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Surveillance of antimicrobial use in a Turkish university hospital

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Aim: To determine antimicrobial use in a university hospital in Turkey and compare it with United States antimicrobial use and resistance (US-AUR) and International Nosocomial Infection Control Consortium (INICC) rates.

Materials and methods: This was a prospective surveillance study done between January 2007 and December 2007. The data are standardized by use of the defined daily dose (DDD) for each antimicrobial group and by calculating use per 1000 patients (antibiotic use density-AD).

Results: Data on 35,936 patients with a total of 215,616 patient-days were analyzed. Ampicillin group (mainly with a beta lactamase inhibitor) has the highest AD in ICU and non-ICU departments (AD was 308 and 244 DDD/1000 patient day, respectively). Compared with the US-AUR rates ADs for ampicillin group, antipseudomonal penicillin group, 1st generation cephalosporins and carbapenems were over the 75th percentile for almost all types of ICU. Fluoroquinolones AD was below the 10th percentile at most ICUs. Inversely compared with INICC data, none of antimicrobial group exceeded the 90th percentile for all ICUs. There was a statistically significant ($P < 0.01$) correlation between incidence densities of all nosocomial infections and ventilator utilization rate with the use of antipseudomonal penicillins, 3rd generation cephalosporins, carbapenems, and glycopeptides at ICUs.

Conclusion: We found a positive correlation with nosocomial infections densities and the use of broad spectrum antimicrobials in ICUs. To use antimicrobials wisely we must implement a comprehensive education program together with infection control measures. A national program for antimicrobial usage may provide more precise data for inter-hospital comparisons.

Key words: Antibiotic surveillance, daily defined dose

Bir üniversite hastanesinde antibiyotik kullanımı surveyansı

Amaç: Türkiye'de bir üniversite hastanesinde antibiyotik kullanımı surveyansını yapmak ve sonuçları Amerika Birleşik Devletleri antimikrobiyal kullanımı ve direnç programı (US- AUR) ve International Nosocomial Infection Control Consortium (INICC) verileri ile karşılaştırmak.

Yöntem ve gereç: Bu prospektif bir surveyans çalışmasıdır. Ocak 2007- Aralık 2007 tarihleri arasında yatarak tedavi gören hastalar çalışmaya dahil edilmiştir. Veriler her antibiyotik grubu için günlük tanımlanmış doz (DDD) kullanılarak standardize edilmiş ve antibiyotik kullanım densitesini (AD) hesaplamak amacıyla 1000 hasta gününe çevrilmiştir.

Bulgular: Yatarak tedavi gören 35936 hastanın toplam 215616 hasta gününün verileri analiz edilmiştir. Yoğun bakım ünitelerinde (YBÜ) ve YBÜ dışında kalan servislerde ampisilin grubu antibiyotikler en yüksek AD'ne sahipti (sırasıyla 308 ve 244 DDD/1000 hasta günü). ABD verileri ile karşılaştırıldığında ampisilin, 1. kuşak sefalosporin, antipsödomonal penisilin, ve karbapenem grubu antibiyotiklerin AD'si hemen hemen tüm YBÜ'i için 75. pörsantilin üzerindeydi. Florokinolon AD ise çoğunda 10. pörsantilin altındaydı. Zıt olarak INICC verileriyle karşılaştırıldığında tüm YBÜ'de hiçbir antibiyotik grubu 90. pörsantilin üzerinde değildi. YBÜ'deki tüm hastane infeksiyonları ve ventilator kullanım oranları ile antipsödomonal penisilin, 3. kuşak sefalosporin, karbapenem ve glikopeptid AD'leri arasında pozitif korelasyon mevcuttu ($P < 0,01$).

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Sonuç: YBÜ'de hastane infeksiyon densiteleri ve geniş spektrumlu antibiyotik kullanımı arasında pozitif bir korelasyon mevcuttu. Bu yüzden antibiyotikleri akılcı kullanmak amacıyla infeksiyon kontrol önlemleri ile beraber kapsamlı bir eğitim programı uygulanmalıdır. Hastaneler arasında karşılaştırma yapabilmek için antibiyotik kullanımının ulusal bir program çerçevesinde takip edilmesinin yarar sağlayacağı düşünülmüştür.

