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Use of antimicrobials in patients in Palliative Care admitted to the Intensive Care Unit: A retrospective study

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ABSTRACT

Introduction: Palliative care (PC) improves the quality of life of patients and their families. The use of antimicrobials is controversial in PC patients, especially in those admitted to the intensive care unit (ICU). **Objective:** To evaluate the use of antimicrobials in PC patients admitted to the ICU. **Methods:** This is a retrospective study, performed from August 2019 to September 2020. Data on demographic profile, hospitalization, PC, and use of antimicrobials were collected from the Erasto Gaertner Hospital database, in Curitiba, Brazil. **Results:** 182 patients were studied, median age of 65 years and 52% men. The median length of stay in the ICU was 3 days; the median total length of stay in the hospital was 6 days and 89.5% of the patients died. The time in ICU of patients treated with antibiotics (14.8%) was significantly longer (p=0.033) than for patients who were not (85.2%). Using or not using antibiotics did not change the outcome. Among those who took antibiotics, death occurred in 81.5% of cases and among those who did not use, 74.8% died (p=0.627). Between the cases that used broad-spectrum antibiotics 17/19 (89.5%) died and the mean hospital stay was 16.2 days. Among cases that used narrow-spectrum 5/9 (62.5%) died and the mean hospital stay was 6.4 days (p=0.033). **Conclusion:** The administration and/or the spectrum of antibiotics in PC patients admitted to the ICU did not change the mortality rate. The administration of antibiotics increased the length of stay in the ICU.

Keywords: death; quality of life; palliative care; oncology.

INTRODUCTION

Palliative care (PC) was defined by the World Health Organization (WHO) as an "approach to promote quality of life to the patients and their familiars while they face problems associated to potentially fatal diseases, that can be achieved through the prevention and relief of suffering by identifying, evaluating and treating underlying conditions as pain, discomfort, and problems related to psychosocial and spiritual suffering"[1]. In the latest years, ICU admissions in the last month of life have been growing up to 30%, requiring specific knowledge from the physicians that encompasses symptom control and end-of-life management, communication with relatives, and setting goals of care ensuring dignity in death and decision-making power[2,3].

The use of antibiotics in PC patients in the ICU is still challenging for physicians[2,4].

Among the various complications that affect end-of-life patients, infections and febrile episodes are very frequent and can lead to a terminal event by themselves[3]. Some authors claim that antibiotics are widely prescribed to PC patients in the terminal stage, even in the absence of meaningful symptoms that could justify a bacterial infection[5-8]. In addition, there are no specific guidelines that approach the use of antibiotics in these patients, which are under the supervision of the PC professional in the ICU setting. Even though the use of these medications can extend life and relieve symptoms, they might not improve health, quality of life, or quality of death, which are primordial objectives of PC[9-11]. Furthermore, many undesirable effects can occur with the administration of antibiotics, such as the use acquisition of multidrug-resistant organisms, adverse reactions, and interactions between the medications and additional suffering[5,12,13].

Thus, the use of antibiotics in PC patients can entail potential benefits and drawbacks, and there are no precise guidelines or recommendations regarding this topic.

This study aims to evaluate the use of antibiotics in patients in the ICU in a PC setting of the Brazilian oncology reference center.

METHODS

This retrospective study was approved by the local Committee of Ethics in Research under protocol number CAAE: 31880820.1.0000.0098 and opinion number 4.132.706. The data was collected in the electronic database of Erasto Gaertner Hospital and by the analysis of medical records.

Patients classified as PC who were admitted to the hospital's ICU from August 2019 to September 2020 were included. Patients with incomplete data in medical records were excluded from the analysis. Data regarding the demographic profile, hospitalization, PC, and use of antimicrobials of patients in PC were collected.

This study used the Charlson Comorbidity Index[14]. The index is based on the mortality rates of patients admitted to the general internal medicine service and predicts survival in patients with multiple comorbidities. When the score is 0, the corresponding estimated 10-year survival rate is 98%, if the final total score is 4, it suggests a 53% estimated 10-year survival, while if the total score is ≥7, the corresponding 10-year survival rate is 0%.

Section 1: demographic and clinical data of patients in PC as age, gender, BMI (Body Mass Index), comorbidities, functional capacity before admission, SOFA (Sequential Organ Failure Assessment) on the first day that antibiotics were administered (D1). The Frailty index (MFI) measures the frailty of an individual by considering multiple health deficits with 17 variables. Simplified Acute Physiology Score III (SAPS-3) index that predicts the probability of death in the ICU setting based on 20 variables).

