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Article *in* Indian Journal of Medical Microbiology · April 2011

DOI: 10.4103/0255-0857.81788 · Source: PubMed

ISSN 0255-0857 VOLUME 29 NUMBER 2 APRIL 2011

INDIAN JOURNAL OF MEDICAL MICROBIOLOGY

Publication of Indian Association of Medical Microbiologists
IJMM On-line at www.ijmm.org

Published by Medknow Publications

Indian Journal of Medical Microbiology, (2011) 29(2): 124-9

Original Article

Evaluation of the therapeutic use of antibiotics in Aegean Region hospitals of Turkey: A multicentric study

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Abstract

Purpose: The antibiotic restriction policy has been validated nationwide since February 2003 by the Ministry of Health because the excessive consumption of antimicrobials causes a high cost. The aim of this study was to evaluate the therapeutic use of antibiotics in Aegean Region hospitals and to assess the impact of this nationwide antibiotic restriction policy. This new policy is based on justification that the infectious disease (ID) physicians should be primarily responsible for the prescription of antimicrobials. **Materials and Methods:** Eight university and government hospitals were included in the study. The criteria of the Council for Appropriate and Rational Antibiotic Therapy (CARAT) were considered. Both patient-based and antibiotic-based analyses were performed. For the analysis of inappropriate use, logistic regression was modeled. **Results:** Therapeutic use was determined in 540 patients by a total of 29 ID physicians. In the study, 30.2% of the patients were given antimicrobials and empirically started antibiotics accounted for 79% cases of therapeutic antibiotic use, and 60% of those were inappropriate ($P = 0.001$). The appropriate use of ID level antibiotics ($P = 0.000$) were very compatible with other antimicrobial groups. **Conclusion:** The study shows that the Turkish government's new intervention policy on antimicrobial prescribing has been effective.

Key words: *Antibiotic restriction policy, appropriate antibiotic usage*

Introduction

There is an increasing concern and awareness of antibiotic resistance problems worldwide. The inappropriate use of these antimicrobials in hospitals contributes to the emergence and spread of drug-resistant microorganisms and increased treatment expenditures.[1] Because the excessive consumption of antimicrobials causes a high cost, the antibiotic restriction policy has been validated nationwide since February 2003 by the Ministry of Health. This new policy is based on the justification that the infectious disease specialist (ID) physicians should be primarily responsible for the prescription of antimicrobials.[2]

The aim of this study was to evaluate the therapeutic use of antibiotics in Aegean region hospitals and to assess the impact of this nationwide antibiotic restriction policy, and then, to develop rational antibiotic implementation protocols to prevent resistance as the Antibiotic Resistance Study Group of Turkish Association of Clinical Microbiology and Infectious Diseases.

Materials and Methods

Hospital setting and study population

Eight university and government hospitals were included in the study. Among these two were teaching and research hospitals, and three of them were university hospitals. Two community hospitals were not education and research oriented. All the patients hospitalized 24-h and were over age 15 who received antibiotics were evaluated by a cross-sectional study.

Current antibiotic implementation policy in Turkey

The Turkish government regulation was based on a two-level restriction (strict infectious disease-ID level and A-72 level) of antimicrobial prescriptions at the hospitals. The strict infectious disease (ID) physician level approval includes liposomal amphotericin B, caspofungin,

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Received: 06-12-2011
Accepted: 2-04-2011

Access this article online	
Quick Response Code:	Website: www.ijmm.org
	DOI: 10.4103/0255-0857.81788

voriconazole, piperacillin–tazobactam, cefoperazone–sulbactam, cefepime, meropenem, imipenem–cilastatin, teicoplanin, and vancomycin. The A-72 level antibiotics include piperacillin, cefoperazone, ceftriaxone, cefotaxime, ceftizoxime, ceftazidime, amikacin, netilmicin, tobramycin, and intravenous formulations of quinolones. For the prescription of this second group, specialists other than ID physicians can utilize these antimicrobials, but if prescribed for a period of longer than 72 hours, ID approval is needed.

Study Design and the Evaluation of Antibiotic Appropriateness

Infectious disease specialists visited the departments on January 16, 2007, in all hospitals. Obtained data from patient's physicians and files included demographic data, department, host information (baseline serum creatinine and liver enzymes, etc.), invasive and surgical procedures, diagnosis, underlying diseases, source and site of infection, microbiological results, details of antimicrobial administration, and indications for treatment. The patients who received prophylaxis were excluded. The patients who received antibiotics for therapy were included. They were reevaluated by the same ID physician 4–6 days later.

