English article

Prescription of antimicrobials for hospitalized older adults: benefit analysis and association with the implementation of limitation of therapeutic effort and palliative care

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RESUMO

ABSTRACT
Background and objectives: Many advances have occurred in the prevention, diagnosis and treatment of infectious diseases, but they are still the main causes of hospitalization and death in older adults. The objective of this study was to verify the benefit of antimicrobial use and its association with the implementation of other therapeutic measures and with the indication of palliative care in the last two weeks of life of hospitalized older adults, in order to subsidize the development of rational models for this group. **Methods:** A retrospective study was carried out by analyzing the medical records of the older adult participants of the cohort epidemiological study "Development of a Care Line for Older Adults at the University Hospital of Santa Maria", which presented death as an outcome. **Results:** Of the 97 individuals evaluated, 89.7% (n = 87) used antibiotics in the last two weeks of life. Among those who used antibacterial agents, 38.9% presented clinical signs of improvement after treatment initiation (n=28). Thus, it was possible to affirm that there was no association between symptom relief and antibacterial use (p = 0.377). Among those who benefited from antibiotic therapy, 46.4% were indicated for respiratory infection and 14.3% for urinary tract infection. We found no dependence between the use of antibacterial drugs and the other therapeutic measures adopted (p = 0.057), nor with the indication of palliative care (p = 0.065). **Conclusion:** There was little evidence of benefit in the use of antibiotics in the studied group, which indicates the need for a different care plan adequacy for this patient profile.
KEYWORDS: Older adult. Antimicrobials. Hospitalization. Palliative care.

INTRODUCTION

Population ageing is a reality faced in developed and developing countries. In Brazil the number of older people has already surpassed the mark of 30.2 million in 2017. In the last 5 years there was an increase of 4.8 million new older adults, which corresponds to a growth of 18% of this age group, only in that time interval.[1,2] It is known that this reality is closely related to advances in the health area that reflected a higher prevalence of chronic non-communicable diseases, with greater consumption of health services, more frequent hospitalizations, longer hospital stays, not always accompanied by increases in quality of life.[3,4]

In this context, there is a worldwide concern about the rational use of drugs, with emphasis on the use of antimicrobials, which correspond to the class of drugs most prescribed to older adults and which influence not only the patient being treated, but the entire ecosystem in which he is inserted, generating microbial resistance, as well as adverse effects when used improperly.[5]

In the United States, a study found that approximately 1.4 million older adults live in long-term care facilities, with 6% to 10% using antibacterials repeatedly, over 50% with at least one antibacterial prescription per year, estimated to be that 25% to 75% of antibacterial prescriptions do not meet clinical guidelines for an appropriate prescription.[6] According to Faria and Ferreira (2015), the suspicion of urinary tract infection (UTI) was the most prevalent with inadequate antibiotic therapy, responsible for 30% to 56% of the antibacterials prescribed, with one third of these prescriptions for asymptomatic bacteriuria.[6] Furthermore, it is noteworthy that there are no clear studies on adverse effects of antimicrobial prescription in this population and that possible consequences include adverse reactions, drug interactions and infection with Clostridium difficile. In addition to the emergence of multi-resistant organisms (a growing public health problem) and the burden imposed by the evaluation and treatment of suspicious infections in patients at the end of life.[7] When prioritizing quality of life and symptom relief, it is important to define the role played by antimicrobials, when used in the context of implementing palliative care, including from the early stages of illness to the final stage of life.[7] Much has been studied about palliative care and its concept has been modified over the years, aiming at an early insertion of the quality of life approach as part of the proposed treatments. Thus, currently, the search for the enhancement of palliative care is sought when, in the process of illness of an individual, there is the presence of a health condition with a limited

life prognosis, with the need to prioritize symptom relief and comfort, orienting the person and not for the present diseases, being focused on the approach of the individual as a whole, and can be provided exclusively or concurrently with curative treatment, depending on the stage of illness in which the individual is, in addition to the necessary therapeutic measures.[8] It is noteworthy that, concomitantly with the implementation of palliative care, the adequacy of therapeutic measures should always occur, avoiding the maintenance of futile measures, which may include both the use of antibacterial agents, as well as the use of parenteral or enteral nutrition, vasoactive drugs, renal replacement therapy, invasive mechanical ventilation and admission to the intensive care unit.[9]

Based on the need to know aspects related to population ageing, differences in the pattern of illness and care in the prescription of medications, this study sought to elucidate how much do older patients benefit from the use of antimicrobials in the final phase of life and to verify how much this use is associated with the implementation of other therapeutic measures or the indication of palliative care.

