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FMUP FACULDADE DE MEDICINA
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Antibiotics in end-of-life care: a systematic review

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Palliative Care Master 2016-2018

Tese de Mestrado apresentada para obtenção do grau de Mestre em Cuidados Paliativos

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Mas não é a ideia de desconhecido que assusta: é a ideia de que não haja desconhecido; apenas o fim.

(Susana Moreira Marques, *in* "Agora e na hora da nossa morte")

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Motivação

Acredito que toda a prática médica deve sustentar-se em evidência científica com o mais elevado padrão de qualidade *possível*. Como é conhecido, a investigação em Cuidados Paliativos é (ainda mais) indissociável de constrangimentos de natureza ética, o que torna infrequente a realização de ensaios clínicos – aqueles que indiscutivelmente produzem evidência mais próxima da causa-efeito –, sobretudo quando prevêem a existência de grupos de controlo e de estratégias de aleatorização. Consequentemente, a prática médica no contexto dos Cuidados Paliativos fundamenta-se na evidência produzida por outras ferramentas de investigação.

É neste enquadramento que surge a presente revisão sistemática. Foi concebida com o único objectivo de reflectir sobre um quesito que não raras vezes se coloca ao profissional de saúde, independentemente da sua profissão, da sua diferenciação médico-cirúrgica e do local onde exerce: num determinado doente em fim de vida com sintomas possivelmente atribuíveis a uma infecção há vantagem em instituir antibioterapia em termos de controlo sintomático e/ou prolongamento da sobrevida?

Dados os pressupostos atrás expostos, não tenho a presunção de chegar a uma conclusão definitiva e incontestável. No entanto, entendo que o exercício de rever a literatura, de compreender o percurso feito pelos autores que se debruçaram sobre o tema e de registar de forma objectiva o resultado desses trabalhos pode constituir um contributo relevante para que a prescrição de antibióticos no fim de vida passe de instintiva a consciente, com tudo de bom que isso poderá trazer àquele indivíduo com uma doença terminal. Considero o meu trabalho proveitoso se esse objectivo se verificar.

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Abstract

Patients receiving palliative and end-of-life care are susceptible to infections and often develop signs and symptoms that suggest this diagnosis. Because infections can be cumbersome, hasten patients decay or even be the terminal event, physicians are frequently posed the dilemma of whether or not to initiate antibiotics in this setting. However, data is not consensual regarding the role of antibiotics in symptom improvement or life prolongation.

The main objectives of this work are to characterize the use of antibiotics in patients at EOL and to clarify their impact on symptom control and survival. With this purpose, we systematically reviewed the available literature published from January 1, 1997 to June 30, 2017. Studies with adult patients with advanced/terminal illnesses followed by hospice/palliative care were included. We extracted data on demographics, patients' underlying condition(s), healthcare setting, antibiotics use prevalences, indications and factors associated with antimicrobials prescription, percentage of symptom improvement and/or survival, and methods used to assess these outcomes.

A total of 27 publications met our inclusion criteria, most of which were retrospective and involved cancer patients admitted to hospice care programs. The use of antibiotics varied from 10 to 97,5%. Some studies addressed symptom improvement, which also varied widely (0-92%) but tended to be greater for urinary tract infection-related symptoms, followed by respiratory tract infection and skin and soft tissue infection. Bacteremias didn't benefit from antibiotics. An even smaller number of publications evaluated factors associated with antibiotics prescription and their impact on survival.

Data is still scarce and with debatable quality for definitely concluding about the impact of antibiotics on symptom improvement or life prolongation. Also, no study specifically evaluated how antibiotics influence quality of life. Future studies need to follow patients prospectively, better define what "symptom improvement" means, rely more on patients' self-report and compare outcomes between treated and non-treated patients.

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1. Introduction

1.1. Palliative Care definition and concept evolution

According to the World Health Organization, Palliative Care (PC) is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems (physical, psychosocial and spiritual). As such, it provides relief from pain and other distressing symptoms; affirms life and regards dying as a normal process; intends neither to hasten or postpone death; integrates psychosocial and spiritual aspects of patient care; offers a support system to help patients live as actively as possible until death; offers a support system to help the family cope during the patients' illness and in their own bereavement; uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated; enhances quality of life and may positively influence the course of illness; is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications". This thorough definition underlines palliative goals of care: to minimize suffering and maximize quality of life, while preserving patient dignity in an as much as possible healthy dying process.(1,2)

The evolution of modern PC and its history is still short. It wasn't until the 1950s, with Dame Cicely Saunders, that care of the dying was first viewed with concern.(3) She built some of her ideas based on careful observation of dying patients during wartime and the results of several end-of-life (EOL) surveys conducted by Marie Curie Memorial Foundation (1952), Gulbenkian Foundation (1960) and John Hinton (1963).(3,4) As a result, St. Christopher's hospice opened in 1967 with capacity for 54 patients, a planned bereavement service and, later, the possibility of providing home care.(3)

"Palliative Care" was first coined in the 1970s by the hand of Dr. Balfour Mount, a surgical oncologist that introduced Dame Cicely Saunders' work to the Canadian health academia. This term replaced "hospice care", which had a negative connotation in the French culture.(3)

Since then, much has been done with regard to certified medical education and quality research. However, many stereotypes still undermine PC implementation around the globe and demand for fierce work. Two important tasks are underway: one is to clarify concepts –

for example, to distinguish PC from EOL care, as PC only means that the disease is incurable and has no timeframe prognosis associated(2) – and the other is to assemble solid scientific evidence to sustain clinical and psychosocial interventions done in the context of PC. In fact, investigation in PC debates itself with a major obstacle when it comes to the quality of scientific evidence: it might be ethically questionable to submit PC patients to clinical trials, particularly if randomization and placebo controls are to be used. As a consequence, healthcare professionals dedicated to PC have the responsibility of (re)evaluating an evolving balance between potential benefits and harms of a variety of otherwise common medical interventions. This is the case with antimicrobial use, one of the last interventions to be withdrawn or withheld in EOL care.(5)

1.2. Infection in Palliative Care

Infective complications play a major role in the morbidity and mortality of PC patients.(2,6–9) Several factors are classically described to explain their vulnerability to infection, namely decreased host resistance, multiple co-morbid illnesses, immobility, malnutrition, dehydration, polypharmacy, presence of invasive devices and frequent healthcare exposures.(1,2,8,10–16) Volicer *et al*, cited by Enck, also stated that infection was a common cause of death in patients with advanced dementia probably due to aspiration subsequent to dysphagia.(17)

However, some of these factors were further studied by Yajima *et al*. These authors examined a small group of Japanese patients with advanced cancer that received PC and died during their hospital stay. They concluded that performance status, fall risk assessment score and the presence of central venous catheter correlated significantly with infection, but not patient age or sex, bedsores, edema, ascites, dysphagia, nausea, malnutrition, treatment history, urethral catheters, drainage or stomach tubes, colostomies and current medical treatments.(9) Although interesting, these results deserve careful analysis, since the study was small, retrospectively reviewed medical charts and involved a specific population admitted to an acute care hospital.

The real burden of infection in PC is still not well described. Pautex *et al* performed an autopsy-based study to list the main anatomical-pathological causes of death in patients with advanced cancer. They concluded that pulmonary infection was the commonest (55%), followed by advanced cancer itself (16%), pulmonary infection together with pulmonary embolism (12%), pulmonary embolism alone (9%), cardiac complications (5%) and others

(1%).(8) Béziaud and colleagues cite other authors to describe an incidence of 29-83% of infections in patients with non-malignant advanced conditions.(2) However, some authors suggest that much of the anti-infective drugs use in PC occurs in the absence of a documented infection. Merel *et al*, for example, found that 31% of PC patients doing antimicrobials did not have a diagnosis of infection.(18) Another study concluded that amongst hospice patients receiving antibiotics in their last week of life only 15% had an unequivocal diagnosis of infection.(19)

This discrepancy stings from the difficulty in diagnosing infection within PC patients. Furuno and colleagues considered that this diagnosis was complicated by the impossibility of detecting new signs and symptoms, as well as the high prevalence of cognitively impaired and non-verbal patients.(1) Béziaud *et al* also addressed this question, concluding that this uncertainty was due to the absence of classical signs of infection (such as fever), to the existence of alternative explanations for blood tests changes (such as elevation of leucocytes secondary to steroids use) and/or to patients presenting with clinical syndromes characterized by vague symptoms and signs (such as malaise, weight loss or confusion).(2) Interestingly, this difficulty seems to be extendable to proxies: in a report by Givens *et al*, based in a prospective cohort study of nursing home residents with advanced dementia (Study of Pathogen Resistance and Antimicrobial Use in Dementia – SPREAD), 496 suspected infections were experienced by 362 residents over a 12-month period, but proxies reported being aware of only 39% of all episodes.(20)

The most commonly observed infections in hospice patients are respiratory tract infections (RTI), urinary tract infections (UTI), gastrointestinal infections, wound infections and bacteremia; the frequency of each type of infection isn't, however, consensual.(2,11,14) Non-infectious fever is also an important consideration among patients with malignancies and dementia: when fever ensues without localizing signs of infection, alternative causes such as drug-related, venous thromboembolism and neoplastic fever should be considered.(2,5)

1.3. Antibiotics use in PC

Healthcare professionals dealing with EOL patients frequently face the need of making difficult decisions that should balance medical, ethical, psychosocial and societal considerations.(21,22) According to Ford and colleagues in a publication from 2005 discussing the ethics behind anti-infective therapy at EOL, the following topics should be appraised: "are antibiotics delaying transition to hospice or prolonging the dying process?

