

Appropriate antimicrobial agent usage: the beginning of a journey

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This study aimed to describe the pattern of antimicrobial agent usage in a general tertiary care hospital in Rio de Janeiro. Some prescriptions were evaluated for its therapeutic indication, dose, route of administration, and duration of treatment based on Antimicrobial Application Sheets and daily medical prescriptions. Consumption was expressed by using Defined Daily Dose per 100 bed-days. Within the 20,182 validated prescriptions, 9,356 were eligible for the study. The first-choice therapy was prescribed 6,175 (66.01%) times. It was verified that 5,455 (58.31%) of the prescribed antimicrobial agents were associated with bacteriologic culture tests, and among 2,484 (45.54%) of such cultures, at least one microorganism was identified. Negative results were obtained in 2,971 (54.46%) processed cultures, in which 1,289 patients (43.49%) had already initiated antimicrobial therapy. From patients with negative cultures, 518 (33.99%) prescriptions had alternative treatments, and from these, 495 (95.96%) could have been changed. Therefore, de-escalation of antimicrobial therapy has not been a practice in the institution. Among prescriptions that needed renal function dose adjustments, this was performed in 81.11%. In general, prescriptions were adjusted for dose (70.03%), route of administration (99.63%) and duration of treatment (74.70%). Piperacillin/tazobactam was the mostly used antimicrobial (3,923 DDD/100 bed-days).

Keywords: Antimicrobial agent management. Prescriptions. Medication usage.

INTRODUCTION

1. Antimicrobial agents are frequently used by hospitalized patients (25-50%) and most are unnecessary or improperly used (Hecker *et al.*, 2003). Antimicrobial Stewardship Programs (ASP) are developed to systematize actions to educate and persuade antimicrobial prescribers of adopting evidence-based protocols in order to contain overuse of antibiotics and antimicrobial resistance. The main goal of an ASP is to monitor the total amount of the local use of antibiotics and use this information to guide and evaluate specific interventions (WHO, 2019).
2. Antimicrobial resistance is a serious and growing global health problem. Hospitals are critical scenarios of antimicrobial resistance development. The control of antimicrobial resistance development goes through restrictive policies combined with effective infection control measures to prevent the spread of resistant microorganisms (Krivoy *et al.*, 2007). De-escalation consists of modifying the empirical antimicrobial therapy after being aware of the isolated microorganism's susceptibility and consists of one of the strategies used to reduce and avoid antimicrobial resistance propagation (Kaye, 2012; Laxminarayan *et al.*, 2013; Schulz, Osterby, Fox, 2013).
3. The first choice of an antimicrobial therapy is challenging because usually requires broad-spectrum agents. Despite the initial broad-spectrum therapy allows that infection cause agent might be treated

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with appropriate antimicrobial agents, such therapy brings some concerns to the health managers in virtue of their expensive price. Therefore, therapy de-escalation is necessary so that the patient can receive a more appropriate treatment given his/her health condition, which might result in a lesser financial impact for the institution (Andrew et al., 2011). This study aimed to evaluate the antimicrobial usage profile in order to guide the implementation of future efficient strategies, ensure rational usage of antimicrobials and improve the quality of care provided to patients.

MATERIAL AND METHODS

Study design

The study was carried out from January 1 to December 31, 2017, in a general military tertiary care hospital with 182 beds, located in the city of Rio de Janeiro. The total number of hospitalizations was 5,033 in the year. During the period, the hospital had a list of standardized drugs in which antimicrobial agents were selected according to the therapeutic needs and criteria of clinical evidence to support their rational usage. The institution had an Antimicrobial Request Form (ARF) including data about the site of infection, antimicrobial prescription (dosage regimen, route of administration and duration of treatment), and antimicrobial susceptibility test (AST), when applicable. This study was a qualitative and quantitative retrospective analysis in which the use of antimicrobial agents was analyzed based on ARFs and medical prescriptions for patients from 18 years old. During 2017, all prescriptions were evaluated and the selected ones were those having at least one systemic antimicrobial treatment prescribed for the hospitalization period. Antimicrobial agents were classified according to the Anatomical Therapeutic Chemical (ATC) Classification Index in the group J01 (antibacterials for systemic use). The qualitative analysis involved the following variables: therapeutic indication, dose, duration of treatment, and route of administration. The quantitative analysis was expressed according to the Defined Daily Doses (DDD) of the analyzed antimicrobials. The WHO

