU	56	74	75.7	0.074
NICU	33	45	73.3	0.206
Pediatrics	541	964	56.1	0.701
Infectious diseases	66	80	82.5	0.016
Other	475	884	53.7	0.826
Surgery	81	219	37.0	<0.001
Total [a]	711	1302	54.6	

PICU, pediatric intensive care unit; NICU, neonatal intensive care unit.
[a] Chi-square 73.6, degrees of freedom 2, $p < 0.001$.

were determined, and the association between the frequency of such errors and the presence of an infectious diseases specialist in the center, infectious disease physician consultation, antibiotic chosen, indication, and hospital wards were assessed.

After excluding unavailable patients, all analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). The significance of differences between groups was evaluated using the Chi-square test with correction when appropriate and *t*-tests as indicated.

Results

A total of 1302 pediatric patients were surveyed in 12 hospitals. Three of the centers were stand-alone pediatric hospitals and the other nine centers were university-affiliated pediatric hospitals, which were part of combined adult–pediatric hospitals. Of the patients studied, most were hospitalized in Hacettepe University (16.6%) and the least number of patients were from Gaziantep University Medical Center (3.5%); the distribution of the patients was comparable with the hospital bed capacity and population served.

Of the 1302 patients surveyed, 711 (54.6%) were receiving antimicrobial drugs. The mean age of patients receiving antimicrobials was 49.51 (±57.78) months. In those participating in the survey, 578 (44.4%) were female and 724 (55.6%) were male. One hundred nineteen (9.1%) patients were in intensive care units (45 (3.5%) were in neonatal intensive care units), 80 (6.1%) were in infectious diseases wards, 884 (67.9%) were in pediatric wards (125 (9.6%) in oncology wards), and 219 (16.8%) were in surgery wards.

Among patients receiving antimicrobials, 283 (39.8%) were receiving one drug, 304 (42.8%) two drugs, 86 (12.1%) three drugs, 25 (3.5%) four drugs, 10 (1.4%) five drugs, and 3 (0.4%) six different drugs.

The most common indication for antimicrobial therapy was respiratory tract infection (RTI; 209 patients, 29.4%). This was followed by empirical therapy in 133 (18.7%) patients, deep-seated infection (DSI; endocarditis, central nervous system infections, etc.) in 75 (10.5%), blood stream infection (BSI; sepsis, bacteremia, etc.) in 69 (9.7%), urinary tract infection (UTI) in 59 (8.3%), intra-abdominal infection in 43 (6.0%), skin and soft tissue infection (SSTI) in 31 (4.4%), and other infection in 36 (5.1%). The indication was not documented in 56 (7.9%) patients.

The highest antimicrobial consumption rate was found in intensive care and the infectious diseases wards; patients hospitalized in the surgery wards were least likely to undergo antimicrobial treatment. The antimicrobial prescription rate was 75.7% in pediatric intensive care, 73.3% in neonatal intensive care, 82.5% in the infectious diseases wards, 53.7% in the general pediatric wards, and 37.0% in the surgery wards (Table 1).

The most commonly used antimicrobial agents were cephalosporins (291 patients, 22.1%) and penicillins (270

Table 2 Antimicrobials prescribed to hospitalized patients

Antimicrobial	Number of patients	Percentage
Cephalosporins	291	22.1
1st generation	13	1.0
2nd generation	15	1.1
3rd generation	219	16.6
4th generation	44	3.3
Penicillins	270	20.5
Narrow- and broad-spectrum	136	10.3
Combinations with β-lactamase inhibitors	134	10.2
Aminoglycosides	218	16.6
Glycopeptides	134	10.2
Carbapenems	150	11.4
Metronidazole	44	3.3
Macrolides	28	2.1
Clindamycin	20	1.5
Fluoroquinolones	11	0.8
Trimethoprim/sulfamethoxazole	13	1.0
Chloramphenicol	6	0.5
Linezolid	5	0.4
Antifungals	88	6.7
Fluconazole	41	3.1
Amphotericin B	42	3.2
Caspofungin	5	0.4
Antivirals	24	1.8
Acyclovir	21	1.6
Ganciclovir	3	0.2
Antituberculous	15	1.1
Total	1317	100

Note: Some patients were ordered more than one antimicrobial.

