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# The effect of a nationwide antibiotic restriction policy on antibiotic usage in a stem cell transplantation unit

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## ABSTRACT

The Turkish Ministry of Health has released a regulation in February 2003 in order to decrease, first the antibiotic expenses and second, inappropriate use of antimicrobial agents. The aim of this study is to assess the impact of this nationwide antibiotic restriction (NAR) in the most active stem cell transplantation unit (SCTU) in Turkey. All patients followed up in SCTU and had received antimicrobial therapy in the period of four months before and after NAR were evaluated retrospectively. The appropriateness of antimicrobial treatments was assessed by two ID specialists and one ID professor. Disagreements between investigators were solved by discussion and review of published guidelines. There were 10 and 25 patients who were on antimicrobial therapy in the 1<sup>st</sup> (before NAR) and 2<sup>nd</sup> (after NAR) group, respectively. Seventeen of the patients had undergone allogeneic stem cell transplantation, while 6 were allogeneic bone marrow recipients and 12 were autologous peripheral stem cell recipients. The antibiotic days per patient was 33.4 and 19.4 in the first and second groups respectively (p=0.036). Although it was not significant, the appropriateness of antibiotic regimens used in the second group was higher than the first group (OR: 5, CI: 0.9-26.4, p= 0.059). The significantly lower antibiotic day per patient in the 2<sup>nd</sup> group may be the result of collaboration between infectious diseases and hematology physicians settled after NAR in our hospital. NAR had reduced the antimicrobial use in our unit mainly by providing collaboration between infectious diseases and hematology departments.

**Key Words:** Restriction policy, Stem cell transplantation, Antibiotic.

## ÖZET

### Ulusal antibiyotik kısıtlama politikalarının bir kök hücre nakli ünitesinde antibiyotik kullanımına etkisi

Türkiye Sağlık Bakanlığı 2003 Şubatında öncelikle antibiyotik masraflarını, ardından uygunsuz antibiyotik kullanımını azaltmak için bir uygulama başlattı. Bu çalışmanın amacı, bu ulusal antibiyotik kısıtlama (UAK) poli-

tikasının Türkiye'deki en aktif kök hücre nakli ünitesindeki etkisini araştırmaktır. Geriye dönük olarak kök hücre nakli ünitesinde takip edilen hastaların bu politikadan dört ay önce ve sonra antibiyotik kullanımları değerlendirildi. Antibiyotik kullanımının uygunluğu iki infeksiyon hastalıkları uzmanı ve bir infeksiyon hastalıkları profesörü tarafından değerlendirildi. İnceleyenler arasındaki uyumsuzluklar tartışma ve yayınlanmış kılavuzlarla çözüldü. UAK öncesi 10, UAK sonrası 25 hasta değerlendirildi. Onyediy olguya allojeneik kök hücre nakli yapılmış iken altı olgu allojeneik nakil bekleyen alıcı ve 12 olgu otolog periferik kök hücre nakli hastası idi. Sırası ile birinci ve ikinci grupta hasta başına antibiyotik kullanım günleri 33.4 ve 19.4 gün idi ( $p= 0.036$ ). Her ne kadar anlamlı değilse de antibiyotik kullanım uygunluğu ikinci grupta biraz daha yüksek idi (OR: 5, CI: 0.9-26.4,  $p= 0.059$ ). İkinci grupta antibiyotik kullanım günü azlığı, infeksiyon hastalığı konsültanı ve hematoloji doktorları ve klinikleri arasındaki yakın ilişkiye bağlı olabilir.

**Anahtar Kelimeler:** Antibiyotik kısıtlaması, Kök hücre nakli.

## INTRODUCTION

There is a growing concern on wisely use of antimicrobial agents. The high cost of the antimicrobial therapy is a threat to viability of health care systems. Inappropriate use of antimicrobial agents results in emergence of resistant pathogens, persistent infections, and adverse events, which all contribute to increased cost. This issue is prominent especially in in-hospital use<sup>[1,2]</sup>. In developed countries some interventions are made to improve use of antimicrobials (e.g. antimicrobial monitoring programs, restriction on some antimicrobials, using empirical therapy guidelines etc.)<sup>[1]</sup>. The Turkish Ministry of Health has released a regulation in February 2003 in order to decrease, first the antibiotic expenses and second, inappropriate use of antimicrobial agents<sup>[3]</sup>. The aim of this study is to assess the impact of this nationwide antibiotic restriction (NAR) in the most active stem cell transplantation unit in Turkey.

## MATERIALS and METHODS

### Antibiotic Policy

In our hospital there was no established restriction policy on antibiotic usage until the release of the NAR by government in February 2003. This regulation categorized the antimicrobial agents into 4 groups (Table 1). The first group contains the antibiotics that can be prescribed by any physician. The second group antibiotics can be prescribed by specialists. The third group antibiotics can

be prescribed by specialists for only three day use and an ID specialist approval is necessary for longer treatments. The last group antibiotics can be prescribed by only ID specialists (Table 1).

### Hospital Setting

The hematopoietic stem cell transplantation unit is located in the Department of Hematology of Ankara University School of Medicine and has 6 beds inside and additional 2 beds outside the unit used for step-down. In the unit approximately 150 transplantation procedures are performed annually.

