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Research paper

Antimicrobial use in patients at the end of life in an Australian hospital

Jane Dyer [a,*], Lucinda Vaux [a], Alex Broom [b], Jennifer Broom [a]

[a] Department of Medicine, Sunshine Coast Hospital and Health Service, Hospital Road, Nambour, QLD, 5470, Australia
[b] School of Social Sciences, University of New South Wales, Sydney, NSW, 2052, Australia

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Ethics

Abstract *Background:* Antimicrobial resistance is increasing and there is an urgent international imperative to optimise use within hospitals. Antibiotic use at the end of life is frequent in the hospital setting, but data on use in Australian hospitals in this context is limited, and optimisation is complicated by clinical/diagnostic, ethical and humanistic considerations. As yet there is little data available on baseline use in hospital end of life settings, an empirical gap we sought to begin to fill here.
Methods: A retrospective review of antibiotic use in patients who died in a Queensland hospital between January 2015 and July 2015.
Results: One hundred and thirty-seven patients were included, of which 73 were male (53.3%) and the median age was 81 years. Of these patients, 86 received antibiotics at the end of life. The most common antibiotic prescribed was piperacillin/tazobactam (41.9%). The most common site of infection was pulmonary (32.8%). Of 86 patients prescribed antibiotics, 29 patients (33.7%) received antibiotics after futility was documented. 83 patients (96.5%) were administered their antibiotics intravenously.
Conclusion: Antimicrobial use at the end of life is frequent, with greater than one third of the patients who died in hospital having their antibiotics continued after discussion of futility. Antimicrobial use in this setting is complex with significant clinical, social and ethical considerations which need to be addressed if antibiotic optimization in this area (and more broadly in the hospital) is to be achieved.
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Highlights

- There is urgent imperative to optimise antimicrobial use due to increasing resistance.
- Limited data is available on antimicrobial use in hospital end of life settings.
- A retrospective study of antibiotic use in patients who died in an Australian hospital.

* Corresponding author. Department of Medicine, Sunshine Coast University Hospital, 6 Doherty St, Birtinya, QLD, 4575, Australia.
E-mail address: jane.dyer@uqconnect.edu.au (J. Dyer).

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- Finding of antibiotic continuation post futility discussion in one third of cases.
- Clinical, ethical and social considerations complicate antimicrobial use in end of life.

Introduction

Antimicrobial use at the end of life is a complex process of balancing the transition to futility, on-going symptom amelioration, antimicrobial de-escalation best practice, as well as a variety of emotional and family-based pressures to continue active treatment (including antibiotics). This complexity is part of the reason there have been no clear guidelines developed for appropriate antimicrobial prescription in this setting. However, there is increasing international recognition of this issue and a desire for discussion around related decision-making frameworks. Infection and fever are common complications in the terminally ill [1—4] and antimicrobials may be viewed as less aggressive or invasive than other technically (or seemingly) life-prolonging interventions such as intubation and cardiopulmonary resuscitation [5—8]. It has been proposed that antibiotics should be considered in end of life discussions to be on par with decisions related to dialysis, hydration and nutrition as well as resuscitation orders [6]. Knowledge of current practice (within hospitals) is lacking to inform guidelines to implement change. Previous studies have examined the use of antimicrobials among patients in end of life care, but have largely focused on specific groups of patients (e.g. those with advanced dementia [9—13] or cancer [3,4,8,14—23]). Further, these studies have mainly been performed in the outpatient setting of hospice care [3,13,18,24—26] or in designated "palliative care units" [2,8,14,15,22,27—29] rather than the setting of inpatient care in general hospital wards [4,19,21,30].

Of the limited available data internationally, studies have shown high use of antimicrobials in end-of-life care settings vis-à-vis clinical best practice, despite potential additional burden they pose to the patient (e.g. via side-effects, potentially prolonging the dying process, and the psychosocial implications of active treatment in the context of futility) [31]. The problem may often be concealed and institutionalized at the end of life, with one small study of nursing facility residents in the United States of America (USA) finding that antibiotics were given in almost one third of residents who had orders for no antibiotics to be provided [32]. Only a limited number of these studies have prospectively examined antibiotic use in end of life care. In a study of patients in a palliative care unit performed over 13 months by Clayton and colleagues, of 41 patients who received parenteral antibiotics, 62% were considered to have an improvement in functional status and/or symptoms, with urinary infections more commonly associated with a beneficial effect compared to other sites of infection. Further, benefit from antibiotics was more common in terminal and stable-phase patients compared to deteriorating or acute-phase patients [28]. A prospective epidemiological investigation performed via survey of palliative cancer patients in Germany, showed 63.8% of 448 patients with suspected infections were treated with antibiotics [33]. In D'Agata and colleagues prospective study of patients with advanced dementia in a nursing home, 42.4% of 99 patients who died were on antibiotics in the two weeks prior to death [9]. None of these prospective studies have examined inpatients directly.