Are these drugs congruent with short-life expectancy and goals of care? Could we be increasing the reservoir of potential resistant pathogens or placing unreasonable costs on a capitated health system by prescribing anti-infectives at EOL?"(23) These topics, the authors add, should set out the discussion, be it on a research basis or when a clinical decision regarding antibiotics prescription has to be taken.

Decisions about life-sustaining treatments use are known to be affected by the perceived effectiveness of a given treatment, the presumed effect on the patient's quality of life, and the wishes, beliefs and expectations of the patient and family.(24) Concerning antimicrobials, prolonged survival and symptom relief are the two potential benefits that most motivate physicians to start them.(8,22,25,26) On the other hand, physicians' decisions regarding withholding antibiotics are influenced by severe dementia, severe pneumonia, low intake of food and fluids, dehydration and a previous episode of pneumonia.(12)

Hinkka *et al* studied the variability in EOL decisions concerning specific treatments and its association with Finnish physicians' personal characteristics, life-experiences and training. They found that although the majority of respondents would withdraw antibiotics, those who disapproved active euthanasia were significantly more likely to continue these drugs. This group believes that maintenance of antibiotics is also a matter of principle.(27)

Research has shown that high rates of hospitalization of severely incapacitated nursing home residents correlate with poorer advance-care planning and lack of adherence to advance directives.(28) Mitchell *et al* showed that only 45,3% of patients or healthcare proxies were asked about their preferences regarding antimicrobials use, and fewer received counselling on this issue.(29)

Ang and colleagues compared attitudes, preferences and decision-making about EOL care between patients, relatives, doctors and nurses in a tertiary hospital from Singapore. They discovered that relatives and nursing staff were more likely to opt for invasive life-sustaining treatments – including antibiotics – than patients themselves. They hypothesized that this decision may have helped relatives and nursing staff to feel satisfied with having tried their best on someone's behalf, but could also be the result of fear of the guilt, regret or sense of negligence at the untimely death of the loved one because of a decision not to treat.(30)

Likewise, Potkins *et al*, in a study that examined the wishes of carers regarding EOL treatment decisions, concluded that the majority wished active treatment to be initiated and those decisions were relatively fixed and insensible to parameters affecting quality of life.(31)

Maida *et al* explored the preferences of advanced cancer patients referred to a regional palliative medicine consultation program and their substitute decision-makers about

commonly offered active and aggressive medical therapies, namely antibiotics. They realized that 50,9% of patients who desired to be given antibiotics tended to be younger and to have a higher performance status.(32)

In a survey with advanced cancer patients integrated in community-based hospice programs, White *et al* found that 79,2% of patients preferred to either avoid antimicrobials or to use antimicrobials with the goal of symptomatic relief only.(33) Kass-Bartelmes & Hughes discovered that patients were more likely to accept short-term or simple treatments such as antibiotics than long-term invasive treatments such as permanent tube feeding.(34) More recently Kissane *et al* studied the Japanese population EOL preferences by doing a national survey and concluded that about half to two thirds expressed a preference for antibiotics.(35)

Data on effectiveness of antibiotics in PC is sparse(12,36), partly because the meaning of effectiveness depends on patients' goals of care. In fact, effectiveness can be regarded as resolution of symptoms, eradication of a putative infection or prolonging life.(1) A study by Cardona-Morrell showed that 38% of patients received what was classified as "non-beneficial medicines", which included antibiotics.(37) Pautex *et al*, in the previously mentioned anatomical-pathological study, found that 64 of 87 patients who received antibiotics in their last two weeks of life still died of pneumonia.(8)

Some authors consider antibiotics useful at least for symptom control, with UTIs being frequently cited as the paradigm of symptomatic infections that benefit with a course of oral or parenteral antibiotics.(11,23,38) Van der Steen and colleagues, in an exhaustive work developed throughout some years, concluded that antibiotic treatment was independently associated with less discomfort shortly before death in dementia patients.(39) Baghban and Juthani-Mehta also denoted that individual patients with painful symptoms attributable to particular infections such as *Herpes Simplex* virus, *Varicella Zoster* virus or oral candidiasis derive great benefit from antimicrobials with a goal of palliation.(5)

Reliable information on safety of antibiotics for PC patients is similarly scant, and side effects of these drugs tend to be trivialized.(17) In fact, antimicrobial use is often viewed as less burdensome that other potentially life-prolonging interventions such as intubation, ventilatory support, dialysis and cardiopulmonary resuscitation.(5,17,40,41) Accordingly, patients and families may incorrectly perceive antimicrobials as "benign" drugs.(1,22)

Adverse outcomes of antimicrobial administration include drug toxicity(8,12,17,22) such as renal failure, ototoxicity and blood dyscrasias; allergic reactions(12); drug-drug interactions (for example, bleeding due to diminished vitamin K levels)(17,22) and the risk of *Clostridium difficile* infection(8,13,17,22). Furuno *et al* reported that 47% to 62% of Oregon

hospice programs assumed that “sometimes” or “often” antibiotics were discontinued due to diarrhea, nausea/vomiting and yeast infections. There was also 14% of respondents who reported sometimes observing *Clostridium difficile* infections in these patients.(5,42)

Moreover, the evaluation (with bladder catheterization, blood draws, chest x-rays, *etc*) and treatment of suspected infections carry additional stress in terminally ill patients, particularly when hospitalization is needed.(8,12,22,23) In fact, the use of intravenous devices for parenteral antibiotics carries the risk of phlebitis, local skin and soft tissue infections and secondary bacteremia. Furthermore, insertion of either central or peripheral venous catheters is painful and may necessitate mechanical restraints in delirious or demented patients.(5,12)

In addition to adverse patient outcomes, societal costs of non-beneficial treatments are significant.(5) In one hand, previous antimicrobial exposure is the most important factor associated with acquisition of multidrug-resistant organisms among patients at EOL, which not only affects the patient but also presents a general public health concern.(8,10,22,23) The development of antimicrobial resistance is even worse when drugs are not properly dosed or when they are used for too long or too short, a not uncommon scenario in PC.(2)

As an example, Levin and colleagues identified certain choices in EOL therapy as risk factors for the acquisition of resistant bacteria in the Intensive Care Unit (UCI) setting. In their prospective observational study in two ICUs with different EOL care they found that non-withdrawal of therapy in very sick ICU patients who ultimately died may have led to increased use of antibiotics and increased incidence of resistant bacteria.(43) Although hypothetical, this mechanism deserves further studies.

In conclusion, the probability of symptom improvement must be weighed against the burdens imposed to patients, as well as the public health concerns regarding antibiotic resistances.(17,44)

Although costs should not be the driving element for any decision in PC, realistic fiscal circumstances must also be taken into account in this setting in the name of distributive justice, just as they are for other patients.(23)

Lastly, Ford and colleagues also expressed the concern that anti-infective drugs might be seen as an excuse to delay addressing patients’ terminal condition and be responsible for creating a false hope for improvement and the belief that the patient’s overall condition is still treatable.(23)

Acute problems in palliative and EOL care are primarily ethical problems, as decisions have to be made on whether to treat fully, to use limited treatments or to not treat at all. This is not, however, a dilemma exclusive to modern clinical practice: in the first edition of *The Principles and Practice of Medicine*, published in 1892, Osler described pneumonia as "the special enemy of old age", an opinion he soon revised by affirming that "pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old man escapes the 'cold gradations of decay' so distressing to himself and to his friends".(cited by (45,46))

We then conclude that conflicting goals of care were discussed in Osler's days as they are now. And, as previously exposed, evidence is conflicting when it comes to the role of antibiotics in symptom control: some authors suggest that they may alleviate suffering, others sustain that antimicrobial agents and aggressive infection treatment may be associated with greater discomfort.(46) As a consequence, benefits of aggressive *versus* conservative management of patients with infection at EOL have not been defined and there is still insufficient evidence to guide sound decision making in this setting.(46)

The aim of this systematic review is to characterize antibiotics use in patients at EOL and to clarify their impact on symptom control and survival based on articles published in the last 20 years. We also expect to identify patient and/or illness factors that positively influence the decision of starting antibiotics.

