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Point Prevalence Survey of Antimicrobial Prescription and Infection in Pediatric and Neonatal Wards of Two Iranian Teaching Hospitals

ORIGINAL ARTICLE

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ABSTRACT

Objective: Point Prevalence Surveys (PPSs) provide useful data on the patterns of in-hospital antimicrobial prescription. Aiming to identify targets for quality improvement, we evaluated prescribing patterns of antimicrobials in the pediatric and neonatal wards of two tertiary referral centers in Iran.

Materials and Methods: Two PPSs on antimicrobial use in children and neonates hospitalized in the Nemazee teaching hospital in Shiraz (south of Iran) and Besat teaching hospital in Sanandaj (west of Iran) were performed for two consecutive years. We used a validated and standardized method based on the Antibiotic Resistance and Prescribing in European Children project.

Results: Out of a total of 266 and 129 admissions in pediatric and neonatal wards, respectively, 61% of pediatric inpatients and 71% of neonates received at least one antimicrobial. The most frequently prescribed antibiotics in pediatric wards were ceftriaxone (29.2%) and vancomycin (15%), and in neonatal wards, ampicillin (34.7%) and cefotaxime (14.7%). Antimicrobial combination therapies and the parenteral route of administration in pediatric wards were 40% and 91.3%, and in neonatal wards, 63% and 100%, respectively. Empirical antibiotic therapies in pediatric and neonatal wards were 93.6% and 96%, respectively.

Conclusion: The high percentage of antimicrobial use, combination therapies, and empirical therapies could be the targets for quality improvement in our hospitals.

Keywords: Prevalence study, antibacterial agents, hospitalized children, antibiotic resistance, Iran

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INTRODUCTION

Antibiotic resistance is a global public health threat (1). Antibiotics are among the most commonly prescribed drugs in hospitalized children and neonates. The magnitude of the prescription rate in any hospital can be an indicator of the overuse of the drug and a potential risk factor for the development of the antibiotic resistance (2). A substantial cross-national variation in the extent and distribution of the exposure to antibiotics in hospital care was demonstrated among 15 European countries in a single study (3). In a large study from the United States, 60% of children received at least one antibiotic agent during their hospitalization (4). In wide point prevalence surveys (PPSs) in Australia and Italy, 46% and 37.2% of neonates, respectively, received at least one antimicrobial prescription (5, 6). Overall, the frequency of antibiotic use in pediatric and neonatal wards was significantly higher in non-European (43.8% and 39.4%) than in European hospitals (35.4% and 21.8%) (7). In developing countries, studies on the patterns of drug use in hospitalized children are limited. In a study by Fahimzad et al., antibiotic use in Iranian hospitalized children was 66.6% (8). In another study, the frequency of antibiotic prescribing in neonatal wards was reported as 72.1% (9).

It has been shown that up to 50% of antibiotic use in hospitals is inappropriate (10). Inappropriate and excessive use of antibiotics among hospitalized patients has been associated with an increased number of resistant pathogens and enormous costs in the health care system. (4, 11, 12). A multicenter antimicrobial surveillance of nosocomial infections in Iran indicated a high rate of isolation of extended spectrum beta-lactamases (ESBL)-producing strains of Enterobacteriaceae (61% of *Klebsiella pneumoniae* isolates and 35% of *Escherichia coli* isolates) and methicillin-resistant strains of *Staphylococcus aureus* (*MRSA*) (37.5%) (13).

PPSs are useful and simple methods for surveillance of antimicrobial use in hospitals. They can help identify the prescribing trends of antimicrobials, recognize the association between the antimicrobial use and resistance data, and identify quality improvement targets to make medical care more efficient and cost-effective (14).

