Original Article

Changes in Antibiotic Use, Cost and Consumption after an Antibiotic Restriction Policy Applied by Infectious Disease Specialists

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SUMMARY: The study was designed to compare antibiotic use, cost and consumption before and after an initiation of an antibiotic-restriction policy in our hospital. The policy was applied in 2003, and the prescription of two groups of antibiotics (intravenously used and expensive antibiotics) was restricted. A prescription for the restricted antibiotics could be obtained with approval by an infectious disease specialist (IDS). All the hospitalized patients who received antibiotics were evaluated by a cross-sectional study with standard criteria. The annual cost and consumption of antibiotics were evaluated. After restriction, the rate of antibiotic use decreased from 52.7 to 36.7% ($P < 0.001$), and the appropriate use increased from 55.5 to 66.4% ($P < 0.05$). Appropriate use was higher for restricted antibiotics (88.4%) than for unrestricted ones (58.2%) ($P < 0.001$), and higher in the presence of ID consultation (97.5%) than in the absence of consultation (55.7%) ($P < 0.001$). Culture-based treatment was increased, and appropriate use in such cases (93.0%) was higher than empirical treatment (33.3%) ($P < 0.001$). After the restriction policy, consumption of antibiotics belonging to the restricted groups was decreased by 44.8%. Total expenditure of all antibiotics was decreased by 18.5%, and the savings were US$332,000 per year. This restriction policy was effective in promoting rational antibiotic prescription and lowering antibiotic cost and consumption in our hospital.

INTRODUCTION

Antibiotics are among the most frequently used drugs worldwide. They are particularly utilized in developing countries, where, on average, 35% of the total health budget is spent on antibiotics (1). In Turkey, the Turkish Pharmaceutical Manufacturers Association recently reported that antibiotics are the most frequently consumed drugs, and constitute approximately 20% of the Turkish drug market (2). However, both in Turkey and in other countries, it is generally accepted that a considerable portion of this consumption is unnecessary (1,3).

Overuse and/or misuse of antibiotics has significant consequences, such as increased cost, bacterial resistance, therapeutic failure drug toxicity and drug interactions (4-7). Excessive use of antibiotics is a well-documented risk factor for the selection of resistant bacteria, and, in general, a close association exists between the rate of resistance development and the quantities of antimicrobial agents used (5,8,9). Therefore, many healthcare institutions have introduced programs aiming at improving rational antibiotic use, initiating education campaigns, regulating drug-auditing practices, restricting dispensing techniques and controls.

A restricted antibiotic prescription policy was applied in our hospital for 1 year. The aim of this study was to evaluate antibiotic use, cost and consumption before and after the restricted antibiotic policy.

MATERIALS AND METHODS

Hospital setting: The study was conducted in a Research Hospital of the Atatürk University Medical School in Erzurum, the largest hospital in the Eastern Anatolian Region of Turkey, in March 2004. The hospital provides tertiary care and has 1,200 beds.

Antibiotic prescription policy: In 2003, an antibiotic restriction policy was applied to reduce the expenditure of antibiotics based on the directive of the Ministry of Health. By this policy, certain intravenous and expensive antibiotics were restricted by legal regulation, and their use required approval from an infectious diseases specialist (IDS). The restricted prescription was applied to the following two groups of antibiotics.

Group 1: Third-generation cephalosporin, amikacin, isepamicin, netilmicin, parentheral quinolones, amphotericin B (conventional) and fluconazol. These antibiotics could be prescribed by any specialist in the first 72 h, but require approval of an IDS if used after 72 h.

Group 2: Expensive antibiotics: piperacillin-tazobactam, ticarcillin-clavulonate, carbapenems, glycopeptides, amphotericin (lipid base) and acyclovir. These antibiotics could only be prescribed by an IDS.

Four IDS regularly visited the wards, and before the approval of antibiotics, consulted each patient receiving those groups of antibiotics. Additionally, in this period, a member of the Infection Control Committee conducted educational studies on rational antibiotic use for the staff.