Anahtar sözcükler: Antibiyotik, surveyans, tanımlanmış günlük doz

Introduction

Mortality from infectious disease has decreased over the last decades with the use of antimicrobials but the early prediction of the approaching end of all bacterial infections has never come true (1). Many organisms have developed resistance to antimicrobials to which they used to be susceptible. Nowadays the major concern about the nosocomial infections in the hospital setting is antimicrobial resistance (2,3). The emergence of resistance is multifactor and the relationship between antimicrobial uses is complex. The World Health Organization (WHO) and the European Commission pointed out the importance of antimicrobial consumption (4,5). It is necessary to detect resistance pathogens but it is also necessary to monitor antimicrobial usage. Surveillance of antimicrobial use is not enough; comparison of the data is also essential. Surveillance data regarding antibiotic use in hospitals in Turkey are absent. In the USA, the National Nosocomial Infections Surveillance (NNIS) System (formerly the National Healthcare Safety Network (NHSN)) antimicrobial use and resistance (AUR) and globally International Nosocomial Infection Control Consortium (INICC) are providing information on the use of antimicrobials (2,3,6).

The present study reports the results on the surveillance of antimicrobial use in our hospital, which is the first of its kind in Turkey, and compares them with those in NNIS and INICC reports.

Materyal and Methods

Study population

The study was conducted in the Akdeniz University hospital, which is the referral hospital in Antalya, Turkey, with 741 clinical and intensive care unit (ICU) beds. Data were collected and analyzed from January 2007 to the end of December 2007. Surveillance of antimicrobial use was done in all hospital and nosocomial infection surveillance was carried out in 6 adult medical and surgical ICUs with a total of 53 ICU beds (2 medical-surgical ICUs with 8 and 16 beds and cardiovascular (CV) ICU with 11 beds, thoracic ICU with 7 beds, coronary care unit with 7 beds, and medical ICU with 4 beds).

Pharmacy data

Data on annual consumption of antimicrobials were obtained from the Pharmacy of the hospital with the help of data processing center. Grams of antimicrobial agents were converted into numbers of defined daily doses used in the defined period. Antimicrobial agents with similar spectrum or clinical indications were grouped as shown in Table 1. A defined daily dose is the average daily dose in grams of a specific antimicrobial agent given to an average adult patient (Table 1) (2). Then we determined the antimicrobial use density (AD), expressed as DDD per 1000 patient days for each antimicrobial group.

$$AD = \frac{\text{total antibiotic use in grams in the defined period}}{\text{defined daily dose}} \times \frac{1000}{\text{patients days in the defined period}}$$

Surveillance data on nosocomial infections

Infection control nurses and an infection control practitioner visited the ICUs 3 times per week and nosocomial infections were defined according to Centers for Disease Control and Prevention criteria (7). Nosocomial infections were considered to be ICU associated if they developed in the ICU or within 48 h of discharge from the ICU and if there was no evidence that the infection was present or incubating at the time of admission to the ICU. To calculate

Table 1. Defined daily dose (DDD) of antimicrobial agents and their groups.