Herein, we report the results of two PPSs of antimicrobial use in children and neonates conducted for two consecutive years, as a part of the project Antibiotic Resistance and Prescribing in European Children (ARPEC-PPS)

Table 1. Bed utilization and proportional use of antimicrobials in different types of wards of two tertiary teaching hospitals within two episodes in Iran

Ward type	Hospital names	Ward names	2011				2012				Total			
			No. of beds	No. of patients	Treated patients		No. of beds	No. of patients	Treated patients		No. of beds	No. of patients	Treated patients	
					No.	%			No.	%			No.	%
Pediatric wards	NTH	GMPW	–	–	–	–	10	5	2	40	10	5	2	40
		SMPWs	70	56	25	45	71	66	41	62	141	122	66	54
		PICU	10	9	9	100	12	12	5	42	22	21	14	67
		Ped S	24	23	17	74	24	21	9	43	48	44	26	59
		Total	104	88	51	58	117	104	57	55	221	192	108	56
	BTH	GMPW	27	16	9	56	27	14	11	78	54	30	20	67
		SMPWs	29	11	7	64	36	22	15	68	65	33	22	67
		PICU	6	5	5	100	6	6	6	100	12	11	11	100
		Total	62	32	21	66	69	42	32	76	131	74	53	72
	Total		166	120	72	60	186	146	89	61	352	266	161	60
Neonatal wards	NTH	GMNW	30	24	11	46	15	14	14	100	45	38	25	66
		NICU	11	11	9	81	11	11	10	91	22	22	19	86
		S NICU	5	4	4	100	4	4	0	0	9	8	4	50
		Total	46	39	24	62	30	29	24	83	76	68	48	71
	BTH	GMNW	21	12	5	42	22	20	13	65	43	32	18	56
		NICU	15	14	13	93	15	15	12	80	30	29	25	86
		Total	36	26	18	69	37	35	25	71	73	61	43	70
	Total		82	65	42	65	67	64	49	77	149	129	91	71
Total			248	185	114	62	253	210	138	66	501	395	252	64

NTH: Nemazee Teaching Hospital; BTH: Besat Teaching Hospital; GMPW: General medical pediatric ward; SMPWs: Specialized general medical wards include the cardiology and endocrinology ward, nephrology and neurology ward, gastroenterology ward, and infectious diseases and immunology ward in the NTH, and the oncology and hematology ward, and infectious diseases ward in the BTH; PICU: Pediatric intensive care unit. Pediatric surgical wards include the pediatric surgery ward and surgical PICU; GNMW: General neonatal medical ward; NICU: Neonatal intensive care unit; S NICU: Surgical NICU

in two teaching tertiary hospitals in southern and western Iran. We aimed to identify the prescribing rate and the pattern of antimicrobials to improve the quality and appropriateness of antibiotic prescribing in our hospitals.

MATERIALS and METHODS

The PPSs on antimicrobial use were conducted in two hospitals in Iran, i) the Nemazee Teaching Hospital (NTH), affiliated with Shiraz University of Medical Sciences, a tertiary referral center in Shiraz, southern Iran, and ii) the Besat Teaching Hospital (BTH), affiliated with the Kurdistan University of Medical Sciences, a tertiary referral center in Sanandaj, western Iran. We conducted these PPSs in October for two consecutive years.

The data about hospitalized patients were collected using the validated and standardized method retrieved from a web-based ARPEC-web PPS (7, 15). Four main pediatric ward types were defined: general pediatric medical ward, pediatric surgical ward, pediatric intensive care unit, and specialized pediatric medical ward. Neonatal wards included a general neonatal medical ward and neonatal intensive care unit.

The PPSs collected details on all neonates (<30 days) and children <18 years old who were present since midnight at least with active antimicrobial prescriptions at 8 am on the day of the survey, and all pediatric and neonatal wards were monitored once within a survey period of 2 weeks. Detailed data were not recorded on holidays and weekends, and pediatric surgical wards were not monitored on the day after weekend in order to gather information about the prophylaxis during the previous 24 hours. Duration of the prophylaxis was either 1 dose, 1 day, or >1 day. The actual data collection was performed using a ward form and a patient form. The ward form included the number of admitted patients and the number of total available beds in each ward. The patient form included patient's age, gender, antibacterial agents for systemic use, dose per administration, the number of doses per day, the route of administration, the type of treatment (empirical versus targeted), underlying diagnosis, the reason for treatment, and the indication for treatment (community-acquired infection, hospital-acquired infection, surgical and medical prophylaxis).