Evaluation of antibiotic use: All the hospitalized patients who received antibiotics were evaluated by a cross-sectional study. Antibiotic orders of all the hospitalized patients were evaluated between 1 and 10 March, 2004. For each patient receiving antibiotic treatment, demographic data, diagnosis, microbiologic results, details of antibiotic administration, indications for treatment or prophylaxis, dosage, dose frequency, and administration route were recorded on the forms. Antibiotic use was divided into three categories: specific

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(based on culture results), empirical (based on clinical evidence), and prophylactic (without evidence of infection). Each antibiotic was evaluated by four IDSs with respect to appropriateness based on standard criteria (a modification of the criteria of Kunin et al. [10] and Jones et al. [11]) and antibiotic guidelines (12).

Irrational use was grouped into eight categories:
1. No indication.
2. Improper dosage or dosage interval.
3. Unnecessary or improper combination.
4. Reserve or broad-spectrum antibiotic.
5. Improper beginning time for prophylactic use or improper duration of treatment.
6. Incorrect choice of antibiotic (antibiotic is not appropriate for diagnosis or disease).
7. More expensive and toxic drug.
8. Any combination of the above.

The results were compared with the results of our previous study carried out before the restriction policy in 2001 (13).

Evaluation of antibiotics in terms of cost and consumption: Before and after (2002 and 2003) the restriction policy, the annual consumption and cost of antibiotics were compared. The data were collected from the hospital pharmacy records. Antibiotic costs were measured in United States dollars (US$). Antibiotic consumptions were evaluated using an international measure, i.e., defined daily doses (DDD)/ 100 patient-days (available online at http://www.whocc.no/ atcddd/) (14).

Statistical analysis: Statistical analysis was conducted with the chi-square test, and a P value of <0.05 was considered significant.

RESULTS

The number of admissions (34,890 versus 35,892) and mean duration of hospitalization (10.04 versus 10.33 days) were similar in 2002 and 2003. Additionally, in this period, hospital infection rates (4% in 2002 versus 4.1% in 2003) and mortality rates (4.2% in 2002 versus 4.0% in 2003) were similar (15,16).

Of 876 hospitalized patients, 318 (36.6%) received antibiotics. Antibiotics were used in 113 (35.5%) patients for surgical prophylaxis, in 5 (1.6%) for medical prophylaxis and in 200 (62.9) for treatment. Of 200 treatments, 71 (35.5%) were culture-based (37 of them were nosocomial infections) and 129 (64.5%) were empiric. The most frequently prescribed antibiotics were ampicillin-sulbactam (15.0%), first-generation cephalosporins (14.7%), nitroimidazoles (11.1%), aminoglycosides (10.5%), and third-generation cephalosporins (9.9%) (Table 1).

Inappropriate use of antibiotics was observed in 107 (33.6%) patients (73 [45.3%] from the surgical ward and 34 [21.7%] from the medical ward [P < 0.05]). Appropriate use was found for 130 of 147 (88.4%) restricted antibiotics and for 167 of 287 (58.2%) unrestricted antibiotics. Inappropriate use was significantly higher in unrestricted antibiotics than in restricted ones (P < 0.001). The rate of antibiotic use decreased from 52.7 to 36.7% (P < 0.001). Appropriate use of antibiotics increased from 55.5 to 66.4% (P < 0.05). The profiles of antibiotic use in the hospital before and after the restriction policy are shown in Table 2.

After restriction, because of the need for approval by an IDS, the number of ID consultations increased dramatically.

As expected, ID consultation resulted in an increase in the percentage of appropriate antibiotic use. Appropriate use of antibiotics was found in 79 (97.5%) of 81 patients who received ID consultation versus 132 (55.7%) of 237 patients who did not (P < 0.001). The rate of culture-based treatment increased from 23.5 to 35.5% after initiation of the antibiotic-restriction policy. The rate of appropriate use in culture-based treatment (93.0%) was higher than that (33.3%) in empirical treatment (P < 0.001) (Table 3).

