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Antibiotic consumption in Turkish hospitals; a multi-centre point prevalence study

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This multi-centre study aimed to determine the antibiotic consumption in Turkish hospitals by point prevalence. Antibiotic consumption of 14 centres was determined using the DDD method. Among hospitalized patients, 44.8% were using antibiotics and the total antibiotic consumption was 674.5 DDD/1000 patient-days (DPD). 189.6 (28%) DPD of the antibiotic consumption was restricted while 484.9 (72%) DPD was unrestricted. Carbapenems (24%) and beta lactam/beta lactamase inhibitors (ampicillin-sulbactam or amoxicillin-clavulanate; 22%) were the most commonly used restricted and unrestricted antibiotics. Antibiotics were most commonly used in intensive care units (1307.7 DPD). Almost half of the hospitalized patients in our hospitals were using at least one antibiotic. Moreover, among these antibiotics, the most commonly used ones were carbapenems, quinolones and cephalosporins, which are known to cause collateral damage. We think that antibiotic resistance, which is seen at considerably high rates in our hospitals, is associated with this level of consumption.

Keywords: Antibiotic, Antibiotic stewardship, Consumption, Hospital

Introduction

Antibiotics are one of the most important discoveries of the twentieth century and are successfully used in the treatment of infections.¹ While the most commonly used medicines are cardiovascular system medicines worldwide, antibiotics are generally the most commonly consumed medicines in developing countries, including Turkey.²

Soon after the introduction of antibiotics, adaptation of bacteria occurred and the term antibiotic resistance has

been included in medical terminology. Penicillin-resistant strains were identified only four years after the introduction of penicillin.³ While multiresistant staphylococci and pneumococci have drawn attention as problematic bacteria since the 1990s, multidrug-resistant gram-negative bacilli have recently become the most important cause of death due to infection, especially in intensive care units.⁴ Antibiotic resistance is associated with antibiotic consumption, and the World Health Organization reports that the irrational use of antibiotics is an important problem worldwide. It is estimated that antimicrobial

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resistance costs the United States 21 to 34 billion dollars and increases the number of days of hospital stay by 8 million/year.⁵ Mortality increases with the development of infections with multidrug-resistant (MDR) bacteria.⁶ This has significance in light of the WHO world health day theme, 2011: 'Anti-microbial resistance: No action today, no cure tomorrow'.⁷

With the increase of medical and surgical intervention facilities in hospitals, the number of patients who are hospitalized and require follow-up in intensive care units has also been increased. Parallel to this, a 2 to 4-fold increase in the consumption of broad-spectrum antibiotics such as cefoperazone-sulbactam, piperacillin-tazobactam, vancomycin, linezolid and carbapenems has been observed.⁸ The increase in the consumption of antibiotics as well as the irrational use of antibiotics and the increase in bacterial resistance associated with these agents have required implementation of systematic programmes for rational use of antibiotics. For this purpose, restriction on prescription of antibiotics has been introduced with legislative regulations implemented in 2003 in Turkey, and only Infectious Disease specialists are authorized to prescribe broad-spectrum antibiotics such as carbapenem, piperacillin-tazobactam, cefoperazone sulbactam, vancomycin and daptomycin.⁹

In addition to the legislative regulations, surveillance of antibiotic consumption patterns to evaluate the current situation is required to ensure the rational use of antibiotics in hospitals. We wonder what is the real use of antibiotics in hospitals in Turkey. The number of studies of antibiotic utilization in hospitalized patients in Turkish hospitals is very limited.² This multi-centre study aimed to determine the consumption of restricted and unrestricted antibiotics in hospitalized patients in Turkish hospitals by a single-day point prevalence.

Patients and Methods

Study design

This multi-centre study was designed as a single-day point prevalence study. To ensure homogeneity between regions, 21 hospitals located in different regions were selected. The infectious disease specialists at the selected hospitals were informed about the study, and they were invited to participate in the study via e-mail. A total of 15 centres (71%) accepted the invitation. Again via e-mail, the centres participating in the study were informed about the date that the study would be performed and the prepared antibiotic consumption form was sent to them. All hospitals were requested to determine both restricted and unrestricted antibiotic utilization in hospitalized patients (from the physicians' orders and nurses' observations) on the same day (12 February 2014). Ambulatory patients were excluded.