The reasons for the treatment were divided into 21 categories, of which the major ones consisted of i) lower respiratory tract infections (LRTI); ii) gastrointestinal infection; iii) sepsis, includ-

Table 2. Reason for antibiotic treatment (diagnosis) in studied children and neonates

Reason for treatment	Pediatric wards		Neonatal wards	
	Frequency	%	Frequency	%
Bacterial LRTI	52	19.1	46	30.7
Sepsis	43	16.1	50	33.3
Treatment for surgical disease	43	16.1	12	8.0
CNS infections	25	9.4	2	1.3
Prophylaxis for surgical disease	13	4.9	10	6.7
GI tract infections	12	4.5	2	1.3
Prophylaxis for medical problems	7	2.6	2	1.3
Joint/Bone infections	5	1.9	2	1.3
Cardiac infections	4	1.5	2	1.3
Other/Unknown	12	4.5	2	1.3
Urinary tract infection (upper and lower)	18	6.7	0	0
Febrile neutropenia/Fever in oncologic patients	14	5.2	0	0
Skin/Soft tissue infections	10	3.7	0	0
Upper respiratory tract infection	3	1.1	0	0
Pyrexia of unknown origin	2	0.7	0	0
Prophylaxis for newborn risk factors	0	0	20	13.3
Total	267	100	150	100

LTRI: Lower respiratory tract infection; GI: Gastrointestinal

ing cases of suspected sepsis syndrome or presumed bacteremia/septicemia; and iv) surgical disease treatment. The antimicrobials were classified according to the World Health Organization's Anatomical Therapeutic Chemical classification system (16). Antimicrobials were grouped into antibacterials, antivirals, and antimycotics.

Collected data were entered into the central database using a web-based application for data entry, validation, and reporting, which was designed by the University of Antwerp, Belgium. Descriptive statistics (SPSS version 16) was used to analyze patients' related data. A paired samples t-test and independent samples t-test were used. Ethics approvals were obtained from the ethics committees of both the above-mentioned health centers.

RESULTS

A total of 13 pediatric and four neonatal wards were surveyed. Bed utilizations and proportional uses of antimicrobials in different types of wards of the two hospitals within two episodes are presented in Table 1. The total bed utilization rate was 76% (266 out of 352) in pediatric wards and 87% (129 out of 149) in neonatal wards. The bed utilization rate for NTH (87%) was higher than BTH (66%) (p=0.0000).

In total, 64% of inpatients (252 out of 395) received at least one antimicrobial, including 61% of pediatric patients (161 out of 266) and 71% of neonates (91 out of 129) (Table 1). The frequencies of antibiotic prescription among the two PPSs were not significantly different (62 vs. 66%, P=0.46). A total antibiotic prescription rate in the pediatric wards of BTH (72%) was higher than in the pediatric wards of NTH (56%) (p=0.03). A total antibiotic prescription rate in neonatal wards of BTH (70%) was similar to the neonatal wards of NTH (71%) (p=0.99). In total, 87% of the treated pediatric patients (144 out of 161) and 84.6% of treated neonates (76 out of 91) were male. The mean age (±standard deviation) of treated pediatric patients was 52 (±54) months, and of treated neonates, it was 12 (±12) days. A total of 47% (43 out of 91) of neonates were younger than 8 days, and 71% (65 out of 91) were younger than 15 days.

The reasons for antibiotic treatment of children and neonates in the two hospitals are presented in Table 2. The LRTI was the most common reason for the treatment in pediatric and neonatal wards. Sepsis was the third most common cause in pediatric wards (12.0%, 29 out of 241) and the second most common in neonatal wards (33.3%, 50 out 150). A total of 31% of neonates with sepsis were younger 8 days (10 out of 32), and 69% were younger than 15 days (22 out of 32).

