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Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance

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Summary *Objectives:* In 2003 Turkish government released a new budget application instruction for regulating the usage of parenteral antibiotics inside and outside of the hospitals. In this study it was aimed to evaluate the effect of this instruction on the overall usage of restricted antibiotics, their cost, overall mortality, bacterial resistance patterns and nosocomial infection rates in intensive care units (ICUs) of our setting for March–October 2002 and March–October 2003 periods.
Methods and results: Overall daily defined dose/1000 patients/day of restricted drugs decreased, whereas unrestricted drugs increased significantly after the instruction. The cost of all analysed drugs in 2003 period was 540,303 USD (−19.6%) less than 2002 period. Nosocomial infection rates in ICUs decreased significantly ($p < 0.05$). When all microbiologically confirmed nosocomial bacteremia cases during the study period were analysed, amoxycilline/clavulanate, ciprofloxacin, cefuroxime, cefotaxime, piperacilline/tazobactam resistance and ESBL rate in *Klebsiella pneumoniae* decreased significantly ($p < 0.05$). Amikacin resistance in *Escherichia coli* and *Acinetobacter baumannii* increased significantly ($p < 0.05$).
Conclusion: Antibiotic control is one of the most important and significant ways to save money, and to prevent antibacterial resistance.

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Introduction

The increasing values of health expenditures is a major problem in Turkey and all over the world.[1–4] In 1996, 26.3% of the total health expenditure in Turkey was spent for drug consumption and it is reported that 22.4% of all drugs used were antimicrobial agents, which means a value of 400,000,000 USD/year.[1]

Antimicrobial agents are often used inappropriately.[1–5] Untoward consequences of inappropriate antibiotic use are well known to infectious diseases clinicians. Adverse drug reactions, emergence of multidrug-resistant organisms and excessive strain on already limited pharmacy budgets are major outcomes of inappropriate antibiotic use.[6–9]

In 2003 Turkish Ministry of Finance which is responsible for payback of over 90% of the population's health expenditures[9] has released a new budget application instruction[10] for regulating the usage of parenteral antibiotics inside and outside of the hospitals. The instruction took effect on March 1st, 2003. According to this instruction the payback of parenteral vancomycin, teicoplanin, meropenem, imipenem, piperacillin/tazobactam, ticarcillin/clavulanate has been restricted without prior approval of infectious diseases specialist (IDS). Payback of ceftriaxone, cefotaxime, ceftizoxime, cefoperazone, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, levofloxacin, netilmicin, amikacin and isepamicin was unlimited, when prescribed for the first 72 h of the treatment, for all specialists (except general practitioners) but further usage required IDS approval. The other antimicrobials could be prescribed without any restriction by all medical doctors.

In this study it was aimed to evaluate the effect of 2003 financial budget application instruction on the usage and cost of antimicrobials that required prior IDS authorization and that were freely prescribed and to analyse the effects of these changes on nosocomial infection rates, overall mortality and antimicrobial resistance.

Method

Setting

Our hospital is a 1788-bedded tertiary-care educational hospital. The total number of inpatients was 52,979 in 2003.

Role of IDSs and microbiology staff

IDSs made the authorizations by bedside consultations. The role of the microbiology staff was to perform the bacteriologic cultures.

Antibiotic expenditure measurement

We retrospectively obtained the amount of the acquisition cost of all antimicrobials as boxes and gram and their cost and the value of overall drug expenditure as Turkish Lira (TL) by using the hospital pharmacy computer database. The evaluated periods were March–October in 2002 and March–October in 2003 (before and after the application). The amount of the antimicrobials used has been calculated as DDD (daily defined dose)/1000 patients/day as follows: (total consumption measured in DDDs/number of days in the period of data collection $\times$ number of patients) $\times$ 1000.[11]

In order to exclude the effect of inflation the cost of antimicrobials in 2002 period was calculated by using 2003/box prices. The total costs has been converted to USD assuming that 1 USD = 1.4 YTL.

We analysed the restricted (vancomycin, teicoplanin, meropenem, imipenem, piperacillin/tazobactam, ticarcillin/clavulanate, ceftriaxone, cefotaxime, ceftizoxime, cefoperazone, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, levofloxacin, netilmicin, amikacin and isepamicin) and unrestricted (cefazolin, cefuroxime, gentamicin, amoxicillin/clavulanate, ampicillin/sulbactam) antimicrobials as separate groups.