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2. Methods

2.1. Literature search

Our methodology was adapted from the work of Rosenberg *et al*(36) and van der Maaden *et al*(47).

We performed systematic searches in PubMed, Scopus, The Cochrane Library, Scientific Electronic Library Online (SciELO), Web of Science and Google Scholar (for grey literature) limited to the period from January 1, 1997 until June 30, 2017. Search terms included controlled terms from MeSH in PubMed and The Cochrane Library, as well as free-text terms. The following search terms were used: (palliative care OR end-of-life care OR terminal care) AND (antibiotics OR antimicrobials OR antibacterials OR anti-infectives).

Additional relevant studies were identified by a manual search of references from articles eligible for inclusion.

2.2. Inclusion and exclusion criteria

Articles were included if they provided data on antimicrobial use in human subjects older than 18 years-old with advanced or terminal illnesses under hospice, palliative or end-of-life care.

We excluded studies that only assessed the use of antimicrobial wound dressings or mouthwashes, studies with patients admitted to nursing homes or other chronic care facilities, survey-based publications evaluating healthcare professionals decision-making regarding anti-infective drugs prescription, studies reporting neither prevalence of antibiotics use nor percentage of symptom improvement, case reports and reviews.

Publications written in languages other than English, French, Italian, Portuguese or Spanish were also excluded.

2.3. Selection process

One author (IAC) screened all potentially relevant titles and abstracts retrieved by the initial search. If possibly eligible, full-text article was analyzed, particularly study objectives, methods and results. Identified publications were further reviewed by two other authors (CP

and EG). Differences in judgment were resolved through a consensus procedure between all three authors.

Due to its methodology, this study was determined to be exempt from institutional review board approval.

2.4. Data extraction and analysis

The following information was extracted from articles meeting inclusion criteria: author(s); year of publication; study design; location of study; sample size and characteristics of patient population (underlying chronic condition, mean or median age and gender distribution); prevalence, indication(s) and factors influencing antimicrobials prescription; and whether symptom response following antibiotics use was considered, which was the definition of symptom response and which methods were chosen to assess it.

As noted by Rosenberg *et al*, prevalence of antimicrobial use was based on total number of patients, infected patients or infective episodes. We determined overall patients to be the standard unit; when episodes of infection or exclusively infected patients were considered for the calculus of prevalence we specifically mention it.

In those publications whose prevalence of antimicrobial use was not explicitly reported we opted to calculate it based on the text content.

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3. Results

We identified a total of 5976 publications in PubMed, Scopus, The Cochrane Library, SciELO, Web of Science and Google Scholar databases, plus 22 from references lists. After removing duplicates, each title and abstract was reviewed and 173 potential articles were identified. We then thoroughly revised all articles' aims, methods (mostly population characteristics, study design and assessment tools) and results (particularly disclosed numbers, their significance and how they were obtained), and selected 27 studies that met all inclusion criteria and were, therefore, eligible for the systematic review (**figure 1**).

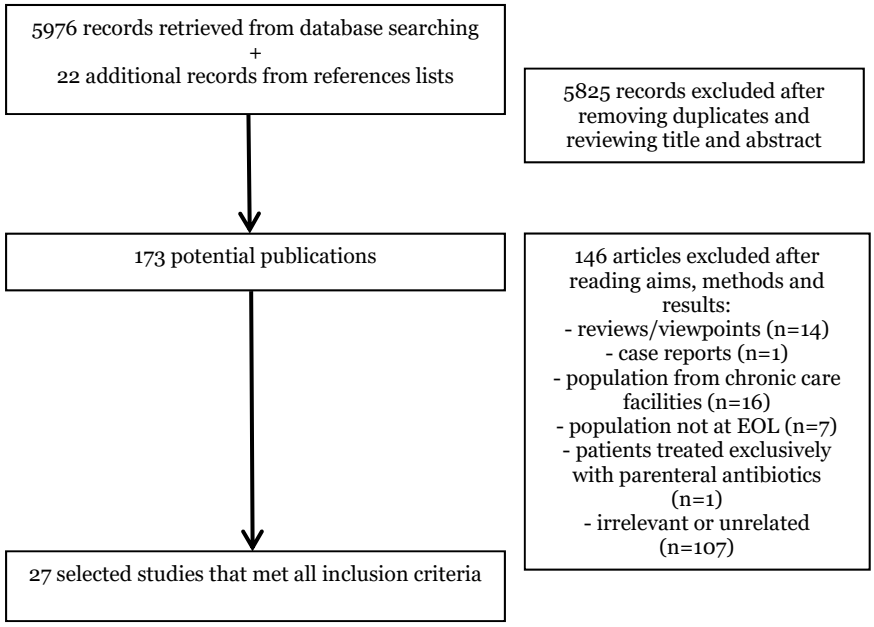

Figure 1. Flowchart of search and selection procedure of publications

A small number of publications were individually discussed because of population issues or exclusive use of parenteral antibiotics.

The characteristics of selected studies are displayed in **table 1**.

Analysis of all 27 articles allowed a total of 15298 pooled patients. The majority (19/27) of publications are retrospective studies(14,15,18,19,48–62); six are prospective(7,33,38,63–65) and two are cross-sectional(42,66). Two studies were published as "letters to the editor"(54,62) and one as an abstract of a poster presented at the 10th PC Congress of United Kingdom(48). We only had access to the abstract of two studies, even after trying to contact the authors (who were either retired, deceased, had no contact available online or had no

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means for being contacted by their former university/hospital).(38,60) Since it was not an exclusion criterion and there was enough information to be extracted, we decided to include these works nevertheless.

When considered individually, sample size of each study ranged from 26 and 3884 (median 248; P25-P75 123-810) patients.

In terms of geographic distribution, thirteen studies were conducted in North America(7,15,18,19,33,38,42,50,54,55,60,63,66), eight in Asia(51–53,56,57,59,61,65), four in Europe(48,49,58,64), one in South America(62) and another one in Australia(14).

The setting where each study took place was diverse: seven studies were done with hospice patients(14,48,53,54,58,61,66); six included patients from PC units(7,15,51,57,62,65) and five evaluated acute care hospitals' patients (18,50,52,56,59); two studies were done with patients from different PC contexts (PC units, outpatient physicians and nursing services, and acute care hospitals)(60,64); two publications derived from both home-based and inpatient hospice care settings(19,49), and another two from community home-based hospice programs(33,63); one study was performed in a rehabilitation center(55), another one was done with patients enrolled in PC programs not otherwise specified(38) and a third was conducted with patients discharged from an acute university hospital to hospice care(42).

Regarding patients' characteristics, 13 studies included only cancer patients(7,15,33,38,49,51,52,56,57,59,62,63,65), another six were performed with patients with different illnesses requiring PC(14,18,19,42,53,58), one study was done with patients with advanced dementia(55), another with patients that died at an acute care setting(50) and a third one involved patients at EOL with no specification about their diagnosis(60); three studies described their sample solely as "hospice patients"(61,64,66) and another two studies (corresponding to a "letter to the editor" and an abstract) didn't characterize their population (48,54).