In pediatric wards, the rate of empirical antibiotic administrations was 94% (226 out 241), and in neonatal wards, it was 96% (144 out of 150). Of 241 antimicrobial prescriptions in pediatric wards, 162 (67.2%) were prescribed for community-acquired infection, 38 (15.7%) for surgical and medical prophylaxis, 40 (16.7%) for hospital-acquired infection, and one (0.4%) for unknown indications. From 150 antimicrobial prescriptions in neonatal wards, 86 (57.3%) were prescribed for community-acquired infection, 28 (18.7%) for surgical and medical prophylaxis, 34 (22.7%) for hospital-acquired infection, and two (1.3%) for unknown indications.

Table 3. Prescription frequency of various antibacterials in children and neonates admitted to two teaching hospitals in Iran

Antibiotic name	Total		Pediatric wards		Neonatal wards	
	Frequency	%	Frequency	%	Frequency	%
Ceftriaxone	78	19.9	78	32.4	0	0
Ampicillin	56	14.3	4	1.7	52	34.7
Vancomycin	52	13.3	34	14.1	18	12.0
Cefotaxime	40	10.2	18	6.2	22	14.7
Meropenem	34	8.7	16	6.6	18	12.0
Clindamycin	28	7.2	26	10.8	2	1.3
Gentamicin	20	5.1	2	0.8	18	12
Metronidazole	15	3.8	12	5.0	3	2.0
Amikacin	12	3.1	2	0.8	10	6.7
Ciprofloxacin	9	2.3	4	1.7	5	3.3
Imipenem	7	1.8	7	2.9	0	0
Azithromycin	6	1.5	6	2.5	0	0
Cefazolin	6	1.5	6	2.5	0	0
Co-trimoxazole	5	1.3	5	2.1	0	0
Ceftazidime	4	1.0	4	1.7	0	0
Cefixime	4	1.0	3	1.2	1	0.7
Acyclovir	3	0.8	3	1.2		
Cloxacillin	2	0.5	2	0.8		
Amphotericin B	2	0.5	2	0.8		
Others	7	1.8	7	2.9	0	0
Total	391	100	241	100	150	100

Other medications applied in pediatric wards include itraconazole, voriconazole, nystatinem, fluconazole, piperacillin/tazobactam, cephalexin, ceftizoxime

Investigating the underlying disease in 241 antimicrobial prescriptions in pediatric wards, there were no underlying diseases in 62 prescriptions (25.7%), and there was at least one underlying disease in 179 prescriptions (74.3%). There were at least two underlying diseases in 48 (19.9%) prescriptions and three in three prescriptions (1.2%). Of 230 underlying diseases, surgical disease malformations were the most common (56, 24.3%), followed by oncologic and hematologic disorders (37, 16.1%), gastrointestinal and congenital heart diseases (17, 7.4% each), chronic neurologic diseases (16, 6.9%), chronic renal diseases (15, 6.5%), chronic lung diseases (11, 4.8%), and others (61, 26.5%).

Investigating underlying diseases in 150 antimicrobial prescriptions in neonatal wards, there were no underlying diseases in only 10 prescriptions (6.7%), and there was at least one underlying disease in 140 (93.3%) prescriptions. There were at least two underlying diseases in 65 (43.3%) prescriptions. Of 205 underlying diseases, respiratory distress syndrome/chronic lung diseases were the most common (64, 31.2%), followed by low birth weight/intrauterine retardation (28, 13.6%), neurological conditions (hypoxia/asphyxia; 27, 13.2%), congenital heart diseases (25, 12.2%), surgical problems (21, 10.2%), chromosomal/single gene and metabolic diseases and hematologic diseases, each 10 (4.9%), and others 20 (9.8%).