Quality of care

Effect of antibiotic expenditure trends on the quality of care was assessed by comparing overall mortality and nosocomial infection rates in ICUs.

Overall mortality

Total number of hospitalized patients and the number of total deaths were extracted retrospectively from hospital statistics department database for the same time periods. (Total number of deaths/total number of patients $\times$ 1000 were calculated.)

Nosocomial infection rates

Our hospital's infection control committee implements targeted active surveillance in internal medicine clinic (97 beds + 13 intensive care unit (ICU) beds), respiratory diseases ICU (8 beds), anaesthesiology and reanimation ICU (28 beds) and pediatrics clinics (77 beds + 23 ICU beds). Nosocomial infection data of these ICUs were collected prospectively by four infection control nurses by daily visits. Center for Diseases Control (CDC) criteria[12] were used for the diagnosis of nosocomial infections. Results of the study periods in 2002 and 2003 were compared.

Antimicrobial resistance

Effect of antibiotic expenditure trends to antimicrobial resistance rates were retrospectively evaluated by comparing the resistance patterns of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneuomoniae*, *Escherichia coli*, *Acinetobacter* spp., *Acinetobacter baumannii* and *Enterococcus* spp. strains isolated from hospitalwide microbiologically confirmed nosocomial bacteremia patients in 2002 and 2003 study periods. Any patient in whom *S. aureus*, *P. aeruginosa*, *K. pneuomoniae*, *E. coli*, *Acinetobacter* spp., *A. baumannii* and *Enterococcus* spp. were isolated in at least one set of blood cultures (sent to the bacteriology laboratory 72 h after hospital admission) was considered to have microbiologically confirmed nosocomial bacteremia. *Enterococcus faecium* and *Enterococcus faecalis* were not analysed separately since only 10% of the strains were identified in species level. Data of

antibacterial resistance and hospital admission dates were extracted from hospital database. Double or more isolates during each episode were counted as one episode.

Blood cultures were performed on Bact-Alert (Bio Merioux). Bacterial identifications were performed by conventional methods and Api systems (Bio Merioux). Antibacterial susceptibility tests were performed by Kirby Bauer disc diffusion method following the recommendations of National Committee for Clinical Laboratory Standards (NCCLS).[13] Mueller–Hinton agar (oxoid) was used for all susceptibility tests. Zone sizes were interpreted as described by NCCLS.[13] Strains which were intermediately resistant were also considered as resistant. Extended-spectrum beta-lacatamases (ESBL) detection was performed by double disk approximation test.[13,14]

Statistical analysis

Data were analysed by Wilcoxon's signed ranks test, Fisher's exact test or the Chi-square tests by SPSS 11.0 package program. A p-value less than 0.05 was considered significant.

Results

Antibiotic expenditure

The analysis of the DDDs/1000 patients/day and cost of restricted antimicrobials used in both study periods revealed a statistically significant ($p < 0.05$) decrease (Table 1), whereas there was a statistically significant increase ($p < 0.05$) in the amount and cost of unrestricted antibiotics (Table 2). There was no ticarcillin/clavulanate in the hospital in both periods.

The costs of restricted antibacterials before and after budget application instruction were 2,615,555 USD and 2,009,902 USD. The difference was 605.663 USD (−23.2%) ($p < 0.05$). When we analysed the total costs of unrestricted antibacterials the total value was 168,735 in 2002 and 234,085 USD in 2003. Difference between the two periods was significant ($p < 0.05$). The cost of all analysed antibacterials in 2002 and 2003 study period was 2,784,290 USD and 2,243,987 USD, respectively. The difference was 540,303 USD (−19.4%). The value of total drug expenditure was 8,953,605 USD for 2002 and 10,225,304 USD for 2003 period and total cost of all analysed drugs comprised 31.0 and 21.9% of all drug expenditure.

When we compared the antimicrobials that required prior approval from the beginning of the treatment (vancomycin, teicoplanin, meropenem, imipenem, piperacillin/tazobactam, ticarcillin/clavulanate) and after 72 h (ceftriaxone, cefotaxime, ceftizoxime, cefoperazone, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, levofloxacin, netilmicin, amikacin and isepamicin) as separate groups the difference was not statistically significant ($p > 0.05$).