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Section 2: admission details as the date of admission, main diagnosis, other diagnoses, use of the invasive device, use of mechanical ventilation, use of a urinary catheter, duration of use of urinary catheter, use of intravascular device, use of vasoactive drug, destination after hospitalization in the ICU, length of hospital stay, outcome on leaving the hospital, destination on leaving the hospital, length of stay.

Section 3: PC data about the decision to limit, intensify, or not intensify therapies, length of stay until choosing PC. Section 4: Data of the infectious site, administration of antibiotics (ATB), and spectrum of ATB used.

The infections were diagnosed by clinical criteria (fever, dyspnea, altered level of consciousness, tachycardia, tachypnea, hypotension, and pain).

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess the normality of the quantitative data using the GraphPad Prism 3.0 software. Quantitative variables were expressed as mean ± standard deviation when within the normal range or medians [min-max] when outside the normal range. The chi-square test and Fisher's exact test were used to compare qualitative data. Continuous variables were compared using the nonparametric Mann-Whitney test and the t-test for independent samples. P values less than 0.05 were considered statistically significant.

RESULTS

During the period, 646 patients admitted to the ICU were studied. After applying the inclusion and exclusion criteria, the final sample was 182 patients. The Charlson Comorbidity Index to evaluate the predicted mortality in 10 years showed a median score

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of 6 (ranging from 2 to 12); 46 (25.3%) patients had a score of 6 and 63 (34.3%) patients had a score higher than 6.

PC patients were separated into three different groups 47.8% were included in the limit procedures group, 32.9% were included in the group whose treatments were not intensified and 19.2% were included in the group whose therapies were discontinued. The median time from admission to the ICU to the start of PC was 1 day (between 0-33 days).

Table 1 shows the clinical and demographic data of the patients studied. The median age was 65 years old and 52.1% of cases were in men. The main comorbidity was a metastatic tumor (50%) followed by arterial hypertension (44.5%). Another analyzed variable was the functionality of the patients, which were classified into three groups: independent (22.5%), need for assistance (39%), and restricted/bedridden (38.5%).

The majority of patients had Modified Frailty Index <3 points and the Simplified Acute Physiology Score (SAPS-3) had a median of 64 [31-101] points and a probability of death with a median of 44.0 [2.08-91.77]. Table 2 provides data on hospitalization. The length of stay in the ICU had a median of 2 days (between 1 – 24 days); 75.8% died before medical release. The total length of stay in the hospital had a median of 6 days (between 1-116 days). The destination after hospitalization in the ICU showed that 55.5% of the studied patients died and 45.6% to the room hospital. As an outcome when leaving the hospital, 75.8% died and 23.1% went to their homes.

Table 3 provides data on the infectious site and which antibiotics were used. Pneumonia was the main infection reported (33.3%) and the proportion between hospital- or community-acquired infections was practically the same. Several types of antimicrobials were used, most of them broad-spectrum.

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Table 4 shows the comparison between patients who used antimicrobials (27/182; 14.8%) and patients whose use of antibiotics was not reported (155/182; 85,2%). Using or not using antibiotics did not change the outcome, and among those who took antibiotics, death occurred in 81.5% of cases and among those who did not use them, 74.8% died (p=0.627). The length of stay in the ICU was significantly longer among patients who used antimicrobials (p=0.014). The other parameters evaluated showed no significant differences.

Regarding the use of antibiotics, among the cases that required the use of broad-spectrum ATB (n=19), two (10.5%) were discharged and 17/19 (89.5%) died; the mean hospital stay of patients that used broad-spectrum ATBs was 16.2 ± 11.83 days, while the mean length of the group who received narrow-spectrum ATBs was of 6.4 ± 4.7 days (p=0.033). From the narrow-spectrum ATB group (n=9), three (37.5%) were discharged and 5/9 (62.5%) died (p=0.063).

DISCUSSION

The decision to intensify or limit therapy for PC patients is a difficult one. The increasing trend of PC and the lack of clear guidelines on the use of antibiotics can lead to more patients receiving potentially unnecessary treatment for infections or not receiving necessary palliative treatments. Our study evaluated the use of antimicrobials in a sample of patients who were admitted to the ICU of a hospital specialized in the treatment of cancer diseases and were under the care of a team specialized in PC. It was observed that 14.8% of these patients received antimicrobials, which is lower than that described by other authors and ranged[3,14-18] from 27% to 84%. However, some of these studies have focused on specific subgroups of patients, for example, cancer patients and patients admitted to hospice.

