SIGNIFICANT DECREASING OF THE SYSTEMIC ANTIBIOTICS' CONSUMPTION ASSOCIATED WITH ANTIMICROBIAL STEWARDSHIP INTERVENTION CONDUCTED IN INFECTIOUS DISEASES UNIVERSITY HOSPITAL FROM EASTEARN EUROPE

SIMIN-AYSEL FLORESCU[1], NICULAE ION NEDELCU[2]*, PETRE IACOB CALISTRU[1], FELICIA PETRUC[2], EMANOIL CEAUŞU[1,2]

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] "Dr. Victor Babeş" Infectious and Tropical Diseases Hospital, Bucharest, Romania

*corresponding author: spcin.babes@gmail.com

Abstract

A growing body of evidences is showing that antibiotic stewardship programs are clearly followed by both optimizing of and also decreasing the adverse events associated to antimicrobials use. The paper reports the effect on systemic antibiotics (AB J01) consumption of an antimicrobial stewardship intervention consisting in a prospective audit and feedback upon the antibiotics prescribed in a 500 beds university hospital. Consumption was expressed as frequency of DDD (daily defined doses) per 1000 patients per day (DDD/1000PD); the needed data were captured from the hospital pharmacy and statistic department. The antibiotics consumption was compared between the reference year (2015) and intervention year (2016). Total consumption of AB J01 decreased from 1236 DDD/1000PD in 2015 to 1193 DDD/1000PD, in other words with 43 DDD/1000PD in absolute numbers or with 3.47% in relative ones. By ATC subgroups the top ranked decline were at: (a) quinolones (J01M) (-25.7%) and (b) aminoglycoside (J01G) (-24.3%), respectively. It was demonstrated that the intervention was associated with a decrease in the general antimicrobial consumption. Presumably more consistent effect on consumption decrease of antibiotics with broad spectrum as carbapenems and/or cephalosporins might require adding of other interventions as "time out", for instance.

Rezumat

Tot mai multe studii arată că programele de tip *antibiotic stewardship* sunt în mod clar urmate atât de optimizarea, cât şi de scăderea reacţiilor adverse asociate cu utilizarea medicamentelor antimicrobiene. Acest studiu raportează efectul asupra consumului de antibiotice sistemice (J01) al unei astfel de intervenţii, constând în audit şi retroinformare privind antibioticele prescrise într-un spital universitar cu 500 de paturi. Consumul a fost exprimat ca fiind frecvenţa DDD (*daily defined doses*) *per* 1000 pacienţi pe zi (DDD/1000PZ); datele necesare le-am preluat de la farmacia spitalului şi serviciul de statistică. Consumul de antibiotice a fost comparat între anul de referinţă (2015) şi respectiv anul intervenţiei (2016). Consumul total de antibiotice (AB) J01 a scăzut de la 1236 DDD/1000PZ în 2015 la 1193 DDD/1000PZ, adică cu 43 DDD/1000PZ în valori absolute sau cu 3,47% în valori relative. Pe subgrupe ATC cele mai mari scăderi au fost la: (a) chinolone (J01M) (-25%) şi respectiv (b) aminoglicozide (J01G) (-24,3%). Studiul demonstrează că intervenţia a fost asociată cu scăderea în consumul general de antibiotice. Prezumtiv, un efect mai consistent asupra scăderii consumului de antibiotice cu spectru larg, precum carbapeneme sau/şi cefalosporine, ar putea necesita adiţionarea altor intervenţii precum cele de tip „*time out*".

Keywords: consumption systemic antimicrobials; antibiotic stewardship

Introduction

There are increasing evidences which demonstrate that hospital based programs dedicated to improving antibiotic use, commonly referred to as "Antibiotic Stewardship Programs (ASPs)", can both optimize the treatment of infections and reduce adverse events associated with antibiotic use [4, 13]. These programs help clinicians improve the quality of patient care [17] and improve patient safety through increased infection cure rates, reduced treatment failures, and increased frequency of correct prescribing for therapy and prophylaxis [11, 15]. They also significantly reduce hospital rates of *Clostridium difficile* infection [1, 12, 21] and antibiotic resistance [5, 7, 10]. Moreover these programs often achieve these benefits while saving hospitals money [4, 16, 18, 19]. In recognition of the urgent need to improve antibiotic use in hospitals and the benefits of antibiotic stewardship programs, in 2014 the Centres for Diseases Control and Preventions (CDC) recommended that all acute care hospitals should implement the Antibiotic Stewardship Programs [9].

The aim of our study was the assessment of the results of an audit and feedback antimicrobial

stewardship intervention conducted in a 500 beds infectious diseases teaching clinic, 2M classified.