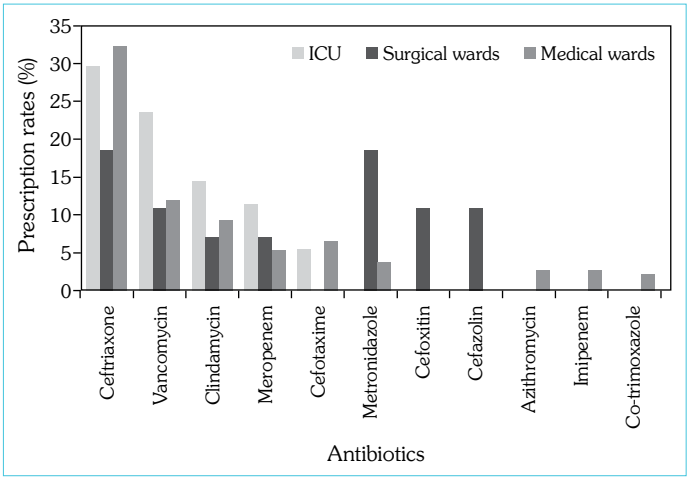

Figure 1. The frequency of antibiotic prescription pediatric intensive care unit (PICU) and surgery and medical wards in pediatric wards

The prescription frequency of various antibiotics in children and neonates admitted to two teaching hospitals in Iran is presented in Table 3. Among antimicrobial prescriptions for children, antibacterials represented 96.3%, antimycotics 2.5%, and antivirals 1.2%. Among antimicrobial prescriptions for neonates, antibacterials represented 100%. The most commonly prescribed antibiotics in the pediatric wards were ceftriaxone (29.2%), followed by vancomycin (15.0%), and in the neonatal wards, it was ampicillin (34.7%), followed by cefotaxime (14.7%).

The most commonly prescribed antibiotics for community-acquired infection in pediatric wards was ceftriaxone (37%), followed by vancomycin (14.2%); for hospital-acquired infection, it was vancomycin (25%), followed by ceftriaxone and meropenem (15% each); for surgical prophylaxis, those were ceftriaxone (26.7%), clindamycin (16.7%), and metronidazole (16.7%) (Fig. 1). The most commonly prescribed antibiotics for community-acquired infections in neonatal wards were ampicillin (39.5%), followed by gentamicin (18.6%) and meropenem (14%). For hospital-acquired infections, it was vancomycin (26.5%), followed by ampicillin (23.5%) and cefotaxime (17.6%). For surgical prophylaxis, it was ampicillin (26.7%), followed by meropenem, amikacin, and vancomycin (13.3% each). Overall sepsis was most frequently treated with ampicillin (40%), cefotaxime (16%), gentamicin (14%), amikacin (8%), and vancomycin (6%). Community-acquired sepsis was treated most frequently with ampicillin (45.2%), cefotaxime (16%), gentamicin (16%), and amikacin (9.7%).

The rates of antimicrobial combinations were detected in 40% (64 out of 161) of treated patients in pediatric wards and 63% (57 out of 91) of treated patients in neonatal wards. The highest rates of combination therapy were detected in the general neonatal medical ward (77%, 33 out of 43) and the pediatric intensive care unit (64%, 16 out of 25). In pediatric wards, combination therapies were 75% for hospital-acquired infection, 40% for community-acquired infections, and 39% surgical prophylaxis. In neonatal wards, combination therapies for hospital-acquired infections were 72%, for community-acquired infections 59%, and for surgical prophylaxis 75%. Of all pediatric patients who were applied antibiotic therapy, 91.3% received parenteral antibiotics, while all neonates except one (0.7%) received parenteral antibiotics.

DISCUSSION

This study showed that the rates of antibiotic uses were high in the pediatric and neonatal wards of two tertiary teaching hospitals located in two different provinces of Iran (61% and 71%, respectively), which is consistent with two multicenter studies from Iran (8, 9). This rate in hospitalized children was significantly higher in the BTH (72%) than in the NTH (56%; P =0.03). A wide range of antibacterial use determined in different hospitals ranged from 32.9% to 100% in pediatric wards and 21.4% to 100% in neonatal wards in Iran (8, 9). These variations could be explained by the characteristics of hospital care systems and the case mix.

