Review Article

Rational antibiotic use

Ozlem Tunger[1], Yeliz Karakaya[2], C. Banu Cetin[1], Gonul Dinc[3], Hakan Borand[4]

[1]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[2] Department of Infectious Diseases and Clinical Microbiology, Nevsehir State Hospital, Nevsehir, Turkey
[3] Department of Public Health, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
[4] Department of Infectious Diseases and Clinical Microbiology, Turgutlu State Hospital, Manisa, Turkey

Abstract

Background: Development of resistance to antimicrobial agents and increase of cost as the result of unnecessary and inappropriate use of antibiotics has become a global health problem. Therefore many strategies, which are aimed at optimizing antibiotic therapy, have been developed until now. In Turkey, an antibiotic restriction policy as a governmental solution was applied to decrease the antibiotic use and especially costs by Ministry of Health in 2003. The aim of this study is to evaluate the rational antibiotic use and the impact of the implementation of new restriction policy, with their reinforcement by infectious disease specialist, on the hospital wide use of antibiotics.

Methodology: The data of the inpatients received antibiotics (n=495) during January-June 2006 were compared with our previous study performed by the same methodology before the restriction policy in 1998. In both studies, prospective active daily surveillance of patients was performed by three infectious disease specialists. The appropriateness of antibiotic therapy was determined using the criteria described by Kunin and Jones. The data were analyzed by using SPSS for Windows.

Results: While the rate of antibiotic use decreased from 16.6% to 11.3%, rational use increased after the restriction policy ($p<0.001$). Besides the specific antibiotic use increasing, prophylactic antibiotic use was found decreased ($p<0.001$). Mostly determined irrationality was the prophylactic uses in both studies. As expected, infectious disease specialist examinations resulted in an increase in the appropriate antibiotic use.

Conclusions: The restriction policy was effective in decreasing the antibiotic consumption and increasing the rational antibiotic prescription in our hospital.

Key Words: Antibiotic, antibiotic usage, rational use, restriction policy

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Introduction

Overuse of antibiotics has been described worldwide in both community and hospital settings particularly in developing countries [1]. In Turkey, it is reported that antibiotics are the most frequently used drugs and constitute approximately 20% of the market value of drugs [2]. However, it is accepted that the majority of this consumption is irrational. Excessive and inappropriate antibiotic use can lead to the emergence of bacterial resistance and increase the economic burden of health care; additionally, many adverse affects of drugs may be seen [3,4].

Irrational antibiotic use was a common problem in Turkey. According to surveillance studies, the percentages of irrational antibiotic use were reported between 40-60% [5-7]. We also determined prevalence of irrational antibiotic use as 54.3% in 1998 in our hospital [8].

Several strategies for controlling antibiotic usage have been proposed, such as formulary replacement or restriction, introduction or order forms, health care provider education, feedback activities, and approval requirement from an infectious disease specialist for drug prescription [9-12]. An antibiotic restriction policy was developed by the Ministry of Health in 2003 in Turkey and it was applied to decrease the antibiotic usage and particularly the economic burden of antibiotics. According to new policy, prescriptions of the parenterally-administered broad-spectrum and expensive antibiotics were limited and their use required approval from an infectious disease specialist.

This study was designed to evaluate the rational antibiotic use and affecting factors in Celal Bayar University Hospital. We also aimed to emphasize the impact of the antibiotic restriction policy by comparing the prevalence of rational antibiotic use in 1998 and 2005.

Table 1. Demographic variables of both studies.

Variables	Study I	Study II
Hospital beds	200	300
Number of wards	17	26
Number of hospitalized patients	937	4380
Age (mean±sd)	50.5 ± 22.2	49.9 ± 21.5
Male (%)	46.2	48.0
Number of patients who received antibiotics (%)*	156 (16.6)	495 (11.3)
Number of prescribed antibiotics	234	776

Materials and Methods

Setting

Celal Bayar University hospital is a 300-bed tertiary referral center in Manisa, a city in the western region of Turkey with a population of about 300,000 inhabitants. Approximately 15,000 patients receive inpatient care annually.

Study design

Rational antibiotic use rates were evaluated according to results of two cross-sectional studies which were conducted in 1998 and 2005 with the same methodology. The results of the first study were also published in 2000 [8].

Subjects and Data Collection

All the hospitalized patients, over 15 years old, who received antibiotics, were evaluated between October and December 1998 in the first survey and between January and June 2005 in the second survey. In both studies, prospective active daily surveillance of patients was performed by three infectious disease (ID) specialists. These specialists regularly visited the wards and consulted with each patient with a suspicion of an infection before the use of antibiotics was approved. Data including demographic characteristics of the patients, laboratory findings, microbiological results, diagnosis of the patients, details of antibiotic administration (the type of drug, dosage, route of administration, dose intervals, and duration of therapy) and indications for antibiotic use were recorded on questionnaire forms.