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Table 1. Description and results of studies that assessed antimicrobials use prevalence and associated symptom improvement among EOL patients

Title	Authors	Year of publication	Study design	Location	Population		Conclusions
					Sample size	*Characteristics*	
Frequency of outpatient antibiotic prescription on discharge to hospice care	Furuno JP, Noble BN, Horne KN, McGregor JC, Elman MR, Bearden DT, Walsh EW, Fromme EK	2014	Cross-sectional (1/01/2010 to 31/12/2012)	Patients discharged from Oregon Health & Science University to hospice care (USA)	845	Cancer 57,6% COPD 17,5% Dementia 15,0% Heart failure 64,5% Cerebrovascular disease 22,0% Renal or liver disease 45,1% **Age ≥ 65:** 50,9% **Male:** 54,6%	**Prevalence:** 21,1% **Indications:** active infection (>3 consecutive days of antibiotics + diagnosis of infection in medical records or positive clinical culture) – 71,8% **Factors influencing prescription:** younger age, cancer diagnosis, higher Charlson comorbidity index score, longer hospital LOS **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
A retrospective review of antimicrobial prescribing and infection prevalence in a PC unit (abstract only)	McKane J, Addie S, McGowan M-C	2014	Retrospective (four month period)	St. Vicent's Hospice (Howwood, UK)	33	NM	**Prevalence:** 76,7% **Indications:** UTI (34%), LRTI (60%) » specified in 88% of cases, empirical in 91% **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Antibiotic treatment in EOL cancer patients – a retrospective observational study at a PC center in Sweden	Helde-Frankling M, Bergqvist J, Bergman P, Björkhem-Bergman L	2016	Retrospective	Palliative Home Care and Hospice Ward of ASIH Stockholm Södra (Sweden)	160	Cancer patients in their last two weeks of life **Age (median):** 71 **Male:** 43%	**Prevalence:** 49,4% **Indications:** treatment/prevention of sepsis, RT symptoms, UT symptoms, GI-tract symptoms, skin infections **Factors influencing prescription:** NM **Symptom improvement:** 36,7% **Definition of symptom response:** reduced fatigue, resolution of fever, patient "gained energy to do things of their choice that were not possible before antibiotic treatment" **Methods used to assess symptom response:** healthcare staff perception
A nationwide analysis of antibiotic use in hospice care in the final week of life	Albrecht JS, McGregor JC, Fromme EK, Bearden DT, Furuno JP	2013	Retrospective (National Home and Hospice Care Survey)	Home and Hospice care, either private or not-for-profit (USA)	3884	Cancer 45% COPD 5% Dementia 11% Heart failure 9% Cerebrovascular disease 5% Renal or liver disease 2% Debility 10% Other 13% **Age ≥ 65:** 83% **Male:** 45%	**Prevalence:** 27% **Indications:** probable/confirmed infection (15%) **Factors influencing prescription:** younger age, longer duration of care, COPD diagnosis **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM

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Antimicrobial use at the EOL among hospitalized patients with advanced cancer	Thompson AJ, Silveira MJ, Vitale CA, Malani PN	2012	Retrospective (1/01/2004 to 31/12/2007)	University of Michigan Comprehensive Cancer Center – UMCCC (USA)	145	Inpatients who died at UMCCC **Age (mean):** 60,3 **Male:** 57,6%	**Prevalence:** 86,9%; 45,2% discontinued prior to death (average of time: 0,8±2,1 days) **Indications:** infection (69,8%), with 27% with fever and 48,4% with positive cultures **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
The pattern of antimicrobial use for PC inpatients during the last week of life	Al-Shaqi MA, Alami AH, Al-Zahrani AS, Al-Marshad B, Bin-Muammar A, Al-Shahri	2012	Retrospective (06/2007 to 07/2008)	Tertiary Palliative Care Unit (Saudi Arabia)	138	Cancer patients who are not for CPR and for whom no disease-modifying therapy is possible **Age (median):** 50,5 **Male:** 43,5%	**Prevalence:** 63% (46,4 on antibiotics, 32,6 on antifungal and 1,5% on antiviral agents) **Indications:** oral thrush (25,4%), wound care (20,4%), empirically (20,4%), positive urine culture (15,5%), chest infection (8,5%), positive blood culture (5,6%), others (4,2%) **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Can anti-infective drugs improve the infection-related symptoms of patients with cancer during the terminal stages of their lives?	Nakagawa S, Toya Y, Okamoto Y, Tsuneto S, Goya S, Tanimukai H, Matsuda Y, Ohno Y, Eto H, Tsugane M, Takagi T, Uejima E	2010	Retrospective (01/2006 to 12/2006)	Osaka University Hospital (Japan)	111	Cancer patients who died during their hospital stay **Age (mean):** 61,3 **Male:** 56,8%	**Prevalence:** 64% **Indications:** 56,4% treatment of infection, 16,9% suspected infection, 10,4% prevention of infection and 16,3% unknown **Factors influencing prescription:** NM **Symptom improvement:** 33,1% (9,2% if in the last week of life) **Definition of symptom response:** self-report of amelioration or completion of anti-infective drugs **Methods used to assess symptom response:** patient self-report or healthcare staff perception; fever resolution or decrease of leukocyte count/CRP levels
Bacterial infections in terminally ill hospice patients	Vitetta L, Kenner D, Sali A	2000	Retrospective (05/1997 to 10/1998)	Caritas Christi Hospice (Australia)	102	Patients admitted to hospice (92,2% malignancies, 7,8% non-malignant illness) **Age (mean):** 72,3 **Male:** 49,0%	**Prevalence:** 34,3% **Indications:** diagnosis of infection, either by symptoms or cultures **Factors influencing prescription:** NM **Symptom improvement:** 40% **Definition of symptom response:** amelioration of symptoms and completion of anti-infective drugs or infection-related death **Methods used to assess symptom response:** healthcare staff perception
An audit on antibiotic use at the end of life in inpatient hospice patients – are we contributing to over-	Lo TJ, Wu HY, Ong WY, Lee A	2015	Retrospective (07/2013 to 09/2013)	Dover Park Hospice (Singapore)	127	Cancer (93,7%) or non-cancer (6,3%) diagnosis with estimated prognosis < 3 months **Age (mean):** 68,5 **Male:** 55,1%	**Prevalence:** 17,3% **Indications:** suspected infection (3,9% with positive cultures) **Factors influencing prescription:** NM **Symptom improvement:** 75,0% (UTI) and 66,6% (LRTI) **Definition of symptom response:** not clearly mentioned **Methods used to assess symptom response:** NM

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Feasibility of retrospective pharmacovigi lance studies in hospice care: a case study of antibiotics for the treatment of UTI	Furuno JP, Noble BN, Bearden DT, Fromme EK	2017	Retrospective (1/01/2015 to 30/09/2015)	For-profit hospice (USA)	520	NM	**Prevalence:** 25,4% **Indications:** symptoms suggestive of infection or infection prophylaxis **Factors influencing prescription:** NM **Symptom improvement:** 0% **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Is it appropriate to withdraw antibiotics in terminal patients with cancer with infection	Chih A-H, Lee LT, Cheng S-Y, Yao C-A, Hu W-Y, Chen C-Y, Chiu T-Y	2013	Prospective observational (1/01/2008 to 30/04/2010)	PC unit of National Taiwan University Hospital (Taiwan)	799	Patients with advanced cancer **Age ≥ 65:** 53,7% **Male:** 57,8%	**Prevalence:** 78% (75,8% one week after admission and 59,1% 2 days before death) **Indications:** diagnosis of infection based on microbe-related symptoms and laboratory or imaging reports **Factors influencing prescription:** NM **Symptom improvement:** NM (but HR of prolonging survival with antibiotics after one week of hospitalization 0,66; HR of prolonging survival if antibiotics administered 2 days prior to death 1,54) **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Antibiotics in Palliative Medicine – results from a prospective epidemiologic al investigation from the HOPE survey	Stiel S, Krumm N, Pestinger M, Lindena G, Nauck F, Ostgathe C, Radbruch L, Elsner F	2012	Prospective epidemiologic al (15/03/2006 to 15/06/2006)	PC services (82.6% PC units, 2.7% oncology units, 10.3% inpatient hospices, 1.8% outpatient physicians, 2.7% outpatient nursing services) (Germany)	448	Patients admitted to PC services **Age (mean):** 67,2 **Male:** 46,7%	**Prevalence:** 63,8% **Indications:** multi-resistant *Staphylococcus aureus* or *Clostridium difficile*, UTI, LRTI, to reduce wound malodour **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Occurrence and treatment of suspected pneumonia in long-term care residents dying with advanced dementia	Chen J-H, Lamberg JL, Chen Y-C, Kiely DK, Page JH, Person CJ, Mitchell SL	2006	Retrospective (1/01/2001 to 31/12/2003)	Hebrew Rehabilitation Center (USA)	240 (229 suspected pneumonia episodes)	Patients with advanced dementia with suspected pneumonia **Age (median):** 91 **Male:** 31%	**Prevalence:** 91% **Indications:** NM **Factors influencing prescription:** lack of a do-not-hospitalize order, aspiration episodes, primary language not English and at least one unstable vital sign **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
The pattern of infection and	Mohammed AA, Al-	2014	Retrospective (10/2010 to	King Abdullah Medical City-	258	EOL cancer patients who are receiving PC	**Prevalence:** 94,2% (60% empirical) **Indications:** active infection