In a multicenter study in Europe, the rates of antimicrobial use were lower than in Iranian hospitals (35.4% among hospitalized pediatric patients and 21.8% among neonates) (7). Other studies in Latvia, Italy, and Russia also showed lower rates of antibiotic prescription in pediatric hospitalized patients (35.4%, 43.9%, and 39%, respectively) (17–19).

The results of two consecutive PPSs in pediatric and neonatal wards in Iran showed differences between the two studied hospitals. In neonatal wards, 71% and 70% of patients in the NTH and BTH received antibiotics, respectively (p=0.99). Such variations may be partly due to differences in hospital systems and patients. Next, in a recent study from Iran, the rate of antibiotic use was high (66.6%), compared to other countries (8, 9). As reported, a more frequent and inappropriate use of antibiotics has contributed to higher levels of emerging antimicrobial resistance (20, 21).

An excessive use of antimicrobial combinations in neonatal wards was detected in our study (77.33%), compared to European hospitals (71%) (7) and Australia (50%) (3). Some parts of the high prescription rates might be inevitable in neonatal, as well as in immunodeficient patients in the hematology–oncology wards, early in the course of treatment when the results of microbiologic tests are unavailable. This is due to the non-specificity of symptoms and signs suggesting sepsis or other life-threatening conditions. In these patients, life-threatening diseases such as sepsis have a very wide spectrum of presentation frequently starting from very subtle symptoms. This leaves a very short time for effective intervention when a full-blown clinical picture develops. Nevertheless, with the continuation of treatment and the evolution of the clinical picture along with the availability of laboratory test results, there should be a modulation in antibiotic prescription. Unfortunately, in most cases, the initial empiric antibiotic regimen would continue inappropriately despite the paucity of documents indicating a bacterial infection. However, in many cases, strict guidelines have been developed to help clinicians to prescribe antibiotics appropriately, even in the absence of microbiological data (22, 23).

In the present study, ceftriaxone and vancomycin were found to be the most frequently prescribed antibiotics in pediatric patients. This is in parallel with the studies from European countries for ceftriaxone, but at a much higher rate (29.2% vs. 8.5%). The overuse of ceftriaxone and other third-generation cephalosporins might be an important cause of a high resistance rate (54%) observed for ceftriaxone in our hospitals (21) and high rate of ESBL producing *Enterobacteriaceae* (61% of *K. pneumonia* and 35% of *E. coli* isolates) in Iran, which is comparable to resistance rates in resource-limited countries with ceftriaxone overuse (13, 24). Our prescription rate is also higher for vancomycin in comparison to European countries (15% vs. 8%), and this clearly leads to a resistance higher rate (25). The prevalence of MRSA in Iran is significantly higher compared to European countries (13). Moreover, some strains of vancomycin-resistant *S. aureus* (24 strains up to year 2012) and a high incidence of vancomycin resistant *enterococci* of up to 71.4% were reported from Iran (20, 26). It seems that more attention to the Centers for Disease Control and Prevention guidelines for vancomycin use is needed, and it should be applied strictly at a national level (27). The appropriate antibiotic usage dictates that most narrow-spectrum antibiotics should be prescribed for targeted therapy. However, our study indicates that most of antibiotic prescriptions in community-acquired infections were on empirical basis (91.7% for children and 95.3% for neonatal wards versus 81.8% and 91.7% for European countries, respectively) (7). Surprisingly low in our study was the prescription rate for co-trimoxazole, the second most common antibiotic in Australia and European countries (1.9% vs. 10%–1.4%) (7). It is an old and inexpensive antibiotic that can be prescribed as a drug of choice against many gram-negative and gram-positive infections, including methicillin-sensitive and even methicillin-resistant *S. aureus*, *brucellosis*, *Shigella*, *Legionella*, *nocardia*, *chlamydia*, and *Pneumocystis jiroveci* infections (28, 29). The susceptibility rate of *S. aureus* to co-trimoxazole in a multicenter study from Iran was only 58%. Thus, the high rate of resistance limits its use in empirical therapy of critically ill patients with suspected staphylococcal infection (13).