Materials and Methods

The annual consumption of systemic antimicrobials ATC J01 (J01 Anatomical Therapeutic Chemical Classification) [22] was used as the meter of the effect of an audit (external assessment) of the currently prescribed antibiotics. Practically each hospital department (paediatrics, adults, HIV/AIDS, pneumology) was visited weekly by a multi-specialties team (infectious diseases clinicians, pharmacist, clinical pharmacology specialist, micro-biologist and epidemiologist) and leaded by the university personnel with broad expertise in the antibiotic use. The team's work was to debate with the clinicians the appropriateness of the antibiotic treatment prescribed to their patients at the date/ moment of the visit and to recommend antibiotic stewardship amendments [2] as needed. The use of current antibiotic treatment protocols for major syndromes was reinforced.

In order to analyse the intervention's effect, the year 2015 was designated as reference period and the year 2016 as the effect period; the amounts of systemic antibiotics dispensed by the hospital pharmacy in the two years were transformed in daily defined doses (DDD) [22] and aggregated later into ATC subgroups as provided in ECDC published reports [8] (ECDC 2004). The consumption of antimicrobials was expressed as the number of DDD per 1000 patient days (DDD/1000PD).

Statistical comparisons of percent was performed with chi-square test provided by US Center for Diseases Control' Epi Info 7 soft (wwwn.cdc.gov/ epiinfo/user-guide/StatCalc/introduction.html), a p value of less than 0.05 being considered as a prove of significance.

Results and Discussion

The consumption of all AB J01 decreased from 1236 DDD/1000PD in the year 2015 up to 1193 DDD/1000PD in 2016, namely with 43 DDD/1000PD in absolute values or with 3.47% in relative one (χ^2: 5.31; p: 0,01).

By ATC subgroups the higher decreasing of the AB J01 consumptions was: (a) in quinolones (-25.7%) and (b) in aminoglycosides (-24.3%), respectively.

Table I

The consumption of systemic antimicrobials per ATC subgroups in infectious diseases hospital, 2016 *vs.* 2015

ATC Subgroups		Calendar year		Abatements	
		2015	*2016*	Absolute	Relative
Code	Name	x	y	y - x	(x - y) * 100
J01A	tetracyclines	24	40	16	71.1
J01C	β-lactam penicillins	204	208	4	1.9
J01D	other β-lactam antibiotics	449	441	-8	-1.7
J01E	sulfonamides and trimethoprim	43	44	1	1.1
J01F	macrolides, lincosamides etc.	94	102	8	8.4
J01G	aminoglycosides	60	45	-15	-24.3
J01M	quinolones	251	187	-65	-25.7
J01X	other antibacterials*	111	126	15	13.4
J01	Total AB	1236	1193	-43	-3.5

* glicopeptide, metronidazole, colistin, linezolid

Currently, the published strategy for antibiotic stewardship includes a complex of interventions [2] summarized below: dedicating necessary human, financial and information technology resources; appointing a single leader responsible for program outcomes; experience with successful programs show that a physician leader is effective; appointing a single pharmacist leader responsible for working to improve antibiotic use; implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. "antibiotic time out" after 48 hours); monitoring antibiotic prescribing and resistance patterns; regular reporting information on antibiotic use and resistance to doctors, nurses and relevant personnel; educating clinicians about resistance and optimal prescribing.

Our clinic had already adopted some of the interventions listed above as for instance written protocols for antibiotic treatment of community acquired infections and preauthorization for some antibiotics. As an improvement of our program for antibiotic stewardship we selected to conduct this prospective audit of the antibiotic prescription because "conducted by persons with expertise in appropriate use of antimicrobials was demonstrated to be highly effective in optimization of the anti-biotic therapy in critical patients and also in the cases in which multiple or with broad spectrum antibiotics were used" [5, 6, 20]; and with no doubt in our clinic we have the needed expertise to develop this type of intervention. Supplementary we like to underscore that this method is different from an antibiotic "time out" because the audits are conducted by other persons than the treating team. An antibiotic

