Design and analysis of longitudinal trials of antimicrobial use at the end of life: to give or not to give?

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Abstract: This perspective review considers analytic features of the design of a longitudinal trial regarding antimicrobial therapy in older terminal cancer patients receiving palliative care. We first overview antimicrobial use at the end of life; both the potential hazards and benefits. Antimicrobial prescribing should consider both initiation as well as cessation of medications when analyzing the burden of medications. Approaches to decision making regarding antimicrobial use are presented and the importance of health literacy in these decision processes. We next present aspects of both feasibility and comparative trial design with a health literacy intervention to reduce antimicrobial use in older terminal cancer patients receiving palliative care. Considerations to clustered randomization and given that infections can reoccur over a trial period, we share suggestions of longitudinal modeling of clustered randomized trial data.

Keywords: antimicrobial therapy, end-of-life care, health literacy, longitudinal analysis, trial design

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Introduction

Systematic reviews have summarized published trials and studies of medication discontinuation in older adults in a variety of settings. Studies have found that older adults are prescribed an increasing number of medications as they age. Thus, prescribing should consider both initiation of a medication, as well as cessation of medications. Recently, a study of terminal cancer patients found that 90% were receiving six or more medications.[1] In this article, we present a perspective on medication use at the end of life, whether to initiate or continue antimicrobial use. Inappropriate antimicrobial use is a widespread problem that requires antimicrobial stewardship interventions to prevent emergence of antimicrobial-resistant pathogens and adverse effects.[2] Patients at the end of life represent one group in whom inappropriate antimicrobial use is commonplace. We hypothesize that the level of 'health literacy,' defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services influences healthcare decisions.[3] Specifically, we consider the design and analytic considerations for a trial that addresses health literacy as part of a multimodal intervention for patients with terminal cancer receiving palliative care that incur infections.

Clinical importance of antimicrobial use at the end of life

In the final weeks of life, 90% of hospitalized patients have antimicrobial therapy initiated.[4,5] Rarely considered as increasing the burden of medications for the terminally ill patient, many physicians consider antimicrobials as a benign intervention even though it may result in adverse events [i.e. adverse drug effects, *Clostridium difficile* infection (CDI), development and transmission of multidrug-resistant organisms (MDROs) in healthcare settings].[4,6,7] In addition to medication burden, discomfort may result from evaluation procedures (e.g. bladder catheterization, blood draws, imaging studies) and treatment (e.g. intravenous lines, mechanical restraints) of

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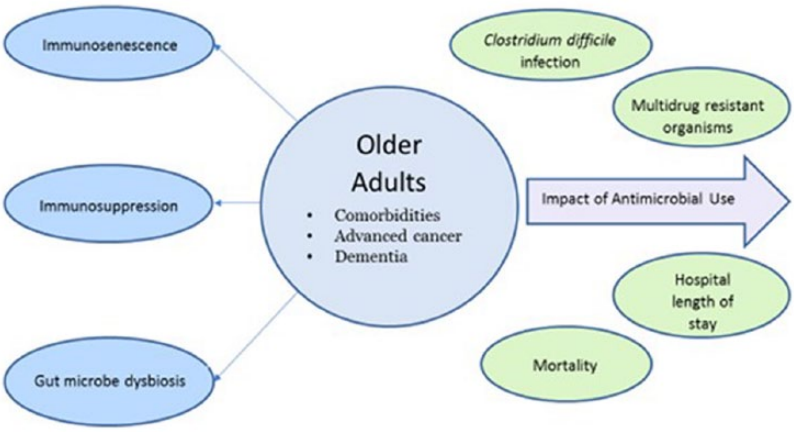

Figure 1. Factors surrounding antimicrobial use at the end of life for older adults with advanced cancer.

suspected infections.[8] Qualitative studies of patients with terminal cancer have shown that with proper counseling, patients and families would consider withholding or withdrawing antimicrobials when increasing signs and symptoms of death are present.[9–13]

Use of antimicrobial therapy at the end of life in different care settings

For patients on palliative care units in the United States and in international settings, the range of patients receiving empiric antimicrobial therapy was 14–84%.[9,14–18] Among nursing home residents with advanced dementia, 42% received parenteral antimicrobial therapy in the final 2 weeks of life.[19] Even in the hospice setting, approximately one quarter of patients received antimicrobials in the final weeks of life.[20,21] For patients with hematologic malignancies dying in hospice, almost 90% of patients received antibiotics in the final week of life.[22] Among hospitalized patients transitioned to comfort measures, 15–20% of patients in one institution were on antimicrobials between 24 and 96 h after a comfort care order set was placed, and oncology patients were the group with the highest use.[23] Urinary tract infections (UTIs) are the most commonly suspected, treated, and mistreated infections at the end of life, followed by respiratory tract infections.[14–16] Antimicrobials are often prescribed empirically based on presenting signs and symptoms without confirmatory imaging studies or laboratory tests.[4,17,24] In many instances, there is inadequate clinical evidence of a bacterial infection to warrant treatment based on published national guidelines.[25] These observations suggest the need for more empirical data to advance best practices.