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antibiotics use in terminal cancer patients	Zahrani AS, Sherisher MA, Alnagar AA, El-Shentenawy A, El-Kashif AT		12/2012)	Holy Capital (Saudi Arabia)		**Age (mean):** 60,5 **Male:** 50%	**Factors influencing prescription:** NM **Symptom improvement:** 17,3% **Definition of symptom response:** NM **Methods used to assess symptom response:** healthcare staff perception
The role of antibiotics in the management of infection-related symptoms in advancer cancer patients (abstract only)	Mirhosseini M, Oneschuk D, Hunter B, Hanson J, Quan H, Amigo P	2006	Prospective	Edmonton PC Program (Canada)	26	Advanced cancer patients **Age:** NM **Male:** NM	**Prevalence:** NM **Indications:** active infection **Factors influencing prescription:** NM **Symptom improvement:** 48,4% **Definition of symptom response:** NM **Methods used to assess symptom response:** Edmonton Symptom Assessment Scale score adapted
Retrospective analysis of antibiotic use and survival in advanced cancer patients with infections	Lam T, Chan KS, Tse CY, Leung MW	2005	Retrospective (01/2002 to 07/2002)	PC Unit of United Christian Hospital (Hong Kong)	87 (120 episodes of infection)	Advanced cancer patients **Age (mean):** 67,4 **Male:** 62,1%	**Prevalence:** 97,5% (unit: episodes of infection) **Indications:** probable infection **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM (but: worse outcome survival with low serum albumin, chest infection, dyspnea as major symptom of infection, empirical antibiotic therapy and parenteral antibiotic route)
A retrospective review of the frequency of infections and patterns of antibiotic utilization on a PC unit	Pereira J, Watanabe S, Wolch G	1998	Retrospective	PC Unit of Edmonton (Canada)	100 consecutive patients	Terminally ill cancer patients **Age (mean):** 64 **Male:** 43%	**Prevalence:** 71,6% (unit: episodes of infection) **Indications:** NM **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Management of healthcare-associated infections at the end of life – a cross-sectional study	Gradalski T, Burczyk-Fitowska B	2017	Retrospective (1/09/2013 to 31/01/2016)	Hospice setting (Krakow, Poland)	1458 (172 healthcare-associated infections)	Hospice patients with healthcare-associated infections; 90% with cancer **Age (mean):** IG 70,2, NIG 68,2 **Male:** IG 48,5%, NIG 47,3%	**Prevalence:** 90% (unit: infected patients) **Indications:** NM **Factors influencing prescription:** NM **Symptom improvement:** 70,3% **Definition of symptom response:** "clinical cure" if all constitutional symptoms and signs of infection ceased, "symptomatic relief" if symptoms disappeared but signs persisted, "symptomatic alleviation" if some symptoms disappeared or diminished, "symptomatic stabilization" and "worsening" **Methods used to assess symptom response:** self-report, healthcare staff perception, blood tests results

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Antibiotic use during the last days of life in cancer patients	Oh DY, Kim JH, Kim DW, Im SA, Kim TY, Heo DS, Bang YJ, Kim NK	2006	Retrospective (1/03/2003 to 30/04/2004)	Seoul National University Boramae Hospital (South Korea)	141	Terminal stage cancer patients **Age (mean):** 64,7 **Male:** 58,2%	**Prevalence:** 84,4% **Indications:** described as complex – combinations of fever, leukocytosis, elevated CRP and clinical decisions **Factors influencing prescription:** NM **Symptom improvement:** 15,1% (fever control 48%, leukocytosis 17%, CRP value 29%, eradication of organism 31%) **Definition of symptom response:** NM **Methods used to assess symptom response:** healthcare staff perception, blood tests results
Antibiotic use in the last week of life in three different PC settings (abstract only)	Oneschuk D, Fainsinger R, Demoissac D	2002	Retrospective	Acute care hospital, tertiary PC unit, hospice units (Canada)	150 consecutive patients	End-of-life patients **Age:** NM **Male:** NM	**Prevalence:** 58% acute hospital setting, 52% tertiary PC unit, 22% hospice **Indications:** NM **Factors influencing prescription:** NM **Symptom improvement:** not clearly mentioned **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Antimicrobial use in patients on a comfort care protocol: a retrospective cohort study	Merel SE, Meier CA, McKinney CM, Pottinger PS	2016	Retrospective (1/06/2012 to 1/08/2014)	Two interrelated academic medical centers (USA)	1881	Patients put on comfort care protocols (34,4% malignancies, 5,2% solid organ/bone marrow transplant, 55,7% renal disease, 79,7% cardiovascular disease, 83,2% pulmonary disease, 33% GI and/or liver disease, 36,2% cerebrovascular disease) **Age (mean):** 64,3 **Male:** 58,2%	**Prevalence:** 77,3% before comfort care protocol » 30,3% 24h after comfort care protocol **Indications:** NM **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM
Antibiotic prescription for fever episodes in hospice patients	Chen L-K, Chou Y-C, Hsu P-S, Tsai S-T, Hwang S-J, Wu B-Y, Lin M-H, Chen T-W	2002	Retrospective (1/07/1999 to 30/06/2001)	Hospice palliative care unit (Taiwan)	481 (93 fever episodes)	Hospice patients **Age (mean):** 67,2 **Male:** 68,4%	**Prevalence:** 84,9% (unit: number of fever episodes) **Indications:** presence of fever as a surrogate of infection **Factors influencing prescription:** NM **Symptom improvement:** 54,4%; survival in antibiotic-treated patients 14,6±13,1 days versus 8,7±9,9 days in non-treated patients (p=0,03) **Definition of symptom response:** fever subsidence **Methods used to assess symptom response:** evaluation of fever
High frequency of antimicrobials use in PC: are we moving in the	Ramadas L, Barroso PF	2017	Retrospective (2010)	PC Unit of the National Cancer Institute of Brazil	870	EOL cancer patients **Age (mean):** 62 **Male:** 48%	**Prevalence:** 41% **Indications:** infectious syndromes (36%), symptom control (48%), prophylaxis (2%), unknown (14%) **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM

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Symptomatic treatment of infections in patients with advanced cancer receiving hospice care	Reinbolt RE, Shenk AM, White PH, Navari RM	2005	Prospective (10/2001 to 10/2003)	Community outpatient, home-based hospice program (USA)	1598 (685 infections)	Advanced cancer patients receiving outpatient hospice care **Age (mean):** 63,1 **Male:** 50%	**Prevalence:** 39,6% (total), 92,4% (unit: number of infection episodes) **Indications:** NM **Factors influencing prescription:** NM **Symptom improvement:** 60-88% for UTI, 15-53% for RTI, 38-50% for mouth/pharynx, 30-46% for skin/subcutaneous, 0% for bacteremia. No significant difference in survival in patients who received antimicrobials versus those who didn't **Definition of symptom response:** clinical improvement in one or more of a number of predefined infection-related symptoms (dysuria, fever, frequency and pain for UTI; cough, dyspnea, fever, sputum production for RTI; fever, mucosal inflammation/pain, odynophagia for mouth/pharynx; fever, pain, skin rash/discoloration for skin and subcutaneous; fever, disorientation and hypotension for bacteremia) **Methods used to assess symptom response:** healthcare staff perception
Antimicrobial use in patients with advanced cancer receiving hospice care	White PH, Kuhlenschmidt HL, Vancura BG, Navari RM	2003	Prospective (six-month period in 2001)	Community-based outpatient hospice and PC program (USA)	255	Advanced cancer patients with an estimated prognosis of less than six months **Age (mean):** 63,1 **Male:** 50%	**Prevalence:** 30,2% **Indications:** presence of infection, defined as symptoms and physical signs that were interpreted as such by the attending physician **Factors influencing prescription:** NM **Symptom improvement:** 60-92 for UTI, 0-50% for RTI, 33-50% for mouth/pharynx, 33-50% for skin/subcutaneous, 0% for bacteremia. Patients' overall survival and infection-related deaths were not significantly affected by the use of antimicrobials or the patients' choices of antimicrobial use **Definition of symptom response:** NM **Methods used to assess symptom response:** healthcare perception
Impact of infections on the survival of hospitalized advanced cancer patients	Thai V, Lau F, Wolch G, Yang J, Quan H, Fassbender K	2012	Prospective (12 months, ending in August 31, 2009)	University of Alberta Hospital Acute PC Consult Team (Canada)	441	Advanced cancer patients **Age (mean):** IG 68 NIG 66 **Male:** IG 59,1% NIG 54,6%	**Prevalence:** 89,7% (unit: infected patients) **Indications:** NM **Factors influencing prescription:** NM **Symptom improvement:** 47,6% (IV antibiotics) and 45,5% (oral antibiotics) with partial response Median survival patients with untreated organ-related infection 27 days versus 48 days in a similar cohort receiving antibiotics Median survival after IV antibiotics: six days for nonresponders, 34 days for partial/indeterminate responders, 108 for good responders (log rank p<0,001) Median survival after oral antibiotics: six days for nonresponders, 25 days for partial/indeterminate responders, 70 for good responders (log rank p<0,001) **Definition of symptom response:** improvement in fever,