ATC/DDD classification, version 2018, was used to calculate the DDD number for each antimicrobial used (WHO, 2018).

Exclusion criteria

The following criteria of prescriptions were used to exclude participants: prescriptions and ARF for outpatients discharged within 24 hours after hospital admission, or who used antimicrobials at emergency room and were not admitted; prescriptions and ARF of inpatients who started the treatment at late 2016 and 2017 and did not complete the time scheduled for the therapy until the end of the referred years, which prevents the correct measurement of the treatment duration variable for the prescribed medication; prescriptions and ARF for antimicrobials not made available by the Hospital Management System (SGH) in virtue of suspension, as well as prescriptions without specified therapeutic indication and without ARF.

Data analysis

The leading investigator collected the data by using the analysis of daily medical prescriptions, ARF, bacteriologic culture and antimicrobial susceptibility testing (AST) results provided by the institution's clinical laboratory. The variables collected were therapeutic indication, dose, duration of treatment and route of administration. For the analysis of the variables, the institutional protocols of urinary tract infection and respiratory tract infection were used. In addition, the electronic databases UpToDate® and The Sanford Guide To Antimicrobial Therapy were used as sources of consultation for the other infection sites. The collected data were recorded in a Microsoft Excel 2007 spreadsheet. The study was approved by Federal Fluminense University's Committee of Ethics (CAAE: 81169917.0.0000.5243, nº 2.606.998).

RESULTS AND DISCUSSION

During the study period, 20,182 prescriptions were validated by the Hospital Pharmacy Section (HFS) of

the institution, and 11,216 (55.57%) contained at least one prescribed systemic usage antimicrobial agent. These data are similar to studies in Brazil (Rodrigues, Bertoldi, 2010), Turkey (Boskurt *et al.*, 2014) and in the USA (Braykov *et al.*, 2014), where 52.4%, 54.4%, and 60% of patients, respectively, used antimicrobials while hospitalized. Several studies have shown greater usage of antimicrobials, such as the ones carried out in Israel (Meyer *et al.*, 2010), Uruguay (Cabrera *et al.*, 2012), and India (Alvarez-Uria, Seeba Zachariah, Thomas, 2014), where 82.5%; 96.48% and 86% of the patients, respectively, had an antimicrobial agent prescribed. However, such usage rates were higher when compared to studies in Croatia (Reilly *et al.*, 2015) and the Netherlands (Willemsen *et al.*, 2007), where 38% and 22.9% of prescriptions had antibiotic therapy included. It is well-known that the use of antimicrobial agents is high in several countries. In Europe, data show less usage of antimicrobials, suggesting most rational usage of such drugs. Brazil presented data similar to the USA, which was also similar to the present study. It is important to consider that these variations may be related to different geographic regions, patient populations, and periods when the studies were carried out.

After the criteria were applied, 1,860 (16.58%) prescriptions were excluded due to the following reasons: hospital discharge in 24 hours (312), beginning of treatment in late 2016 (111) or late 2017 (35), antimicrobial suspended without actually beginning treatment in the SGH (30), as well unspecified therapeutic indication without ARF (1,372). Hence, the resulting number of eligible prescriptions were 9,356 (83.42%).

