Int J Clin Pharm (2015) 37:452–456
DOI 10.1007/s11096-015-0096-1

SHORT RESEARCH REPORT

Evaluation of restricted antibiotic use in a hospital in Romania

Patricia Tarcea Bizo[1] · **Diana Dumitras**[2] · **Adina Popa**[1]

Received: 14 March 2014 / Accepted: 4 March 2015 / Published online: 2 April 2015

Abstract *Background* Antibiotics are the most frequently used drugs among hospitalised patients. Antimicrobial resistance is a major health issue and therefore antibiotic consumption should be under strict surveillance. *Objective* To evaluate the use of restricted antibiotics in an academic hospital in Romania. *Methods* Retrospective evaluation of the use of 11 restricted antibiotics issued based on the antibiotics formularies for the year 2012. Therapeutic guidelines and the summary of product characteristics were used for the evaluation. The appropriateness antibiotics use was verified, according to three main criteria: appropriate indication (type of treatment, localization and type of infection), dose and duration of treatment. Descriptive statistics and multiple logistic regression analysis were performed. *Results* 664 prescribing formularies were analyzed, of these 319 were from the intensive care unit (48.04 %). The most prescribed antibiotics were vancomycin (171, 25.75 %), imipenem (151, 22.74 %) and meropenem (116, 17.47 %). Overall, 285 prescriptions (42.92 %) were considered inappropriate. Vancomycin, meropenem and imipenem were prescribed inappropriate in 49.71, 46.55 and 44.06 % of such cases. Of the total 285 prescriptions deemed as inappropriate, for 49.82 % the dose was incorrect, 20 % were inadequate in terms of treatment duration and 15.44 % were wrongly indicated. Inappropriate use was significantly higher among empirical prescriptions than the documented ones (69.75 vs. 30.25 %, $p < 0.001$). Multiple stepwise logistic regression identified that the duration of the treatment was significant for inappropriate antibiotic use ($p < 0.05$). The risk of inappropriate use in the case of empirical prescriptions is higher than for documented prescriptions (OR 5.78, $p < 0.001$, CI 3.65–9.15). *Conclusions* the results suggest the need to intensify the control of the use of restricted antibiotics. The implementation of drug formularies in hospitals and the involvement of the clinical pharmacist may ensure rational antibiotic therapy.

Keywords Anti-bacterial agents · Drug therapy · Drug utilisation review · Inappropriate use · Order forms · Restricted antibiotics · Romania

Impact of findings on practice

- In Romania, it is necessary that measures to improve the use of antibiotics are implemented
- To decreases the number of inappropriate prescriptions for antibiotics in Romanian hospitals, routine microbiological susceptibility testing should be implemented as soon as possible

Introduction

Antimicrobial resistance is a major public health problem because antibiotic use has consequences both for the patient and for the community as a whole [1, 2]. Antibiotics are the most frequently prescribed drugs to hospitalized patients [3].

The inappropriate use of antibiotics increases the number of infections caused by multidrug-resistant organisms

✉ Patricia Tarcea Bizo
tarceapatricia@gmail.com

[1] Universitatea de Medicina si Farmacie Iuliu Hatieganu, Cluj-Napoca, Romania

[2] University of Agricultural Science and Veterinary Medicine, Cluj-Napoca, Romania

which are associated with worse therapy outcomes, longer hospital stay and higher treatment costs [4].

Therefore, antibiotic use and antibiotic resistance surveillance systems are essential prerequisites for targeted interventions to cope with the problem of antibiotic resistance [2]. In Romania, few hospitals have local antimicrobial guidelines or a restriction policy for antibiotics.

A recent study conducted by the European Centre for Disease Prevention and Control (ECDC) shows that the antimicrobial resistance rate increased in Europe between 2009 and 2012, Romania being one of the countries reporting the highest resistance rates for second-line (restricted) antibiotics such as carbapenems [5]. Although some countries took aggressive measures to contain the spread of antimicrobial resistance, extensively-resistant organisms continue their rapid proliferation. Antimicrobial stewardship programs have seen some measures of success but are limited to acute-care settings in high-income countries. In addition while the high resistance rate of organisms to restricted antibiotics is increasing, no new antimicrobial drugs are being developed [6].