The appropriateness of the antibiotic usage was primarily based on case evaluation by recording the data on a prereviewed questionnaire sheet. The criteria of the Council for Appropriate and Rational Antibiotic Therapy (CARAT) were considered.[3] With the criteria, the first consideration was if there was an indication for an antimicrobial agent. The signs and symptoms of infection, age of the patient, patient's medical history, and the presence or absence of comorbidities were documented. Evidence-based results, therapeutic benefits, safety, cost-effectiveness, and optimal drug were observed. The duration of therapy could not be judged because the investigation was designed as a cross-sectional one; this was the limitation of the study. Two ID physicians from the hospital where the study was coordinated evaluated all the prescriptions by observing the records of ID physicians in each center. If there was a disagreement, the third ID physician at a senior position resolved the conflict by consensus. The Sanford Guide to Antimicrobial Therapy was used as a reference handbook.[4] The clinicians were also advised to use surveillance data on regional antibiotic resistance patterns in selecting the optimal therapeutic agent and information about previous antibiotic utilization, and this was taken into account, if informed. Also, antibiotic implementation according to culture-proven results was recommended. Unnecessary combinations of antibiotics were considered inappropriate even if each antibiotic used was effective.

Data Analysis

Both, patient-based and antibiotic-based analyses were performed. In the patient-based data sheet, each row was devoted to a patient, and in the antibiotic-based data sheet, each row was devoted to an antibiotic. We preferred to use patient-based data for the analysis of inappropriateness to avoid duplicity of antibiotics in a combined antibiotic use. However, in the evaluation of the antibiotic restriction policy, we preferred antibiotic-based data.

Logistic regression, chi-square test, and Student's *t*-test were performed, and a *P*-value of <0.05 was considered to be significant. For univariate analysis, the chi-square test and Student's *t*-test were used. For the analysis of inappropriate use, logistic regression was modeled. An inappropriate use was defined as the dependent variable, and the independent variables were age, kind of hospital, underlying disease, source and site of infection, etc. The model was made by the backward selection of independent variables. Software package STATA 7.0 (College Station, TX, USA) was used for the analysis.

Results

The hospitals had a 200–1000 bed range. Among 2841 patients hospitalized at the study day, a total of 858 patients (30.2%) were using antimicrobials. Therapeutic use was determined in 540 patients by a total of 29 ID physicians.

Univariate analysis of indicators for the appropriateness of antibiotic therapy was defined as type of hospital, patients' gender, age, immune status, department, and device used. An inappropriate and appropriate antibiotic use was found significantly in the community ($P < 0.008$) and teaching and research hospitals ($P < 0.029$), respectively [Table 1]. The appropriate antibiotic use in the intensive care unit was meaningful ($P < 0.024$). When the univariate analysis was evaluated according to the invasive device used, the patients having urinary catheters ($P = 0.000$) were found to receive antibiotics more properly than the patients with other devices. Although the immuncompromised status was an independent indicator of an appropriate antibiotic use, diabetes mellitus was associated with the appropriate antibiotic use.

Univariate analysis of indicators for the appropriateness of antibiotic therapy was defined according to the source and site of infection and antibiotic utilization. Community-acquired and hospital-acquired infections were 68% and 32%, respectively [Table 2]. It was considered that there was no indication for an antimicrobial agent in 66 patients (12.2%). Among community-acquired infections, the most frequently observed infections were lower respiratory tract (33%), intra-abdominal (16%), and lower urinary tract infections (15%). Hospital-acquired infections were demonstrated as lower respiratory tract (33%), surgical site (21%), and lower urinary tract infections (%9), according to the frequency of appearance. The most common sites of infections among the infection sites were lower respiratory tract (33%), lower urinary tract (13%), and intra-abdominal (12%) regions.

The appropriate antibiotic use was found significant in lower respiratory tract infections which accounted for the highest (33%) number of infections. The lower urinary tract infection was highly associated with inappropriate antibiotic therapy ($P < 0.018$). The inappropriate receiving of empirical therapy ($P < 0.001$) and appropriate use of antibiotics in microbiologically documented infections ($P = 0.000$) were demonstrated as significant. Bacteriological cultures showed either no growth or normal flora in 11.8% of cases. The overall, inappropriate antibiotic utilization was found 68% in the study.