Microbiological culture and AST results were associated with 5,455 eligible prescriptions (58.31%), a fact related to the concern of the clinical staff when prescribing antimicrobial agents based on the infection-causing microorganism. Results found here are analogous to those found in a study in the USA, where microbiological cultures were collected in 59% of patients (Braykov *et al.*, 2014), but lesser expressive than a study in Israel that showed more than 80% of culture performance (Cabrera *et al.*, 2012). In 3,901 (41.69%) prescriptions, empirical treatment started without culture results, demonstrating that the prescribed therapies

were based on the sources of infection. Therefore, the absence of microbiological culture is not justifiable. This antimicrobial usage pattern may be related to health professional attitudes, which can be crucial to prevent the infection spread in severe cases. In certain clinical indications, such as severe sepsis and septic shock, empirical broad-spectrum antibiotic therapy should be started quickly since it increases patients' survival rate. However, some guidelines recommend that prescribers reevaluate initial therapy as soon as AST results are available in order to reduce the number and spectrum of antibiotics (Dellinger *et al.*, 2008) and, therefore, the potential resistance development and institutional cost (Meyer *et al.*, 2010).

The amount of 2,484 (45.54%) prescriptions had been associated with positive culture, having at least one microorganism recovered, and 2,971 (54.46%) had negative culture results. For negative results, it was evaluated whether the sampling of clinical specimen occurred before or after the beginning of antibiotic therapy. Among 1,289 (43.39%) prescriptions, the culture was performed after therapy beginning, therefore, negative results may be related to the prior empirical therapy. The lack of culture sampling before the beginning of therapeutic regime may be due to healthcare team's attitudes about the importance of obtaining specimen cultures before starting antibiotic therapy and in virtue of patient's clinical conditions. Adopting a proper sample collection and sample processing practices in health care settings can minimize the impact of these results on the appropriate use of antimicrobials (Ombelet *et al.*, 2019). Negative microbiological results strongly suggest the absence of infection and present great opportunities to avoid the unnecessary usage of antimicrobial agents.

From the AST results, 1,524 (61.35%) prescriptions had recovered microorganisms susceptible to the chosen antibiotic, representing an adequate therapeutic indication. Similar results of proper use were found in studies in Turkey (Boskurt *et al.*, 2014). However, several studies (Krivoy *et al.*, 2007; Braykov *et al.*, 2014; Cabrera *et al.*, 2012; Dong-Ying Wu *et al.*, 2015; Gidamudi *et al.*, 2015) did not present susceptibility data to demonstrate a more meaningful comparison with this study. Within the 1,524 prescriptions mentioned, 1,006 (66.01%) had the

first-choice regimen for therapeutic indication prescribed. Within the 518 (33.99%) prescriptions in which alternative therapeutic regimens were recorded, 495 (95.56%) had no antimicrobial de-escalation. De-escalation of therapy is not a current practice in the institution since less than 10% of the alternative therapeutic regimens were changed according to the AST results. However, suitable therapeutic regimens were prescribed although it has not been the first choice, which may be related to patient clinical conditions not covered in the study. An increased variation in the incidence of de-escalation has been observed and it is greater in developed countries and, perhaps, more engaged for antimicrobial therapy usage rationality. These differences may be related to situations in which the prescribers avoid modifying the therapy due to the favorable evolution of the patient clinical condition or when there is a strong clinical suspicion of bacterial infection without a positive culture (Kollef *et al.*, 2006). The practice of de-escalation in the studied hospital analyzed should be encouraged as this measure contributes significantly to the rational usage of antimicrobials.