Table 3 Inappropriate antibiotic usage according to indication and microbiological test results

Indication	Patients receiving antibiotics		Antimicrobials given according to microbiological test results[a]			
	Number	Percent	Number	Antimicrobials ordered	Percent	*p*-Value
Respiratory infection	209	29.4	17	375	4.5	0.002
Empirical[b]	133	18.7	0	259	0	
Deep-seated infection[c]	75	10.5	24	135	17.8	0.018
Blood stream infection[d]	69	9.7	26	148	17.6	0.017
Urinary tract infection	59	8.3	32	75	42.7	<0.001
Intra-abdominal infection	43	6.0	13	101	12.9	0.445
Skin and soft tissue infection	31	4.4	9	54	16.7	0.180
Other	36	5.1	6	75	8	0.579
Undocumented	56	7.9	8	95	8.4	0.617
Total[e]	711	100	135	1317	10.2	

[a] Microbiological tests: culture, serology, PCR, etc.
[b] For febrile neutropenia, premature newborns with early membrane rupture, etc.
[c] Endocarditis, central nervous system infection, etc.
[d] Sepsis, bacteremia.
[e] Chi-square 63.5, degrees of freedom 7, $p < 0.001$.

patients, 20.5%) (Table 2). The rate of prescribing antimicrobials according to microbiological test results was lowest in RTIs (4.5%, $p = 0.002$) and highest in UTIs (42.7%, $p < 0.001$) (Table 3). Although the frequency of using antimicrobials depending on the test results was lower than that in RTIs, the rate of usage according to microbiological test results was statistically higher in DSIs (17.8%, $p = 0.018$) and BSIs (17.6%, $p = 0.017$) than for the other indications.

Out of 711 patients receiving antimicrobials, 332 patients (46.7%) were found to be receiving at least one inappropriately prescribed drug. Fluoroquinolones were used in 11 patients and caspofungin in five in spite of their limited indications. We determined that fluoroquinolones were the most inappropriately used antibiotics (81.8%, $p = 0.021$); first-generation cephalosporins (7.7%), glycopeptides (31.3%), metronidazole (25%), and clindamycin (28%) were used more appropriately than the others ($p = 0.005$, 0.001, and 0.005, respectively) (Table 4).

The presence of a pediatric infectious disease specialist in the center did not affect the rate of inappropriate antimicrobial use ($p > 0.05$), however, patient consultation with an infectious disease physician was found to be related to a

Table 4 Comparison of the 11 most commonly used antibacterial drugs for inappropriate indication and/or dosage use

Antibiotic	Numbers of antibiotics				Percentage of inappropriately used antibiotics	*p*-Value
	Inappropriate indication	Inappropriate dosage	Inappropriate indication and/or dosage	Used in total		
Cephalosporins	102	8	105	291	36.1	0.547
1st generation	1	0	1	13	7.7	0.005
2nd generation	5	0	5	15	33.3	0.765
3rd generation	82	7	85	219	38.8	0.982
4th generation	14	1	14	44	31.8	0.050
Penicillins	113	14	118	270	43.7	0.348
Narrow- and broad-spectrum	53	6	55	136	40.4	0.822
Combinations with β-lactamase inhibitors	60	8	63	134	47.0	0.245
Aminoglycosides	82	9	87	218	39.9	0.858
Carbapenems	58	2	58	150	38.7	0.966
Glycopeptides	39	5	42	134	31.3	0.001
Metronidazole	11	0	11	44	25	0.005
Macrolides	18	0	18	28	64.3	0.068
Clindamycin	7	1	7	25	28	0.005
Trimethoprim/sulfamethoxazole	6	2	6	13	46.2	0.732
Fluoroquinolones	8	2	9	11	81.8	0.021
Total[a]	444	43	461	1184	39.9	0.005

[a] Chi-square 27.1, degrees of freedom 10, $p = 0.005$.