Potential hazards of antimicrobial use

Antimicrobial use is often viewed as benign compared with other life-sustaining treatments (e.g. intubation, dialysis), and both its initiation and withdrawal are often overlooked in deprescribing. However, antimicrobials are not always benign and may result in adverse events, including drug reactions, CDI, and transmission of MDROs in healthcare settings (Figure 1).[4,6,7,26] Patients with malignancy, particularly those undergoing transplant, are at high risk for developing CDI.[27] CDI or asymptomatic *C. difficile* colonization is associated with an alteration of the gut microbiota and reduction in the numbers of potentially protective bacterial taxa in the gut.[28] In addition, changes to normal gut flora creates an opportunity for acquisition and colonization with MDROs and subsequent possible infection. Aging alone contributes to gut microbe dysbiosis;[29] hence, the combination of antimicrobial exposure, immunocompromised state; and aging may create an environment for even more profound risk of MDRO infection and CDI (Figure 1). When the goals of care transition to comfort, additional hazards of antimicrobial therapy include prolonged hospitalization. Recognizing the magnitude of the risks of antimicrobial use at the end of life, decisions about whether to initiate or withdraw antimicrobial therapy should be foremost in the patient and provider discussion (Figure 1). Providers are confronted with many competing concerns and motivations, including a desire to respect a patient and family's wishes, alleviate pain and suffering, prevent adverse effects, prevent emergence of MDROs, treat potentially curable infection, and reduce burdensome treatments.[30]

Potential benefits of antimicrobial use at the end of life

Two theoretical benefits motivate providers to prescribe antimicrobials to terminally ill patients: prolonging survival and relieving symptoms. However, there are limited data to provide evidence regarding these outcomes. Small observational studies suggest that hospice patients who receive antimicrobial therapy for suspected infections have prolonged survival compared with untreated patients.[10,17] However, for many of these patients, comfort, not survival, is the main goal of care. The role of antimicrobial therapy in achieving comfort is not well established. A systematic review identified eight observational studies that examined whether antimicrobials provided symptom relief to terminally ill patients. Methods of symptom assessment varied widely among the studies, and symptom improvement varied by indication for treatment.[24] Dysuria from a UTI had the greatest improvement; hence, antimicrobials may be beneficial on a case-by-case basis.[31,32] However, because of heterogeneous cohorts and contrasting findings, no clear overriding conclusions could be made. Among advanced-dementia patients with suspected pneumonia, those not treated with antimicrobials had greater comfort, though shorter survival, compared with the treated group.[33] The survival benefit was the same regardless of the route of antimicrobial administration (oral, intramuscular, or intravenous). Treatment of suspected UTI in advanced dementia had no survival impact.[25] Given these findings, nonantimicrobial options to treat symptoms should be considered.

Withholding or withdrawing antimicrobial therapy in terminally ill cancer patients

Studies in patients with terminal cancer have shown that with proper counseling, patients and families often are amenable to withholding or withdrawing antimicrobials when increasing signs and symptoms of death are present.[9–12] In a study of patients with advanced cancer receiving hospice care, older patients with poorer performance status were more likely to choose symptomatic treatment of infections only (48.2% of respondents) or no antibiotic therapy (31% of respondents).[32] In another study of 1277 cancer patients in hospice care aged 65 and older, 14% received antibiotics in the final week of life, consistent with the finding that older adults and their families may be amenable to withholding or withdrawing antimicrobial therapy to align with the goals of care.[34] Yet, a study in Taiwan identified that the vast majority of patients with terminal cancer felt that antibiotics were helpful to all patients with terminal cancer.[35] A study of end-of-life needs by terminally ill older adult patients found that patients ranked the need to include them in determining the care policy significantly higher than physicians did.[36] They further reported that 86.4% wanted to know the truth about their condition, 60% did not want life extension and 57% wished to die at home. Thus, health literacy interventions that incorporate setting goals of care and counseling may allow patients and families to make informed choices.