"time out" prompts a reassessment of the continuing need and choice of antibiotics when the clinical picture is clearer and more diagnostic information is available. All clinicians should perform a review of antibiotics 48 hours after antibiotics are initiated to answer these key questions: "Does this patient have an infection that will respond to antibiotics?" If so, "Is the patient on the right antibiotic(s), dose, and route of administration? Can a more targeted antibiotic be used to treat the infection (de-escalate)? How long should the patient receive the antibiotic(s)?".
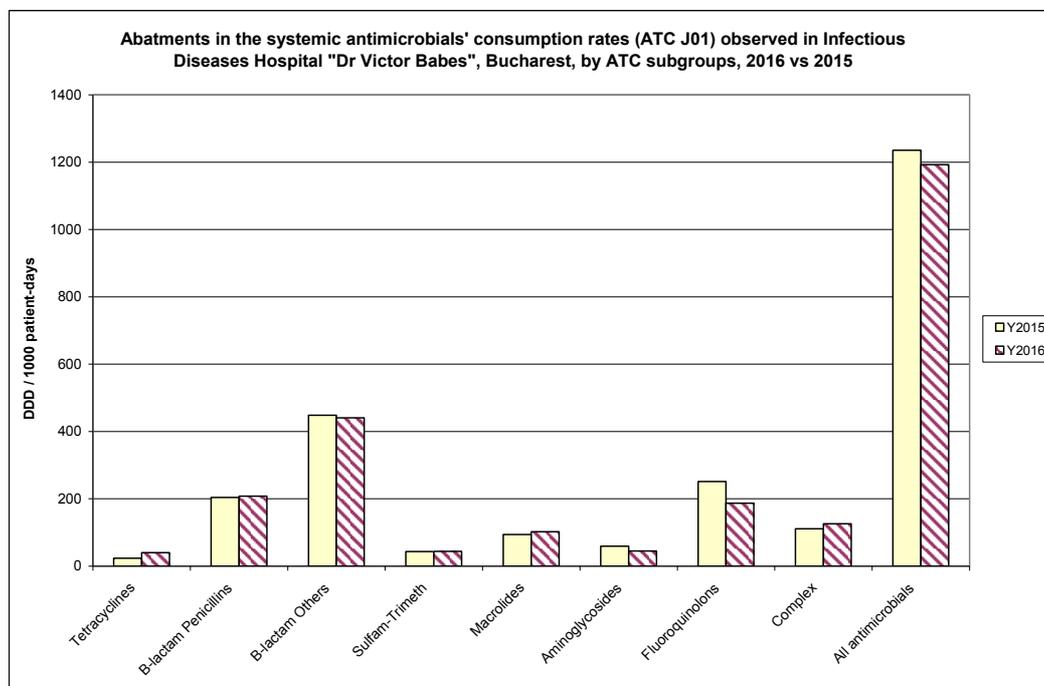

Figure 1.
Deviations in the consumption rates of systemic antimicrobial by ATC subclasses, 2016 *versus* 2015

Total antimicrobials consumption decreased, achieving the main strategic objective of the antimicrobial stewardship team. Decrease was done mainly by consistent underutilization of fluoroquinolones and aminoglycozides and to a lesser extended of the other subgroups of antimicrobials. Reducing the consumption of fluoroquinolones, with consequent drop of selection pressure of resistant microbial strains and also decreasing the risk of inducing *Clostridium difficile* colitis represented the second aim of the antimicrobial stewardship work. Furthermore the targeted antimicrobial therapy, based on both optimal and also in line with local, national and European guidelines of first intention therapy and stimulating the de-escalation of the antimicrobial therapy, based on the susceptibility of microorganisms isolated, have determined variations in the use of other subgroups of antibiotics. Thus appeared the tendency of augmenting the use of betalactam antibiotics, tetracycline and macrolides, which were involved more frequently and more reasonable in the treatment of upper respiratory tract infections, community pneumonia and endocarditis with negative blood culture. The clinically and epidemiologically orientated treatment of bone joints system cases was followed by an increase of glyco-peptides and lincosamides consumption.

From a strategic point of view, the fact that in spite of the significant decrease of the global quantity of antibiotics in the post-intervention period, we registered an increased consumption in some individual anti-biotic classes, it must be mentioned that, as it was reported by other authors [3, 14], this phenomenon is an expected outcome when in ASP strategy the "audit and feedback" intervention follows the "preauthorization" one, namely our case.

Conclusions

The intervention conducted in this study was temporally associated with a significant decrease of the consumption of all systemic antibiotics. However, the decrease in consumption of broad spectrum antibiotics like cephalosporin and carbapenems was modest (-1.7%); a more consisted impact upon administration of these therapeutically important antibiotics needs probably an extension of the antibiotic stewardship with other interventions like "time out" or/and documentation of the nature, dose and duration of the antibiotic prescribed [2].

Finally, we consider that this global decrease of the antimicrobial consumption at the clinic's level and changes into different types of antibiotics used is a fairly good start of antimicrobial stewardship activity, which however, had to continue targeting a more efficient antibiotic therapy for lowering the unpleasant consequences, as antibiotics resistance and important adverse events.