METHODS

A retrospective study was developed through the analysis of medical records of older adults participating in the epidemiological cohort study called "Development of a line of care for older adults at the University Hospital of Santa Maria (HUSM)", under CAAE no. 48212915.50000.5346, this study followed the ethical principles of CNS Resolution 466/12, in which patients signed an Informed Consent Form. The objective was to address the clinical and epidemiological aspects of patients aged 60 years or older, admitted to the HUSM, in Santa Maria-RS, from October 2015 to May 2016, comprising 493 older adults in total.

All older adults who presented the outcome of death were included for the definition of the sample, which consisted of 100 older adults. The analysis was performed using a form to collect the following variables: age, sex, date of hospitalization and discharge, infectious focus, use of antibacterials, microbiological cultures, identified pathogens, prescribed classes of antibacterials and indication of treatment (categorized into five groups: treatment or prevention of sepsis; respiratory tract symptoms; genito-urinary tract symptoms; gastrointestinal tract symptoms; skin infections), health problem responsible for hospital admission (categorized according to CID-10), positive effects of treatment, which were measured by a subjective scale, in which it was considered "positive", if the patient had any

clinical improvement, and other therapeutic measures instituted (orotracheal intubation, mechanical ventilation, cardiorespiratory resuscitation, blood transfusion, renal dialysis, use of vasoactive drugs, intravenous hydration and nutrition, and indication of palliative care). Sepsis prevention was considered when no obvious infectious focus was evident, but the patient had fever, leukocytosis, elevated C-reactive protein and an impaired general condition (tachypnea, sensory changes, tachycardia, among others), so antibiotic therapy was started even without evidence of infection somewhere and even though this is not the standard concept of sepsis. Data regarding positive effects were collected from medical or nursing records through subjective assessment of the team, such as relief of dyspnea or cough, improvement of fever or inappetence, ability to talk, improvement of pain or urinary complaints in cases where which was used for this purpose and reduced episodes of delirium when these were observed. There being a report in the medical or nursing evolution of improvement in any of the signs or symptoms already mentioned, it was considered that the patient had a positive effect. There being no records, they were classified as "absent or unknown".[9]

With the exception of data on hospitalization date, date of hospital discharge and pathology responsible for hospital admission, all data are equivalent to the last two weeks of the patient's life.[10]

Exclusion criteria were patients who presented incomplete medical records (with less than 1/3 of the necessary information) and those who used antibacterials for less than 72 hours, which resulted in the exclusion of three patients, totaling a sample of 97 individuals.[11] Statistical analysis for categorical and non-categorical variables was performed using the Statistical Package for the Social Sciences (SPSS) for Windows 17.0. The variables were described using absolute and relative frequencies, as well as mean and standard deviation, when applicable. When the association between descriptive variables was performed, univariate analysis was used with the Chi-square test or Fisher's exact test, with significance levels below 5% ($p \leq 0.05$).

RESULTS

This study included 97 individuals, with a predominance of young older adults, since only 34% were 80 years old or older, with a mean of 74.94 + -9.269 (median of 73 years, with a minimum age of 60 and a maximum of 96 years), being 55.7% male. As for the implemented care plan, antibacterials were prescribed for 89.7% of individuals, with a prescription of 3.62

+ -1.584 therapeutic measures, 55.7% with a prescription of at least four therapeutic measures, with 67.9% without indication of palliative care. As for the number of days of antibiotic use in the two weeks before death, it was 8.39 + -4.723 days (median of 9.0, minimum of 1 and maximum of 14 days), with 50.74% using it for 7 days and 28.7% in those 14 days before death. As for the health problems responsible for hospital admission, according to the CID-10, neoplasms, cardiovascular and respiratory diseases stand out, as described in Table 1.

Table 1. Health problems responsible for hospital admission

Pathology	N (%)
Neoplasms	22 (22.7)
Diseases of the digestive system	10 (10.3)
Genitourinary Diseases	3 (3.1)
Respiratory Diseases	12 (12.4)
Others	4 (4.1)

As for the pharmacological classes of antibacterials used, we can observe that betalactams were the most used with 92% (n = 80), followed by beta-lactamase inhibitors with 58.6%. The frequency of used classes of antibacterials in the last two weeks of life are shown in Table 2.

Table 2. Use of antibacterial drug classes in the last two weeks of life

Characterization by the use of antibiotics		
Use of antibiotics	Yes	86 (88.7)
	No	11 (11.3)
Beta Lactamics		80 (92.0)
Inhibitors Beta Lactamase		51 (58.6)
Glycopeptides		34 (39.1)
Nucleic acid synthesis inhibitors		18 (20.7)
Membrane function inhibitors		11 (12.6)
Protein synthesis inhibitors		19 (21.8)

During hospitalization, 86.6% of the patients collected some type of culture, and we found no association between the culture request and the antibiotic prescription (p = 0.452). As shown in Table 3, blood culture was performed in 72 individuals, corresponding to 74.2% of the samples, of which 31.9% presented positive results, with a higher prevalence of Gram-positive cocci, representing 60.9% (n = 14), and the request for blood culture did not influence the decision to use antibacterials (p = 0.206). In other words, antibiotics were prescribed and maintained regardless of the culture result.

