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Stewardship program for restricted use of antimicrobials in the elderly: a cohort study in a quaternary hospital in Brazil

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Abstract

Objective: The *stewardship* strategy refers to a consistent practice to promoting responsible antimicrobial use. Optimizing the use of antibiotics is critical to mitigating adverse effects and combating bacterial resistance. The pillars of an *stewardship* program include: i) clinical pharmacist and infectologist with expertise; ii) educational measures for prescribers, nurses and pharmacists; iii) prophylaxis and therapeutic protocol; iv) monitoring of indicators. In this scenario of antimicrobial rational use, the older population are more susceptible to infection because immunocenescence and, therefore, greater use of antimicrobials is expected. Thus, the aim of the present study is to evaluate the prescription compliance of antimicrobial whose use is restricted in a hospitalized elderly population. **Method:** observational, controlled study in a Brazilian hospital, from January 2021 to January 2022. Based on the electrotonic antimicrobial form, the compliance of the prescriptions was evaluated. The definition used for elderly corresponded to individuals over 60 years old, according to the Brazilian Nation Principles for Older Persons, ordinance number 2528, of October 2006. Restricted drugs were considered: carbapenems, polymyxin, ceftazidime-avibactam, linezolid, tigecycline, ceftaroline, echinocandins and amphotericin. **Results:** A total of 1.688 requests for restricted use were received, of which 53% corresponded use in elderly group. Neutropenic fever was more common in young people and the inpatient unit was the sector with the highest percentage of antimicrobials. Furthermore, teicoplanin was the main drug that required intervention. **Conclusion:** Faced with the increase in bacterial resistance, the rational use of antimicrobials is extremely important, especially in older age group.

Key-words: elderly, *stewardship*, rational use of drugs, patient care

Programa *stewardship* de antimicrobianos de uso restrito em idosos: estudo de coorte em um hospital quaternário do Brasil

Resumo

Objetivo: A estratégia denominada stewardship refere-se a um conjunto de intervenções coerentes direcionadas a promover o uso responsável de antimicrobianos. A otimização do uso de antibióticos é fundamental para tratar de forma correta as infecções, mitigar efeitos adversos aos pacientes e combater a resistência bacteriana. Os pilares de um programa de stewardship incluem: i)farmacêutico clínico e infectologista com expertise; ii) medidas educativas aos prescritores, enfermeiros e farmacêuticos; iii) protocolos de profilaxia e terapia estruturados, iv) monitorização de indicadores. Nesse cenário de uso racional de antimicrobianos, os idosos são a população mais susceptível a infecção pela imunocenescência e, portanto, espera-se maior uso de antimicrobianos. Dessa forma, o presente trabalho tem por objetivo avaliar a conformidade da prescrição de antimicrobianos de uso restrito em uma população idosa hospitalizada. **Método:** estudo observacional, conduzido em um hospital no Rio de Janeiro, Brasil, de janeiro de 2021 a janeiro de 2022. A partir do formulário eletrônico de requisição de antimicrobianos, a conformidade das prescrições era avaliada. A definição utilizada de idoso correspondeu a indivíduos acima de 60 anos, segundo critérios da Política Nacional de Saúde da Pessoa Idosa, Portaria nº 2528, de outubro de 2006. Foram considerados fármacos de uso restrito: carbapenêmicos, polimixina, ceftazidima-avibactam, linezolida, tigeciclina, ceftarolina, equinocandinas e anfotericinas. Resultados: Um total de 1.688 requisições de antimicrobianos de uso restrito foram recebidas, dessas 53% corresponderam a uso em idosos. Neutropenia febril foi mais comum em jovens e unidade de internação foi o setor com maior percentual de antimicrobianos. Outrossim, teicoplanina foi o principal fármaco que necessitou de intervenção. **Conclusão:** Frente ao aumento da resistência bacteriana, é de extrema importância o uso racional dos antimicrobianos, principalmente nas faixas etárias mais elevadas.