Overall mortality

There was no difference between the mortality rates between two periods (%0.58, 208/35754 in 2002 and %0.62, 233/37055 in 2003 period $p > 0.05$). The number of patient days in 2002 and 2003 study periods was 285.606 and 308.852, respectively.

Resistance patterns

Amoxycilline/clavulanate, ciprofloxacin, cefuroxime, cefotaxime, piperacilline/tazobactam resistance and ESBL rate in *K. pneumoniae* decreased significantly. Amikacin

Table 1 The amount of the restricted antimicrobials used as DDD, and costs in USD in 2002 and 2003 study periods ($p < 0.05$)

Antibiotic	DDDs/1000 patients/day			Cost		
	2002	2003	Diff. (%)	2002	2003	Diff. (%)
Ceftriaxone	0.961	0.846	−12	173,031	162,559	−6
Cefoperazone	0.064	0.039	−39	30,359	19,579	−35
Cefotaxime[a]	0.013	0.030	+230	3803	9094	+239
Ceftizoxime	0.182	0.102	−44	54,732	31,761	−42
Cefoperazon/sulbactam	0.218	0.154	−29	146,702	108,832	−26
Ceftazidime[a]	0.087	0.097	+11	29,948	34,444	+15
Cefepime	0.894	0.288	−78	291,480	97,453	−78
Piperacillin/tazobactam	0.230	0.219	−5	175,487	173,020	−1
Netilmicin	0.133	0.068	−49	21,710	11,709	−46
Isepamicin[b]				22,750	15,445	−32
Amikacin[a]	0.362	0.405	+11	26,311	29,302	+11
Levofloxacin	0.111	0.088	−21	39,523	32,363	−18
Ciprofloxacin	0.388	0.240	−32	282,855	157,615	−44
Imipenem	0.227	0.140	−38	190,399	120,889	−36
Meropenem	0.620	0.584	−6	636,882	622,412	−2
Vancomycin	0.180	0.130	−28	75,960	57,176	−25
Teicoplanin	0.675	0.506	−25	413,623	326,249	−21
Total	5.127	3.782	−26	2,615,555	2,009,902	−23

[a] Antimicrobials, usage of which increased in 2003.
[b] DDD not established, total consumption 657 g in 2002, 463 g in 2003.

Table 2 The amount of unrestricted antimicrobials used as DDD 2002 and 2003 study periods ($p < 0.05$)

Antibiotic (g)	DDDs/1000 patients/day			Cost		
	2002	2003	Diff. %	2002	2003	Diff. %
Ampicillin/sulbactam	0.305	0.482	+58	31,874	52,220	+64
Amoxicillin/clavulanate[a]	0.228	0.389	+70	1206	2330	+93
Cefazolin	1.195	1.542	+29	103,694	138,673	+34
Cefuroxime	0.130	0.164	+26	27,775	35,934	+29
Gentamicin	0.222	0.283	+27	4186	4928	+18
Total	2.08	2.86	+37	168,735	234,085	+39

[a] Amoxicillin/clavulanate was found only for 1 month in both analysed periods.

resistance in. *E. coli and A. baumannii* increased significantly (Table 3).

Nosocomial infections

Surveillance data comprised a total of 13.223 and 20.064 patient days for 2002 and 2003 study periods. Nosocomial infection rates in ICUs decreased significantly ($p < 0.05$) (Table 4).

Discussion

Inappropriate antibiotic usage is a global problem.[1–4] Buke et al.[3] reported the inappropriate antibiotic usage as 48% in internal medicine intensive care unit of our hospital in the period when IDS prior authorization was not required. Etiler et al.[1] found the inappropriate antibiotic usage as 43% and found the direct cost of inappropriate usage as 996 USD/day in Antalya. Tunger et al.[2] reported the inappropriate antibiotic usage as 49% in a university hospital in Manisa. For improving antibiotic usage IDSs developed many strategies[1] such as national guidelines,[15–18] antibiotic control committees, surveillance, feed back of antimicrobial resistance ratios[19] and prior authorization of IDS for selected antimicrobial agents.[20,21] Preventing the antibacterial resistance and reducing the cost are goals for antibiotic policies. The ideal is to have all patients treated with the most effective, least toxic, and least costly antibiotic for the optimal time.[20] IDS consultation service has an important role in the management of community-acquired infections requiring hospitalization and nosocomial infections. IDS consultations may increase the rate of correct diagnosis, appropriate antibiotic usage and antibiotics ordered by IDSs are less likely to be inappropriate.[6,7,22–24] It has been reported that the requirement for approval of an IDS for the use of restricted antibiotics is the most effective method.[23] In 2003 Turkish government which is responsible for payback of over 90% of Turkish population's health expenditures has chosen requirement of prior authorization by IDSs for the use of several antibiotics.