Approach to decision making regarding antimicrobial use

The first step to addressing antimicrobial use at the end of life in advanced cancer patients is assess where a patient and their family are in the decision-making process regarding end-of-life care. If the goals of care are still curative in nature, antimicrobials are almost always indicated, as this would be consistent with goals of care. However, as a patient decides to opt for more palliative measures or for Do Not Resuscitate orders to be in place, addressing antimicrobial use may be indicated. At this stage, it is important to inform patients and their families that infections are expected near the end of life and are often a terminal event. Elements of health literacy around antimicrobial use include an understanding that even if an infection were cured, the underlying illness remains.[36] Another element for patients and their family is understanding what the evaluation of a suspected infection entails and to provide them with real-life examples that may results in unnecessary antimicrobial use. The hazards of diagnosing and treatment should be openly discussed, as well as the potential benefits while sharing the uncertainty of these in a dialog the patient and family can engage in.[37,38] Although most physicians are aware of the hazards associated with antimicrobial use, some lack the skills and training to address antimicrobials at the end of life, while others feel that these burdens are minimal in the context of other, more complex decisions that are made at the end of life. Hence, any intervention regarding antimicrobial use at the end of life should involve education and training of patients, families, and healthcare providers regarding a purely palliative approach to care.

This alignment of the patient's and their family's choices with goals of care guides treatment

decisions. When comfort care is the priority, no evaluation for a suspected infection is conducted. However, if the patient's choice is to maximize survival, consideration is given as to whether the potential benefits of antimicrobials may prevail over its burdens. In such a case, evaluation for infection is conducted and continuation with antimicrobial therapy by the least invasive route is preferable.[37] Survival may not differ from parenteral therapy with less patient discomfort and lower healthcare expenditures.[33,37] As each terminally ill older patient may have differing goals, underlying illness and tolerances for uncertainty, there is no single approach regarding the use of antimicrobial agents.[39] However, by physicians, patients, and families assessing goals of care and understanding what treatments entail, care can be aligned with goals.

Health literacy of antimicrobial use

Previous literature and trials on medications use for patients receiving palliative care has largely focused on chronic use medications for primary prevention or active treatment for a chronic condition. The percentage of Americans over 65 taking at least five prescription medications has doubled over the past decade to nearly 40%.[40] Another body of literature focuses on initiating antimicrobial use, but rarely in the context of medication burden. Even fewer articles discuss the withdrawal of antimicrobials. Traditionally, prescription medication use has been at the discretion of the physician; however, in palliative care settings, goals-of-care discussions with the patient and family can open the door to discussion about medication initiation and withdrawal. A recent paper found that adults with adequate health literacy were less likely to have taken antibiotics in the past year than those with low health literacy.[41] Other work has shown that health literacy is inversely associated with a desire for aggressive end-of-life care and filling antibiotic prescriptions after emergency care.[42,43]

Considerations of a health literacy trial of antimicrobial use for older adults with advanced cancer

Feasibility trial design

Intervention trials typically progress from testing feasibility of the intervention to comparative trials. Recently, Ailabounic and colleagues presented a feasibility trial for deprescribing in residential aged care facilities with a primary outcome of a change in the Drug Burden Index.[44,45] Many trials have primary outcomes of reducing the number of medications, but to a lesser extent, include clinical outcomes.[46] Without evidence that a medication can be withdrawn, estimating the difference in clinical outcomes may be moot. Feasibility trials provide the foundation for both investigators and stakeholders (e.g. patients, families of patients, physicians, care facilities) to establish the acceptability of potential intervention elements, as well as appropriate conduct of informed consent.

The planning of the feasibility trial provides an opportunity to develop the medication management plan, which may be based on screening tools to identify high-risk medications or the Good Palliative–Geriatric Practice algorithm.[47,48] Many of these tools provide patient-centered screening to continue with the same dose, reduce the dose, shift to another medication or stop the medication. Thompson and Farrell noted that most guides and algorithms considered the timing and reasoning for medication discontinuation but lacked an explicit description of how to discontinue.[49]

During a feasibility trial on antimicrobial use, different health literacy intervention elements intended to support patients and families with the knowledge of whether they prefer to withdraw or not initiate an antimicrobial may be tested. Incorporating input from stakeholders, inclusive of healthcare providers, patients, families, and institutions, into the design of potential intervention elements should be part of the feasibility process.