Group	Antimicrobial agent	DDD*
Penicillin group	Penicillin G	1.2 × 106 U
	Procaine Penicillin G	2.4 × 106 U
	Penicillin G benzathine	1.2 ×106 U
	Penicillin V	1 g
Ampicillin group	Ampicillin (parenteral)	2 g
	Ampicillin (oral)	2 g
	Ampicillin/sulbactam	2 g
	Amoxicillin (oral)	1 g
	Amoxicillin/Clavulanic Acid (oral)	1 g
Antipseudomonal penicillin	Piperacillin	14 g
	Piperacillin/Tazobactam	14 g
1st generation cephalosporins	Cefazolin	3 g
	Cefadroxil (oral)	2 g
	Cephalexin (oral)	2 g
2nd generation cephalosporins	Cefoxitin	6 g
	Cefuroxime	3 g
	Cefuroxime axetil (oral)	1 g
	Cefaclor (oral)	1 g
	Cefprozil (oral)	1 g
3rd generation cephalosporins	Cefotaxime	4 g
	Ceftazidime	4 g
	Ceftizoxime	4 g
	Ceftriaxone	2 g
	Cephoperazone/sulbactam	4 g
	Cefixime (oral)	0.4 g
Carbapenem group	Meropenem	2 g
	Imipenem cilastatin	2 g
Fluoroquinolones	Ciprofloxacin (parenteral)	0.5 g
	Ciprofloxacin (oral)	1 g
	Ofloxacin (parenteral)	0.4 g
	Ofloxacin (oral)	0.4 g
	Levofloxacin (parenteral)	0.5 g
	Levofloxacin (oral)	0.5 g
	Moxifloxacin (parenteral)	0.4 g
	Moxifloxacin (oral)	0.4 g
Trimetophrim/sulfamethoxazole	Trimethoprim component (oral)	0.4 g
	Trimethoprim compound (parenteral)	0.4 g
Glycopeptides	Vancomycin (parenteral)	2 g
	Teicoplanin	0.4 g

*DDD = daily defined dose

nosocomial infection rates, the number of patients in the ICU, the total number of patient-days, urinary catheter-days, ventilator-days, and central line-days were collected each month. The overall nosocomial infection rates per patient and per patient-day were calculated by dividing the total number of nosocomial ICU infections by the total number of ICU patients (×100) and patient-days (×1000), respectively. For pneumonia, blood stream infection (BSI), and urinary tract infection (UTI), each device-associated infection rate was calculated by dividing the total number of device-associated infections by the total number of device-days and then multiplying the result by 1000. Device utilization ratios for ventilators, central lines, and urinary catheters were calculated by dividing the total number of device-days by the total number patient-days.

Statistical methods

The pharmacy data were collected by using the Medi-ecz program, which was written by our data proceeding center. Nosocomial infections data were abstracted from standard form and analyzed using Epi-info software (version 6.04b: CDC). Correlation coefficients between antimicrobial use density with device associated infection rates and device utilization rates were calculated by using SPSS 10.0 (Statistical Package for the Social Sciences).

Results

In 2007, 35,936 patients were hospitalized with a total of 215,616 patient-days. Antimicrobial use was analyzed as all ICUs and also according to the type of ICUs in order to compare the results with those in NNIS and INICC reports. The ampicillin group (mainly with beta lactamase inhibitor) was the antimicrobial with the highest AD in all ICUs except CV ICU, where first generation cephalosporins had the highest AD. Ampicillin group antibiotics AD were over the 90th percentile at cardiovascular, thoracic, medical, and coronary ICUs according to the NNISS report. Antipseudomonal penicillin (piperacillin) AD was over the 90th percentile except the coronary unit. First generation cephalosporins' percentile was over 90 at cardiovascular and thoracic ICUs. Carbapenem group antibiotics AD were over the 90th percentile except thoracic ICU. Fluoroquinolones and trimetophrim/sulfamethoxazole ADs were not exceeding the 90th percentile at any ICU and fluoroquinolones AD was even below the 10th percentile at most ICUs (Table 2). The highest AD was observed in the ampicillin group (mainly with beta lactamase inhibitors), followed by 1st generation cephalosporins in all ICUs. For all ICUs compared with INICC report ADs were between the 25th and 90th percentiles except for quinolones, which was below the 25th percentile (Table 3). The most commonly used antibiotic group was the ampicillin group, with AD of 244 at non-ICU departments. Quinolones and TMP/STZ ADs were over the 90th percentile according to the INICC report but at most the 25th percentile according to the NNISS report. Inversely carbapenems AD was over the 90th percentile according to the NNISS report whereas it was only the 25th percentile according to the INICC report (Table 4).

Device utilization ratios and incidence densities for specific device associated infections in all types of ICUs and their correlations with the ADs are shown in Tables 5 and 6. There were positive correlations between incidence densities of all nosocomial infections and ventilator utilization rate with the use of antipseudomonal penicillins, 3rd generation cephalosporins, carbapenems, and glycopeptides at ICUs ($P < 0.01$).