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							symptoms, imaging and/or blood work; response categorized as good, partial/indeterminate or poor **Methods used to assess symptom response:** not clearly mentioned
Antibiotic policies and utilization in Oregon Hospice Programs	Novak R, Noble BN, Fromme EK, Tice MO, McGregor JC, Furuno JP	2015	Cross-sectional (August to November 2013)	Oregon hospice programs (USA)	39 hospice programs (diverse daily census)	Patients admitted to hospice care **Age:** NM **Male:** NM	**Prevalence:** 10% (proportion of current census receiving antibiotics) **Indications:** UTI (median 75%) > skin and soft tissue infections (median 25%) > pneumonia (median 18,5%) **Factors influencing prescription:** NM **Symptom improvement:** NM **Definition of symptom response:** NM **Methods used to assess symptom response:** NM

COPD: Chronic obstructive pulmonary disease
CPR: Cardiopulmonary resuscitation
CRP: C-reactive protein
EOL: End-of-life
GI: Gastrointestinal
HZ: Hazard ratio
IG: Infected group
LOS: Length of stay
NIG: Non-infected group
NM: Not mentioned
PC: Palliative Care
UT(I): Urinary tract (infection)
RT(I): Respiratory tract (infection)
LRTI: Lower respiratory tract infection
UK: United Kingdom
USA: United States of America

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3.1. Prevalence of antibiotics use

All publications except one(38) analyzed the prevalence of antibiotics' prescription for EOL patients with suspected or confirmed infection, which varied between 10 and 97,5%.

Most studies (13/27) only included patients with malignant diseases.(7,15,33,38,49,51,52,56,57,59,62,63,65) The average prevalence of antibiotics use among cancer patients was 66,9% (±22,8). Regarding the remaining 14 studies, seven had no description of patients' characteristics(48,50,54,60,61,64,66), one included advanced dementia patients(55) and six had diverse patients, with a mixture of malignant and non-malignant diseases(14,18,19,42,53,58). The average prevalence of antibiotics use in the last six articles, involving a sum of 8297 patients, was 36,7% (±26,8).

A prospective study by Chih *et al*, involving 799 consecutive patients with advanced cancer admitted to a PC unit of Taiwan, showed that the use of antibiotics was approximately the same at admission (78%) and one week later (75,8%), but decreased to 59,1% two days before death.(65) Merel *et al*(18), in a recent publication, also showed that 77,3% of 1881 inpatients who transitioned to a "comfort care protocol" (which suggests "to stop measuring vital signs and laboratory testing and provides standard orders for symptom management") received antimicrobials at admission. This percentage dropped to 30,3% after 24 hours of being in the protocol and remained similar across time. It is worth noting, as the authors point out, that this "comfort care protocol" provides no guidance on antimicrobial use.

Some studies defined episodes of infection as the unit to determine the prevalence of antibiotics use. Pereira, Watanabe and Wolch(15) analyzed medical charts of 100 consecutive terminally ill cancer patients admitted to a PC unit of Edmonton, Canada, and realized there was a total of 74 separate infections (43 patients had one infection, eight patients had two separate infections, three patients suffered three separate infections and one patient experienced four separate infections). Considering those 74 events, authors found that 71,6% were treated with antibiotics. In 10 of the 21 remaining cases, reasons for not starting antibiotics were documented: five due to very poor general condition/imminent death, three due to unavailability of oral route and subsequent decision of not starting parenteral treatment and two cases because of patient and/or family refusal of antibiotics institution.

Chen *et al* documented 93 fever episodes amongst 481 patients admitted to the hospice PC unit of Taipei Veterans General Hospital, of which 84,9% were treated with antibiotics.(61)

Reinbolt and colleagues also found a high percentage of infection episodes treated with antibiotics: in a study involving 1598 patients with advanced cancer receiving outpatient

hospice care, there was 685 infections affecting 623 different patients, and in 633 (92,4%) an antimicrobial was started.(63) This high percentage only finds parallel in the work of Lam and colleagues(57), who showed, in their retrospective study with advanced cancer patients admitted to a Hong Kong PC unit, that 97,5% of 120 episodes of infection were treated with antibiotics.

3.2. Indications for antibiotics use

Indications for antibiotics prescription are commonly addressed throughout the analyzed studies, but most of them cite "infection" – either active, possible, probable or suspected – as the key one.(11,12,21,34–40,49,51)

For White and colleagues(33), infection was defined as the "presence of symptoms and physical signs that were interpreted by the attending physician to have been caused by a microbial agent and was documented as such in the patient's chart". Chih *et al* defined infection as a clinical judgement based on "microbe-related symptoms, with the assistance of laboratory or imaging reports, when available".(65) Furuno and colleagues, in a study with 845 patients discharged from a university hospital to an hospice setting, opted for more stringent criteria and defined active infection as: 1) being on antibiotics for at least three consecutive days, 2) a written diagnosis of infection in medical records or 3) a positive clinical culture.(42) Chen *et al* studied 93 fever episodes in 481 hospice patients, defined as "a period in which the oral body temperature was higher than 38,5ºC".(61) Oh and colleagues defined fever, leukocytosis and bacteremia, and established a cut-off value for CRP elevation, but they didn't clarify which parameter or combination of parameters were required for an infection to be considered.(59)

Some studies chose to describe specific types of infection, instead of a generic label; the most commonly cited were urinary and respiratory tract infections(48,49,51,64,66), and wound care(51,64). A limited number of publications also included gastrointestinal infections(49), oral thrush(51), skin and subcutaneous infections(49,66) and sepsis(49,66) as explicit indications for initiating antibiotics.

Ramadas *et al*(62), in their retrospective study at the PC unit of National Cancer Institute of Brazil, defined indications in a practical way: infectious syndromes (36%), symptom control (48%), prophylaxis (2%) and unknown (14%).

3.3. Factors influencing prescription

Factors influencing antibiotics prescription are seldom mentioned throughout the 27 publications. Furuno *et al*(42) concluded that patients with younger age, a diagnosis of cancer (65,7 *versus* 55,5%, p=0,01), higher Charlson comorbidity index scores (mean±standard deviation 7,6±4,1 *versus* 6,7±3,8, p=0,006) and longer (>7 days) hospital lengths of stay (50,0% *versus* 41,7%, p=0,047) were significantly more likely to be discharged to hospice care with a prescription of an anti-infective drug.

After reviewing the 2007 National Home and Hospice Care Survey, Albrecht and colleagues(19) confirmed younger age (mean±standard deviation of 76±0,7 *versus* 78±0,5 years) and longer duration of care (mean±standard deviation of 60±7 *versus* with 48±4 days) as relevant factors influencing antibiotics prescription; patients with COPD were also more likely to receive antibiotics, compared with cancer, heart failure and cardiovascular disease, dementia, debility, cerebrovascular disease, renal and liver diseases, or other diseases (p=0.008).

In a retrospective study aimed to describe the role of pneumonia during the terminal trajectory of dementia in 240 patients residing in an American rehabilitation facility, Chen et al(55) realized that the lack of a "do-not-hospitalize" order, aspiration episodes, primary language not English and at least one unstable vital sign were variables independently associated with more aggressive management, including antibiotic treatment.

3.4. Symptom response (definition, percentage and methods of assessment)

Twelve studies reported some kind of symptom response measurement. Of these, three studies were prospective(33,38,63) and the remaining was retrospective(14,49,52–54,56,58,59,61).

Quantification of symptom improvement varied from 0% to 92%.

Two studies published by the same group two years apart(33,63) detailed which symptoms improved after a course of antimicrobials (first percentages presented after the work of White *et al*, followed by the results of Reinbolt *et al*): 60-92% and 60-88% of UTI symptoms, 0-50% and 15-53% of RTI symptoms, 33-50% and 38-50% of mouth/pharynx-related symptoms, 33-50% and 30-46% of skin/subcutaneous infection manifestations and 0% for bacteremia. Lo and colleagues(53) also detailed the response rate according to infection site, which was 100% for peritonitis (one patient), 75% for UTI (eight patients), 66,6% for RTI (18 patients)

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and 0% for skin/subcutaneous infection (one patient). In their retrospective study with terminal stage cancer at Seoul National University Boramae Hospital, Oh and colleagues(59) described 15,1% of symptomatic amelioration, 48% of fever control, 31% of organism-proven cases cleared up and 17% of leukocytosis plus 29% of CRP elevation improvement after antibiotic use.