In an attempt to control the usage of restricted antibiotics, the hospital where we conducted our research implemented an order form for these drugs.

Aim of the study

The aim of this study was to assess the appropriateness of the restricted antibiotic use associated with diagnosis and bacteriological findings.

Ethical approval

Ethical approval was granted by the ethics committee of the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca.

Method

Design

We conducted a retrospective study evaluating the pattern of restricted antibiotics prescription in a hospital.

Hospital-setting

The study was conducted in a universitary tertiary hospital with in Cluj-Napoca, Romania. The 1777 beds hospital includes ICU, Surgery, Neurosurgery, Dermatology, Orthopedics, Nephrology, Cardiology and Internal Medicine departments.

Antibiotic policy

An order form for antibiotics was designed by the hospital pharmacy and implemented by the hospital in 2007 with the aim to restrict prescription of certain antibiotics: vancomycin, meropenem, imipenem, ertapenem, levofloxacine, moxifloxacine, linezolid, piperacylin—tazobactam, teicoplanin and tigecyline. This form must be completed by the physician with information about the patient and the disease and then submitted to the hospital pharmacy. The hospital has no other local antimicrobial guidelines or antimicrobial stewardships programs.

Data collection and evaluation

The antibiotic order forms received by the hospital pharmacy between January and December 2012 were evaluated. Data collected from the order forms included: patient demographics, patient serum creatinine, microbiological and clinical information (etiology, localization of infection), prescribed antibiotic dosing regimen, the intended use of the antibiotic (surgical prophylaxis, empiric treatment, treatment with susceptibility testing). This information was analyzed for each patient in order to evaluate the appropriateness of the antibiotic treatment. Because no local antibiotic formulary is available, national and international guidelines for antibiotic therapy were used for the evaluation, namely and the Sanford guide [7] and the Summary of Product Characteristics [8]. Inappropriate antibiotic use was described in the following cases:

- Wrong dosage: when the dose was inappropriate according to data found in literature and patient particularities
- Wrong duration: when the duration of treatment was inappropriate
- Wrong indication: when there was no need of a prophylactic or therapeutic antibiotic; when the choice of antibiotic was inappropriate, because the spectrum was not appropriate according to the identified or suspected pathogen; when another non-restricted antibiotic could have been used instead of the chosen antibiotic

Statistical analysis

Descriptive statistics, multiple stepwise logistic regression, and χ^2-test were performed. The multiple stepwise logistic regression test was conducted with inappropriate use as an outcome variable and gender, age, weight, route of administration, duration of treatment and empirical use as explanatory variables and a p value of <0.05 was considered to be significant. The difference of inappropriate use

between empiric and documented treatments were examined using the χ^2 test. STATA 10.0 software package (College Station, Texas, USA) was used for the analysis.

Results

A total of 664 antibiotic formularies were analyzed. Most prescriptions 319/664 were issued by the intensive care unit, representing 48 % of all formularies, 97/664 (14.6 %) prescriptions from the surgical ward and 108/664 (16.2 %) from neurosurgery.

Of the patients who received antibiotics, 275/657 (41.8 %) were females and 382/657 (58.1 %) males. The mean age of the patients was 55.7 years, and the mean weight of the patients was 77.8 kg (Table 1).

Bacterial data are available for 272/664 (41.2 %) prescriptions. The most common bacteria responsible for infections was *Staphylococcus aureus*, identified in 72/272 (26.4 %) cases. Other frequently identified bacteria were: *Pseudomonas aeruginosa* in 18/272 (6.6 %) cases, *Klebsiella pneumoniae* in 25/272 (9.2 %) cases, *Acinetobacter* spp. in 18/272 (6.6 %) cases and *E. Coli* in 15/272 (5.5 %) cases.

The type of the infection was described in 468 cases. Most of the antibiotics were prescribed for abdominal infections 89/468 (19 %), skin and soft tissue infections (95/468, (20.3 %) cases, pulmonary infections 76/468 (20.3 %) cases and urinary tract infections 31/468 (6.6 %) cases.