The studies about antibiotic restriction policies are usually about economic issues and the decrease in the antibiotic usage. Comprehensive effects of these changes to the bacterial resistance, mortality and nosocomial infection rates are usually not coanalysed.[25] From this point of view we tried to look from a global perspective to all mentioned variables. We used the daily defined dose/patient for evaluating the antimicrobial usage. DDD is a good marker used for the evaluation of drug consumption and prevents the patient number bias. For antiinfectives (or other drugs normally used in short periods) it is often considered most appropriate to present the antibiotic amounts as numbers of DDDs/patient/year.[11]

Our data show that consumption of restricted antibiotics decreased, whereas consumption of unrestricted antibiotics increased. The total cost of all analysed drugs in 2003 period was 540,303 USD less than 2002 period. Decrease in the totally restricted and partially restricted antibacterials were similar. These findings are in concordance with those described by other researchers.[20,21,23,24,26–30] In GATA (a military medical faculty in Turkey) a more extended restriction policy including the second generation cephalosporins and all beta lactam/beta lactamase combinations has been implemented since 2000 and resulted in a decrement of more than 7,000,000 USD in the antimicrobial expenditures in four years.[26]

The emergence of antimicrobial resistance is the result of a series of complex events. While this is in part, a natural biological response of microorganisms to the selection pressure exerted by the antibacterial use, it creates a significant challenge in insuring an optimal balance between the current and future use and effectiveness of antibacterials.[25] Changes in antimicrobial resistance are a known result of antibiotic restriction policies. As seen in this study, this change may be an increase or decrease.[20,28] Since we did not implement any other intervention, the most probable reason is the shift of antimicrobial usage from broad-spectrum agents to narrow-spectrum agents. Among Gram-negatives amikacin resistance in *A. baumannii* and *E. coli* increased significantly. Amoxycilline/clavulanate, ciprofloxacin, cefuroxime, cefotaxime, piperacilline/tazobactam resistance and ESBL rate in *K. pneumoniae* decreased significantly. There are three antibiotics consumption of which increased after restriction policies: amikacin, ceftazidime and cefotaxime. Although overall ceftazidime usage increased, ESBL rate decreased significantly in *K. pneumoniae*. The decrease in ESBL rate in *K. pneumoniae* may be responsible for the decrease in resistance to other antimicrobials.[14] Ceftazidime usage is a well-known risk factor for ESBL production.[14] In spite of increase in ceftazidime and cefotaxime consumption, ESBL rates decreased significantly in *K. pneumoniae*. This is an interesting finding and may in part be attributed to the nearly stabile i.e. relatively increased usage of piperacillin/tazobactam usage.[14] Our data show that