Ampicillin and cefotaxime were the most frequently prescribed antibiotics in neonates in our study. A recent report indicates that ampicillin and gentamicin are the most commonly prescribed antibiotics in European, Asian, and Latin and North American neonates (7). Reports from Australia indicate penicillin and gentamicin as the most common antibiotics prescribed in this group (5, 7). Guidelines from the United States and European countries advocate a combination of narrower spectrum penicillin plus gentamicin versus a more broad-spectrum combination of ampicillin plus cefotaxime in treating neonatal sepsis (30, 31). These reflect the fact that the majority (>81%) of early- and late-onset neonatal sepsis cases in these countries were caused by group B Streptococcus that had been sensitive to a combination of ampicillin and gentamicin (>93%). In a study from NTH, all the isolates of *E. coli*, the most frequent gram-negative pathogen causing early- and late-onset sepsis in neonates, were resistant to ampicillin (32). In low birth weight neonates, especially in developing countries, it seems that a combination of cefotaxime plus ampicillin may be more appropriate. The rationale for this is a higher prevalence rate of gram-negative bacteria in low birth weight infants (30, 33). A high resistance rate of gram-negative bacteria to ampicillin and gentamicin reported from our hospitals suggests that ampicillin plus cefotaxime are more appropriate for low birth weight in our neonatal wards (13, 21). Unfortunately, meropenem was widely prescribed for neonates in our centers 18/150 (12%). The reason for switching to carbapenems was mostly the fear of clinical failure in a patient that was already treated with wide-spectrum antibiotics. The carbapenems are sometimes started at an emergency room in Iran, and in most cases, the antibiotics were started empirically as prophylaxis in

patients having noninfectious underlying diseases and risk factors. It seems that in the absence of clues dictating microbiological failure, the criteria for clinical failure should be defined more precisely to avoid antibiotic overuse. Moreover, regimens including broad-spectrum antibiotics such as cefotaxime and imipenem should be based on more precise criteria, and their long-term prescription should be avoided (30, 33). Negative blood cultures by automated systems like Becton Dickinson Diagnostic Instrument Systems, Sparks, Md. (BACTEC) have reasonable negative predictive values, and in most hospitalized infants in the absence of clinical and hematologic findings compatible with sepsis, they can largely decrease the duration of antibiotic therapy. C-reactive protein (CRP) is another marker that has been used in neonatal wards to rule out sepsis. Indeed, two CRP levels below 10 mg/dl taken 8–48 hours apart after 48 hours from the onset of symptoms have a negative predictive value of 99% and can be largely relied on to discontinue antibiotic treatment (33).

The LRTI was the most prevalent cause of hospitalization and antibiotic treatment in pediatric group. The patients were treated mostly with ceftriaxone (35.3%), clindamycin (15.7%), vancomycin (11.8%), meropenem (9.8%), and azithromycin (7.8%). This finding is consistent with that found in European countries, which reported LRTI as a common cause of inappropriate antibiotic prescription (6, 34). In comparison, the prescription rates were significantly higher for vancomycin and clindamycin and significantly lower for macrolides in our hospitals (6). This might increase the cost and clinical failure. A study from Italy documented a significant role for *Mycoplasma pneumonia* (35%) as the etiology of LRTI in 613 children aged between 2 and 14 years, which necessitated the use of macrolides (35). Another study from Athens, Greece, revealed similar results in school-aged children (36).

Clindamycin is indicated for *S. aureus* and anaerobic infections. These organisms rarely cause community-acquired pneumonia. A large recent series of studies from the United States found staphylococcus infection in only 22/2533 of the LRTI cases (37). Vancomycin is indicated for *S. aureus* and rarely for highly resistant pneumococcal infection (38). *Streptococcus pneumonia* is the most common cause of bacterial pneumonia in all ages (39, 40). However, the antibiotic choices are not different between sensitive and resistant cases of *S. pneumonia* in the management of LRTI. The lung has a very rich blood supply that delivers antibiotics in high concentrations to the site of infection and thereby overcomes the concentration-dependent resistance of S. pneumonia. "To date, no association with resistance and treatment failure has been demonstrated in children" (39). Vancomycin and clindamycin are not indicated at such a high rate in the absence of clues dictating staphylococcal infections. In this situation and in the face of clinical failure, the second antibiotic that should be added to drug regimen is a macrolide (39).