Among prescriptions in which antimicrobial agents did not require dose adjustment according to the patient's creatinine clearance (N = 5,811; 62.11%), 4,999 (86.03%) showed adequate dose, 404 (6.95%) were inadequate. In 408 (7.02%) prescriptions, it was not possible to assess the adequacy of the dose due to inadequate indication or inadequate indication due to resistant microorganism. Among prescriptions in which the antimicrobials required dose adjustment according to the patient's creatinine clearance (N = 2,117; 22.63%), there was dose adjustment in 1,717 (81.11%). Within the prescriptions adjusted as per renal function, 1,553 (73.36%) were appropriately adjusted, and 164 (7.75%) were inappropriate. It was not possible to evaluate the referred variable in 1,428 (15.26%) prescriptions because there was no creatinine test requested during treatment (N = 531; 5.67%), as they were related to inappropriate therapeutic indication (N = 176; 1, 88%) or to the inappropriate therapeutic indication due to recovered microorganism (N = 721; 7.71%). The absence of requests for creatinine tests in approximately 6% of prescriptions is noteworthy, especially regarding extremely nephrotoxic drugs, such as gentamicin, which

were prescribed in almost half of the prescriptions without assessing the patient's renal function.

Considering the route of administration, 9,321 prescriptions (99.63%) were appropriate. This variable is often not associated with prescription errors, but it is one of the requirements involved in the rational use of antimicrobials.

Regarding the variable 'duration of treatment', 6,989 (74.70%) prescriptions were adequate and 1,062 (11.35%) were inadequate. In 1,305 (13.95%), it was not possible to evaluate the referred variable because it was related to the inadequate indication for the proposed therapy (N = 345; 3.69%) and the inappropriate indication due to recovered microorganism (N = 960; 10.26%).

Among prescriptions appropriately adjusted for the treatment duration, an antimicrobial agent was used in 3,214 (45.99%) within the time provided in the ARF. This fact demonstrates that the ARF is useful for monitoring the treatment time when it is followed. Among 1,467 (20.99%) prescriptions without antimicrobial therapy suspension within the time prescribed by the ARF, in 370 (25.22%) there was an extension of the treatment time with a new ARF, and in 1,097 (74, 78%) there was no extension of the treatment duration. Approximately 12% of the prescriptions were inadequate concerning the correct use of the antimicrobial within the recommended treatment time for a given clinical indication. The study data are smaller when compared to that of Israel, which demonstrated that 74% (2002) and 35% (2003) of the treated patients did not complete the treatment duration (Krivoy *et al.*, 2007). However, the data of this study are higher than a Swiss study where 2.1% and 3% of antimicrobials prescribed had an improper and extensive treatment duration, classified as inadequate (Cusini *et al.*, 2010). The use of antimicrobials for excessively long periods is a frequent cause of inadequate use (Moussau *et al.*, 2006). In 2,308 (33.02%) prescriptions was not possible to evaluate the referred variable since 866 (12.39%) are related to patients discharged from the hospital before the end of the expected therapy duration, 369 (5.28 %) had the therapy replaced, 769 (11%) had no ARF, and 304 (4.35%) did not have the duration of treatment specified in the ARF. The lack of treatment duration's information in approximately 15%

of prescriptions represents an obstacle for the rational use of antimicrobials and demonstrates the need for improvements in the processes for controlling the use of antimicrobials in the institution.

Table I indicates the DDD per 100 bed-days calculated by the class of antimicrobial agents in the

period. Penicillins with β -lactamases inhibitors were the mostly used group of drugs, followed by carbapenems, β -lactamases-resistant penicillins, third-generation cephalosporin, fluoroquinolones, macrolides, polymyxin, glycopeptides, imidazole derivatives, and extended-spectrum penicillin.

TABLE I - Consumption of antimicrobials for systemic use, expressed in DDD per 100 bed-days at a Tertiary General Hospital in Rio de Janeiro in 2017