Measures

In both studies, indications for antibiotic use were grouped into the following three categories: empirical (based on clinical evidence of infection), prophylactic (administration of antibiotics without evidence of infection) and specific uses (based on culture results).

The appropriateness of antibiotic therapy was determined using the criteria described by Kunin and Jones [13,14]. The universal guides were accepted as a reference for the diagnosis of infections and appropriate therapeutic recommendations in our study [15].

According to new policy implemented in 2003, the restricted antibiotics were divided into two groups as follows:

Group 1: Third-generation cephalosporins, parenterally-administered quinolones, amikacin, isepamicin, netilmicin, amphotericin B (conventional) and fluconazol. This group of antibiotics could be prescribed by any specialist in the first 72 hours of management, after which the approval of an infectious disease specialist was required.

Group 2: Carbapenems, glycopeptides, piperacillin-tazobactam, ticarcillin-clavulonate, amphotericin B (lipid base), and acyclovir. These antibiotics were prescribed only by infectious disease specialists.

Data Analysis

The data were analyzed by using SPSS for Windows. The χ^2 test was used to compare rational antibiotic use prevalence of different groups.

Results

The compared demographic variables of both studies are shown in Table 1. Although the number of wards and the hospitalization capacity of the hospital were increased, the rate of antibiotic use decreased from 16.6% to 11.3% ($p < 0.001$) after the restriction policy was set in place.

Table 2 summarizes the appropriateness of antibiotic use observed in this study as compared with the appropriateness of antibiotic use observed in the study that was performed before the antibiotic restriction policy was enforced. Appropriate use of antibiotic was significantly high in study 2 ($p<0.001$). Both before and after the introduction of the restriction policy, the most frequent causes

Table 2. Distribution of appropriateness of antibiotic use.
[a] Column percent
*** p<0.001, χ^2 test, appropriateness of antibiotic use percentages were compared between study I and II.**

Appropriateness of antibiotic use	Study 1 n (%)[a]	Study 2 n (%)[a]
Appropriate use *	107 (45.7)	709 (91.4)
Probably appropriate use	11 (4.7)	4 (0.5)
Unjustified, excessive length of treatment	4 (1.7)	6 (0.8)
Unjustified, use of any antimicrobial not indicated	28 (12.0)	12 (1.5)
More effective drug recommended	27 (11.5)	26 (3.5)
Unjustified, short length of treatment	36 (15.4)	17 (2.1)
Less expensive drug recommended	4 (1.7)	1 (0.1)
Various combinations of points listed above	17 (7.3)	1 (0.1)
Total	234 (100.0)	776 (100.0)

of irrational antibiotic use were similar, as follows: short treatment period (15.4% in study 1; 2.1% in study 2), unnecessary use (12.0% and 1.5%, respectively) and recommendation of a more effective antibiotic (11.5% and 3.5%, respectively).

Appropriateness of antibiotic use for therapeutic indications in both studies is summarized in Table 3. As the specific antibiotic usage rate increased, the rate of prophylactic antibiotic use decreased after the initiation of the restriction policy (p<0.001). While rational antibiotic use was statistically significant in the indication for specific use in both studies (p<0.05 in study 1; p<0.001 in study 2), the irrational antibiotic use identified most often was prophylactic use.

Appropriateness of antibiotic use according to wards is shown in Table 4. Although the rate of antibiotic usage in medical wards was higher than in other wards in both studies (67.5%, 69.1%, respectively), inappropriate antibiotic use was significantly higher in patients who had been hospitalized on surgical wards before and after the restriction policy was initiated (p<0.001).

The most commonly used antibiotics were similar in both studies. These were β lactam-β lactamase inhibitor combinations, quinolones and third generation cephalosporins (Table 5). In study 1, the rate of irrational antibiotic use was high in all antibiotic groups (p>0.05). However, in study 2, the use of first-, third-, and fourth-generation cephalosporins was statistically inappropriate (p<0.001).

Table 3. Appropriateness of antibiotic use for therapeutic indications.