Table 1: Analysis of inappropriate antibiotic therapy according to various parameters

Parameters	Ratio (%)	*P*-value
Hospitals		
Community	93/154 (60)	0.008
Teaching and Research	111/241 (46)	0.029*
University	73/145 (50)	0.789
Patients		
Female	139/245 (57)	0.021
Male	138/295 (47)	
Age > 50 years	175/367 (47)	0.014
Age < 50 years	102/173 (59)	
Underlying diseases		
Immunosuppression	36/71 (50)	0.915
Diabetes mellitus	44/120 (36)	0.000
Departments		
Internal Medicine	150/280 (54)	0.272
Surgery	99/188 (53)	0.643
Intensive Care	28/72(38)	0.024*
Device used		
Mechanical ventilation	16/41 (39)	0.102
Urinary catheter	52/150 (35)	0.000*
Central venous catheter	26/50 (52)	0.917

*Figures show statistically significant appropriate usage.

In logistic regression analysis of inappropriate antibiotic use, community-acquired infection, community hospital, age, immunosuppression, lower urinary tract infection, and empirical antibiotic use were included in the model as independent variables. Bed-size and immuncompromised status were not significant for the inappropriate antibiotic use ($P > 0.05$). Antibiotics given empirically were less likely to be appropriate than those with microbiologically documented [odds ratio (OR) = 6.76, $P = 0.000$, confidence interval (CI) = 3.99–11.41]. Antibiotic utilization in community hospitals was more inappropriate than that in teaching hospitals (OR = 1.93, $P < 0.011$, CI = 1.16–3.21). The inappropriate antibiotic use was significantly higher in patients who had lower urinary tract infections (OR = 2.02, $P < 0.024$, CI = 1.09–3.72).

Among 754 antibiotic prescriptions, 374 were found to be inappropriate (50%). Ceftriaxone, ciprofloxacin, ampicillin–sulbactam, metronidazol, and cefazolin were the most frequently inappropriately used antibiotics [Table 3]. The implementation of appropriate antibiotic usage according to the defined antimicrobial level is shown in Figure 1. The appropriate use of ID level antibiotics was very compatible with other antimicrobial groups ($P = 0.000$). A-72 level antimicrobials, which if prescribed for a period longer than 72 h needed an ID approval, were the least inappropriately used antimicrobials.

Discussion

The selection of appropriate antimicrobial therapy requires the knowledge of infectious diseases, and a thorough understanding of the likely microbial cause of the infection, the properties of the antimicrobials

Table 2: Analysis of inappropriate antibiotic therapy according to the source and site of infection and according to antibiotic utilization

Parameters (%)	Ratio (%)	*P*-value
Source of infection		
Community acquired (68)	152/323 (47)	0.741
Hospital acquired (32)	73/151 (48)	0.794
Site of infection		
Lower respiratory tract infection (33)	70/158 (44)	0.037*
Lower urinary tract infection (13)	40/61 (66)	0.018
Intra-abdominal infection (12)	29/56 (52)	0.938
Surgical site infection (7)	15/34 (44)	0.387
Upper urinary tract infection (7)	14/32 (44)	0.379
Bloodstream infection (3)	10/19 (53)	0.906
Antibiotic utilization		
Empirical (79)	256/425 (60)	0.001
Microbiologically documented (21)	11/115 (10)	0.000*

*Figures show statistically significant appropriate usage.

Table 3: The inappropriate use of antibiotics according to the frequency of consumption