Table 5 Evaluation of inappropriate antimicrobial drug use by pediatric infectious disease consultation, hospital ward, and indication

	Number of patients with:				Percentage of inappropriate use	Chi-square, degrees of freedom, *p*-value
	Inappropriate indication	Inappropriate dosage	Inappropriate indication and/or dosage[a]	Antimicrobial treatment		
Pediatric infectious disease specialist at the center						
Absent	182	42	215	461	46.6	0.01, DF 1, $p = 0.980$
Present	118	7	117	250	46.8	
Pediatric infectious disease consultation						
Absent	247	36	265	552	48.0	7.36, DF 1, $p = 0.008$
Present	53	13	57	159	35.8	
Wards						
Intensive care unit	28	5	28	56	50	46.71, DF 4, $p < 0.001$
Neonatal intensive care unit	17	1	17	33	51.5	
Oncology	21	3	21	66	31.8	
Pediatrics	175	29	201	475	42.3	
Surgery	59	11	65	81	80.2	
Indication						
Respiratory infection	112	26	118	209	56.5	23.91, DF 8, $p = 0.006$
Deep-seated infection[b]	39	6	41	75	54.7	
Blood stream infection[c]	25	4	26	69	37.7	
Urinary tract infection	13	5	16	59	27.1	
Intra-abdominal infection	17	6	20	43	46.5	
Skin and soft tissue infection	6	10	10	31	32.3	
Empirical[d]	55	5	56	133	42.1	
Undocumented	22	2	22	56	39.3	
Other	17	2	17	36	47.2	
Total	306	66	326	711	45.9	

[a] Some patients were ordered antimicrobials both with the wrong indication and dosage.
[b] Endocarditis, central nervous system infections, etc.
[c] Sepsis, bacteremia.
[d] For febrile neutropenia, premature newborns with early membrane rupture, etc.

lower rate of inappropriate use ($p = 0.008$) (Table 5). The highest rate of inappropriate antimicrobial use was observed in surgery units (80.2%), while in contrast, inappropriate prescription was found less frequently in the oncology wards (31.8%; $p < 0.001$). When we look at the indications for antimicrobial treatment, antimicrobials were most appropriately used in UTI patients (72.9%, $p = 0.006$).

Discussion

The appropriate use of antimicrobials plays a key role in efforts aimed at establishing a good and cost-effective healthcare system in pediatric hospitals. The observation of an increasing antibacterial resistance in Turkish hospitals[11,12,15] prompted this survey of inappropriate use of antibacterial drugs in the Turkish pediatric population. Because our study centers provide a service to approximately 32% of the pediatric population of Turkey, we believe that our results may be used to give a general view of the situation in Turkish pediatric hospitals.

In a multicenter study undertaken in adult hospitals in Turkey, the frequency of antimicrobial prescription was found to be 30.6% in hospitalized patients.[11] In our study, 54.6% of patients were receiving antimicrobial treatment, and it seems that pediatric patients are receiving antimicrobials more frequently than adult patients in hospitals in Turkey. This frequency is similar to those reported from developing countries, such as 77.8% in China and 65.0% in Costa Rica.[16,17] Although the antimicrobial prescription rate was found to be higher in adult surgical wards compared to other adult hospital wards in Turkey and also in Germany as a developed country,[11,18] surgery wards had the lowest rate of antibiotic use in our study (37.0%, $p < 0.001$). This may be related to the types of surgical operations in pediatric patients, which have a lower requirement for prophylactic and empirical antimicrobial therapy. In the present study, the

higher rates of antimicrobial treatment in the infectious diseases wards (82.5%, $p = 0.016$) and the pediatric and neonatal ICUs (in spite of the lack of statistical significance; 75.7%, $p = 0.074$ and 73.3%, $p = 0.206$, respectively), may be not surprising; however we believe that these rates are far outside the acceptable range when compared to reported prescription frequencies of 6.55% and 14.4% from two different pediatric ICUs in Israel and some other studies in recent years.[19]

We found that the empirical use of antimicrobial drugs was the second most common indication for therapy after respiratory infections, and this is comparable to results found in the literature.[20] The high rate of empirical therapy is possibly related to the low positive results of microbiological tests, which especially for culture constitutes a vicious circle, as higher and previous antimicrobial use will affect the sensitivity of these tests.