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It was observed that 63% of patients who received antibiotics had a diagnosis of infectious disease. Albrecht et al.[3] reported that only 15% of the patients studied had infections. Infections and febrile episodes are frequent worries about terminal patients and can represent a mortal event[3]. Thus, antimicrobials are frequently prescribed to patients who are in CP, even without clinical symptoms[3,5,8]. Possible benefits, such as life extension and/or symptom relief, may motivate the prescription of antimicrobials for these patients. However, the evidence to support any benefit is sparse[10,11].

The infection sites reported in the patients in this study agreed with the findings by other authors[18]. Respiratory infections were the main infectious sites reported. Vitetta et al.[17] and Evers et al.[19] also reported respiratory infection as the main diagnosis found. The diagnosis of infection in PC patients, especially those with cancer, is not always easy[17]. Drugs such as non-steroidal anti-inflammatory drugs, analgesics, and corticosteroids can disguise febrile conditions. Furthermore, fever can occur due to non-infectious etiologies, such as the neoplasm itself and thromboembolic conditions, commonly associated with cancer[16].

The use of narrow or broad-spectrum antibiotics in palliative care settings is controversial[3,13]. Possible adverse consequences of antimicrobials include drug reactions, drug interactions, infection with *Clostridium difficile*, acquisition of organisms resistant to multiple drugs, and difficulty in assessing the individual's end of life[13]. For many patients, the use of antimicrobials may be indicated for comfort[17]. In our study, ceftriaxone and metronidazole were the most used antimicrobials. In other studies, ceftriaxone was the most used, followed by piperacillin/tazobactam and cefotaxime[18]. The antimicrobial used may vary according to local epidemiology, site of infection, availability, and cost, and it is important to individualize cases[19].

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Patients who used antimicrobials had a median length of stay significantly longer compared to those who did not. A length of stay 120% times greater was observed among patients who used antimicrobials versus those who did not. Another study showed a 34% longer length of stay among patients who used antimicrobials than those who did not[20]. Assessing patients in CIT, other authors indicated that the inappropriate use of antibiotics increases the length of hospital stay[21]. It should be considered that in patients in PC, in whom the use of medication is aimed at relieving symptoms, these additional days of hospitalization may represent the extension of potential suffering.

In our study, the median age of the studied patients was 65 years, which is about 10 years higher than that observed in other studies[3,20]. Males represented 52% of the cases analyzed in this study, similar to that described by other authors[20]. Metastases and cardiovascular diseases accounted for the majority of conditions that led patients to hospitalization, in agreement with other authors[3].

In our sample, the median score was 6 using the Charlson Comorbidity Index. Lam et al.[22] studying antibiotic use in advanced cancer patients, used the same score and found a median of 1.5, showing that our patients were considerably more ill even though the median age was similar between the studies (65 years and 67.4 years). This probably happened because 50% of the patients in this study had solid tumors with metastasis which account for 6 points in the index while in Lam's study, there were no metastasis reported.

This study has some limitations due to its retrospective design. Missing data in the registry system, such as the antibiotic used, the time to start the antimicrobial and the time between admission and the decision for PC, are factors that limited the results of the study. Choosing the most appropriate antibiotic for the patient's needs is not always possible, since the decision to suspend or escalate antibiotics is based on the articulation of

the team of intensive care and/or PC physicians. Thus, the team's decision time can affect the patient's outcome, giving the work a possible bias. The hospital where the study took place is notable for the care of cancer patients and the culture of palliative care is widespread. However, studies in other centers are still lacking to make further comparisons possible.

Decision-making about the use of antimicrobials at the end of life should be carried out with advance care planning and treatment preferences documented in advance directives and/or during the discussion of the goals of care[13]. In the absence of evidence-based guidelines, the decision to use antimicrobials at the end of life must be individualized and the approach adopted must be aligned with the patient's stated care goals, the level of uncontrolled pain, the main diagnosis and its stage, and the degree of multisystem deterioration[9]. Although the reasons for continuing therapy are unclear, one possibility is that providers may not want to pursue active discussions with patients' families about discontinuing antimicrobials, as these medications are often perceived by patients, families, and even by providers, as benevolent, inexpensive and almost basic treatment. The discussion about the withdrawal of antimicrobials can be perceived by the physician as a challenging and delicate task and perhaps, for that reason, even discouraging[23,24]. Thus, the use of antimicrobial treatment for patients with CP, the use of antimicrobial in a so fragilized patient remains challenging.