Antibiotic consumption form

The first part of the form contained questions about demographic data (total bed number, bed number in intensive care units, internal services and surgery services, and the

number of patients hospitalized in these departments on the study day) of the hospitals. The second part of the form contained antibiotic use information. The antibiotics were divided into two groups: restricted antibiotics (allowed to be prescribed only by infectious disease specialists) and unrestricted antibiotics (allowed to be prescribed by any physician). All centres were requested to report antibiotic consumption (in milligrams) in the intensive care units, internal services and surgery services.

Restricted antibiotics (allowed to be prescribed only by infectious disease specialists)

Imipenem, meropenem, doripenem, ertapenem, vancomycin, teicoplanin, daptomycin, linezolid, colistin, piperacillin-tazobactam, sulbactam, cefepime, cefoperazone-sulbactam, intravenous quinolones and tigecycline.

Calculation of antibiotic consumption

Antibiotic consumption was analysed according to the 'Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD)' method recommended by the World Health Organization, and expressed as DDD/1000 patient-days (DPD).

Statistics

Information from each centre was entered into MS Excel. The data were collected and mean values and percentages were calculated. Chi-square test was used to analyse qualitative variables and Student's *t*-test was used to analyse quantitative data. *p*-values < 0.05 were considered significant.

Results

Since one of the centres that had accepted to participate did not send data, the study was completed with the data from 14 (66%) centres in total. A total of 6306 hospitalized patients (515 in intensive care units, 2835 in internal services and 2956 in surgery services) were evaluated in terms of antibiotic use on the study day.

It was seen that 2827 (44.83%) of the patients were taking at least one antibiotic. 1125 (39%) of them were using restricted and 1832 (64.8%) were using unrestricted antibiotics. The frequency of antibiotic use by hospital departments is shown in Table 1.

Total antibiotic usage on the study day was 674.5 DPD [189.6 (28%) DPD for restricted antibiotics, and 484.9 (72%) DPD for unrestricted antibiotics]. The most commonly used restricted antibiotics were carbapenems (24%) followed by piperacillin-tazobactam (19%) and intravenous quinolones (18%).

For the unrestricted antibiotics, the most commonly used ones were beta lactam/beta lactamase inhibitor combinations including ampicillin-sulbactam or amoxicillin-clavulanic acid combination (22%). The second most commonly used unrestricted antibiotics were third generation cephalosporins (19%) (ceftriaxone 85.9 DPD,

Table 1 Antibiotic use prevalence in intensive care units and services

	Intensive care units	Internal services	Surgery services	p-value
	n: 515 (%)	n: 2835 (%)	n: 2956 (%)	
Number of patients using antibiotics	367 (71.3%)	1088 (38.4%)	1372 (46.4%)	<0.001
Number of patients using restricted antibiotics	264 (51.3%)	604 (21.3%)	244 (8.3%)	<0.001
Number of patients using unrestricted antibiotics	118 (22.9%)	533 (18.8%)	1161 (39.3%)	<0.001

ceftazidime 3.4 DPD, ceftizoxime 1.6 DPD and cefotaxime 1.3 DPD), and the third was cefazolin, a first generation cephalosporin (17%). The consumptions of restricted and unrestricted antibiotics are shown in Figs. 1 and 2, respectively.

When the departments within the hospitals were compared, the most common antibiotic consumption was in intensive care units. The total antibiotic usage was 1307.7 DPD [786.7 DPD restricted (60%), 521 DPD unrestricted (40%)] in intensive care units, while 593 DPD [190.8 DPD restricted (32%), 402.2 DPD unrestricted (68%)] was used in internal services and 650.5 DPD [84.5 DPD restricted (13%), 566 DPD unrestricted (87%)] was used in surgery services.

Of the restricted antibiotics used in the participating hospitals, 74% were used in ICUs, and the most commonly used ones were colistin, carbapenems and piperacillin-tazobactam (196.1 DPD, 181.8 DPD and 135 DPD, respectively).