Nakagawa and colleagues(52) investigated the relationship between the timing of anti-infective drug use and symptom improvement, concluding it was less pronounced during the last week of life (33,1% of overall improvement *versus* 9,2% during the last week of life).

Some studies examined the impact of antibiotics on survival. Chih *et al*(65) realized that antibiotic administration prolonged survival in patients with hospital stays longer than one week (hazard ratio 0,66, 95% confidence interval of 0,46-0,95), but negatively impacted survival if they were started two days prior to death (hazard ratio 1,54, 95% confidence interval of 1,22-1,94). Thai and colleagues, in a prospective study designed to determine the impact of recent infection (sepsis, organ-related infection or both) on survival of 441 advanced cancer patients, realized that 95,5% of infected individuals, compared with 93,9% of non-infected, died during the study period. They also saw that the occurrence of suspected or confirmed sepsis in the last four weeks combined with a poor response to antibiotics had a significant impact on survival: septic patients had a median survival of approximately 15 days, *versus* 42 days in the non-septic group ($p < 0,001$).(7)

Chen *et al*(61) documented 54,4% of clinical improvement (defined as fever subsidence) after a course of antibiotics and described a significant ($p=0,03$) difference between the survival of patients treated with anti-infectives (14,6±13,1 days) and the survival of non-treated patients (8,7±9,9 days). The overall mean survival after an episode of fever was 13,8±12,8 days.

Lam *et al*(57) examined the pattern of antimicrobials use and factors that could affect outcomes following infection. After comparing patients with infective episodes that survived more than 14 days with those that didn't, they concluded that low serum albumin, chest infection, dyspnea as the major symptom of infection, empirical antibiotic therapy and parenteral antibiotic route were significantly associated with worse survival.

The definition of symptom response, when available, varied considerably between publications. In their retrospective study with 160 cancer patients in the last two weeks of life, Helde-Frankling *et al*(49) collected data on different forms of symptom relief after antibiotic treatment from medical and nursing records; examples of "positive effects" were reduced fatigue, resolution of fever or "patient having energy to do things of their choice that

were not possible before antibiotic treatment". Both Nakagawa *et al*(52) and Vitetta *et al*(14) defined symptom improvement based on medical and nursing records of symptom amelioration and completion of the antibiotic course. Vitetta *et al*(14) also considered infection-related death as a direct measure of antibiotic response. Gradalski and colleagues(58) classified clinical outcomes within the infected patients group as "clinical cure" if all constitutional symptoms and signs of infection ceased, "symptomatic relief" if all symptoms disappeared but signs persisted, and "symptomatic alleviation" if some symptoms disappeared or diminished. Two more categories were included ("symptomatic stabilization" and "worsening"), for which no specific definition was provided. Reinbolt and colleagues(63) provided a detailed list of symptoms according to infection site: dysuria, fever, frequency and pain for UTI; cough, dyspnea, fever and sputum production for RTI; fever, mucosal inflammation/pain and odynophagia for mouth/pharynx; fever, pain and skin rash/discoloration for skin and subcutaneous; fever, disorientation and hypotension for bacteremia.

Most publications didn't mention which method was used to assess symptom response. When it was assessed, many studies(14,33,49,52,56,58,59,63) based their evaluation in healthcare staff perception, complemented at times by patient self-reports(58), vital signs measurement(52,61) or blood tests results(52,58,59). Mirhosseini and colleagues(38) used the "other" category of the Edmonton Symptom Assessment Scale (ESAS) – a validated metric for quantifying symptom intensity – to document infection-related symptoms experienced by the patient.#

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4. Discussion

We systematically reviewed the available literature published between 1997 and 2017 in order to summarize data concerning 1) antibiotics use, 2) factors associated with its prescription and 3) outcomes attributable to antimicrobials in the context of EOL care.

As previously mentioned, our methodology was mainly based on the work of Rosenberg and colleagues(36), which reviewed articles reporting antimicrobial use in hospice and palliative care settings released from 2001 to 2011. They concluded there was limited data on antibiotics effectiveness for symptom improvement but a tendency towards success in amelioration of UTI-related symptoms. They also cautioned against the methods used to assess symptom burden, since they varied greatly between studies and often relied on subjective clinical assessment.

We expected antibiotics prescription in PC in general and EOL care in particular to be a fairly common practice. After thoroughly analyzing 27 publications, we found that antibiotics use vary between 10 and 97,5% (mean: 57,9±27,9%; median: 63%), depending on study population and cultural setting. Prevalence rates higher than 80% mostly occurred in acute care or rehabilitation settings.(50,55,56,59) All studies considering episodes of fever/infection or infected patients for the calculus of prevalence also exceeded 80%.(7,57,58,61,63)

This prevalence variability might be explained by the heterogeneity of study designs, by the uneasiness of recognizing the EOL, by little evidence being available to guide practice and by the influence of culture and ethnicity. For example, Chen *et al* showed that nonwhite and non-English speaking persons generally chose more aggressive care.(55) Besides, the results of this review suggest that location of care also affects the decision to treat infection. We strongly believe that this wideness reflects an also wide antimicrobial prescription pattern in real practice.

Regarding *the meaning* of these prevalences, several reasons can elucidate why, in average, more than half of EOL care patients are prescribed antibiotics. Firstly, many physicians perceive antimicrobials as usual care, potentially providing symptomatic relief and postponing death. Additionally, diagnosis of infection is complicated by the ambiguity of signs and symptoms, the existence of causes other than infection and the unreliability of microbiological yields(53). All these points taken together push healthcare professionals to strive with the will of treating potentially reversible events and the ethical priority of avoiding

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therapeutic futility. Consequently, they err on the side of caution and to treat all supposedly infected patients.(7)

Secondly, both patients and their families tend to think that infections are not related to cancer and are always reversible, and therefore should be treated. That assumption influences their preference in favor of antibiotics, even when expected outcome is explained to be minimal. They may also rely on the same idea of benevolence(50) and innocuity of antimicrobials and regard these drugs as a mean of "symbolic comfort", which makes it hard for healthcare providers to pursue active discussions about discontinuing them.

Lastly, the fact that acute care settings seem to be linked with higher prevalences of antimicrobial use may derive from the also higher probability of PC patients be accompanied by healthcare personal less experienced in this medical field. Accordingly, one study showed that healthcare professionals with less experience in palliative and EOL care chose aggressive and interventional treatments more often, rather than observation or symptom control.(56)

Concerning factors influencing antibiotics prescription, literature remains sparse. The most frequently cited factors were younger age, longer hospital lengths of stay and higher Charlson comorbidity index scores.

We consider that younger patients are given antibiotics more often because in a theoretical "natural life cycle" these patients would be farther from death. This is a difficult theory to prove, and definitely a more emotional than rational decision.

Regarding longer hospital lengths of stay, the aforementioned link between frequent healthcare contact and higher probability of acquiring infection makes it reasonable that patients staying longer in healthcare facilities have higher percentages of healthcare-associated infections, and hence are more often treated with antibiotics.

We didn't find a consistent association between a given diagnosis and higher probabilities of starting antibiotics.

Comparing outcomes from different studies is a difficult task because of major differences in medical setting, patient populations, study design and proposed definitions for infection and symptom improvement. Furthermore, only 14 of all selected publications specifically addressed outcomes.

Symptom improvement varied from 0 to 92% (mean: 46,8±25,3%; median: 50%). For these mean and median calculations we considered all percentages available (more than one, depending on type of infection, in the works of White *et al* and Reinbolt *et al*). When percentages were presented as an interval we chose the highest value.

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We found that antibiotics are *probably* good for controlling UTI-related symptoms; the same might not be true for other infections. Evidence is consensual that sepsis/bacteremia is poorly controlled by antimicrobials in this particular population.

In fact, two prospective studies included in our systematic review suggested that prescribing antimicrobials for UTIs improved symptoms in a large number of patients but the same drugs were less successful for symptom control in RTIs, mucositis and skin infections.(33,63) It was also proposed that in some patients a lack of response may be due to co-morbid conditions such as immunocompromised state, malnutrition, failure of host barriers, decreased level of consciousness, immobility or even cancer itself.(33)

Mirhosseini *et al* showed that antibiotics mildly improved infection-related symptoms. Despite this, one quarter of all patients died within one week of antibiotic administration.(38)

Gradalski and colleagues reviewed medical charts of patients admitted to an acute PC ward and categorized them into infected and non-infected groups according to the presence of clinical manifestations most probably caused by microbial agents (based on the revised McGeer criteria). They found that "evident symptomatic improvement" [defined as the sum of "clinical cure" (when all constitutional symptoms and signs of infection ceased), "symptomatic relief" (all symptoms disappeared but signs persisted) and "symptomatic alleviation" (some symptoms disappeared or diminished)] was achieved in 70% of all healthcare-associated infections.