### Collection of Data

All patients who had received antimicrobial therapy in the period of four months before and after NAR were evaluated retrospectively. The appropriateness of antimicrobial treatments was assessed by two ID specialists and one ID professor. Disagreements between investigators were solved by discussion and review of published guidelines<sup>[4,5]</sup>.

Any antibiotic treatment fulfilling one of the following criteria was judged as inappropriate:

1. No need for an antibiotic (the patient had no evidence of infection or indication for prophylaxis),
2. The spectrum of the antibiotic was overly broad,
3. The spectrum of the antibiotic was not broad enough,

**Table 1. Antimicrobial agents grouped according to NAR**

1 <sup>st</sup> group	2 <sup>nd</sup> group	3 <sup>rd</sup> group	4 <sup>th</sup> group
Amoxicillin	Acyclovir (pe)	Amphotericin B	Ganciclovir
Amoxicillin-clavulanate	Famcyclovir	(non-lipid formulation)	Amphotericin B
Ampicillin	Clarithromycin (pe)	Amikacin	(lipid-formulations)
Ampicillin-sulbactam	Lamivudine	Azlocillin	Vancomycin
Clindamycin	Nafcillin	Aztreonam	Teicoplanin
Chloramphenicol	Ribavirin	Fluconazole (pe)	Imipenem
Metronidazole	Rifabutin	Carbenicillin	Meropenem
Ornidazole	Rifampin (po, pe)	Levofloxacin (pe)	Piperacillin-tazobactam
Penicillin	Cefoxitin	Mezlocillin	Ticarcillin-clavulanate
Cefuroxime	Streptomycin	Moxifloxacin (pe)	Anti HIV drugs
Cefazolin	Valacyclovir	Netilmicin	
Tiamphenicol	Antituberculous drugs	Ofloxacin (pe)	
		Pefloxacin (pe)	
		Piperacillin	
		Cefepime	
		Cefoperazone	
		Cefoperazone-sulbactam	
		Cefotaxime	
		Ceftizoxime	
		Ceftriaxone	
		Ciprofloxacin (pe)	
		Tikarcillin	
		Tobramycin	

pe: Parenteral, po: Per oral

4. The spectrum of antibiotics was overlapped,

5. There was an equally effective drug available at a lower cost,

6. The dosage of the antibiotic was inappropriate,

7. The duration of the therapy was inappropriate.

#### Statistical Analysis

Chi-square test was performed to compare categorical variables and a p value of < 0.05 was accepted as significant. Incidence rate ra-

tio analysis was performed for antibiotic day per patient. Software package STATA 7.0 (College station, TX) was used for analysis.

#### RESULTS

There were 10 and 25 patients who were on antimicrobial therapy in the 1<sup>st</sup> (before NAR) and 2<sup>nd</sup> (after NAR) group, respectively. Median age was 36 years (range: 20-59) in both groups. Seventeen of the patients had undergone allogeneic stem cell transplantation, while 6 were allogeneic bone marrow recipients and 12 were autologous peripheral stem cell recipients. The antibiotic days per

patient was 33.4 and 19.4 in the first and second groups respectively ( $p= 0.036$ ). Although it was not significant, the appropriateness of antibiotic regimens used in the second group was higher than the first group (OR: 5, CI: 0.9-26.4,  $p= 0.059$ ).

## DISCUSSION

Inappropriate use of antimicrobial agents in hospitals makes a big amount in health expenditures. It is reported that 25-33% of the hospitalized patients receive antibiotic therapy and 22-65% of these therapies are inappropriate<sup>[2]</sup>. Due to prolonged neutropenia and immunosuppression, the patients in hematopoietic stem cell transplantation units are at risk for severe infections and receive broad-spectrum antimicrobial agents. As infections in stem cell recipients progress rapidly and usually the etiologic agent can not be isolated, the antimicrobial therapy should be initiated empirically and promptly. Although this practice has reduced the infectious mortality, it might result in overuse of antibiotics and in the emergence of drug resistant microorganisms<sup>[6]</sup>. Both universal and national guidelines are published for the therapeutical approach to patients with febrile neutropenia and are adopted to our hospital<sup>[4,5]</sup>. In our study, empirical therapies were in accordance with the febrile neutropenia guidelines in both groups, however, although not significant statistically, appropriateness was higher in 2<sup>nd</sup> group [7/12 (58%) vs 20/23 (86%),  $p= 0.059$ ]. The most common reason for inappropriateness in both groups was, using antimicrobial agents longer than needed. As a result, the antibiotic day per patient was significantly lower in the 2<sup>nd</sup> group than the 1<sup>st</sup> group (33.4 days in the 1<sup>st</sup>, 19.4 days in the 2<sup>nd</sup> group,  $p= 0.036$ ). This may be due to the collaboration between infectious diseases and hematology physicians settled after NAR in our hospital.

To our knowledge, this is a pioneer preliminary study in Turkey assessing the impact

of NAR in a hematopoietic stem cell transplantation unit. However the study has some limitations. First of all, the study period was not long enough thus number of the patients was low. Secondly, the social security systems in which the patients were included were different from each other, thus the cost of the same antimicrobial agent showed significant difference from patient to patient. This made the antibiotic cost hard to analyze.

## CONCLUSION

NAR had reduced the antimicrobial use in our unit mainly by providing collaboration between infectious diseases and hematology departments.

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