Antibiotic usage was higher in large hospitals (>500 beds) than small ones (<500 beds) ($p < 0.05$). While unrestricted antibiotics were used more in small hospitals than large ones, restricted antibiotics were used more in large hospitals than small ones ($p < 0.05$). Among restricted antibiotics, carbapenems and antibiotics effective for methicillin-resistant staphylococcus aureus (vancomycin, teicoplanin, linezolid and daptomycin) were used more in large hospitals than small ones ($p < 0.05$). On the other hand, among unrestricted antibiotics, cefazolin was used more in small hospitals than large ones ($p < 0.05$) (Table 2).

Discussion

Improvement of antibiotic use is one of the top priority issues in terms of patient safety and public health.¹⁰ For this purpose, many antibiotic use policies have been developed and implemented. One of the main efforts that should be made to ensure rational use of antibiotics is to determine the antibiotic amounts used in the country.¹¹ Unfortunately, the antibiotic amounts used across the country cannot be tracked in many countries (except for several countries such as Denmark, The Netherlands, Sweden and Norway). In some countries, including Germany, USA and France, attempts have been made to determine antibiotic consumption by conducting multi-centre studies.¹² The antibiotic consumption in Turkish hospitals has generally been investigated by conducting single-centre studies. In the present study, 14 centres were selected across Turkey in an

effort to determine the trend and prevalence of antibiotic use in the country.

We found in our study that 44.8% of the patients were using at least one antibiotic. A multi-centre study conducted in 2002 in our country reported that 30.6% of the hospitalized patients were using at least one antibiotic.¹³ Another (single-centre) study conducted in our country reported that 47% of the patients were using at least one antibiotic, similar to the results of our study.¹⁴ Based on these data, it is seen that nearly half of the patients hospitalized in our hospitals are using antibiotics. This situation should be carefully examined, and measures and antibiotic management programmes should be developed to prevent irrational use.

Since the daily doses of antibiotics are different from each other, the World Health Organization recommended the use of the ATC/DDD method for standardization of the amounts of antibiotics used.¹⁵ Using this method, we found the antibiotic consumption to be 674.5 DPD. In France, a study that included 530 hospitals found that 633 DPD antibiotics were consumed in training hospitals.¹² In their study that compiled 2-year data from 25 hospitals in 7 southern and eastern Mediterranean countries including Turkey, Borg et al. found the median value of antibiotic consumption to be 112 DDD/100 bed-days. In the mentioned study, the consumption was found to be >50 DDD/100 bed-days in 24 hospitals (except for one), moreover, the antibiotic consumption was >100 DDD/100 bed-days in 13 of these.¹⁶ The Australian national antimicrobial annual report states that the antibiotic consumption was 943 DPD in the country in 2013.¹⁷ In Dutch hospitals, the antibiotic consumption was reported to be 713 DPD.¹⁸ As can be seen, the antibiotic consumption in our hospitals is higher than some European countries, while being lower than others. We think that antibiotic consumption is associated with the antibiotic management programmes implemented in countries rather than with the development level. In our country, the authorization to initiate broad spectrum antibiotics has been given to infectious disease specialists in accordance with the antibiotic management programme, which was effective as of 2003. Studies demonstrated that the consumption of and expenses relating to antibiotics have been reduced with the implementation of this programme.^{19,20} Our results show that the consumptions of restricted antibiotics (which are allowed to be prescribed only by an infectious disease specialist) and unrestricted antibiotics are 189.6 DPD and

Consumption of antibiotics not requiring IDS consent (DDD/1000 patient-day)