Palavras chaves: Idosos, Stewardship, uso racional de medicamentos, assistência ao paciente

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Introduction

The concept of One Health in the microbial resistance scenario is defined as a collaborative effort by various health science professionals, together with related disciplines and institutions, whether locally, nationally or globally, to achieve optimal health for people, pets, wild life, plants and the environment. Several efforts have been initiated to mitigate microbial resistance as a global public health crisis[1]. Antimicrobial resistance increases the medical care costs with longer hospitalization times and the need for more intensive care. If no action is taken, by 2050, nearly 500,000 people will die due to infections by resistant bacteria. Given this scenario, the World Health Organization (WHO) promotes antimicrobial awareness and understanding to encourage better practices[2].

In this sense, multidisciplinary Antimicrobial Stewardship programs have been implemented worldwide with the aim of improving prescriptions based on rational use of these medications. This proposal is based on using the appropriate drug for the infectious topography, in the correct dose, for the correct time and respecting the antimicrobial spectrum[3].

It is known that, due to the morphophysiological changes typical of aging, older adults attend health services more frequently and, consequently, are subjected to greater exposure to antimicrobials[4]. According to the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*, IBGE), nearly 33.7% of the Brazilian population will consist of aged individuals in 2060[5]. Therefore, encouraging and implementing Stewardship programs for patients over 60 years of age is essential to render antimicrobial prescriptions safe and accurate for this population. That said, this study aimed at evaluating compliance of the prescription of restricted use antimicrobials in a hospitalized aged population and, thus, discuss and promote better practices in antimicrobial use.

Methods

This descriptive study represents a retrospective review of a single quaternary teaching hospital in the metropolitan region of Rio de Janeiro, Brazil. The hospital unit handles 9,000 emergency room visits per month and has 300 beds and 4 intensive care units for adults. In December 2020, the Stewardship program was implemented at the hospital unit. By definition, an Antimicrobial Stewardship program is a set of actions that promote optimal use of antimicrobials in order to ensure sustainable access to effective patient therapy and reduce unfavorable outcomes. The main objectives of this program should be to guarantee the therapeutic efficacy of antimicrobial treatments, minimize the occurrence of adverse events, reduce the incidence of bacterial resistance, and reduce both the hospitalization times and the costs related to unnecessary treatments[6].

According to the National Guideline for the Elaboration of a Management Program for the Antimicrobial Use in Health Services of 2017 by ANVISA (National Health Surveillance Agency), the *Stewardship* team should ideally be comprised by: Infectologist Physician devoted to the activity; Clinical Pharmacist devoted to the activity, institutional top management, representative of the Hospital Infection Control Service, representative of the Medical team, representative of the Nursing team, Microbiology laboratory, Information Technology, and coordination areas of strategic sectors for the use of antimicrobials in intensive care units, operating rooms and hospitalization units[7].

All antimicrobial therapy recommendations described in the care protocols were based on diverse scientific evidence from the Brazilian, American and European Societies of Infectious Diseases.

The Observation Group consisted of adult patients over 60 years of age and the Control Group was comprised by individuals aged between 18 and 59 years old, hospitalized, who had received restricted use antibiotic therapy from January 2021 to January 2022. Patients who died or were transferred without validation of the prescription by the *Stewardship* team or those without sufficient data for statistical analysis were excluded. All epidemiological characteristics were compared according to age group. The categorical variables were presented as proportions.

Based on the evaluation of the antimicrobial request form, the professionals linked to the *Stewardship* evaluated the following: i) the need for escalation or de-escalation of the empirical or targeted therapy according to the microbiological profile of the unit and to culture results; ii) possibility of adjusting duration; iii) verification of dose and drug interactions; iv) switching from venous to oral therapy; and/or v) discontinuing the drug.

After consulting the form and reviewing the medical record, a database was built in Excel containing the following data: name, age, gender, hospitalization sector, evaluation month, evaluation year, antimicrobial prescribed, infectious topography, cultures collected and respective results, as well as the assessment made by the *Stewardship* team, type of intervention required, and whether the intervention was accepted by the assistance team. The interventions were carried out by telephone, notes in the medical records and, ultimately, via notifications in the system for in-hospital quality.

Antimicrobials for restricted therapeutic use were considered: meropenem, ertapenem, ceftazidime + avibactam (torgena), polymyxin b, linezolid, tigecycline, teicoplanin and ceftaroline[8]. According to the classification proposed by the World Health Organization (WHO) for developing countries, aged patients were considered those over 60 years old and very aged patients those over 80 years old[9]. In relation to the clinical syndromes evaluated, the topography was considered indeterminate when it was not possible to define it even after exhaustive investigation. The study is part of the Stewardship project, approved by the Research Ethics Committee under CAAE number: 47504821.0.0000.5455.