Discussion

The present study provides the first detailed information of its kind on antimicrobial use in a Turkish hospital. Although there are some multicenter studies on antibiotic consumption in Mediterranean hospitals, which included some Turkish hospitals, their data do not contain hospital data separately (8,9). The ampicillin group (mainly with a beta lactamase inhibitor) has the highest ADs in all ICUs (except cardiovascular ICU). In Turkey there is no antistaphylococcal penicillin on the market. Therefore, penicillin with a beta lactamase inhibitor instead of antistaphylococcal penicillin is used. Nevertheless, penicillins with a beta lactamase inhibitor were the antimicrobial group with the highest ADs in most reports including INICC and SARI (surveillance of antimicrobial use and antimicrobial resistance in intensive care units) (3,10). According to US-AUR data the most widely used antibiotic group was also ampicillin group except

Table 2. Antimicrobial used density according to the type of ICUs and their percentiles according to US-AUR report.

Antimicrobial group	AD*	US-AUR percentile
Penicillin group		
MS ICU 1[+]	9	25-50
MS ICU 2	-	
CV ICU[§]	-	
Thoracic ICU	-	
M ICU[¶]	-	
Coronary unit	-	
Ampicillin group		
MS ICU 1	285	50-75
MS ICU 2	301	75-90
CV ICU[+]	382	>90
Thoracic ICU	982	>90
M ICU	389	>90
Coronary unit	299	>90
Antipseudomonal penicillin		
MS ICU	145	>90
MS ICU	141	>90
CV ICU[+]	51	>90
Thoracic ICU	50	>90
M ICU	120	>90
Coronary unit	51	75-90
1st generation cephalosporins		
MS ICU 1	186	75-90
MS ICU 2	167	75-90
CV ICU[+]	493	>90
Thoracic ICU	591	>90
M ICU	46	75-90
Coronary unit	13	10-25
2nd generation cephalosporins		
MS ICU 1	-	
MS ICU 2	-	
CV ICU[+]	1	<10
Thoracic ICU	-	
M ICU	-	
Coronary unit	-	

Table 2. (Continued).

Antimicrobial group	AD*	US-AUR percentile
3rd generation cephalosporins		
MS ICU 1	292	>90
MS ICU 2	177	75-90
CV ICU+	50	25-50
Thoracic ICU	57	25-50
M ICU	145	50-75
Coronary unit	26	10-25
Carbapenem group		
MS ICU 1	180	>90
MS ICU 2	110	>90
CV ICU+	57	>90
Thoracic ICU	35	25-50
M ICU	130	>90
Coronary unit	33	>90
Fluoroquinolones		
MS ICU 1	19	<10
MS ICU 2	10	<10
CV ICU+	8	10-25
Thoracic ICU	18	25-50
M ICU	45	<10
Coronary unit	29	<10
Trimetophrim/sulfamethoxazole		
MS ICU 1	62	50-75
MS ICU 2	34	50-75
CV ICU+	17	50-75
Thoracic ICU	14	50-75
M ICU	10	75-90
Coronary unit		
Glycopeptides		
MS ICU 1	248	>90
MS ICU 2	153	>90
CV ICU+	61	25-50
Thoracic ICU	50	25-50
M ICU	172	25-50
Coronary unit	24	25-50

*AD = antimicrobial used density +MS ICU = medical surgical intensive care unit
§CV ICU = cardiovascular intensive care unit ¶M ICU = medical intensive care unit

Table 3. Antimicrobial used density in all ICUs and its percentile according to INICC.

Antimicrobial group	AD*	INICC percentile
Penicillin group	1	50
Ampicillin group	308	75-90
Antipseudomonal penicillin	76	50-75
1st generation cephalosporins	190	75-90
2nd generation cephalosporins	0.13	25-50
3rd generation cephalosporins	101	25-50
Carbapenem group	70	25-50
Fluoroquinolones	13	<25
Trimetophrim/sulfamethoxazole	26	75-90
Glycopeptides	93	50-75

*AD = antimicrobial used density

Table 4. Antimicrobial used density in non- ICUs and their percentiles according to NNIS and INICC.