Both before and after the antibiotic-restriction policy, the most frequent causes of inappropriate use of antibiotics were improper beginning time for prophylactic use or improper duration of treatment, and unnecessary or improper combination (Table 4).

After the antibiotic-restriction policy, total antibiotic consumption decreased by 14.2% (from 37.34 to 32.02 DDD/ 100 patient-days). Antibiotic usage decreased by 53.1% (from 13.66 to 6.4 DDD/100 patient-days) for Group 1 antibiotics and by 20.5% (from 4.68 to 3.72 DDD/100 patient-days) for Group 2 antibiotics. There was a decrease of 44.8% (from 18.34 to 10.12 DDD/100 patient-days) in restricted groups (Table 5). Before applying the restricted prescription policy, third-generation cephalosporins were the most widely used class of antibiotics. After restriction, the use of third-generation cephalosporins decreased by 64.8% (from 10.62 to 3.73 DDD/100 patient-days). In the restricted groups of antibiotics, except antifungal, consumption of all antibiotics (aminoglycosides, quinolones, (parentheral), third-generation cephalosporins, glycopeptides, carbapenems, piperacillin/ tazobactam, ticarcillin/clavulonate) had decreased by various percentages (Table 6). The use of antifungals increased from 0.19 to 0.27 DDD/100 patient-days in Group 1 and from 0.06 to 0.08 DDD/100 patient-days in Group 2.

In the unrestricted group, consumption of antibiotics increased by 15.2% (from 19.0 to 21.9 DDD/100 patient-days). In this group, while the use of some of the antibiotics (quinolones, nitroimidazoles, phenicols, rifampicin, streptomicin) decreased, the use of others (penicillins, 1st- and 2nd-generation cephalosporins, macrolides, co-trimaxazole, gentamicin) increased (Table 6).

The total expenditure of all antibiotics decreased by 18.5%, resulting in a savings of US$332,000 per year (from

Table 1. Comparison of the frequently prescribed antibiotics in 2001 and 2004 (daily)

Antibiotics	2001 n = 498	2004 n = 476	P
	no. (%)		
Ampicillin-sulbactam	105 (27.8)	71 (15.0)	<0.05[2]
Third-generation cephalosporins[1]	83 (22.0)	47 (9.9)	<0.002[2]
Aminoglycosides[1]	70 (18.5)	50 (10.5)	>0.05
Quinolones[1]	44 (11.6)	33 (6.9)	>0.05
Nitroimidazoles	28 (7.4)	53 (11.1)	>0.05
Amoxicillin/clavulonate	25 (6.6)	14 (2.9)	>0.05
Carbapenems[1]	22 (5.8)	18 (3.8)	>0.05
Penicillin G	22 (5.8)	27 (5.6)	>0.05
Glycopeptides[1]	18 (4.8)	15 (3.2)	>0.05
Co-trimaxsazole	14 (3.7)	11 (2.3)	>0.05
Second-generation cephalosporins	12 (3.2)	26 (5.5)	>0.05
First-generation cephalosporins	9 (2.4)	70 (14.7)	<0.001[2]
Others	27 (7.1)	41 (8.6)	>0.05

[1]: Restricted antibiotics.

[2]: There were statistically significant difference.

