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The need for an antibiotic stewardship program in a hospital using a computerized pre-authorization system

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ABSTRACT

Objectives: Antimicrobial stewardship programs (ASPs) have an important role in the appropriate utilization of antibiotics. Some of the core strategies recommended for ASPs are pre-authorization and prospective audit and feedback. In Turkey, a unique nationwide antibiotic restriction program (NARP) has been in place since 2003. The aim of this study was to measure the effect of a prospective audit and feedback strategy system along with the NARP.

Methods: A prospective quasi-experimental study was designed and implemented between March and June 2017. A computerized pre-authorization system was used as an ASP strategy to approve the antibiotics. During the baseline period, patients with intravenous (IV) antibiotic use ≥72 h were monitored without intervention. In the second period, feedback and treatment recommendations were given to attending physicians in the case of IV antibiotic use ≥72 h. The modified criteria of Kunin et al. and Gyssens et al. were followed for appropriateness of prescribing. Days of therapy (DOT) and length of stay (LOS) were calculated and compared between the two study periods.

Results: A total of 866 antibiotic episodes among 519 patients were observed. A significant reduction in systemic antibiotic consumption was observed in the intervention period (575 vs. 349 DOT per 1000 patient-days; $p < 0.001$). On multivariate analysis, prospective audit and feedback (odds ratio 1.5, 95% confidence interval 1.09–2.04; $p = 0.011$) and pre-authorization of restricted antibiotics (odds ratio 1.7; 95% confidence interval 1.2–2.31; $p = 0.002$) were the predictors of appropriate antimicrobial use. Mean LOS was decreased by 2.9 days ($p = 0.095$).

Conclusions: This study showed that the antimicrobial restriction program alone was effective, but the system should be supported by a tailored ASP, such as prospective audit and feedback.

Introduction

Antibiotics are one of the most frequently used drugs among hospitalized patients. Excessive and inappropriate use of antibiotics results in the emergence of resistant microorganisms, adverse events, drug interactions, increased length of stay, and increased costs (Fishman, 2006). Antimicrobial resistance is an emerging threat to public health worldwide and limits the choices of treatment; furthermore, it increases the mortality rate because of complications (Barlam et al., 2016). To overcome the unnecessary use of antimicrobials, an antimicrobial stewardship program (ASP) should be implemented. Such programs are coordinated interventions to improve and measure the appropriate use of antimicrobials with an optimal regimen, dose, and duration (IDSA, 2015).

The favorable effects of ASPs on prescribing and microbiological outcomes have been shown repeatedly in the literature (Davey et al., 2013). However the practice in Turkey for combating inappropriate antibiotic use provides a unique experience. In February 2003, the Ministry of Health of Turkey initiated a nationwide antibiotic restriction program (NARP) based on a computerized pre-authorization system. According to this program, parenteral carbapenems, piperacillin–tazobactam, glycopeptides, colistin, and antifungals (except fluconazole) have been

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restricted without prior approval of an infectious disease specialist (IDS). Physicians from all medical specialties can prescribe parenteral third-generation cephalosporins, quinolones, and amikacin antimicrobials for the first 72 h, but further use requires IDS approval. According to recent reports, Turkey has the highest rate of antibiotic consumption among the OECD countries (Organization for Economic Co-operation and Development) (OECD, 2018; Versporten et al., 2014). The aim of this study was to assess the contribution of antimicrobial stewardship interventions in addition to the NARP.

Methods

The study was conducted in a university hospital with 650 beds. A prospective, quasi-experimental study was designed and implemented between March and June 2017. Wards were grouped as medical, surgical, and intensive care units (ICUs). Medical wards included in the study were internal medicine and neurology, while surgical wards were general surgery, urology, gynecology/obstetrics, neurosurgery, and thoracic surgery. Patient characteristics such as age, sex, weight, height, admission and discharge dates, antibiotics prescribed and their dosages, and antibiotic indications were recorded in a standardized form. Indications for antibiotics were: (1) surgical prophylaxis; (2) medical prophylaxis, including prophylaxis of immunosuppressive patients during chemotherapy; (3) empirical treatment, i.e., initial treatment for suspected bacterial infections prior to microbiology results becoming available; (4) preemptive treatment, for patients with radiological or laboratory findings of infection, but no microbiological documentation; (5) microbiologically documented infection. Decisions on the authorization of restricted antimicrobials, including the initiation and discontinuation of antibiotic therapy, were performed by the routine infectious diseases consultants.