Antimicrobial group	AD*	INICC percentile	US-AUR percentile
Penicillin group	14	75-90	10-25
Ampicillin group	244	50-75	75-90
Antipseudomonal penicillin	27	75-90	50-75
1st generation cephalosporins	108	>90	75-90
2nd generation cephalosporins	9	75-90	<10
3rd generation cephalosporins	67	25-50	50-75
Carbapenem group	31	25	>90
Fluoroquinolones	36	>90	<10
Trimetophrim/sulfamethoxazole	11	>90	10-25
Glycopeptides	20	25-50	25-50

*AD = antimicrobial used density

Table 5. Device utilization ratios and incidence densities for specific device associated infections in ICUs.

	MS ICU*	MS ICU2	CV ICU+	Thoracic ICU	M ICU	Coronary
Number of beds	8	16	11	7	4	7
Incidence density of NI	46.33	33.32	7.08	11.35	21	7.84
Ventilator utilization rate	0.6	0.55	0.16	0.24	0.51	0.16
VAP§	33.41	16.22	10.14	21.22	14.22	17.14
CVC¶ utilization rate	0.88	0.83	0.56	0.36	0.64	0.14
CVC associated BSI**	2.16	1.06	0.6			3.4
Urinary catheter utilization rate	0.98	0.94	0.82	0.56	0.90	0.44
Urinary catheter associated UTI++	6.62	7.15	1.23	2.34	2.41	6.56

*MS ICU = medical surgical intensive care unit;
+ CV ICU = cardiovascular intensive care unit;
§VAP = ventilator associated pneumonia;
¶CVC = central venous catheter
**BSI = blood stream infection
++UTI = urinary tract infection

Table 6. Correlation coefficients between antimicrobial use densities with device associated infection rates and device utilization rates at ICUs.

	Antimicrobial use density							
	Ampicillin group	Antipseu+	1st generation	3rd generation	Carbapenem	Quinolon	TMP	Glycopeptide
Number of beds	-0.251	-0.091	-0.065	-0.064	-0.139	-0.416	0.132	-0.109
Incidence density of all NI	-0.370	0.922*	-0.323	0.933*	0.907*	-0.065	0.806	0.929*
Ventilator utilization rate	-0.350	0.968*	-0.427	0.918*	0.908*	0.152	0.722	0.935*
VAP§	0.021	0.428	-0.076	0.612	0.541	-0.049	0.750	0.571
CVC¶ utilization rate	-0.376	0.849	-0.09	0.859	0.845	-0.242	0.829	0.867
CVC associated BSI++	-0.532	-0.011	-0.544	0.058	-0.006	0.005	-0.101	-0.058
Urinary catheter utilization rate	-0.446	0.813	-0.138	0.792	0.841	-0.129	0.716	0.847
Urinary catheter associated UTI§§	-0.527	0.493	-0.619	0.459	0.323	-0.120	0.446	0.325

*Correlation is significant at a level of 0.01 +Antipseu = antipseudomonal §VAP = ventilator associated pneumonia
¶CVC= central venous catheter ++BSI = blood stream infection §§UTI = urinary tract infection

cardiothoracic and medical ICUs (2). The highest AD (982) for the ampicillin group was at the thoracic ICU. Thoracic surgeons use ampicillin–sulbactam for every patient in whom thoracic tube was employed until the patient was discharged. In the cardiovascular ICU the highest AD belongs to 1st generation cephalosporins, which are the primary choice for surgical prophylaxis. Evaluating and analyzing these

results, we recognized that cardiovascular surgeons are giving prophylaxis until all catheters are removed. Education programs and seminars were organized in order to apply good surgical prophylaxis. In addition a surgical prophylaxis guideline was prepared.