Of the 11 restricted antibiotics, the most frequently prescribed were vancomycin with 171/664 (25.7 %) prescriptions, followed by imipenem with 143/664 (21.5 %) prescriptions and meropenem with 116/664 (17.4 %) prescriptions (Fig. 1). 646/664 (97.2 %) of all antibiotics were prescribed parenterally.

Table 1 Main patient characteristics

Gender	
Male	382 (58.1 %)
Female	275 (41.8 %)
Age (years)	
Mean	55.7
Minimum	16
Maximum	91
Weight (kg)	
Mean	77.8
Minimum	35
Maximum	170
Creatinine clearance (ml/min)[a]	
>60 ml/min	235 patients, 63.5 %
30–60 ml/min	69 patients, 18.6 %
10–30 ml/min	56 patients, 15.1 %
<10 ml/min	10 patients, 2.7 %

[a] Creatinine values were not registered in the order forms for all patients

The mean duration of the antibiotic treatment is 6.6 days. Most frequently, in 28.2 % (187/664) cases, the antibiotic was given for 4 days.

Of the total number of forms, 285/664 (42.9 %) contained inappropriate prescriptions and 379/664 (57 %) were considered to be appropriate. By analyzing the most prescribed antibiotics separately, we noticed that in the case of vancomycin 85/171 (49.7 %) of the prescriptions were considered inappropriate. Imipenem was used inappropriately in 63/143 (44 %) cases and the use of meropenem was considered inappropriate in 54/116 (46.5 %) cases. 330/664 (50.6 %) of all prescriptions were empirical and only 321/664 (49.3 %) were prescribed based on antimicrobial resistance testing. In the case of empirical use of restricted antibiotics, 236/330 prescriptions (68.4 %) were considered inappropriate, but only 134/321 (41.7 %) of the prescriptions based on susceptibility tests were considered inappropriate. The main characteristics of inappropriate prescribing were: wrong dosage 142/285 (49.8 %) prescriptions, wrong duration of treatment 57/285 (20 %) prescriptions and wrong indication 44/285 prescriptions (15.4 %) in cases where non-restricted antibiotics could have been used instead. Most prescriptions are inappropriate because their dosage regimen and carbapenems were the most frequently prescribed in inappropriate doses (21/142 prescriptions, 14.7 %). In 12 out of the 21 cases the dosage was not adapted to the patient's renal function.

The χ^2-test showed that there is a statistically significant difference between the empirical and the documented treatments ($p < 0.001$). Multiple stepwise logistic regression identified that gender, age and weight of patients and the administration route were not significant for inappropriate use ($p > 0.05$). The duration of treatment was significant for inappropriate antibiotic use (OR 1.11, $p < 0.05$, CI 1.02–1.20). The risk of inappropriate use in case of

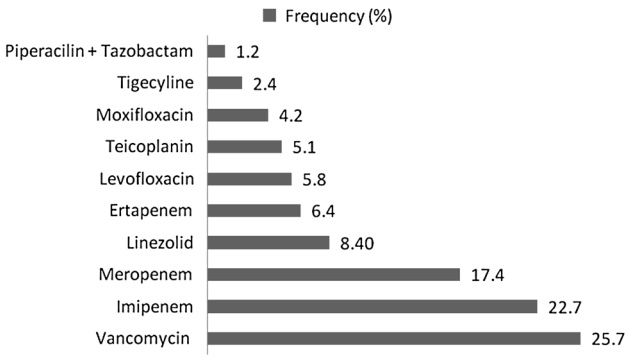

Fig. 1 Frequency of restricted antibiotics prescriptions

empirical prescriptions was higher than for documented ones (OR 5.78, $p < 0.001$, CI 3.65–9.15).

Discussion

Our study shows that 285 (42.9 %) of the issued prescriptions were inappropriate, which is consistent with previous studies evaluating antibiotic use in hospitals that have shown that up to 50 % of the prescriptions can be inappropriate. In order to optimize antibiotic use, a number of measures can be taken, including implementing order forms for restricted antibiotics, as was the case in the hospital in which we conducted our research [9, 10].