Table 2. The profiles of antibiotic use before and after the restriction policy

Antibiotic use	2001 no. (%)			2004 no. (%)			P
	Medical ward (n = 393)	Surgical ward (n = 324)	Total (n = 717)	Medical ward (n = 529)	Surgical ward (n = 338)	Total (n = 867)	
Total use of antibiotics	169 (43.0)	209 (64.5)	378 (52.7)	157 (29.7)	161 (47.6)	318 (36.7)	<0.001
Prophylactic	23 (13.6)	130 (62.2)	153 (40.5)	5 (3.0)	113 (70.2)	118 (37.1)	>0.05
Treatment	146 (86.3)	79 (46.7)	225 (59.5)	152 (96.8)	48 (29.8)	200 (62.9)	>0.05
Empiric	111 (76.0)	61 (77.2)	172 (76.4)	96 (63.2)	33 (68.7)	129 (64.5)	<0.05
Culture-based	35 (23.9)	18 (22.7)	53 (23.5)	56 (36.8)	15 (31.3)	71 (35.5)	<0.05
Appropriate use	114 (67.4)	96 (45.9)	210 (55.5)	123 (78.3)	88 (54.7)	211 (66.4)	<0.05
Inappropriate use	55 (32.5)	113 (54.1)	168 (44.4)	34 (21.7)	73 (45.3)	107 (33.6)	<0.05
Prophylactic	10 (43.5)	95 (73.1)	105 (68.6)	1 (20.0)	58 (51.3)	59 (50.0)	<0.001
Empiric	37 (33.3)	15 (24.6)	52 (30.2)	30 (31.2)	13 (39.4)	43 (33.3)	>0.05
Culture-based	8 (22.9)	3 (16.7)	11 (20.8)	3 (5.4)	2 (13.3)	5 (7.0)	<0.001

n, number of hospitalized patient.

Table 3. Antibiotic use with respect to restricted antibiotics and infection consultation after antibiotic policy (in 2004)

Usage	ID consultation no. of patients (%)		P	no. of antibiotics (%)		P
	Yes	No		Restricted	Unrestricted	
Appropriate use	79 (97.5)	132 (55.7)	<0.001	130 (88.4)	167 (58.2)	<0.001
Inappropriate use	2 (2.5)	105 (44.3)	<0.001	17 (11.6)	120 (41.8)	<0.001
Total	81	237		147	287	

ID, infectious disease.

Table 4. The causes of irrational antibiotic use in 2001 and 2004

Causes of irrational antibiotic use	no. of cases (%)	
	2001	2004
No indication	24 (14.3)	9 (8.4)
Reserve or broad-spectrum antibiotic	13 (7.7)	4 (3.7)
More expensive and toxic drug	6 (3.6)	7 (6.5)
Imporer dosage or dosage interval	19 (11.3)	5 (4.7)
Imporer beginning time for prophylactic use or imporer duration of treatment	42 (25.0)	34 (31.7)
Incorrect choice of antibiotic	4 (2.4)	8 (7.5)
Unnecessary or imporer combination	24 (14.3)	15 (14.0)
Various combinations of inappropriateness	36 (21.4)	25 (23.4)

Table 5. Comparison of yearly consumption and cost of antibiotics before and after the restriction policy

Antibiotic class	DDD/100 patient-days		% difference	Cost (US$)		% difference
	2002	2003		2002	2003	
Group 1	13.66	6.40	−53.1	690,000	366,000	−47.0
Group 2	4.68	3.72	−20.5	812,000	711,000	−12.4
Total	18.34	10.12	−44.8	1,502,000	1,077,000	−28.3
Unrestricted	19.0	21.9	+15.2	294,000	387,000	+31.6
Total	37.34	32.02	−14.2	1,796,000	1,464,000	−18.5

DDD, defined daily doses.

US$1,796,000 in 2002 to US$1,464,000 in 2003). With respect to the restricted antibiotics, the expenditure on the drugs in Group 1 decreased by 47.0%, and that on the drugs in Group 2 decreased by 12.4%. The expenditure of antibiotic decreased by 28.3% (from US$1,502,000 to US$1,077,000) in the restricted groups and increased by 31.6% (from US$294,000 to US$387,000) in the unrestricted ones (Table 5).

Tables 7 and 8 show the antibiotic resistances of micro-organisms isolated in our hospital in 2002 and 2003. In this period, some resistance patterns of both Gram-negative and Gram-positive microorganisms were significantly decreased.