Antimicrobials	Frequency	Percentage	Cumulative
Ceftriaxone	52	13.90	13.90
Ciprofloxacin	51	13.64	27.54
Ampicillin–sulbactam	44	11.76	39.30
Metronidazol	27	7.22	46.52
Cefazolin	26	6.95	53.48
Levofloxacin	23	6.15	59.63
Cefuroxime	21	5.61	65.24
Gentamicin	17	4.55	69.79
Clindamicin	14	3.74	73.53
Cefoperazon–sulbactam	14	3.74	77.27
Imipenem/cilastatin	12	3.21	80.48
Teicoplanin	12	3.21	83.69
Piperacillin/tazobactam	10	2.67	86.36
Ceftazidim	7	1.87	88.24
Amikacin	6	1.60	89.84
Claritromicin	6	1.60	91.44
Cefoperazone	6	1.60	93.05
Amoxicillin/klavulonic acid	5	1.34	94.39
Meropenem	5	1.34	95.72
Moxifloxacin	3	0.80	96.52
Ceftizoxim	3	0.80	97.33
Amoxicillin	1	0.27	97.59
Ampicillin	1	0.27	97.86
Fluconazole	1	0.27	98.13
Lincomicin	1	0.27	98.40
Netilmicin	1	0.27	98.66
Penicillin G	1	0.27	98.93
Cefotaxime	1	0.27	99.20
Cefprozil	1	0.27	99.47
Telitromicin	1	0.27	99.73
Itraconazole	1	0.27	100.00
Total	374	100.00	

available for treating these infections, pharmacokinetic profile, tolerability, and safety.[5,6] In addition, the choice of appropriate antimicrobial therapy is complicated by a number of factors, particularly use of antibiotics prior to hospitalization and pathogen resistance.[6] Once the infecting pathogen has been identified, antimicrobial therapy can be of a more limited spectrum.

Approximately 25–40% of all hospitalized patients receive antibiotics in the United States each year.[5,7] Previous studies evaluating antibiotic use in hospitals have shown that up to 50% of prescriptions can be inappropriate.[1,5,8] Thuong *et al*.[1] in a study with restricted antimicrobials from France, presented that of the 192 prescriptions, 16% received empirical therapy, 49% empirical and secondarily documented, and 35% initially documented therapy. The inadequacy of culture-proven susceptibility results presumes to be the highest effect for inappropriateness of antibiotic usage.

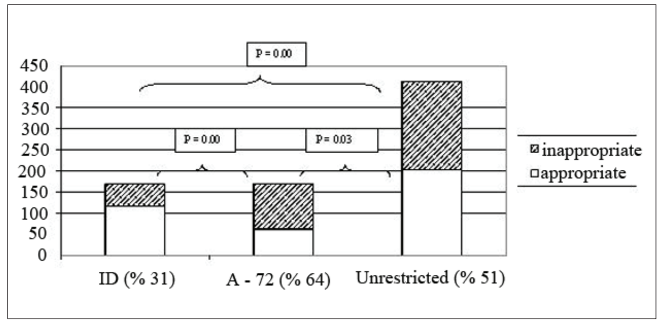

Figure 1: Implementation of appropriate antibiotic usage according to the defined antimicrobial level

In the present study, 30.2% of the patients were given antimicrobials and empirically started antibiotics accounted for 79% cases of therapeutic antibiotic use, and 60% of those were inappropriate ($P = 0.001$). Appropriate antibiotic use was highest when documented microbiologically, and 92% of those prescriptions were appropriate. In a previous study from Turkey with results similar to ours, antibiotic usage was 36.6% and the ratios of appropriateness in culture-based and empirical antibiotic treatments were found to be 93.0% and 33.3% ($P = 0.000$), respectively.[9] Inappropriate use was significantly higher among unrestricted antibiotics than restricted ones in the two previous[9,10] and in the present investigations. Erbay *et al.*[10] demonstrated a better appropriate antibiotic use (64.2%), overall. Tünger *et al*.[11] also found the ratio of rational antibiotic use as 45.7%.

The overall, inappropriate antibiotic utilization was found to be 68% in the present study. Compared with the published data from Turkey, the lower rate of inappropriateness in the present study is partly due to the strict definition of appropriate antibiotic treatment used. In a previous study from Korea, 85.6% of the prescriptions were inappropriate, with 73.7% being inappropriate for therapeutic use and 100% inappropriate for prophylactic use.[12]

The potential for the misuse and abuse of antibiotics was recognized shortly after their introduction into clinical use. The recent introduction of new antibiotics increased the inappropriate use of these agents. Most of the studies reported in the literature use different criteria for the appropriateness of antibiotic usage. This makes it difficult to compare data gathered in different institutions.[7] In our study, one of the factors that led to the inappropriate use of antimicrobial agents was the failure to obtain appropriate cultures. This could explain why the lower urinary tract infections were highly associated with inappropriate antibiotic therapy ($P < 0.018$). Improving the antibiotic use in hospitals is a challenging task for Turkish ID physicians because it is difficult to change the prescribing practices.