Our PPSs showed high proportions of surgical prophylaxis by longer than a day duration in our hospitals (97%). Prolonged surgical prophylaxis rates range from 78% for Europe to 84% for Latin America (7). There is no evidence supporting the usefulness of surgical prophylaxis for longer than 24 hours (41), and for such a case, the drugs most commonly used in our center were third-generation cephalosporins (35.3% and 23.5% for ceftriaxone in pediatrics and neonates, respectively). European countries use ceftriaxone most commonly, but by a very lower limit of 14.6%. In North America and Australia, the first-generation cephalosporins were the most commonly prescribed antibiotics (61.1% and 47.0%, respectively) (7). Other commonly prescribed antibiotics in our centers were clindamycin (14.7%), metronidazole (15.2%), and cefoxitin (9.1%). This is in contrast with the credible clinical guideline that recommended cefazolin for surgical prophylaxis, especially for orthopedic and gastrointestinal surgeries (the most common surgical procedures in our hospitals) (42). This figure for our hospitals was only 11.8% for all the first-generation cephalosporins. Using broad-spectrum antibiotics and a prolonged duration of antibiotic therapy for surgical prophylaxis are poor quality indicators (7).

In conclusion, the identified targets for quality improvement in antimicrobial prescribing include excessive use of (third-generation) cephalosporins in pediatric and neonatal wards, Prolonged duration of surgical prophylactic use >1 day (for pediatric and neonatal patients), excessive use of broad-spectrum cephalosporins for surgical prophylaxis, excessive use of antimicrobial combinations, a high proportion of parenteral antimicrobial use and inappropriate use of narrow- versus broad-spectrum antibiotics.

A strategic planning for antibiotic stewardship programs is strongly needed in our centers and might include the following steps:

- Documentation of all clinical pathways that lead to antibiotic prescription in our hospitals
- Microbiological and etiological confirmation of common bacterial and also viral illnesses that lead to hospitalization
- Clarification of the reason for treatment and antibiotic prescriptions in every case
- Setup of a surveillance system for antibiotic resistance at hospital and national level for systematic data collection
- Developing guidelines for evidence-based management of infectious diseases (43)
- Assimilation of these programs in the curriculum of medical faculties
- Judicious use of inflammatory markers such as procalcitonin for differentiation of bacterial and viral diseases (44)
- Implementation of annual PPS programs as a useful, simple, and cheap way for quality assessment and finding targets for improvement in hospitals at national levels (6)

Our study has several limitations. First, the study could not assess the duration of antibiotic therapy. This is a key variable and determinant factor of appropriateness of antibiotic prescription. Moreover, the retrieved data were from university tertiary hospitals. We did not assess data from primary- or secondary-level hospitals, so we cannot generalize our findings as quality indicators of antibiotic stewardship to the whole covered population. The paucity of microbiological data about antibiotic resistance patterns at our hospitals or even at the national level is another limitation. It challenges our judgment about appropriateness of antibiotic stewardship programs.

CONCLUSIONS

Quality improvement is necessary in hospital antibiotic prescriptions. A high percentage of antimicrobial use, in combination and as empirical therapies, could be a target for quality improvement in our health centers. In addition, the targets for improvement also require a surveillance system for antibiotic resistance, developing of guidelines for antibiotic choices in various infectious diseases based on local microbiological data, and reinforcement of hospital microbiological laboratories. A continuous medical education for antibiotic stewardship programs, emphasizing risks and long-term sequelae of inappropriate antibiotic prescription, especially for surgical prophylaxis, is of paramount importance.

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