References

1. Bishop J., Parry M.F., Hall T., Decreasing *Clostridium difficile* infections in surgery: impact of a practice bundle incorporating a resident rounding protocol. *Conn Med.*, 2013; 77(2): 69-75.
2. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014. www.cdc.gov.
3. Cosgrove S.E., Seo S.K., Bolon M.K., Sepkowitz K.A., Climo M.W., Diekema D.J., Speck K., Gunaseelan V., Noskin G.A., Herwaldt L.A., Wong E., Perl T.M., CDC Prevention Epicenter Program, Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multi-center intervention. *Infect. Control Hosp. Epidemiol.*, 2012; 33(4): 374-380.
4. Davey P., Brown E., Charani E., Fenelon L., Gould I.M., Holmes A., Ramsay C.R., Wiffen P.J., Wilcox M., Interventions to improve antibiotic prescribing practices for hospital inpatients. *The Cochrane database of syst. rev.*, 2013; 4: CD003543.
5. Diaconu C., Bălăceanu A., Moroşan E., Sepsis biomarkers: past, present and future. *Farmacia*, 2015; 63(6): 811-815.
6. Diaz Granados C.A., Prospective audit for antimicrobial stewardship in intensive care: impact on resistance and clinical outcomes. *Am. J. Infect. Control*, 2012; 40(6): 526-529.
7. Elligsen M., Walker S.A., Pinto R., Simor A., Mubareka S., Rachlis A., Allen V., Daneman N., Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. Infect Control Hosp Epidemiol., 2012; 33(4): 354-361.
8. European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014. www.ecdc.europa.eu.
9. Fridkin S., Baggs J., Fagan R., Magill S., Pollack L.A., Malpiedi P., Slayton R., Khader K., Rubin M.A., Jones M., Samore M.H., Dumyati G., Dodds-Ashley E., Meek J., Yousey-Hindes K., Jernigan J., Shehab N., Herrera R., McDonald C.L., Schneider A., Srinivasan A., Centers for Disease Control and Prevention (CDC), Vital Signs: Improving Antibiotic Use Among Hospitalized Patients. MMWR. Morbidity and mortality weekly report, 2014; 63(9): 194-200.
10. Griffith M., Postelnick M., Scheetz M., Antimicrobial stewardship programs: methods of operation and suggested outcomes. *Expert review of anti-infective therapy*, 2012; 10(1): 63-73.
11. Kaki R., Elligsen M., Walker S., Simor A., Palmay L., Daneman N., Impact of antimicrobial stewardship in critical care: a systematic review. *J. Antimicrob. Chemother.*, 2011; 66(6): 1223-1230.
12. Luca M.C., Roşu F., Hurmuzache M., Luca A.Ş., Leca D., Iancu L.S., Ochiuz L., Updates in the assesment of risk factors in *Clostridium difficile* infection in patients with infectious diseases. *Farmacia*, 2016; 64(1): 112-115.
13. Malani A.N., Richards P.G., Kapila S., Otto M.H., Czerwinski J., Singal B., Clinical and economic outcomes from a community hospital's antimicrobial stewardship program. *Am. J. Infect. Control*, 2013; 41(2): 145-148.
14. Mehta J., Haynes K., Wileyto E.P., Gerber J.S., Timko D.R., Morgan S.C., Binkley S., Fishman N.O., Lautenbach E., Zaoutis T., Centers for Disease Control and Prevention Epicenter Program, Comparison of prior authorization and prospective audit with feedback for antimicrobial stewardship. *Infect. Control Hosp. Epidemiol.*, 2014; 35(9): 1092-1099.
15. Nowak M.A., Nelson R.E., Breidenbach J.L., Thompson P.A., Carson P.J., Clinical and economic outcomes of a prospective antimicrobial stewardship program. *AJHP*, 2012; 69(17): 1500-1508.
16. Roberts R.R., Hota B., Ahmad I., Scott R.D. 2nd, Foster S.D., Abbasi F., Schabowski S., Kampe L.M., Ciavarella G.G., Supino M., Naples J., Cordell R., Levy S.B., Weinstein R.A., Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin. Infect. Dis.*, 2009; 49(8): 1175-1184.
17. Sick A.C., Lehmann C.U., Tamma P.D., Lee C.K., Agwu A.L., Sustained savings from a longitudinal cost analysis of an internet-based preapproval antimicrobial stewardship program. *Infect. Control Hosp. Epidemiol.*, 2013; 34(6): 573-580.
18. Stach L.M., Hedican E.B., Herigon J.C., Jackson M.A., Newland J.G., Clinicians' Attitudes Towards an Antimicrobial Stewardship Program at a Children's Hospital. *J. of the Ped. Infect. Dis. Soc.*, 2012; 1(3): 190-197.
19. Standiford H.C., Chan S., Tripoli M., Weekes E., Forrest G.N., Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. *Infect. Control Hosp. Epidemiol.*, 2012; 33(4): 338-345.
20. Toth N.R., Chambers R.M., Davis S.L., Implementation of a care bundle for antimicrobial stewardship. *AJHP*, 2010; 67(9): 746-749.
21. Valiquette L., Cossette B., Garant M.P., Diab H., Pepin J., Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin. Infect. Dis.*, 2007; 45(Suppl.2): S112-121.
22. World Health Organization, Collaborating Centre for Drug Statistics Methodology. ATC Index with DDDs. Oslo, Norway: WHO, 2004.