ATC Code	ATC Classification	DDD per 100 bed-days	Prescriptions ^a	% ^b
J01GB	Aminoglycoside antibacterials	0.488	178	1.90
J04AB	Antimycobacterials (Rifampicin)	0.220	93	0.99
J01DH	Carbapenems	3.648	1211	12.94
J01DB	First-generation cephalosporins	0.438	111	1.19
J01DC	Second-generation cephalosporins	0.956	267	2.85
J01DD	Third-generation cephalosporins	3.110	900	9.62
J01DE	Fourth-generation cephalosporins	0.792	137	1.46
J01DI	Other cephalosporins and penems	0.072	23	0.25
J01MA	Fluoroquinolones	2.961	816	8.72
J01XA	Glycopeptide antibacterials	1.638	698	7.46
J01XD	Triazole derivatives	1.479	437	4.67
J01FF	Lincosamides	0.288	235	2.51
J01FA	Macrolides	2.413	782	8.36
J01XE	Nitrofurans derivatives	0.787	114	1.22
J01XX	Other antibacterials (Linezolid)	0.259	81	0.87
J01XB	Other antibacterials (Polymyxins B)	2.084	340	3.63
J01CE	Beta-lactamase sensitive penicillins	0.034	16	0.17
J01CA	Penicillins with extended spectrum	1.244	136	1.45
J01CF	Beta-lactamase resistant penicillins	3.418	210	2.24
J01CR	Penicillins + beta-lactamase inhibitors	3.515	1084	11.59
J01CR	Penicillins + beta-lactamase inhibitors (Piperacillin+Tazobactam)	3.923	1227	13.11
J01EC	Intermediate-acting sulfonamides	0.297	172	1.84
J01AA	Tetracyclines	0.310	88	0.94
Total		34.374	9356	100

^a Numbers of prescriptions in which the antimicrobial class was prescribed.

^b Percentage referring to prescriptions in which the antimicrobial class was prescribed/total of prescriptions.

Penicillin drugs with β -lactamases inhibitors (piperacillin+tazobactam) were the most widely used class of antimicrobials (DDD/100 bed-days = 3.923), presenting a higher consumption when compared with other Brazilian studies, 2.93 DDD/100 bed-days (Rodrigues, Bertoldi, 2010) and 0.87 DDD/100 bed-days (Castro *et al.*, 2002). The greater use of active antimicrobials for *Pseudomonas spp.* in the study may be related to the hospital microbiota and the clinical conditions of patients. However, in 42.02% of prescriptions, piperacillin+tazobactam could have been preserved with the de-escalation of therapy, in order to avoid the development of resistant strains and to reduce hospital costs. It is noteworthy in the present study that broad-spectrum antimicrobials, such as piperacillin+tazobactam and meropenem, are among the mostly used ones and usually their use is preserved in most hospitals.

In this hospital, antimicrobial agents usage was considered satisfactory since more than half of the prescribed drugs were based on microorganisms that caused the infection. Indeed, more than half of the therapeutic indications corresponded to the first-choice therapy. On the other hand, de-escalation of therapy should be stimulated by the Hospital Infection Control Committee in order to avoid antimicrobial resistance development and to preserve broad-spectrum antimicrobial agents. Encouraging the appropriate sample collection and sample processing practices, as well as the enhancement of microbiological diagnosis, reduces the empirical usage and contributes to an adequate prescription. The adoption of such measures will provide a more rational usage of antimicrobial agents in the hospital analyzed.

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REFERENCES

Alvarez-Uria G, Seeba Zachariah S, Thomas D. High prescription of antimicrobials in a rural district hospital in India. *Pharm Pract (Granada)*. 2014;12(2):384-7.

Andrew FS, Scott TM, Emily CW, Joshua AD, Richard MR, Marin HK. Inappropriate antibiotic therapy in Gram-negative sepsis increases hospital length of stay. *Crit Care Med*. 2011;39(1):46-51.

Boskurt F, Kaya S, Tekin R, Guslun S, Deveci O, Dayan S, et al. Analysis of antimicrobial consumption and cost in a teaching hospital. *J Infect Public Health*. 2014;7(2):161-9.

Braykov NP, Morgan DJ, Schweizer ML, Uslan DZ, Kelesidis T, Weisenberg SA, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. *Lancet Infect Dis*. 2014;14(12):1220-27.