DISCUSSION

There are three important considerations for establishing rational antibiotic use: efficacy, safety and low cost. Four types of intervention strategies to improve drug use can be applied: educational, managerial, financial and regulatory

Table 6. Changes in the use of antibiotics

Restricted antibiotics	DDD/100 patient-days		% difference	Unrestricted antibiotics	DDD/100 patient-days		% difference
	2002	2003			2002	2003	
Aminoglycosides	1.91	1.53	−19.8	Penicillins	6.53	7.64	+16.9
Quinolones(parenteral)	0.94	0.87	−7.4	1-, 2-Gen Cep*	2.13	4.80	+125.3
3-Generation Cep.*	10.62	3.73	−64.8	Macrolides	0.27	0.53	+96.2
Antifungal drugs	0.19	0.27	+42.1	Quinolones (oral)	0.30	0.23	−23.3
Glycopeptides	2.20	1.92	−12.7	Nitroimidazoles	1.95	1.27	−34.8
Carbapenems	2.22	1.54	−30.6	Co-trimaxazole	0.47	0.73	+55.3
Piperacillin/tazobactam	0.18	0.16	−11.1	Gentamicine	2.81	3.76	+33.8
Ticarcillin/clavulonate	0.008	0	−100	Phenicols	0.18	0.13	−27.7
Acyclovir	0.02	0.02	0	Rifampicin	4.21	2.71	−35.6
Amphotericin B (lipid)	0.06	0.08	+33.3	Streptomicin	0.15	0.13	−13.3
Total	18.34	10.12	−44.8	Total	19.0	21.9	+15.2

Gen Cep, Generation cephalosporins.

Table 7. Antimicrobial resistance rates of Gram-negative microorganisms in 2002 and 2003

	2002/2003 % (P)			
	E. coli ($n = 199/261$)	*P. aeruginosa* ($n = 112/313$)	*Enterobacter* spp. ($n = 111/258$)	*Acinetobacter* spp. ($n = 7/44$)
Amikacin	17.1/10.3 (0.03)*	38.4/26.8 (0.30)	23.4/16.7 (0.14)	71.4/61.4 (0.69)
Ceftriaxone	28.6/36.4 (0.08)	71.4/75.7 (0.31)	52.3/55.4 (0.65)	85.7/81.8 (1.00)
Ceftazidime	25.6/39.8 (0.001)*	66.9/77.3 (0.44)	55.4/57.4 (0.73)	85.7/84.1 (1.00)
Sulbactam/ampicillin	46.7/51 (0.39)	75.9/80.2 (0.34)	61.3/61.6 (1.00)	71.4/63.6 (1.00)
Ciprofloxacin	43.7/38.3 (0.25)	71.4/60.7 (0.52)	33.9/44.6 (0.06)	85.7/79.5 (1.00)
Imipenem	2.5/2.7 (1.00)	26.8/20.8 (0.18)	27.0/2.3 (0.0001)*	71.4/15.9 (0.005)*
Meropenem	2.5/4.2 (0.44)	38.4/24.9 (0.01)*	27.0/15.5 (0.0001)*	14.3/29.5 (0.67)

*A P value of <0.05 was considered significant.

Table 8. Antimicrobial resistance rates of *Staphylococcus* in 2002 and 2003

	2002/2003 % (P)				
	Penicillin	SAM	Cefazolin	Oxacillin	Eritromicin
S. aureus ($n = 226/420$)	88.9/79.7 (0.004)*	69.0/71.4 (0.52)	69.0/ 71.4 (1.00)	61.9/65 (0.40)	83.2/73.8 (0.08)*
CNS ($n = 178/308$)	91.0/82 (0.008)*	74.2/73.7 (1.00)	74.2/73.7 (0.40)	69.1/73 (1.00)	86.0/76.2 (0.01)*

CNS, Coagulase-negative staphylococci.
*There were statistically significant difference.

(17). These strategies include education, control of the hospital formulary, written justification forms, automatic stop order ongoing utilization review, restriction, required consultation, control of laboratory susceptibility testing, and limitation of contact time between physicians and pharmaceutical representatives (18-20).