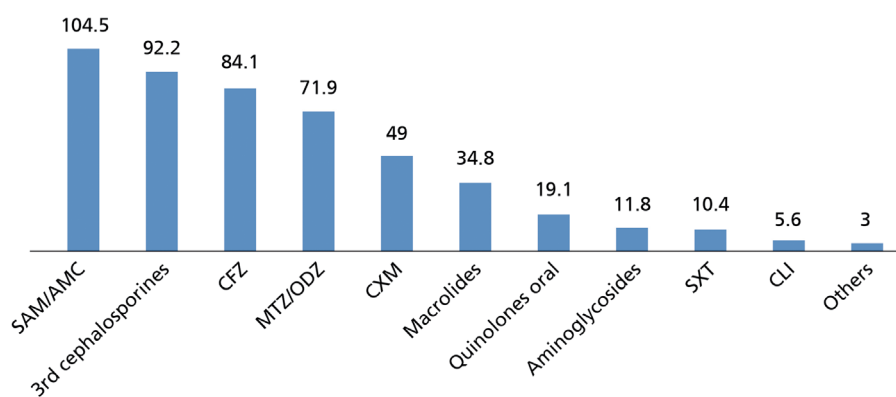


Figure 1 Consumption of antibiotics requiring consent of an infectious disease specialist.

Consumption of antibiotics requiring IDS consent (DDD/1000 patient-day)

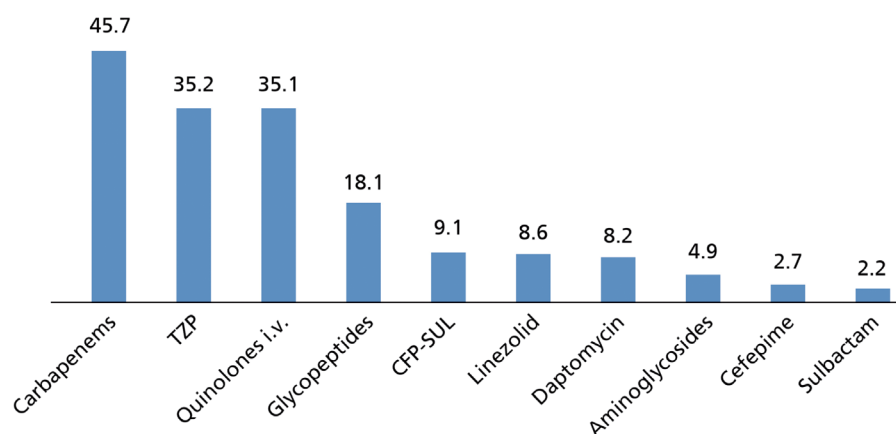


Figure 2 Consumption of antibiotics not requiring consent of an infectious disease specialist.

Table 2 The effect of hospital size on antibiotic consumption

Parameters	Bed capacity < 500	Bed capacity > 500	p-value
Hospitalized patients	1457	4849	
Patients taking antibiotics	618 (42.4%)	2209 (45.6%)	0.03
Patients taking restricted antibiotics	215 (14.8%)	910 (18.8%)	0.0004
Patients taking unrestricted antibiotics	449 (30.8%)	1383 (28.5%)	0.09
Carbapenems <i>DPD</i>	32.8	49.6	0.04
vancomycin, teicoplanin, daptomycin, linezolid <i>DPD</i>	16.4	40.5	0.006
Intavenous Quinolones <i>DPD</i>	53.6	29.6	0.23
Colistin <i>DPD</i>	6.5	23.7	0.02
TZP <i>DPD</i>	22.6	39	0.07
SAM/AMC <i>DPD</i>	136.3	92.3	0.46
Cefazolin <i>DPD</i>	116.5	74.4	0.09
Oral Quinolones <i>DPD</i>	30.5	15.7	0.36
Aminoglycosides <i>DPD</i>	13.6	11.2	0.40

DPD: DDD/1000 patient-day, TZP: Piperacillin-tazobactam, SAM: ampicillin-sulbactam, AMC: amoxicillin-clavulanic acid.

484.9 DPD, respectively. Therefore, programmes aiming to reduce antibiotic use in hospitals should cover not only the broad spectrum antibiotics but also other antibiotics.