Conclusion

In summary, in our sample, the use of antibiotics or the type of antibiotics used for PC patients admitted to the ICU did not change the mortality rate. Using antibiotics increased the length of stay but did not significantly change the outcome.

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Table 1: Demographic and clinical data of studied patients (n=182)

Variable	**Median** [min - max]	
Age	65 [1-89]	
BMI	22.9 [14.2-36.3]	
	N	**%**
Male	93	51.1
Comorbidity	**N**	**%**
Solid. metastatic tumor	91	50
Arterial hypertension	81	44.5
Immunosuppression	59	32.4
Solid tumor loco regional	57	31.3
Diabetes mellitus	35	19.2
Hematologic neoplasm	34	18.7
Smoking (in the last 12 months)	23	12.6
Severe COPD	16	8.8
Hypothyroidism	12	6.6
Malnutrition	12	6.6
Others	46	25.3
Functional capacity before hospitalization	**N**	**%**
Independent	41	22.5
Need for assistance	71	39
Restricted/bedridden	70	38.5
SAPS-3	**Median** [min - max]	**Average**
Points	64 [31-101]	-
Probability of death	44.0 [2.08-91.77]	44.4

SAPS-3 = Simplified Acute Physiology Score
BMI = Body Mass Index

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Table 2: Data on patient admission to palliative care studied (n=182)

Proceeding	n	%
Invasive Device Usage		
Not referred to	95	52.2
Yes	87	47.8
Use of mechanical ventilation		
Not referred to	118	64.8
Yes	64	35.2
Use of urinary catheter		
Not referred to	164	90.1
Yes	18	9.9
Use of intravascular device (N)		
Deep Venous - Internal Jugular	26	14.3
Deep Vein – Subclavian	18	9.9
Arterial – Radial	2	1.1
Use of vasoactive drug (N)	40	22
Destination after hospitalization		
Death	92	55.5
Infirmary or room	83	45.6
Residence	6	3.3
Hospice / Support house	1	0.5
The outcome when leaving the hospital		
Death	138	75.8
Discharged from hospital	44	24.2
Destination when leaving the hospital		
Death	138	75.8
Residence	42	23.1
Hospice / Support house	2	1.1
	Median [min-max]	
Length of hospital stay (days)	6 [1-116]	
Duration of urinary catheter use - median [min - max]	2.5 [0-42]	
Total duration of mechanical ventilation - median [min - max]	2 [0-98]	
Length of stay in the ICU (days)	2 [1-24]	

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Table 3: Data on the infectious site and the use of antimicrobials in the group of patients

under palliative care in the ICU (n=182)

	n	%
Infections	27	14.8
Site of infection		
Pneumonia	9	33.4
Urinary	6	22.2
Peritonitis	5	18.5
Bloodstream infection	3	11.1
Abdominal	1	3.7
Undetermined	1	3.7
Surgical site infection	1	3.7
Biliary tract infection	1	3.7
Source		
Community	14	51.8
Hospital	13	48.2
Antimicrobial		
Ceftriaxone	15	20
Metronidazole	8	10.7
Cefepime	7	9.3
Meropenem	7	9.3
Azithromycin	5	6.7
Piperacillin + Tazobactam	5	6.7
Vancomycin	4	5.3
Fluconazole	3	4
Others	21	28,2
Antimicrobial Spectrum		
Broad	19	25.4
Narrow	8	10.7

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Table 4: Comparisons between patients who used or did not antimicrobials during their ICU stay

	Not referred to (n=155)		Used (n=27)		
	n	**%**	**n**	**%**	**p**
Sex					
Female	77	49.7	12	44.4	0.679
Male	78	50.3	15	55.6	
Functionality					
Independent	39	20.6	9	33.4	0.227
Need for assistance	60	38.7	11	40.7	
Restricted/bedridden	63	40.7	7	25.9	
Outcome					
Discharge	39	25.2	5	18.5	0.627
Death	116	74.8	22	81.5	
Palliative care decision					
Limit	73	47.1	14	51.9	0.806
Do not intensify	51	32.9	9	33.3	
Remove	31	20	4	14.8	
Antibiotic use	**Not referred to (n=155)**		**Used (n=27)**		
	Median [IQR]		**Median** [IQR]		**p**
Age	66 [53-74]		62 [50-71]		0.191
Comorbidity Index	6 [3-7]		6 [4-9]		0.311
Length of stay	5 [2-9]		11 [4-19]		**0.014**

IQR: Interquartile Range
SAPS-3 = Simplified Acute Physiology Score
BMI = Body Mass Index

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