Cabrera AS, Sosa L, Arteta Z, Seija V, Mateos S, Perna A, et al. Uso racional de antimicrobianos en el departamento de medicina interna de un hospital universitario: resultados de una experiencia piloto. *Rev Chil Infect*. 2012;29(1):7-13.

Castro MS, Pilger D, Ferreira MBC, Kopittke L. Tendências na utilização de antimicrobianos em um hospital universitário, 1990-1996. *Rev Saúde Pública*. 2002;36(5):553-8.

Cusini A, Rampini SK, Bansal V, Ledergerber B, Kuster SP, Ruef C, et al. Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: a prevalence survey. *Plos ONE*. 2010;5(11):14011-18.

Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med*. 2008;34(1):17-60.

Dong-Ying Wu L, Walker SAN, Elligsen M, Palmay L, Simor A, Daneman N. Antibiotic Use and Need for Antimicrobial Stewardship in Long-Term Care. *Can J Hosp Pharm*. 2015;68(6):445-49.

Gidamudi SS, Jadhav SA, Khanwelkar CC, Vandana M, Thorat VM, Desai RR, et al. Antimicrobial Utilization Pattern of Urinary Tract Infection in Tertiary Care Hospital. *Asian J Pharm Clin Res*. 2015;8(6):161-4.

Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. *Arch Intern Med*. 2003;163(8):972-78.

Kaye KS. Antimicrobial de-escalation strategies in hospitalized patients with pneumonia, intra-abdominal infections, and bacteremia. *J Hosp Med*. 2012;7(1):13-21.

Kollef MH, Morrow LE, Niederman MS, Leeper KV, Anzueto A, Benz-Scott L, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest*. 2006;129(5):1210-18.

- Krivoy N, El-Ahal WA, Bar-Lavie Y, Haddad S. Antibiotic prescription and cost patterns in a general intensive care unit. *Pharm Pract (Granada)*. 2007;5(2):67-73.
- Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis*. 2013;13:1057-98.
- Meyer E, Schwab F, Pollitt A, Bettolo B, Schroeren-Boersc B, Trautmann, M. Impact of a change in antibiotic prophylaxis on total antibiotic use in a surgical intensive care unit. *Infection*. 2010;38(1):19-24.
- Moussau R, Borgie CAJM de, Van Den Broek P, Hustinx WN, Bresser P, Van Den Berk GEL, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ*. 2006;332(7554):1355-61.
- Ombelet S, Barbé B, Affolabi D, Ronat JB, Lompo P, Lunguya O, et al. Best Practices of Blood Cultures in low- and middle-income countries. *Front Med*. 2019;6(131):1-27.
- Reilly JS, Price L, Godwin J, Cairns S, Hopkins S, Cookson B, et al. National Participants in the ECDC pilot validation study. A pilot validation in 10 European Union Member States of a point prevalence survey of healthcare-associated infections and antimicrobial use in acute hospitals in Europe, 2011. *Euro Surveill*. 2015;20(8):21045-50.
- Rodrigues FA, Bertoldi AD. Perfil de Utilização de antimicrobianos em um hospital privado. *Ciênc Saúde Coletiva*. 2010;15(1):1239-1247.
- Schulz I, Osterby K, Fox B. The use of best practice alerts with the development of an antimicrobial stewardship navigator to promote antibiotic de-escalation in the electronic medical record. *Infect Control Hosp Epidemiol*. 2013;34:1259-65.
- World Health Organization Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) Classification and Defined Daily Doses (DDD). [Internet] [cited 2018 sep 11]. Available from: <http://www.whocc.no/atcddd/atcssystem.html>.
- World Health Organization. WHO. ¶2019. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. Available from: <https://apps.who.int/iris/handle/10665/329404>.
- Willemsen I, Groenhuijzen A, Bogaers D, Stuurman A, Keulen PV, Kluytmans J. Appropriateness of Antimicrobial Therapy Measured by Repeated Prevalence Surveys. *Antimicrob Agents Chemother*. 2007;51(3):864-7.

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