ICUs are the departments in hospitals where antibiotics are most commonly used. It was reported that at least one antibiotic is given to 41–85% of the patients hospitalized at

ICUs and the use of antibiotics at ICUs is 10 times higher than in the services.²¹ Our study also showed that the departments where antibiotics are most commonly used are ICUs. Approximately 71% of the patients hospitalized at ICUs were using at least one antibiotic while 38.4% and 46.4% of the patients (respectively) hospitalized at internal services and surgery services were using at least one antibiotic. The antibiotic consumption in ICUs was 1307.7 DPD (786.7 DPD was restricted), about two times higher than the surgery and internal departments. The fact that infections seen in ICUs are severe, the complexity of the decision-making process and the employment of physicians whose knowledge of antibiotics is limited makes the implementation of antibiotic management programmes difficult in these departments. For these reasons, the studies conducted reported that 30 to 60% of the antibiotics used at ICUs are unnecessary, inappropriate or suboptimal.²² Ongoing on-the-job training of physicians serving in ICUs to increase their knowledge of antibiotics, and daily visits of infectious disease specialists to ICUs to both regulate the antibiotic therapies of the patients and to be a role model for the physicians serving in these departments may contribute to the rational use of antibiotics in ICUs.

The most commonly consumed restricted antibiotics in our hospitals were, in decreasing order of use, carbapenems, piperacillin-tazobactam and intravenous quinolones. One of the most commonly used unrestricted antibiotics was cephalosporins. It is known that fluoroquinolones, carbapenems and cephalosporins affect the microflora of the hospitals by causing collateral damage, and resistant pathogens such as multidrug-resistant (MDR) *Acinetobacter baumannii*, MDR-*Pseudomonas aeruginosa*, carbapenemase-positive *Klebsiella* spp. undergo selection in hospitals resulting in increased colonization.^{23,24} It was demonstrated that restricting the use of carbapenems in hospitals reduces the prevalence of *Acinetobacter* infection in ICUs.²⁵ Based on these findings, we think that the MDR gram-negative bacterial problem in our hospitals, especially in ICUs, may be associated with the use of carbapenem, fluoroquinolone, colistin and cephalosporin at such high levels. We predict that reducing the use of these antibiotics through active use of antibiotic management programmes will reduce the MDR bacterial problem.

According to our findings, carbapenems were the most commonly used restricted antibiotics (45.7 DPD). With the legislative regulations introduced in 2003 in our country, only Infectious Disease specialists are authorized to prescribe carbapenems. Carbapenems are the most commonly used antibiotics in hospitals in Turkey but they have collateral damage effect. According to the World Health Organization's reports, Turkey is one of the countries in which carbapenem-resistant Enterobacteriaceae and carbapenem-resistant *Acinetobacter* are most commonly seen.⁵ To reduce antibiotic resistance, we should re-consider the use of carbapenem. Moreover, we think that a re-training on the indications and outcomes of the use of carbapenems

should be given to Infectious Disease specialists, who are the only physicians authorized to prescribe carbapenems.

According to our results, hospital size affects the use of restricted antibiotics. Broad-spectrum antibiotics such as carbapenems, vancomycin, teicoplanin, linezolid, daptomycin and colistin, which have more side effects, were used more frequently in larger hospitals than in smaller ones. The similar usage of unrestricted antibiotics such as oral quinolones, first generation cephalosporins and aminoglycosides, regardless of the hospital size, showed that these antibiotics were prescribed in similar proportion by all physicians. All these findings show a linear relationship between bed capacity of hospitals and antibiotic consumption. In conclusion, 'If you have many beds there are so many antibiotics'.

The most important limitation of our study is that only the amounts of consumed antibiotics were examined without evaluating the appropriate or inappropriate use of antibiotics. In addition, pre-surgery prophylactic use and therapeutic use were not distinguished. If we could distinguish between these points, we could be able to point to the level of irrational use of antibiotics in our hospitals.

In conclusion, almost half of the hospitalized patients in our hospitals use antibiotics. Carbapenems are the most commonly used restricted antibiotic, and for the unrestricted antibiotics, the most commonly used ones were beta lactam/beta lactamase inhibitor combinations including ampicillin-sulbactam or amoxicillin-clavulonic acid combination and third generation cephalosporins. The high level of antibiotic use in our hospitals is associated with the resistant pathogens seen in our country. Antibiotic management programmes that will ensure rational use of both restricted and unrestricted antibiotics should be implemented and maintained, and tracking and feedback should be performed relating to consumption.

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