Table 3 Resistance rates of strains isolated by blood culture

Bacteria/antimicrobial	Resistance rates		*p*-Value
	2002	2003	
Staphylococcus aureus			
Methicillin	68.0% (87/120)	72.6% (85/117)	NS
Gentamicin	60.2% (77/128)	67.5% (79/117)	NS
Ofloxacin	54.0% (67/124)	62.9% (73/117)	NS
Penicillin	93.7% (120128)	96.5% (113/117)	NS
Enterococcus spp.			
Levofloxacin	59.7% (49/82)	71.1% (37/52)	NS
Gentamicin	51.2% (42/82)	57.7% (41/71)	NS
Penicillin	43.9% (36/82)	52.1% (37/71)	NS
Teicoplanin	6.1% (5/82)	9.8% (7/71)	NS
Vancomycin	6.1% (5/82)	9.0% (7/71)	NS
Klebsiella pneumoniae			
ESBL	50.0% (33/66)	25.5% (13/51)	<0.05
Amikacin	28.8% (19/66)	15.7% (8/51)	NS
Amoxycilline/clavulanate	71.2% (47/66)	51.8% (26/51)	<0.05
Cefuroxime	59.1% (39/66)	32.0% (16/50)	<0.05
Ciprofloxacin	33.3% (23/66)	12.0% (6/50)	<0.05
Cefotaxime	50.0% (33/66)	27.5% (14/51)	<0.05
Cefepime	42.4% (28/66)	22.0%(11/50)	NS
Imipenem	0% (0/66)	0% (0/51)	NS
Meropenem	0% (0/66)	0% (0/51)	NS
Piperacilline/tazobactam	68.2% (45/66)	37.3% (19/51)	<0.05
Pseudomonas aeruginosa			
Imipenem	22.0% (11/50)	17.1% (6/35)	NS
Meropenem	16.0% (8/50)	11.4% (4/35)	NS
Amikacin	25.0% (12/48)	31.4%(11/35)	NS
Ceftazidime	32.0% (16/50)	27.8% (10/36)	NS
Ciprofloxacin	15.2% (7/46)	18.9% (7/37)	NS
Cefepime	38.6% (17/44)	29.7% (11/37)	NS
Netilmicin	27.5% (11/40)	23.8% (5/21)	NS
Piperacilline/tazobactam	34.0% (17/50)	32.4% (12/37)	NS
Cefoperazone	28.9% (11/38)	25.0% (2/8)	NS
Acinetobacter spp.			
Amikacin	58.15% (25/43)	33.3% (7/21)	NS
Ceftazidime	83.7% (36/43)	76.2% (16/21)	NS
Ciprofloxacin	74.4% (32/43)	57.1% (12/21)	NS
Cefepime	68.4% (26/38)	61.9% (13/21)	NS
Piperacilline/tazobactam	83.7% (36/43)	76.2% (16/21)	NS
Netilmicin	43.2% (16/37)	20.0% (1/5)	NS
Cefoperazone/sulbactam	12.9% (12/28)	50.0% (2/4)	NS
Imipenem	62.2% (23/37)	57.1% (8/14)	NS
Meropenem	65.1% (28/43)	47.6% (10/21)	NS
Acinetobacter baumannii			
Amikacin	47.2% (34/72)	65.5% (38/58)	<0.05
Ceftazidime	81.9% (59/72)	87.9% (51/58)	NS
Ciprofloxacin	75.0% (54/72)	74.1% (43/58)	NS
Cefepime	73.6% (53/72)	70.7% (41/58)	NS
Piperacilline/tazobactam	86.1% (62/72)	86.4% (51/59)	NS
Netilmicin	57.6% (34/59)	39.4% (13/33)	NS
Cefoperazone/sulbactam	39.0% (16/41)	52.2% (12/23)	NS
Imipenem	60.9% (42/69)	51.2% (22/43)	NS
Meropenem	62.5% (45/72)	49.2% (29/59)	NS

(*continued on next page*)

Table 3 (*continued*)

Bacteria/antimicrobial	Resistance rates		*p*-Value
	2002	2003	
Escherichia coli			
ESBL	16.2% (11/68)	28.3% (26/92)	NS
Ciprofloxacin	35.7% (20/56)	51.2% (44/86)	NS
Amoxycillin/clavulanate	32.8% (22/67)	43.5% (40/92)	NS
Cefuroxime	26.5% (18/68)	30.0% (27/90)	NS
Cefotaxime	19.4% (13/67)	27.5% (25/91)	NS
Amikacin	0% (0/66)	6.5% (6/92)	<0.05
Netilmicin	3.2% (2/62)	6.2% (5/81)	NS
Cefepime	15.9% (10/63)	23.3% (21/90)	NS
Piperacillne/tazobactam	23.1% (15/65)	25.0% (23/92)	NS
Imipenem	0% (0/65)	0% (0/92)	NS
Meropenem	0% (0/65)	0% (0/92)	NS

NS: not significant, $p > 0.05$.

antibiotic restriction policies may result in acute significant changes in the antibacterial resistance rates.

Turkey is a high inflation country[31] in order to exclude the effect of inflation the cost of antimicrobials in 2002 period was calculated by using 2003/box prices.