Inappropriate use of antimicrobials has economic and ecological implications for society (11,12). Hospitals are the principal interest because of the frequent and extended use of antimicrobials. In order to use antibiotics properly the first step is to calculate the amount of antimicrobials that has been used. The second step is to compare data in order to recognize problems and then to improve antimicrobial use. Here we used US-AUR and INICC data as a benchmarking instrument. We chose these data for various reasons. Firstly, they used the same antimicrobial groups; secondly, US-AUR data have the advantage of having data from all types of ICUs; finally, INICC represents multinational data. But they have some disadvantages too. For example, the NNIS system report does not contain antimicrobial use data since 2004 and their antimicrobial group selection was not properly equal to WHO ATC group and some antimicrobials are not available in the market in Turkey (for example antistaphylococcal penicillins). Although INICC data are multinational most of the participating hospitals are from Latin America, which may or may not resemble our hospital. For most antimicrobial group the AD was over the 90th percentile according to US-AUR data but it is in the normal range according to INICC data (2,3). Especially antipseudomonal penicillin (piperacillin, mostly as piperacillin tazobactam) and carbapenems ADs were higher than US hospitals. We have noted both higher device utilization ratios and higher device associated infections than those reported by the NNIS system (data are shown in Table 5 but are not compared). Antimicrobial use must be reevaluated together with the rate of nosocomial infections and resistant microorganisms. In contrast to these antimicrobials quinolone use density was lower in our institution compared with US-AUR and INICC data in ICUs (2,3). This may be in part due to the fact that quinolones are mostly used in outpatients or non-ICU departments and the usage of intravenous forms are under the control of infectious disease specialist according to the health practice rescript in Turkey.

In ICU and non-ICU departments as well the ampicillin group had the highest AD, followed by 1st generation cephalosporins. When compared with INICC the use of 1st generation cephalosporins was in the 75th-90th and >90th percentile, for ICU and non-ICU departments respectively. Although a recent consensus statement from the National Surgical Infection Prevention Project recommended surgical prophylaxis not to be extended beyond 24 h in most cases, in our institution in most cases surgical prophylaxis extended beyond 24 h (13). After this result we decided to implement an education program and prepared a surgical prophylaxis guideline.

Incidence densities of all nosocomial infections and ventilator utilization rates were correlated at ICUs with the use of antipseudomonal penicillins, 3rd generation cephalosporins, carbapenems, and glycopeptides. These are broad spectrum antimicrobials and probably were used to treat nosocomial infections, which are likely to be more resistant pathogens. This may explain the correlation with the incidence densities of nosocomial infections. It is difficult to explain the correlation with the ventilator utilization rate. One can speculate that the high utilization rate is likely to result in high ventilator associated pneumonia rate, which is highly mortal, which in turn is likely to result in a high empirical use of broad spectrum antibiotics.

Since 1993, the institutional policies of hospital infection control have been implemented by an infection control team (14). Until 2006 antibiotic policies were decided and implemented by that team in collaboration with the infectious disease department. In 2006 an antimicrobial control subcommittee was created. The implementation of nosocomial infection surveillance has gained widespread acceptance in Turkey and there is a national program for monitoring nosocomial infections but there is no national program for monitoring antimicrobial use. It may be more practical to have national comparative data for antimicrobial use. Some countries in Europe, for example Sweden and Germany, improve their national project on antimicrobial use in ICUs. The Swedish STRAMA project (ICU section of the Swedish Strategic Program for the Rational Use of Antimicrobial Agents and Surveillance of Resistance) and the German SARI Project (Surveillance of Antimicrobial Use and

Antimicrobial Resistance in Intensive Care Units) are government sponsored. The main objective of these 2 surveillance systems is to provide information on the use of antimicrobials in risk areas such as ICUs, and to supply data on the incidence percentages of resistant bacterial pathogens and to serve as a benchmark for hospitals in their countries (15,16).

In conclusion, this is the first report on antimicrobial consumption from a Turkish university hospital separately. The main finding of our study was a positive correlation between nosocomial infections densities and the use of broad spectrum antimicrobials. Moreover, a high AD for 1st generation cephalosporins was noted in ICU and non-ICU departments. To use antimicrobials wisely we must implement a comprehensive education program together with infection control measures. A national program for antimicrobial usage may provide more precise data for inter-hospital comparisons.

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