The rather ad hoc use of antimicrobials at the end of life is perhaps understandable given that there is still conflicting evidence in the literature regarding whether there are actually improvements in symptom control [31] and survival [2,3,18,22,25,34] with the use of antimicrobials in end of life context. These studies are not comparable with marked differences in methodology and patient population. However, antimicrobial use at the end of life is also important in terms of what it represents in terms of broader attempts at tempering (unnecessary) use of antimicrobials. This includes reconciliation of sites of sub-optimal use with broader public health concerns of antimicrobial resistance resulting from inappropriate antibiotic use [12,15,35—38].

The purpose of this study was to retrospectively evaluate antibiotic use in hospital inpatients during their end of life admission. To our knowledge, no-one in Australia has examined antibiotic consumption in end of life care in the inpatient setting.

Methods

Study design and setting

A retrospective review of antimicrobial use in inpatients >18 years of age who died was undertaken between January 2015 and July 2015 in a 450 bed regional referral hospital in Queensland, Australia.

Case inclusion and exclusion criteria

Deceased patients were identified from monthly mortality meeting lists for the medical and surgical services. Exclusion criteria included admission under the direct care of the palliative care team who had protocols for antibiotic cessation.

Data collection

Retrospective review of medical records was undertaken, collecting the following data:

Baseline demographics: Age, Gender, Admitting Team, Specialty unit, Duration of admission, Presence of acute resuscitation plan (ARP), Antibiotic status on ARP, Presence of end of life pathway, Presence of antibiotic allergy, Relevant comorbidity.

Futility Data: Death Expected, Days prior to death futility of life discussed (see definition below).

Infection Characteristics: Infection present, category of infection, antibiotic route, antibiotic choice, whether antibiotics continued post futility, whether antibiotics

escalated post futility, number days prior to death antibiotics ceased.

Infection was deemed to be present if there was clinician chart documentation of terms such as infection, sepsis, bacteraemia, urinary tract infection, cellulitis, pneumonia, gastroenteritis and/or osteomyelitis. Death was deemed to be expected if futility of life continuation had been discussed prior to the patient dying. Futility of life timing was recorded from the first chart documentation of terminology related to palliation, dying, terminally ill, moribund, poor prognosis, cessation of medical interventions, comfort cares or futility of treatment continuation.

Results

Baseline demographics

The study included 137 patients (male n = 73, 53% female n = 64, 47%) with a median age of 81 years (range 33–99 years). The mean duration from admission to death was 7.1 days (range 0–36 days). 15 patients (10.9%) did not have an acute resuscitation plan (ARP). Of those with an ARP, 27% did not have antibiotic preferences specified. 24 patients (17.5%) had documented antibiotic allergies. 65 patients (47.4%) were placed on an "End of life pathway". 9 patients (6.6%) were deceased in the care of the intensive care unit. Patient demographics are summarised in Table 1.

Table 1 Baseline demographics.

Variable	n	%
Gender		
Male	73	53.3%
Female	64	46.7%
Age		
<40	1	0.7%
40-65	15	10.9%
65-80	49	35.8%
80-95	64	46.7%
>95	8	5.8%
Team		
Medical	96	70.1%
Surgical	41	29.9%
Duration Admission		
<1	2	1.5%
1 to 7	86	62.8%
7 to 14	34	24.8%
>14	15	10.9%
Acute Resuscitation Plan (ARP)		
Yes	122	89.1%
No	15	10.9%
Antibiotic Status on ARP		
Provide	66	48.2%
Do not provide	19	13.9%
Not specified	37	27.0%
No ARP	15	10.9%
Specialty Unit		
General Medicine	33	24.1%
Stroke	18	13.1%
Respiratory	11	8.0%
Geriatrics	9	6.6%
Gastroenterology	5	3.6%
ICU	9	6.6%
Cardiology	7	5.1%
General Surgery	31	22.6%
Orthopaedics	7	5.1%
Haematology	1	0.7%
Urology	3	2.2%
Oncology	3	2.2%
Relevant Comorbidity		
Malignancy	29	21.2%
Dementia	11	8.0%
Cirrhosis	7	5.1%
CVD	42	30.7%
COPD	13	9.5%
Chronic pulmonary disease (not COPD)	2	1.5%
CKD	2	1.5%

CVD = cardiovascular disease.
COPD = chronic obstructive pulmonary disease.
CKD = chronic kidney disease.

Infection Characteristics

51 patients (37.2%) were not prescribed antibiotics or had their antibiotics ceased prior to futility discussions. Of the 117 antibiotic prescriptions in the remaining 86 patients, the most common antibiotic prescribed was piperacillin/tazobactam (41.9%). The most common site of infection was pulmonary (32.8%). The vast majority of patients received their antibiotics via the intravenous route (96.5%). 35 patients (40.7%) patients received more than one type of antibiotic. The Infectious Diseases service was consulted on antibiotics in 8 patients. Infection characteristics are summarised in Table 2.