In our country, an antibiotic restriction policy was initiated for 1 year to reduce antibiotics expenditures. The policy stipulated that the use of certain expensive antibiotics would require approval by IDS. As a result of the new policy, ID consultations increased, and the rate of appropriate use of antibiotic increased to 97.5% for patients who received ID consultation but was a low 55.7% for those who did not. The rate of culture-based treatment also increased from 23.5 to 35.5% after restriction, and the appropriate use of antibiotics in patients receiving culture-based treatment (93.0%) was higher than that in patients receiving empirical treatment (33.3%).

Previous reports on hospitals applying an antibiotic policy reported that the rate of appropriate use of antibiotics increased after intervention (21,22). It has also previously been reported that hospitals in which ID consultation was available showed an increased rate of rational antibiotic use (22,23). In other studies, the rational use of antibiotics also was significantly higher in culture-based therapy than in empirical therapy (2,22,23).

In the present study, the rate of appropriate use of antibiotics increased from 55.5 to 66.4% when ID consultation. The rate for appropriate use was 88.4% for restricted antibiotics versus 58.1% for unrestricted ones. The rate of antibiotic use decreased from 52.7 to 36.7% in our hospital. Both before and after initiation of the antibiotic-restriction policy, the most frequent causes of inappropriate use of antibiotics were improper beginning time for prophylactic use, improper duration of treatment, and unnecessary or improper combination. Improper beginning time and improper duration of therapy were observed in surgical prophylaxis. Since the antibiotics used in surgical prophylaxis were not included in this restriction policy, we think that the policy was ineffective in solving the problem of inappropriate use in surgical

prophylaxis. For the solution of this problem, we recommend the preparation of local surgical guidelines and continuous education.

Before restriction policy, the third-generation cephalosporins were the second most frequently used antibiotics, and after the policy, the use of this group decreased and was replaced by the first-generation cephalosporins.

After antibiotic policy, antibiotic consumption and expenditure decreased significantly for all of the antibiotics concerned. The consumption decreased by 13.9% and expenditure by 18.5% in total use. The usage decreased by 44.8% in the total of restricted groups, but increased in the unrestricted groups only by 15.3%. This increase may be accounted for by the replacement of conventional antibiotics with new, expensive and broad-spectrum ones. For example, while the usage of third-generation cephalosporins significantly decreased (by 64.8%), that of the first- and second-generation cephalosporins increased (by 125%) and replaced third-generation cephalosporins. While amikacin and neutromycin usages decreased (by 19.8%), gentamicin usage increased (33.8%) and replaced them. In the restricted antibiotics, only the usage of antifungals increased. This may be due to an increase in the candida infections.

The total savings were US$332,000 (18.5%). The cost of antibiotics in the restricted groups decreased by 47.0% in Group 1 and by 12.4% in Group 2 antibiotics.

In 2002 and 2003, hospital infection rates were similar, and mortality rate of the hospitalized patients did not increase despite the restricted prescription of antibiotics. Upon the comparison of resistance patterns of various microorganisms, we observed that some resistance rates were decreased. Appropriate use of antibiotics may delay or prevent the emergence and spread of resistant pathogens. We hope in the future that these rates will decrease further.

Antibiotic restriction policy combined with or without other strategies showed that an antibiotic policy provides a decrease of consumption and thus cost of the drugs (24-30). In a hospital, only antibiotic guideline applied without restriction also saved and had decreased usage of antibiotics (31,32). In other hospitals applying ID consultation services to improve use of antibiotics, successful results have also been obtained (22,33-35). Although our antibiotic use policy was time-consuming and labor intensive, both the IDS and hospital pharmacist were very eager to apply it, since it was expected to result in improved infection control and a decrease in antibiotic resistance. Proper application was possible by the cooperation of the IDS and the hospital pharmacist.

This policy was successfully applied in our hospital with respect to consumption, cost, and rational use of antibiotics by continuous consultation services of IDS, education, and the cooperation of the hospital pharmacist.

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