There are few publications assessing the effect of guidelines on antibiotic use but the best method to improve antimicrobial use is not known. The importance of a multidisciplinary continuous process and the crucial role of ID physicians are often emphasized.[13,14] As demonstrated by Hoşoğlu *et al.*,[2] Turkish government's new intervention policy on antimicrobial prescribing has resulted in a reduction in antimicrobial use, which is financially effective. In another study from Turkey by Ozkurt *et al.*,[9] it has been shown that 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 ($P < 0.001$) for restricted antibiotics (88.4%) than for unrestricted ones being 58.2%.[9] Culture-based treatment was increased and appropriate use in such cases (93.0%) was higher than empirical (33.3%) treatment.[9] In summary, antibiotics ordered empirically were found to be less appropriate than those ordered with evidence of culture and susceptibility results.

When the source and site of infection were evaluated, Berild *et al.*[13] found that 35% of the treated infections were hospital acquired, and lower respiratory tract and urinary tract infections accounted for more than half of all antibiotic use. Bacteriological samples were obtained in 85% of patients and 55% of the cultures appeared as either no growth or growth of normal flora in that study, whereas a low percent of bacteriological cultures (11.8%) showed either no growth or normal flora in our study. Those findings which were regarding the site of infection of that point-prevalence study were very close to the present study's figures. In addition, in a study from Israel, univariate indicators for the appropriateness of treatment were similar to our results, so that the comparison could be made more effectively.[15] The most common indications for antimicrobial use were respiratory tract infections (27%), urinary tract infections (15%), sepsis (11%), and intra-abdominal (10%) infections,[15] as in today's study. In contrast, in that prospective study, the appropriateness of the use of restricted drugs was lower (70%) than of unrestricted ones (84%) and the overall appropriateness of treatment was 80%.[15]

In one study, patients were seen by ID consultants and were more likely to receive effective and appropriate empirical therapy (66% vs. 55%), to have their antimicrobial therapy narrowed or otherwise adjusted after culture results (58% vs. 33%) became available.[14] This could be taken into consideration, because changing from inappropriate to appropriate treatment once culture results have become available can improve outcomes but not to the same extent as initial appropriate antimicrobial treatment.[16] In Tünger *et al.*'s[11] study, the most commonly used antibiotics were β-lactam–β-lactamase inhibitor combinations (18.4%), quinolone (17.5%), and third-generation cephalosporins (13.7%). In the present study, in the order of the frequency of consumption, ceftriaxone (13.9%), ciprofloxacin (13.6%), and ampicillin–sulbactam (11.7%) accounted for the first-line three antibiotics, which were in the same antimicrobial classes as in the previously mentioned study.

The design and implementation of a successful antimicrobial management program have the potential to decrease costs while improving patient and population health outcomes. However, the rising prevalence of resistance and its clinical and economic impact are increasingly noticed by all clinicians and administrators. Since few new drugs will become available for the multidrug-resistant pathogens, the therapeutic options will become increasingly limited. The focus on antimicrobial management strategies will continue to shift from decreased cost to efforts to limit resistance.[8] Approaches that should be taken into account would include educational programs, development of prescribing guidelines, monitoring of drug resistance patterns, limitations on reports of sensitivity tests, and requirement of expert approval before or after prescribing some drugs.[1,10]

In conclusion, the study shows that Turkish government's new intervention policy on antimicrobial prescribing has been effective. In one study, it is shown that irrational antibiotic use was high for unrestricted antibiotics in intensive care units of a tertiary care hospital in Turkey.[17] In addition, the policy has resulted in a reduction in antimicrobial use.[2] Being very important, the appropriate use of ID level antibiotics ($P = 0.000$) was very compatible with other antimicrobial groups in this study. It has been stated that a collaborative team for improving antimicrobial use in hospitals is very necessary. Key members should include ID specialist physicians, clinical pharmacists, the microbiology laboratory staff, hospital epidemiologists, and infection-control personnel to provide continuing education to hospital employees.[5] In addition, it seems desirable that each hospital conducts surveillance studies on antimicrobial usage, to identify unique indicators of inappropriate drug use which could be employed as educational tools to improve antibiotic use by physicians.[15,16] This approach will provide information on the efficacy of the hospital's infection control program and restricted antibiotic policy.

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Source of Support: Nil, **Conflict of Interest:** None declared.