Each intravenous (IV) antibiotic use corresponded to a single episode. The assessment of the antibiotic prescriptions was performed by two infectious diseases physicians, one of whom was blind. The assessment was done according to clinical guidelines and the modified criteria of Kunin et al. and Gyssens et al. (Gyssens et al., 1992; Kunin et al., 1973): (1) agree with the choice of antibiotic, but the dosage is inappropriate according to the literature; (2) disagree with the choice of antibiotics because the spectra of the antibiotics overlap; (3) disagree with the choice of antibiotic because the spectrum is not broad enough; (4) disagree with the choice of antibiotic because the spectrum is overly broad; (5) disagree with the need for an antibiotic.

During the baseline period (March to April 2017), the medical records of the study patients who received more than 3 days of IV systemic antimicrobial therapy were observed without intervention. During the intervention period (May to June 2017), the ASP team audited the medical records of study patients. Feedback and treatment recommendations were given to each patient in the wards. These interventions included stopping extended surgical prophylaxis or unnecessary antibiotics, correcting inappropriate antibiotic dosages, and de-escalation/escalation according to the modified Kunin and Gyssens criteria (Gyssens et al., 1992; Kunin et al., 1973).

Antimicrobial use was expressed as the days of therapy (DOT) per 1000 patient-days. The numerator was the antimicrobial days, which was the sum of the days of antibiotic use. The denominator was the patient days (Centers for Disease Control and Prevention, 2017; Centers for Disease Control and Prevention, 2018; Cohen et al., 2008). One DOT represented the administration of a single antimicrobial on a given day regardless of the number of doses. If a single patient received two antibiotics, this was recorded as two DOTs. The data were normalized to 1000 patient-days. Monthly unit DOTs and the length of stay (LOS) of the patients were compared between the two periods. The primary outcome was the effect of prospective audit and feedback on the duration of IV antibiotic usage, and the secondary outcome was LOS. The study protocol was approved by the local ethics committee of Marmara University School of Medicine. A waiver of consent was granted, since all patients were routinely evaluated by the IDS team and the person could be enrolled in the study without any additional risk beyond their standard care.

Statistical analysis

In the univariate analysis, categorical data were tested by Chi-square test and the *t*-test was used for the comparison of the means of two groups. In the multivariate analysis, logistic regression analysis was performed to determine the predictors of appropriate antibiotic use. The independent variables included in the model were the effect of the intervention (post vs. pre intervention), antibiotics restricted by NARP, and medical vs. surgical ward. Stata version 11 was used for the statistical analysis (Stata, version 11, TX, USA). The level of statistical significance was set at <0.05.

Results

A total 519 patients who had been prescribed IV antibiotics for longer than 72 h were enrolled and a total 866 antibiotic episodes were observed (Table 1). Of the 519 patients, 280 were male (54%). The mean age of the patients was 56 years (standard deviation 18 years).

In both periods, 15 different groups of antibiotics were prescribed. The most frequently prescribed antibiotic group was third and fourth-generation cephalosporins (18%), followed by ampicillin–sulbactam (13%), piperacillin–tazobactam (12%), carbapenems (10%), quinolones (8%), first-generation cephalosporins (6%), glycopeptides (5%), aminoglycosides (4%), and colistin (1%).

The indications for antibiotic use were preemptive (42%), documented infection (26%), empirical (17%), surgical prophylaxis (12%), and medical prophylaxis (2%). Further analysis of these indications revealed that 98% of surgical prophylaxis was inappropriate due to an extended antimicrobial duration. Seventy percent of 151 empirical antibiotics were inappropriate, and the most common reason was the absence of a source of infection. In contrast, justifications for medical prophylaxis, preemptive use, and documented infections were mostly appropriate (90%, 91%, and 91%, respectively). Respiratory tract (34%), intra-abdominal (14%), urinary tract (10%), bloodstream (8%), and skin and soft tissue (7%) were the infection sites identified.