The finding that nosocomial infection rates decreased significantly is of interest. To our knowledge there is no published data showing such a relationship. In our study the nosocomial infection rate data are limited to ICUs. Although total antibiotic consumption is approximately 10 times greater in ICUs[32] than general hospital wards, this may create a bias regarding the situation of whole parts of the hospital. Point prevalence studies are advised in big hospitals.[33] We conducted two point prevalence studies in June 2002 and January 2004. There were no changes in the overall nosocomial infection rates (49/1063 vs. 59/1185, $p > 0.05$).[34] This may be attributed to the more common antibiotic usage in ICUs. In addition similarity in prevalence is not an obligation for similarity in incidence. There are several interventions associated with decrease in nosocomial infection rates. Infection control committees, antibiotic control committees, surveillance, data collection and analysis, patient isolation, personnel screening, personnel vaccination, educational programs for hand washing, urinary sound or IV catheter usage are several of the methods advised for the prevention of hospital infections.[33,35] Infection control committee was founded in 1995 and antibiotic conrol committee was founded in 1994 in our hospital. Because of the lack of available legal sanctions both committees were not very successful like many others from our country.[35] There were only two remarkable epidemics both due to vancomycin resistant Enterococci (VRE) during the study periods. Universal isolation precautions were implemented for management of these epidemics. Hand washing behaviour[36] and knowledge on the usage of indwelling urinary catheters[37] are poor in our personnel. Several interventional programs are planned for improving the situation. Personnel screening is not implemented routinely except VRE epidemics. Although a self-decrease or a subtle effect of the prevention methods during the VRE epidemics cannot be excluded, according to us the most probable reason is the shift and decrease in the antibacterial usage patterns.

Unfortunately there are several limitations of our study. We chose only microbiologically confirmed nosocomial bacteremia-related strains since nosocomial bacteremia is the most common nosocomial infection in our hospital (Table 4). The long-term influence of requiring prior authorization may not be as strong as the beginning[29] but this study comprises 8 months periods in 2002 and 2003. In addition although four full time consultants and one night shift consultant were in charge during the study periods, we cannot exclude a possible increase in the time for starting an antimicrobial. Absence of infection-related mortality is another restricting variable, but since autopsy rate is very low in Turkey,[38] it would be impossible to give an exact rate of infection-related mortality. Finally we did not analyse the cost of possible additional savings related to

Table 4 Nosocomial infection (NI) rates in the two study periods

	2002	2003	*p*-Value
	Cumulative NI incidence	Cumulative NI incidence	
Overall NI rate	51.3% (330/643)	25.0% (293/1171)	<0.05
Nosocomial bacteremia	23.4% (151/643)	8.5% (100/1171)	<0.05
Nosocomial pneumonia	13.04% (84/643)	5.8% (68/1171)	<0.05
Nosocomial urinary tract infection	7.9% (51/643)	3.1% (37/1171)	<0.05

changes in nosocomial infection and bacterial resistance rates or possible extra savings by decreasing the number of total doses, nursing time, etc.

The costs of prior authorization requirement are not easily defined. The major expense is personnel time and major difference is in IDS and hospital pharmacist time.[19] No additional hospital pharmacist was added to the staff. Since number of consultations increased over seven times between 2002 and 2003 (584 vs. 4204), one additional IDS was added to the infectious diseases staff. The cost of additional staff and additional consultations are approximately 46,000 USD/year.

These findings indicate that requiring prior authorization by IDS for use of selected antimicrobial agents resulted in a shift in antimicrobial usage from expensive, broad-spectrum agents to less expensive, narrow-spectrum agents. This shift created an estimated reduction of 540,303 USD in total pharmacy expenditures for 8 months, did not effect the overall mortality and length of hospital stay and decreased the nosocomial infection incidence in ICUs and decreased antimicrobial resistance in several bacteria. There was an increase in the consumption of unrestricted antibacterial agents. To our knowledge this is the first report about the global effects of antibiotic restriction policies on global nosocomial infection rates. Whether these effects will be stable in long term or will be supported by observations of other institutions is not known. Our experience leads us to recommend antibiotic control as one of the most important and significant ways to save money, to increase the standards of care by decreasing nosocomial infections and prevent antibacterial resistance. A more stringent restriction policy may be advised for a further decrease in the antimicrobial resistance.

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