Futility Data

Of the 86 patients prescribed antibiotics, a total of 29 patients (33.7%) were continued on antibiotic therapy after the futility discussions. Only one of these 29 patients (3.4%) had their antibiotics escalated after the futility documentation. 7 of the 9 patients in intensive care received antibiotics, and 2 of these 7 patients (28.6%) had their antibiotics continued post futility. 13 of the 19 patients (68.4%) with acute resuscitation plans specifying that antibiotics were not to be provided received antibiotics during their admission. Timing of antibiotic cessation prior to death is depicted in Fig. 1.

Futility was documented for 123 patients (89.8%), meaning death was deemed not to be expected in 10.2% of patients. The first occurrence of futility documentation occurred an average of 2.6 days prior to death with a median of 1 days (range 0–19 days) prior to death. A significant proportion (44.2%) of those patients who were on antibiotics at time of futility discussions were on antibiotics in the final 24 h of life.

Discussion

There is no clinical consensus on the treatment of infections in end of life care [22] yet antimicrobial use is

Table 2 Infection characteristics.

Variable	n	%
Infection Site		
Pulmonary	45	32.8%
Urinary	8	5.8%
Bone	3	2.2%
Skin	4	2.9%
GI	18	13.1%
Hepatobiliary	2	1.5%
Unknown	6	4.4%
No infection identified	51	37.2%
Antibiotic (Multiple allowed)		
Piperacillin/tazobactam	49	41.9%
Ceftriaxone	18	15.4%
Vancomycin	14	12.0%
Azithromycin	8	6.8%
Benzylpenicillin	5	4.3%
Gentamicin	5	4.3%
Cefazolin	4	3.4%
Flucloxacillin	4	3.4%
Meropenem	2	1.7%
Doxycycline	2	1.7%
Ciprofloxacin	2	1.7%
Amoxicillin	1	0.9%
Norfloxacin	1	0.9%
Trimethoprim	1	0.9%
Cephalexin	1	0.9%
(Nil)	51	
Route		
IV	83	96.5%
PO	3	3.5%

common amongst patients who die in hospital. In this study, even when recognition was made to futility of ongoing medical intervention, the use of antibiotics was continued in one third of patients.

Our finding of predominance of pulmonary [9,14,16,39], urinary [1,2,29] and gastrointestinal sources as the etiology of infection requiring antimicrobial treatment is consistent with previous literature [17,18,21,28]. The most common antibiotic prescribed was piperacillin/tazobactam followed by ceftriaxone. Only 2.6% of antibiotic prescriptions were fluoroquinolones, which is less than other studies of antibiotic at end of life care with fluoroquinolone antibiotic prescription rates as high as 32–38% [9,24,30], although all these studies were performed in the USA. Our results may reflect Australian local prescribing practices and antibiograms. The majority of patients in our study received antibiotics through the parenteral route. This is higher than in small prospective studies of parenteral antibiotic use where parenteral rates ranged from 40 to 51% of antibiotic prescriptions [9,30,33]. However, previous studies have been mainly performed in the outpatient setting.

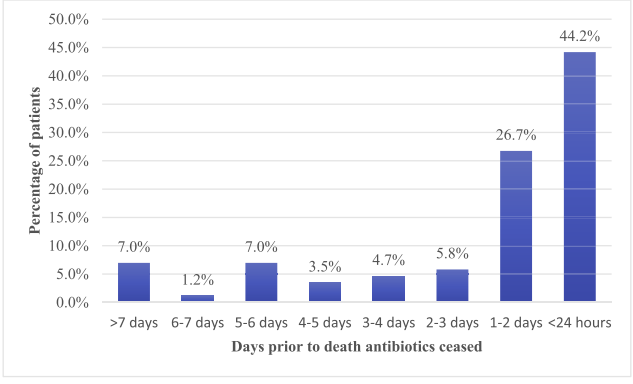

Fig. 1 Time prior to death antibiotics ceased (n = 86).