Results

There were 14,068 hospitalizations during the study period and 5,282 (37.5%) corresponded to aged patients. A total of 1,688 requests for restricted use antimicrobials were received, of which 1,438 (901 in older adults and 537 in young adults) were included for analysis in a scenario of 649 patients. Males accounted for 51% (35.7% older adults x 20.5% young adults) and antimicrobial use in febrile neutropenia and abdominal infection was a protective factor for the aged patients (OR: 0.43 and 0.40). The epidemiological and clinical characteristics are described in Table 1.

Table 1. Clinical and demographic characteristics of the patients who resorted to restricted use antimicrobials, from January 2021 to January 2022, n=649

Patient, n(%)	Total		OR	95% IC	p-valor
	Idoso	Adulto Jovem			
Gender					
Male	232(35.7)	133(20.5)	0.83	0.60 - 1.15	0.28
Female	192(29.5)	92(14.1)			
Age median (years old)	75(60 - 102)	44(19 - 59)			
Clinical syndrome					
Respiratory tract	133(31)	59(26)	1.28	0.89 - 1.84	0.17
Urinary tract	48(11)	16(7)	1.66	0.92 - 3.0	0.08
Primary Bloodstream Infection	41(10)	17(8)	1.30	0.72 - 2.36	0.36
Skin and soft parts	25(6)	10(4)	1.34	0.65 - 2.85	0.43
Febrile neutropenia	22(5)	27(12)	0.40	0.22 - 0.72	<0.001
Abdominal	19(4)	22(10)	0.43	0.22 - 0.81	0,008
Central Nervous System	4(1)	2(1)	1.06	0.19 - 5.84	0.94
Others	132(31)	72(32)	0.96	0.67 - 1.35	0.82

Note: "Others" grouped topographies not covered in the previous options

Most prescriptions of restricted use antimicrobials were made in the inpatient unit, followed by the general ICC and by the COVID-19 ICC. Prescription compliance was higher in young adults when compared to older adults (56% vs. 66%). In addition, the main reasons for intervention were prolonged duration, need for escalation and empirical use of a greater than necessary spectrum. When specifically analyzing the antimicrobials, the highest inadequacy rates were found in teicoplanin prescriptions among the population aged over 60 years old; in addition, there was greater difficulty adjusting the therapy after the intervention by an infectologist for the aged patients. Such data are described in Table 2.

Table 2. Characteristics of the restricted use prescriptions, from January 2021 to January 2022, n=1,688

Prescription, n(%)	Total		OR	95% CI	p-valor
	Older adult	Young adult			
Prescription sector					
Hospitalization unit	242(27)	109(20)	1.42	1.09 - 1.83	0,007
GENERAL ICC	223(25)	78(15)	1.93	1.45 - 2.57	<0.001
COVID-19 ICC	193(21)	118(22)	0.96	0.74 - 1.25	0.80
Cardiology ICC	100(11)	35(7)	1.79	1.19-2.67	0,003
Transplantation Unit	71(8)	118(22)	0.30	0.22 - 0.41	<0.001
Neurological ICC	40(4)	57(11)	0.39	0.25 - 0.59	<0.001
Post-Operative ICC	32(3.5)	22(4)	0.86	0.49 - 1.49	0.59
Evaluation					
Compliant	509(56)	352(66)	0.68	0.54 - 0.85	<0.001
Non-compliant	392(44)	185(34)			
Reason for intervention non-compliance					
Duration	61(16)	48(26)	0.73	0.49 - 1.09	0.13
De-escalation	54(14)	44(24)	0.71	0.47 - 1.07	0.10
Spectrum	50(13)	27(15)	1.10	0.68 - 1.79	0.67
No infection	36(9)	23(12)	0.91	0.53 - 1.56	0.75
Empirical treatment	38(10)	19(10)	1.20	0.68 - 2.10	0.52
Targeted treatment	71(18)	34(18)	1.26	0.82 - 1.93	0.27
Others	82(21)	10(5)			
Non-compliant antimicrobial					
Meropenem	149(38)	71(38)	1.30	0.95 - 1.76	0.09
Teicoplanin	101(25.8)	42(23)	1.48	1.02 - 2.16	0.03
Polymyxin B/Colistin	30(7.7)	16(9)	1.12	0.60 - 2.07	0.71
Echinocandins	33(8)	18(10)	1.09	0.61 - 2.00	0.75
Others	79(20)	38(21)			
Intervention accepted					
Meropenem	70(47)	40(56)	0.72	0.63 - 0.82	<0.001
Teicoplanin	38(38)	42(100)	0.69	0.60 - 0.79	<0.001
Polymyxin B/Colistin	12(40)	9(56)	0.70	0.61 - 0.80	<0.001
Echinocandins	15(45)	9(50)	0.60	0.50 - 0.72	<0.001