Overall, the rate of inappropriate antibiotic use was 30% (261 episodes); the rate was 33% (162 episodes) in the observation period and 27% (99 episodes) in the intervention period ($p = 0.036$). The unnecessary use of antibiotics was 54% in both study periods. The most common reasons for inappropriateness were extended

Table 1
Distribution of patients and antibiotic episodes in the wards.

	Patients $n = 519$ (%)	Antibiotic episodes $n = 866$ (%)
Medical wards	299 (58%)	567 (65%)
Internal medicine	280 (54%)	542 (62%)
Neurology	19 (4%)	25 (3%)
Surgical wards	220 (42%)	299 (35%)
Thoracic surgery	62 (12%)	67 (8%)
General surgery	50 (10%)	73 (9%)
Neurosurgery	40 (8%)	43 (5%)
Gynecology/obstetrics	36 (7%)	71 (8%)
Urology	32 (6%)	45 (5%)

surgical prophylaxis (32%), necessity of de-escalation (10%), necessity of escalation (3%), and inappropriate doses (1%). During the observation period, the inappropriate use of antibiotics was 23% for restricted drugs, while it was 39% for unrestricted antibiotics ($p < 0.001$). In the intervention period, these rates were 19% (restricted drugs) and 31% (unrestricted drugs), respectively ($p = 0.013$).

The most frequent microorganisms were Pseudomonas aeruginosa (20%), Escherichia coli (15%), Enterococcus spp (9%), Klebsiella pneumoniae (8%), Acinetobacter baumannii (5%), and Candida spp (3%).

The mean DOT was 349 days in the intervention period and 576 days in the observation period ($p < 0.001$). The LOS decreased, although this was not statistically significant (17.4 days in the intervention period vs. 20.3 days in the observation period; $p = 0.095$).

During the intervention period, the DOT decreased significantly in all wards, except gynecology/obstetrics and general surgery ($p < 0.001$). Since the antimicrobial modifications were done before 72 h in the ICUs, they were analyzed separately. The DOT also decreased significantly in both the medical ($p = 0.02$) and surgical ($p = 0.001$) ICUs during the intervention period (Table 2).

In the multivariate analysis, the feedback strategy after ≥72 h of IV antibiotic use (odds ratio (OR) 1.5, 95% confidence interval (CI) 1.09–2.04; $p = 0.011$), antibiotics restricted by NARP (OR 1.7, 95% CI 1.2–2.31; $p = 0.002$), and being hospitalized in a medical vs. surgical ward (OR 3, 95% CI 2.2–4.11; $p < 0.001$) were found to be predictors of appropriate antibiotic use (Table 3).

Discussion

This study demonstrated a decrease in inappropriate antibiotic use from 33% during the observation period to 27% during the intervention period ($p = 0.036$). In both periods, restricted antibiotics were used less inappropriately. Thus, the NARP alone had a significant role in decreasing inappropriate antibiotic use in both periods. Similarly, Ozkurt et al. found that inappropriate antibiotic use was higher among unrestricted antibiotics than restricted ones in a previous study performed in Turkey (Ozkurt et al., 2005). Other studies showed that the NARP was effective in lowering costs and preventing antibiotic resistance (Altunsoy et al., 2011; Arda et al., 2007). Previous studies have reported the system of approval by IDS to be the most effective control method for minimizing antimicrobial use (Hirschman et al., 1988; McGowan, 2004).

In the multivariate analysis, performing prospective audit and feedback after 72 h of IV antibiotics as an ASP intervention and antibiotics restricted by NARP were found to be the independent predictors of appropriate antibiotic use. Prospective audit and feedback and restrictive approaches have been found to be the most effective ways to reach the goals of the ASP (Barlam et al., 2016; Davey et al., 2013).

In the present study, the main reason for inappropriateness was unnecessary antibiotic use (54%). Previous studies have demonstrated that the administration of antibiotics to uninfected patients accounts for 32–60% of irrational antibiotic use (Dunagan et al., 1991). Fleming-Dutra et al. reported that nearly half of hospitalized patients receive at least one antimicrobial and up to 30–50% of this antimicrobial use is unnecessary (Fleming-Dutra et al., 2016).