On the contrary, Stiel *et al* concluded that a clear tendency towards the usefulness or the lack of usefulness of a course of antibiotics could not be found.(64) This group classified the absence of suitable outcome parameters as a major limitation of studies in this field and proposed the decrease of pathogenic germs colonization and the improvement in the patient performance status as candidate outcome parameters.

The same group also proposed patients' self-assessment of symptoms and suffering to be explored in upcoming studies. In fact, another study showed that patients and physicians disagreed on the symptoms most affected by antimicrobials, with patients selecting dysuria and physicians selecting cough.(38) Interestingly, the only study considering patient self-report of symptom amelioration found that one third of all patients benefited from antibiotics prescription. The same publication is also noteworthy for measuring the impact of antibiotics in the last week of life, concluding that no symptom improvement occurred.(52)

No study was designed to appraise if curing an infection with antibiotics is the most effective method for palliation of infection-related symptoms.

There was also no study addressing the issue of quality of life, which would have to consider the intricate balance of positive and negative points of prescribing antibiotics in EOL care.

Data on the effect of antibiotics on survival was also conflicting and the paucity of studies evaluating this outcome even bigger (six out of 27).(7,14,33,61,63,65) As such, we can't either affirm or exclude that doing antibiotics at the EOL prolongs survival.

The two similar prospective studies by White *et al* and Reinbolt *et al* revealed that patients' overall survival and infection-related deaths were not significantly affected by the use of anti-infective drugs.(33,63)

Vitetta and colleagues found that patients with documented infection had longer median survivals. The authors considered, however, that the most plausible explanation was that the probability of infection increased with duration of survival.(14)

Thai and colleagues demonstrated that a favorable antibiotic response in hospitalized advanced cancer patients with confirmed/suspected sepsis or organ-related infection improved survival. They proposed a time-limited trial of antibiotic treatment if the principle factor causing the patient's decline was infection.(7)

Patients with longer lengths of stay to whom antibiotics were administered were shown to have longer survivals.(19,67) The underlying rationale was not formally explored yet, but we believe that these patients develop infections as a *consequence* of the prolonged hospital stay. Citing Albrecht and colleagues(19), it is also possible that patients who didn't receive antibiotics were more severely ill and, therefore, survived for a shorter period.

A single study(57) concluded that for those treated with antibiotics, therapy adapted to antibiotic sensitivity was better in terms of survival than empirical therapy.

In line with Rosenberg *et al*(36) observations, we also identified methodological limitations in reviewed articles that weaken their conclusions. It is important to note that most major limitations derive from retrospective studies being the commonest type of publication. We agree it can be ethically complex to develop interventional and randomized studies, but these limitations have to be debated.

The first relevant limitation is the fact that all retrospective studies relied on subjective healthcare professionals' notes to quantify or qualify patients' symptoms and their changes, rather than applying validated symptom measurement tools. In fact, only one study applied a validated method of symptom assessment, namely the Edmonton Symptom Assessment Scale.(38) The problem of this assessment method is its highly subjective nature. It is not useful for distinguishing infection-related symptoms from symptoms derived from the

“chronic”, underlying disease. In fact, and again in line with Rosenberg *et al* conclusions, no study made an adjustment for potential confounding effects of underlying disease or other drug exposures regarding symptom improvement evaluation. Likewise, cases with symptom relief may be underestimated, as this information is seldom written in clinical records. Furuno and colleagues, for example, found that symptoms are rarely documented in the first place and never explicitly stated as resolved after treatment.(54)

Another major limitation stems from the significant heterogeneity in the measurement of antimicrobial use and symptom improvement. That inconsistency compromises the usefulness of this data in clarifying benefits and disadvantages of anti-infective drugs in the PC population.

Lastly, absence of a control group to compare the impact of instituting and not instituting antibiotics is also a major flaw of retrospective studies. More and better prospective cohort studies are needed to compare outcomes between patients with infective symptoms who received antimicrobials with those that didn’t.

This work is naturally limited by not including studies published in languages other than English, French, Italian, Portuguese or Spanish. In addition, systematic reviews are susceptible to publication bias, in that studies reporting a positive association between antimicrobial use and symptom reduction or prolonged survival may be more likely to be submitted and accepted for publication than studies suggesting little or no benefit.(36)

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5. Conclusion

Starting antibiotics for infections in EOL patients is a complex and controversial issue. Although rather prevalent – our systematic review shows that more than one in two patients is given antimicrobials -, literature is not consensual regarding symptom improvement or life prolongation following antimicrobials administration.

It is known that antibiotics are used with the intention of increasing comfort even when death is imminent.(68,69) However, it is still not possible to predict whether antibiotics will produce a cure or if withholding them will result in death. Moreover, there is no evidence that if antibiotics produced a cure it would lead to symptom control in this particular population.

Our systematic review corroborates the tendency towards amelioration of UTI-related symptoms after an antibiotic course. That tendency is less remarkable for all other infection-related symptoms and is absent for bacteremia. However, since the vast majority of studies relied on healthcare professionals' perception of symptom improvement, it's not clear if it correlates with actual patients' perceptions. We are deeply convinced that further adequate research, namely prospective observational studies based in patients' self-report, will shed some light on this issue.

We also conclude that it is *possible* that antibiotics extend the number of days lived, but we share the plausible concern about the discomfort that comes with prolonging an extenuating and painful EOL and the need for diagnostic tests and invasive devices.

Marcus and colleagues affirmed that a given intervention might simultaneously be futile in achieving one goal and successful in attaining another.(45) The World Health Organization also proposed the principle of *proportion*, by which treatments that prolong life are contra-indicated when they cause more harm than good. In view of that, we believe that the ultimate aim of high quality EOL care is to deliver treatment concordant with patients' goals and preferences. As a corollary, antibiotics use at the EOL should be approached using a framework of shared decision-making with patients and families, similar to other EOL treatment choices, in order to delineate an individual, case-sensitive and total treatment plan. (5,11,66) It should be done as part of advance-care planning, in contrast with the common scenario of taking decisions at the time of a crisis.(22)

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The first step consists in providing evidence-based information to patients and families, focusing on the fact that infections near the EOL are expected and usually a terminal event. It should also be explained that diagnosing an infection can entail some invasive procedures.(22) The next step is to help patients and families decide which approach best suits their goals of care. If their preferences are for treatments that optimize comfort, it is reasonable to recommend that no evaluation be initiated in the event of a suspected infection.(11,22) Conversely, if the patient's goal is to live as long as possible and potential benefits of antimicrobials are believed to outweigh their burdens, it is then reasonable to proceed with clinical assessment and to start antibiotics by the least invasive route.(22)

We partially agree with Béziaud and colleagues, who proposed not starting antibiotics in the following situations (reproduced with adaptations): 1) if a sound minded patient, after being correctly and honestly informed, freely expresses the wish of not receiving antimicrobials; 2) if prescribing antibiotics implies invasive devices or physical restraints; 3) if the diagnostic workup is too invasive and/or imposes too much suffering; 4) if it's plausible that the cause of high body temperature is not an infection.

The main motivation for this work was to emphasize that the role of antibiotics in EOL care cannot be underestimated and we feel that ignoring it is not viable for present and future patients. For many terminally ill patients it is indisputable that no intervention will prolong life, including antibiotics. Treating patients indiscriminately, even those who do not benefit from antibiotics, comes with a high societal cost by rising the prevalence of resistant microorganisms and undue financial burden. Therefore, some authors defend that public debates should be promoted to increase general awareness about the adverse ecological effects of unnecessary antibiotic treatment at the EOL and to the need of living wills detailing preferences on this specific topic.(10) Van der Steen and colleagues also defended that more attention has to be paid to PC in medical curricula, journals and standards of care, with the intention of spreading knowledge about effective PC strategies of symptom control.(26)

Lastly, we agree with Juthani-Mehta that there is an ongoing need for collaborative discussions between PC and Infectious Diseases physicians, which could be materialized in flexible and individualized algorithms of decision.(22)

We then conclude that the decision of whether or not to use antibiotics for treating infections in EOL patients is highly individualized and depends almost exclusively on patients' goals. In fact, there is limited data to support the effectiveness of antibiotics in alleviating symptoms and prolonging survival, none regarding the impact of antibiotics on quality of life and antibiotic-derived adverse events are likely underappreciated.

We end this dissertation by citing Pautex *et al*: “the difficulty does not lie in the decision to administer or not administer an antibiotic, but to estimate when will the ‘point of no return’ be”.

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