Note: ICC: Intensive Care Center

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Discussion

The data presented in this study are extremely important for the search for rational antimicrobial use in the Brazilian aged population. These findings need to be discussed in the context of global and Brazilian demographic change. The higher incidence of young patients with febrile neutropenia and abdominal symptoms can be explained by the fact that the hospital is a reference center for bone marrow transplantation and Oncology in the state of Rio de Janeiro, welcoming many young patients with oncohematological disease.

Surprisingly, the largest percentage of restricted use antimicrobials in the aged population was found in the inpatient unit. These data suggest reflecting on institutional and public Palliative Care policies for the aged population. Increased life expectancy and associated changes in end-of-life morbidity predict major challenges for health care[10].

The population over 60 years old had more inappropriate prescriptions. This fact is similar to studies carried out previously. In 2003, in France, Zahar *et al.* pointed out 35% of inadequacy in antimicrobial prescriptions[11]. In Turkey, a study carried out by Tunger *et al.* in 2000 at a teaching hospital indicated a 54.3% of inadequate prescriptions[12]. The high inadequacy rate found both in developed and developing countries must be understood in the context of the difficulty diagnosing sepsis in aged patients. In this situation, one of the most common manifestations found is fever. However, as they age, individuals tend to reduce body temperature and fever is no longer part of the condition presented by the patients in more than 50% of the sepsis cases, hindering the diagnosis[13].

Prolonged duration was the main reason for non-compliance. Although most bacterial infections can be treated with a 7-day regime, the treatment tends to extend in time and this fact is more influenced by the medical decision than by the patient's profile. An analysis of prescriptions in long-term institutions from Canada pointed out that the professionals who prescribed antimicrobials for more than 7 days were male and general practitioners with more than 30 years of clinical practice[14]. These data reinforce the importance of including interventions based on continuing education in Stewardship programs.

The low acceptance of interventions by the prescribers for aged individuals can be explained by the following reasons: i) the previous history of hospitalization and/or colonization by resistant bacteria in this population; ii) greater severity of the disease in older adults at the time of the intervention; and iii) reluctance to discontinue broad-spectrum antibiotics with clinical improvement, even in the presence of culture data to support de-escalation[15-16].

An important detractor in aged patients was the prescription of teicoplanin. The basic principle of antimicrobial therapy is to determine the causative agent of the infection and its antimicrobial sensitivity profile, and the diagnosis should be based on clinical, epidemiological and laboratory results[17]. The main microorganisms identified in infections among older adults are enteric Gram-negative[18]. Therefore, one of the pillars of Stewardship programs is empirical therapy based on institutional protocols that respect the local microbiological profile. Empirical therapy adhering to the guideline is associated with a relative reduction in the mortality risk[19].

Conclusion

Given the above, the main study limitation was that it was conducted in a single center. Therefore, the findings cannot be generalized to other hospitals in Brazil. In addition to that, this cohort did not evaluate the outcome. Other studies should be carried out to relate the impact of inadequate prescription of antimicrobials and death in older adults. However, the current study provides useful information to help understand the effect of increased life expectancy among Brazilians regarding the prescription of restricted-use antimicrobials and improves the management of Stewardship programs for the aged population.

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Collaborators

ACF, TPN, MEMM: Data collection; JMSS and DBS: Project design and data analysis, ADF, PRPF, MG, JMA and NCZS: Data review and writing of the article.

Declaration of conflicts of interest

The authors declare that there is conflict of interest in relation to this article.

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