Table 3. Results of blood culture in relation to the most prevalent microorganisms.

		N (%)
Performing blood culture	Yes	72 (74.2)
	No	25 (25.8)
Blood Culture Result	Positive	23 (31.9)
	Negative	49 (68.1)
Gram-positive bacilli	Yes	3 (13.0)
	No	20 (87.0)
Cocos Gram-positivos	Yes	14 (60.9)
	No	9 (39.1)
Gram-negative bacilli	Yes	4 (17.4)
	No	19 (82.6)
Fungi	Yes	2 (8.3)
	No	22 (91.7)

Urine cultures were collected in 74.22%, totaling 72 individuals, of which 50% (n = 36) presented positive results for infection, with a higher prevalence of fungi followed by Gram-negative bacilli, as can be seen in Table 4. There was no association regarding urine culture and antibacterial use (p = 0.55).

Table 4. Results of urine culture in relation to the most prevalent microorganisms

		N(%)
Performing Uroculture	Yes	72 (75.0)
Uriculture Result	Positive	36 (50.0)
	Negative	36 (50.0)
Gram-negative bacilli	Yes	14 (38.9)
	No	22 (61.1)
Gram-positive coconuts	Yes	8 (22.2)
	No	28 (77.8)
Fungi	Yes	19 (52.8)
	No	17 (47.2)

As for the therapeutic measures instituted, we observed that in relation to nutrition, the most prescribed type of diet was enteral by nasogastric tube or nasoenteric tube, totaling 72 patients, with 8 patients with full oral route, three by gastrostomy, three with parenteral nutrition and one patient remained on a suspended diet during hospitalization. About 42.3% (n = 41) of the patients received blood transfusions, 48.5% (n = 47) used mechanical ventilation, 12.4% (n = 12) underwent dialysis, 60.8% (n = 59) used some vasoactive drug and 92.8% (n=90) received intravenous hydration. About 22.7% (n = 22) of the individuals underwent cardiopulmonary resuscitation. We found no association between the use of antibacterials and the other therapeutic measures adopted for the patient (p = 0.05), however 59.3% of the patients who used antibiotics underwent four or more therapeutic

measures. The association between the use of antibacterial and therapeutic measures can be seen in Table 5.

<p style="text-align:center">Table 5. Use of antimicrobials and other therapeutic measures instituted</p>

Antimicrobial use and therapeutic measures			
Antibacterial use	Yes N (%)	No N (%)	*p*
Blood transfusion	37 (90.2)	9.8% (n=4)	0.467
Mechanical ventilation	43 (91.5)	8.5%(n=4)	0.394
Dialysis	97 (100)	--	0.214
Vasoactive Drugs	95 (93.2)	4 (6.8)	0.077
Cardiopulmonary resuscitation	20 (90.9)	2 (9.1)	0.524
Parenteral nutrition	97 (100)	--	0.694
Hydration	79 (87.8)	11 (12.2)	0.418
Nasoenteric probe	62 (86.1)	10 (13.9)	0.165

Regarding the effect of using antibacterials, according to the laboratory tests performed, patients were evaluated in relation to the reduction of C-reactive protein, improvement of leukocytosis and reduction of rods in the blood count. There was an association only with the improvement of leukocytosis and reduction of the rods in the blood count ($p = 0.012$), without association with the reduction of C-reactive protein ($p = 0.447$). Of the patients who used antibiotics, 39.4% (n = 29) presented some clinical sign indicating improvement after the start of treatment, which we analyzed through the medical team's records as symptom relief, improvement of fever, better acceptance of the diet or any other evidence of clinical improvement, suggesting that there is no relationship between symptom relief and antibacterial use in older adults in the last two weeks of life ($p = 0.397$). Regarding the definition of palliative care by the assistant team, we identified about 32.2% (n = 26) as in palliative care, and of these 21 individuals used antibacterials in the last two weeks of life, with no association of the prescription of antibacterial with indication for palliative care ($p = 0.065$). Of the patients in which we observed a clinical sign of improvement with the use of antibacterials, 46.4% (n = 13) received treatment with indication due to respiratory focus.

When comparing the results of respiratory tract infections and UTI, it was more likely to have a positive effect on the treatment of UTI, since all those treated for UTI had relief of symptoms.

DISCUSSION

This study showed that antibacterial treatment led to an improvement in symptoms in 38.9% of older patients in the last two weeks of life, a data expected according to a previous observational study conducted in 2016 with a larger sample of patients (n = 160).[12] Even in those patients with negative cultures, there was no difference in the benefit observed with the use of antibacterials. Adverse effects to the treatments applied were not found in medical records.