The retrospective literature for antibiotic use at end of life in palliative care units has shown rates of 63–90% of patients are continued on antibiotics in the last week of life [15,27]. Inpatient research has also demonstrated similar results with respect to high rates of antibiotic use in end of life care. In cancer inpatients in Seoul, Korea, Oh and colleagues found that 63.8% of the 141 patients reviewed had antibiotics used until the day of death [19]. In Thompson and colleagues study of hospitalised patients in Michigan, USA with advanced cancer, 90% of these patients received antibiotics during the week prior to their death and 35.4% continued to receive antimicrobials after a transition to comfort cares with antimicrobials mostly discontinued less than one day prior to death [21]. In a larger cohort study in Washington, USA, Merel and colleagues showed that of 1881 inpatients who were placed on comfort cares, 77% used antimicrobials during their admission [30]. They found that at 24 h after comfort cares were began, 15.6% of patients were still on antimicrobials. In general medical inpatients, a Korean study by Kwak and colleagues found that antibiotics were continued in 59.6% of patients after "do not resuscitate" orders were obtained [36]. These previous studies are consistent with our finding of 33.7% of patients continuing antibiotics after futility discussions and 44.2% of those patients continuing on antibiotics to the final 24 h of life. These results demonstrate a relative high prevalence of antibiotic use in the inpatient setting at end of life, even when the goal is comfort, and death is expected.

The goals for antibiotic prescription at the end of life can include symptom control and improving survival when quality of life is maintained. Although our study did not examine outcomes from antibiotic prescription, systematic reviews have demonstrated inconsistency in the literature regarding patient outcomes with respect to symptom and survival improvement [17,31]. In terminally ill patients where other aggressive therapies are deemed inappropriate, physicians may feel it is easier to prescribe rather than withhold antimicrobials in the setting of suspected infection [16]. Judgement of the turning point of when antimicrobial use becomes futile is challenging and there is likely uncertainty held by physicians for the ethical and legal issues related to withholding and withdrawing of antimicrobials [40,41]. However, there is a responsibility of prescribing physicians to effectively communicate burdens of antimicrobial use to patients and their families to allow informed decision-making processes. Ultimately, initiation of antimicrobial prescription should be an evidence based, goal directed and shared decision making process amongst patients, family and physicians, similar to other life sustaining therapy choices [5]. Ideally this process should be performed in advance, rather than in time of crisis with

shared understanding that even if infection is cured, the underlying terminal illness will remain [5].

Reinbolt et al. propose that patients and family should expresses their wishes concerning treatment of infection on entering palliative care, just as is done for other decisions including cardiopulmonary resuscitation, intubation, and blood transfusions [3]. Secondly, if the patient desires, symptom control should be the major indication for the use of antimicrobials in treatment of infections in this setting. Another group proposed a similar algorithm for management of patients at the end of life with suspected infections that begins with a discussion about antimicrobial use during a comprehensive goals of care discussion [42]. If the patient goal is prolongation of life, then evaluation and treatment for infection is offered if there is a non-futile survival benefit. If the patient is moved to complete palliation, then targeted antimicrobial therapy is only offered when there are symptoms directly attributable to an infection.

Our study has several limitations. Firstly, data collection was of a retrospective nature and relied on accurate and detailed documentation in patient charts for patient futility discussion and treatment. This did not allow for understanding of prescribing intentions of the patient's treating doctors or decision making of the patient and their next of kin. Secondly, all the patients in our small study included were from a single, tertiary-care centre in South East Queensland and antibiotic prescription in this cohort is not necessarily representative of the wider Australian population. Thirdly, judgement of futility was made based on a subjective decision which we acknowledge could vary significantly amongst prescribers and observers. Finally, numerous factors that are not documented in medical records would likely play a role in antibiotic prescription decision making. This includes but is not limited to patient and family preferences influenced by many underlying psychosocial factors and physician emotional prescribing influences and biases, which is an area for future research. There are no randomized controlled trials examining outcomes of antimicrobial use in end of life care, and trials of this nature would be limited by ethical issues.

Despite these limitations, our study generates hypotheses and adds to the limited literature evaluating antimicrobial use amongst inpatients dying in hospital, regardless of underlying diagnosis. This study reaffirms the need for further high quality research in this area.

Conclusion

Antimicrobial use at the end of life in hospitals is high, with over one third of patients who died in hospital having antibiotics continued after discussion of treatment futility. This is an emotive and controversial area of medicine with significant social and ethical considerations which need to be addressed if antibiotic optimization in this area is to be achieved. This study provides an opportunity for further prospective, multicentre studies assessing the benefits and harms of antimicrobial consumption in dying inpatients to optimise outcomes. In addition, the appropriateness of antimicrobial prescribing practice in this population needs to be evaluated, ideally using a recognised research tool, such as the National Antimicrobial Prescribing Survey. Finally, the bigger picture of antimicrobial stewardship and resistance in end of life care may be partly addressed by qualitative evaluation of determinates in antimicrobial decision making for patients, family and physicians.

Ethics

Requirements for Metro North Health Research Ethics Committee (HREC/17/QPCH/467) were fulfilled (exemption from formal ethical review granted).

Authorship statement

JB conceived the study. JD drafted the study design, acquired and analysed the data and wrote the manuscript. LV assisted in data collection. JB and AB critically reviewed the manuscript. All authors have given permission for their inclusion.

Conflicts of interest

None to declare.

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Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idh.2018.12.001.

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