In the present study, the majority of the patients and antibiotic consumption occurred in the internal medicine ward. The most frequently prescribed antibiotic group was third and fourth-generation cephalosporins. Since the parenteral form of ceftriaxone was not restricted for the first 72 h of therapy by the NARP, the consumption of this antibiotic was unsurprisingly high in this study. In a study that included Eastern European countries, Versporten et al. found that the country most commonly prescribing cephalosporins was Turkey (Versporten et al., 2014).

This study demonstrated a total mean decrease in DOT with the intervention, from 575 DOT to 349 DOT ($p < 0.001$), reflecting a decrease in the consumption of parenteral antibiotics. Although other outcomes were not investigated in this study, it is safe to assume that with this intervention, antibiotic-related adverse events, the prevalence of resistant microorganisms, and antibiotic costs would also have decreased. Several studies have demonstrated a decrease in inappropriate antibiotic usage with the implementation of an ASP (Chrysou et al., 2018; Ting et al., 2018). Chrysou et al. found that after implementing an ASP, total antibiotic use decreased by 16.7% owing to a 19.1% reduction in unrestricted antibiotics and 13.8% in restricted antibiotics (Chrysou et al., 2018). In the present study, when each ward was assessed separately, it was found that the DOT was significantly decreased in all wards, except in gynecology/obstetrics and general surgery.

A decrease in LOS from 20.3 to 17.4 was demonstrated with the intervention, but this was not statistically significant ($p = 0.095$), probably due to the sample size. In a meta-analysis, it was shown that interventions reduced LOS by 1.12 days (Davey et al., 2013). In another study, it was demonstrated that a prospective audit and feedback intervention reduced median LOS in patients with community-acquired pneumonia by nearly 0.5 days (DiDiodato and McArthur, 2017). The overall reduction in LOS was 19.4%. The effectiveness and economic impact of ASPs have also been shown in previous studies (Dik et al., 2015; Schuts et al., 2016). In a meta-analysis, it was found that there was a reduction in the duration of antibiotic therapy ranging from 0.6 to 3.3 days and it was not associated with clinical outcomes (Lee et al., 2018).

There are several limitations to this study. First, a time-series analysis was not performed, but logistic regression was performed. There was no seasonal change during the study period, as it was

Table 2
Comparison of DOTs for the effects of the intervention.

	RR	95% CI	*p*-Value
Internal medicine	0.74	0.70–0.77	<0.001
Thoracic surgery	0.74	0.65–0.84	<0.001
Gynecology/obstetrics	0.91	0.81–1.01	0.10
Urology	0.64	0.53–0.76	<0.001
Neurosurgery	0.29	0.24–0.34	<0.001
General surgery	0.93	0.82–1.07	0.36
Neurology	0.43	0.31–0.59	<0.001
Medical ICU	0.89	0.80–0.98	0.02
Surgical ICU	0.85	0.78–0.93	0.001

DOT, days of therapy; RR, risk ratio; CI, confidence interval; ICU, intensive care unit.

Table 3
Univariate and multivariate analyses for the predictors of appropriate antibiotic use.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Prospective audit and feedback	1.4	1.02–1.84	0.036	1.5	1.09–2.04	0.011
Antibiotics restricted by NARP	2	1.51–2.82	<0.001	1.7	1.2–2.31	0.002
Medical vs. surgical wards (excluding ICU)	3.2	2.34–4.28	<0.001	3	2.2–4.11	<0.001

OR, odds ratio; CI, confidence interval; NARP, nationwide antibiotic restriction program; ICU, intensive care unit.

performed during the four spring months. Second, the duration of the study was too short to assess changing antibiotic resistance patterns and *Clostridium difficile* infections. In a systematic review, Kaki et al. found that ASP interventions reduced antimicrobial resistance if they were applied beyond 6 months (Kaki et al., 2011). Finally, observing outcome measures such as mortality and complications such as re-admissions would not be possible in a shorter time. The results of this study emphasize the significance of an ID approval system.

In conclusion, although the NARP alone had a significant role in decreasing inappropriate antimicrobial use, the implementation of prospective audit and feedback as an ASP strategy along with the NARP may further improve appropriate antimicrobial use.

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Ethical approval

The study protocol was approved by the local ethics committee of Marmara University School of Medicine (reference number 09.2017.231).

Conflict of interest

The authors declare that they have no conflicts of interest.

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