Another study indicates that 77% of patients who were in transition to a comfort treatment protocol received antimicrobials during hospitalization, corroborating the idea that antibacterial use is relatively high in hospitalized patients near the end of life, even when the objective is comfort. In this same study, 24 hours after the definition of comfort measures, only about 15.6% of the patients still used antibacterials.[13] In our study, the moment for defining palliative care in relation to the permanence of use was not evaluated, which could alter the expected result for the main outcome. Despite the large number of positive cultures, there was no association with the appearance of symptoms in this studied group, and the presence of positive urine culture did not mean treatment for asymptomatic bacteriuria. We did not consider laboratory tests in the assessment of the patient's benefit in relation to the use of medication, taking into account that in patients that there is no possibility of cure, clinical benefits should be evaluated in relation to the therapies used.

In contrast to a study previously mentioned in which 48% of cancer patients were treated with antibacterial in the last week of life, our results showed therapy in 89.7% of patients in the last two weeks[12]. This difference can be justified by the fact that that study evaluated patients who already had a definition for limiting therapeutic effort. The definition of palliative care was inferred when, at any time during hospitalization, the assistant team together with the family chose not to adopt new measures of therapeutic effort for a given patient, in view of the advanced condition of the underlying pathology and the impossibility of treatments of dressings. Those measures already in place were not necessarily interrupted at the time of the decision, such as the use of antibacterial or vasoactive drugs. We found these definitions in 26.8% of older adults in the period. In an analysis carried out in 2007 at a Hospice Care service, 91% of patients who received antibacterials had advance guidelines, compared with 92% of those who did not receive antibacterials (p = 0.4).[14]

The European Center for Disease Prevention and Control study made it possible to identify the most frequent hospital infections, that being lower respiratory tract infections /

pneumonia, UTI and infections of the surgical site, and respiratory tract infections. Those were also the ones that had the most indication for antimicrobials.[15] In a study by Moreira et al.[16] in 2007, they observed that the class of antibacterials most used was betalactams (24.1%), corroborating the same result, due to the great use of this class, since betalactams accounted for 50% of the total sales of antibacterials in 2004 and also have a broad spectrum of antibacterial activity, clinical efficacy and excellent safety profile, since they act on the enzyme transpeptidase, unique in bacteria.[16]

Other studies claim that almost 90% of hospitalized patients with advanced cancer receive antimicrobials during the week before death and approximately a quarter of patients who have been established "palliative care" receive antimicrobials during the final weeks of life.[17] A prospective study reported greater comfort, although shorter survival, among patients with advanced dementia and suspected pneumonia who were not treated with antimicrobials compared to those who were treated. In this study, we did not asses the prevalence of dementia in the sample to make an association with the benefit.[17] Recent data indicate that 33% to 38% of end-of-life patients receive interventions even without benefit. Including in this statistic the use of antimicrobials, which tends to be one of the last interventions withdrawn, with 27% to 88% of patients receiving antimicrobials during the last weeks of life.[18]

Thus, antimicrobials are commonly prescribed for patients in palliative care, often until the last moment, even when there are no indicators of infection, considering that, due to the weakness and deficits in the immune system common to these individuals, sometimes transfer symptoms similar to infectious conditions and sepsis.[7] However, the imprudent prescription of drugs that do not provide relief in individuals in the last weeks or days of life, as verified through this study with antimicrobials, tend to generate costs and can drain resources that could be used in long-term care, in addition to the charges to the financial resources for the health system. On the other hand, it is known that there are more effective comfort measures than the prescription of antibacterials, such as the use of anxiolytics, analgesics and adaptations of the environment so that there is comfort for both patients and families.

Another concern with the inefficiency of the use of antibacterial in terminally ill patients is the propensity for microbial resistance, especially in an in-hospital environment. This study had limitations, due to the difficulty in obtaining some data, justified by characteristics typical of the emergency room environment, such as high patient turnover,

transfer dynamics and the absence, sometimes, of those responsible for the information of the data in skillful time. Another limitation of this study was due to the fact that we monitored the clinical evolution of the patient through the review of medical records, being dependent on their proper filling. However, in this way, it was possible to portray, in a more reliable and realistic way, the profile of the patients evaluated, providing a basis for future studies. Therefore, we suggest that more research should be planned in order to compare the response of symptoms and the survival of older patients at the end of life who receive antimicrobials and those who did not, so that we can achieve a greater theoretical basis in order to build a rational antibacterial prescription model for this group, avoiding dysthanasia. We also conclude that, when prescribing the antibacterial for older adults in the final stage of life, it is essential to evaluate each condition individually, as the benefits are not clear and may vary according to the pathology and symptoms of each patient.

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Ivana Beatrice Mânica da Cruz: planning, design, review, and final approval of the manuscript.
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