Indication	Study 1*			Study 2[†]		
	Rational n (%)[a]	Irrational n (%)[a]	Total n (%) [b]	Rational n (%)[a]	Irrational n (%)[a]	Total n (%) [b]
Empiric use	81 (48.5)	86 (51.5)	167 (71.4)	535 (91.0)	53 (9.0)	588 (51.9)
Specific use	8 (72.7)	3 (27.3)	11 (4.7)	159 (97.0)	5 (3.0)	164 (14.5)
Prophylactic use	18 (32.1)	38 (67.9)	56 (23.9)	15 (62.5)	9 (37.5)	24 (2.2)
Total	107 (45.7)	127 (54.3)	234 (100.0)	709 (91.4)	67 (8.6)	776 (100.0)

[a] Row percent
[b] Column percent
[#]p<0.001, χ^2 test, rationality between study I and study II
*** p<0.05, χ^2 test**
[†] p<0.001, χ^2 test

Table 4. Appropriateness of antibiotic use according to wards

Ward	Study 1*			Study 2*		
	Rational n (%)[a]	**Irrational n (%)[a]**	**Total n (%) [b]**	**Rational n (%)[a]**	**Irrational n (%)[a]**	**Total N (%) [b]**
Medical	87 (55.1)	71 (44.9)	158 (67.5)	503 (93.8)	33 (6.2)	536 (69.1)
Surgical	20 (26.3)	56 (73.7)	76 (32.5)	206 (85.8)	34 (14.2)	240 (30.9)
Total	107 (45.7)	127 (54.3)	234 (100.0)	709 (91.4)	67 (8.6)	776 (100.0

[a] Row percent
[b] Column percent
*** p<0.001, χ^2 test**

Discussion

The major consideration for proper usage of antimicrobial agents, which is a main concern of modern medicine, is to select the optimal agent at the proper dosage and duration. Secondary, but still important concerns are to minimize the emergence of resistance and to provide health services at a reasonable cost. Although the overall accomplishments have been outstanding, there is considerable evidence that antimicrobial agents are often abused and used excessively [16,17].

Studies indicate that about one third of all hospitalized patients receive antimicrobial

Table 5. Appropriateness of different antibiotic groups use.

	Study 1[*]			Study 2[†]		
	Rational n (%)[a]	**Irrational n (%)[a]**	**Total n (%)[b]**	**Rational n (%)[a]**	**Irrational n (%)[a]**	**Total n (%)[b]**
Penicillin	12 (63.2)	7 (36.8)	19 (8.1)	10 (90.9)	1 (9.1)	11 (1.4)
First-generation cephalosporins	-	4 (100.0)	4 (1.7)	10 (71.4)	4 (28.6)	14 (1.8)

Second-generation cephalosporins	9 (40.9)	13 (59.1)	22 (9.4)	29 (93.5)	2 (6.5)	31 (4.0)
Third-generation cephalosporins	11 (34.4)	21 (65.6)	32 (13.7)	93 (80.2)	23 (19.8)	116 (14.9)
Fourth-generation cephalosporins	-	3 (100.0)	3 (1.3)	6 (75.0)	2 (25.0)	8 (1.0)
Quinolones	22 (53.7)	19 (46.3)	41 (17.5)	162 (93.6)	11 (6.4)	173 (22.3)
Aminoglycosides	4 (30.8)	9 (69.2)	13 (5.6)	51 (98.1)	1 (1.9)	52 (6.7)
Macrolides	15 (60.0)	10 (40.0)	25 (10.7)	20 (90.9)	2 (9.1)	22 (2.9)
β-lactam/β-lactamase inhibitors	20 (46.5)	23 (53.5)	43 (18.4)	102 (98.1)	2 (1.9)	104 (13.4)
Carbapenems	2 (100.0)	-	2 (0.9)	85 (87.6)	12 (12.4)	97 (12.5)
Glycopeptides	2 (66.7)	1 (33.3)	3 (1.3)	71 (98.6)	1 (1.4)	72 (9.3)
Others	10 (37.1)	17 (62.9)	27 (11.6)	70 (92.1)	6 (7.9)	76 (9.8)
Total	107 (45.7)	127 (54.3)	234 (100.0)	709 (91.4)	67 (8.6)	776 (100.0)

[a] Row percent, [b] Column percent
[#] In order to analyze the different antibiotic groups, cells having count lower than five were combined according to similar antibacterial activity.
***p>0.05, χ^2 test**
[†] p<0.001, χ^2 test

therapy, which accounts for between 3% and 25% of all prescriptions, and up to 41% of the drug budget in hospital care [17,18]. Similarly, while 11.3% of the patients received antibiotics in study 2, antibiotics were prescribed in 16.6% in study 1.