Most of the prescriptions analyzed in this study came from the intensive care unit and from the surgical wards, which proves that these units are the greatest antibiotic consumers and that in many cases antibiotics are excessively used [11]. The most common pathogen found responsible for the infections in our study was *Staphylococcus aureus* (72 cases, 32.43 %). This correlates with the fact that the most prescribed antibiotic is vancomycin, which is an antibiotic used mostly to treat infections caused by multi-resistant *Staphylococcus aureus* strains [7, 11]. Unfortunately the published data shows that the resistance rate to vancomycin is higher in Romania than the European mean [5]. *Pseudomonas aeruginosa*, *E. Coli*, *Acinetobacter* and *Klebsiella pneumoniae* are also among the bacteria found responsible for most of the infections. Carbapenems are broad-spectrum antibiotics used as first-choice drugs empirically when a gram-negative infection is suspected [12].

Despite the introduction of the restrictive order form in the hospital, in our retrospective analysis 326 (49.2 %) of the prescriptions were still inappropriate. The most important problem is associated with the empirical prescriptions, where the percentage of inappropriateness is much higher than for the prescriptions based on susceptibility testing 236 (63.7 %) to 134 (36.2 %). This suggests that susceptibility testing, when possible, decreases the risk of inappropriate use [4].

The duration of the treatment was significant for inappropriate use, especially in the case of empirical prescriptions where the treatment is not recommended to exceed 3 days (based on the antibiotic formulary issued by the hospital). Once the pathogen(s) were identified and their susceptibilities have been determined, the empiric antibiotic(s) that were started should be stopped or reduced in number and/or narrowed in spectrum. This strategy, termed "de-escalation therapy", appears theoretically correct, capable of promoting therapeutic appropriateness and reducing costs [13].

In our study the dosage regimens were inappropriate in 142 (49.8 %) cases, especially for carbapenems. In 12/21 cases of inappropriate prescribing the doses of carbapenems were not adapted to the patient's renal clearance. In the case of carbapenems, the adaptation of dosage regimens to the creatinine clearance is very important, because their elimination is mainly renal and can be severely affected by a decreased renal function [12].

Although the formularies for restricted antibiotics were designed and introduced in order to control and optimize their use, the lack of infectious diseases specialists and local antimicrobial guidelines maintained the number of inappropriate prescriptions at a high level. Studies showed that the interventions of infectious diseases specialists and of the clinical pharmacist lead to the improvement of antibiotic prescribing to hospitalized patients, generating better outcomes and reducing antimicrobial resistance and hospital-acquired infections. The most common interventions were: implementation of compulsory order forms, expert approval (clinical pharmacist and infectious disease specialist), guidelines implementation, rapid laboratory testing, removal or restriction of drugs, reviewing and prescription changing by the clinical pharmacist, as well as therapeutic drug monitoring [13, 14]. Another measure that may be taken into consideration to improve the prescribing of antibiotics is computerized physician order entry (CPOE) which allows the detection of mistakes in prescribing in real time [15]. In Romania, hospitals have a program which allows online prescribing, but the existing information is insufficient for the pharmacist to evaluate the treatment. A combination of both restrictive and educational measures appears to be necessary to improve overall antibiotic usage in hospitals [14].

Although our study has provided information about the antibiotic prescribing practices in hospital and the results could contribute to the awareness of these practices and also to the reduction of inappropriate prescribing, we admit several limitations. First, the lack of evaluation of the factors that influenced physician adherence to the guidelines. Second, because some of the prescription formularies were incomplete there was no possibility of gathering complete information in the retrospective study. Third, this is a single-center study carried out in a large university hospital and our results might not be generalized to centers that do not share similar characteristics.

Conclusion

Despite the introduction of the restrictive order form in the hospital, our retrospective analysis showed that 49.2 % of the prescriptions were still inappropriate, especially in the case of the prescriptions issued without susceptibility testing. The large number of inappropriate prescriptions show the need to intensify the control of restricted

antibiotics use. Other favorable factors such as the implementation of drug formularies in hospitals and the involvement of the clinical pharmacist in order to ensure rational antibiotic therapy may improve the quality of patient care and radically reduce the cost of therapy. All these measures are especially important in our country because of the high antibiotic resistance rates, which are above European average.

Acknowledgments The authors would like to thank the head of the hospital pharmacy, Ms. Carmen Span for granting us access to the prescription formularies.

Funding None.

Conflicts of interest None declared.

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