The unnecessary use of antimicrobial drugs has been reported as 14% to 43% in hospitalized patients.[11,15] We calculated unnecessary use in the inappropriate usage rate, however if we believe that unnecessary therapy is the most frequent error in antimicrobial prescriptions, it can be concluded that unnecessary antimicrobial use in our pediatric patients is more common than in previous reports. Errors in therapy were noted in 30% of the medical orders and 63% of the surgical orders.

Our study showed that only 21.5% of the surveyed patients were receiving one antimicrobial, whereas combination therapy was given to 33% of the patients. This is comparable to the results of a study in adults in Turkey and the general literature.[11,12] This high proportion of combination therapy may be related to the prescription of empirical treatment without the support of microbiological test results in order to increase the spectrum of action.

Although the presence of a pediatric infectious disease specialist in the center did not affect the rate of inappropriate use of antimicrobials, consultation with a specialist did decrease inappropriate use significantly ($p = 0.008$). To the best of our knowledge, this is the first study evaluating this factor, and consulting with patients to determine whether they need antimicrobial treatment can decrease the rate of unnecessary antimicrobial prescription. Although it is difficult to explain the similar rates of inappropriate antimicrobial usage in the centers that had infectious disease physicians and in the centers that did not, low consultation rates in the latter may be a reason.

Although the rate of antimicrobial drug use was lowest in the surgical wards, inappropriate use was most common in these services (80.2%, $p < 0.001$). The high rate of prophylactic antimicrobial use may be the cause of this inappropriate treatment.[7,17] On the other hand, oncology wards had the lowest rate of inappropriate antimicrobial treatment. This is probably as a result of the more frequent consultation of oncology patients with infectious disease departments because of their underlying high-risk diseases. Antimicrobial drugs were used more appropriately in patients with UTIs (27.1%, $p = 0.006$) than the other infections. The presence of more microbiological evidence in UTIs (42.7%, $p < 0.001$) than in the other infections may be thought of as the reason for this. These results show the importance of collaboration among the departments of infectious diseases, microbiology, infection control, general pediatrics, oncology, and surgery.

In the pediatric patients, the most commonly used antimicrobials were the penicillins and cephalosporins, as has been found in adult cases.[9,11] However, fluoroquinolones were the drugs most commonly used inappropriately. This is related to the use of these antibiotics despite the limited approved indications, and may be a cause of the fact that bacterial resistance against β-lactams and quinolones has increased significantly in Turkey in recent years; fluoroquinolone resistance has reached up to 40% in invasive *E. coli* isolates.[21] Plasmid-mediated quinolone resistance in particular has been thought of as responsible for the emerging problem in extended-spectrum β-lactamase (ESBL)-positive *Enterobacteriaceae* in our region.[22] High-level fluoroquinolone resistance has also been reported in *Streptococcus pneumoniae* in Turkey.[23]

On the other hand, glycopeptides, clindamycin, and metronidazole were the antibiotics that were most appropriately used. The rare indications for their use, being the second or third choice of drug, with these antibiotics usually used after treatment with first-choice antimicrobials such as penicillins, cephalosporins, and aminoglycosides, and infectious disease consultation are probably the reasons for their appropriate use.

In conclusion, there is the need for microbiological support for clinicians to increase the rate of appropriate prescription. Increasing the number of pediatric infectious disease specialists, practical antimicrobial treatment guidelines, and continuing education for general pediatricians, oncologists, and surgeons are also important to resolve the problem of inappropriate antimicrobial use. Although continuous surveillance using hospital pharmacy data is available in many developed countries, point prevalence studies are advantageous because they may be more feasible in those countries lacking automated systems. These studies must be done repeatedly and the results of these surveys should be used in formulating the antimicrobial treatment policies in the pediatric hospitals.

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