The Turkish Pharmaceutical Manufacturers Association recently reported that antibiotics are the most commonly consumed drugs, and constitute approximately 20% of the Turkish drug market [2]. A variety of mechanisms have been used to enhance the appropriate use of antimicrobial agents. A widely used initial strategy is the formation of multidisciplinary groups, such as Pharmacy and Therapeutics Committees or Antimicrobial Subcommittees, which are responsible for all antimicrobial policies for the health care facility. Other techniques include the use of antimicrobial order sheets, automatic stop orders, therapeutic substitution, antibiotic restriction systems, and the use of selective antimicrobial susceptibility reporting systems. Many of these strategies have been reported to be effective in the management of antimicrobial usage [12,16]. An antibiotic restriction policy combined with or without other strategies showed that an antibiotic policy provides a decrease of consumption and thus the cost of the drugs [19].

In Turkey, an antibiotic restriction policy was applied to reduce the expenditure of antibiotics based on the directive of the Ministry of Health in 2003. By this policy, certain intravenous and expensive broad-spectrum antibiotics were restricted by legal regulation and their use required approval from an infectious disease specialist. Previous reports on hospitals applying an antibiotic policy had shown that the rate of appropriate use of antibiotics increased after intervention [6,7]. As a result of the new policy, in our hospital, besides the decreasing of the rate of antibiotic use, the rate of rational antibiotic use increased from 45.7% to 91.4%.

Ideally good antibiotic prescribing practice should reflect the use of the most effective, least toxic, and least costly antibiotic for the precise duration of time needed to cure the infection. Unfortunately, up to 40% to 60% of these antibiotics are prescribed inappropriately in some respect [3,16]. The four particular areas of irrational antibiotic prescribing remain: inadequate recognition of infections, leading to prescription of unnecessary drugs; inappropriate route of antibiotic; the choice of antibiotic; the dose and protracted duration of antibiotics [17,20]. In our hospital, both before and after initiation of the antibiotic-restriction policy, the most frequent causes of inappropriate use of antibiotics were short duration of treatment, unnecessary use, and recommendation of a more effective antibiotic.

Studies showed that a high proportion of antibiotic prescribing occurs in general medical wards [17,21]. In the two studies presented here, most of the patients receiving antibiotics were on medical wards (67.5%, 69.1%, respectively). However, the rates of inappropriate antibiotic use on surgical wards were significantly higher than those in medical wards. The high rate on surgical wards may be ascribed to difficulties in diagnosis of surgical infections [22].

The rate of specific use also increased from 4.7% to 14.5% after the introduction of the restriction policy, and the appropriate use of antibiotics in patients receiving specific antibiotic use was higher than that in patients receiving empirical and prophylactic usage in both studies. Although the most frequent cause of irrational antibiotic usage was prophylactic antibiotic usage before and after restriction, the rate of prophylactic antibiotic usage in particular decreased from 23.9% to 2.2% after restriction and this significant decrease of prophylactic antibiotic use directly reflects the increasing rate of appropriate use.

A variety of studies indicate that ID physicians working with multi-disciplinary teams have a significant effect on improving the quality of antibiotic prescribing and costs [23,24]. The actual composition of any team providing advice on antibiotic prescribing should be dependent on local practice and resources, but must include an ID specialist, a clinical microbiologist, and a pharmacist. Studies showed that the clinical value of microbiological information is significantly enhanced when it is considered together with information provided by a specialist in infectious diseases [25]. Culture and antimicrobial sensitivity test results were obtained in a shorter period and interpreted by communicating directly with the microbiological laboratory in our study after the introduction of the restriction policy. The significantly higher rate of rational use in the patients in whom a culture was performed clearly emphasized the necessity of appropriate diagnostics including culture and sensitivities.

Studies showed that third-generation cephalosporins are being widely used in hospitals for empirical and prophylactic therapy [26]. Indeed, cephalosporins were determined as the most frequently and the irrationally used antibiotics in both studies in our hospital. However, in the second study, the use of carbapenems and glycopeptids was increased. The difference in the consumption of this antibiotic could be defined by the increase in the proportion of seriously ill patients, such as immunocompromised patients.

In the presented study, our institution's successful experience in enforcing a policy for restricting use of antimicrobial agents is described. After the restriction policy began, use of antimicrobial drugs declined and the rate of rational antibiotic usage increased. In addition to the restriction policy, additional interventions such as postgraduate training programmes, elaboration of local prophylactic guidelines, and the constitution of an antibiotic monitoring team compromising a pharmacist, clinical microbiologist and infectious disease specialist could be beneficial in order to idealize rational antimicrobial use for future national programs.

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Corresponding Author: Ozlem Tunger, MD, Associate Professor, Department of Infectious Diseases and Clinical Microbiology, Celal Bayar University Medical Faculty, Manisa, Turkey 45020
Tel: +90.236.2370053
Fax: +90.236.2370213
Email: otunger@hotmail.com

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