In this feasibility phase, investigators need to consider the heterogeneity of the potential participants. If the primary goal is to develop an intervention reducing antimicrobial use intended to be next applied in a pragmatic comparative trial, then a heterogeneous participant pool may be suitable. On the other hand, if the intervention is to reduce antimicrobial use which in turn impacts clinical or patient-centered outcomes, then a homogeneous participant pool may estimate a signal of the intervention. In a potential trial, a more homogeneous group of participants that have advanced cancer and are receiving palliative chemotherapy during a second hospitalization for clinical decompensation and experiencing an infection are the target population (Figure 2). All patients with advanced cancer on palliative

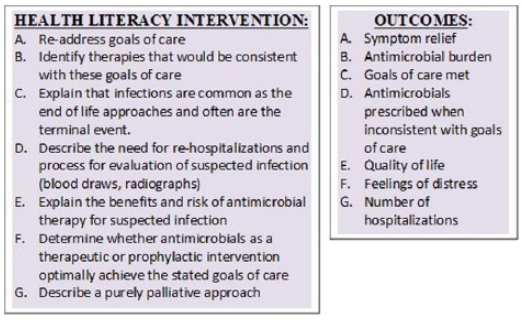

Figure 2. Overview of proposed health literacy intervention and outcomes among older advanced cancer patients receiving palliative care during the second hospitalization for clinical decompensation.

chemotherapy that can provide self-consent would be eligible. This intervention would have to be incorporated into other advance care-planning discussions that would be required for all participants, as this discussion is only appropriate in the context of other advance directives.

Feasibility trials are not intended to estimate efficacy, but rather stakeholder satisfaction, a potential for implementation, participant screen to enroll ratio and completion rates, amount of missing data and ascertainment of reasons for missing data, and variances of the treatment arms. Measuring outcomes may be informative for which intervention component may go on for further testing (Figure 2). The CONSORT group has developed guidelines to support the planning of feasibility trials[50] (Figure 2).

Comparative trial design

Based on the findings of the feasibility trial, intervention components are selected for a comparative trial. Comparative trials may range from smaller targeted trials (single condition, single setting, homogeneous sample) to pragmatic trials. Depending upon the intensity of the intervention, health literacy interventions may lend themselves to larger-scale pragmatic settings.[51,52] For a pragmatic trial that may be implemented across a healthcare system, models such as the 'health literate care model' should be considered.[53]

Typically, the initial comparative trial is a single center, relatively homogenous sample. However, should there be a risk of contamination because blinding is infeasible, then wards within a hospital or hospitals may be randomized resulting in a cluster randomized trial. These designs need to account for the correlation of participants within a cluster.[54] As it may be apparent to participants which arm they are in, single blinding is also an option, where outcome assessment is blinded to treatment arm.[52]

For the proposed trial addressing antimicrobial use, to reduce the likelihood of contamination, a cluster randomized, single-blinded, parallel-group design is most straightforward. However, elements of adaptive trial design must be considered given that older adults with advanced cancer receiving palliative care may have a number of sequential infections over the trial. During an infection episode, a sequence of decisions regarding patient care will need to be undertaken (e.g. if the patient is unresponsive to the initial treatment decision, do we withdraw antimicrobials or switch to a different course? If the patient's condition worsens, are intravenous antimicrobials switched to oral alternatives?). Thus, the health literacy intervention may need to be provided throughout the trial and not only upon entry. The set of health literacy options at each decision point (e.g. if a patient is unresponsive to the initial treatment decision, should counseling be increased?) needs to be clarified. What would trigger a change or additional element of the health literacy intervention? These are referred to as tailoring variables and can be factors such as worsening health, symptoms, or level of comfort. Hence, a sequence of *a priori* decision rules links these to provide information about which of the health literacy intervention elements is most appropriate for the patient at the time of the decision.

Defining the outcomes

As in all comparative trials, the primary outcome(s) and the frequency of measures of it influence the design and analysis. As participants may have multiple infections over the course of the trial and the goals of care may evolve for each participant over time, each infection episode would be a recurrent event and within-participant correlation must be modeled. Furthermore, as older adults with advanced cancer are at high risk of dying, palliative comfort care may be a goal of care, as might hospice care; thus, suitably modeled as meeting the goals of care (if indicated) and not considered lost to follow up. Ongoing studies by our group are identifying clinically relevant outcomes, their rates, and effect sizes that could be tested in a clinical trial. Potential outcomes are shown in Figure 2.

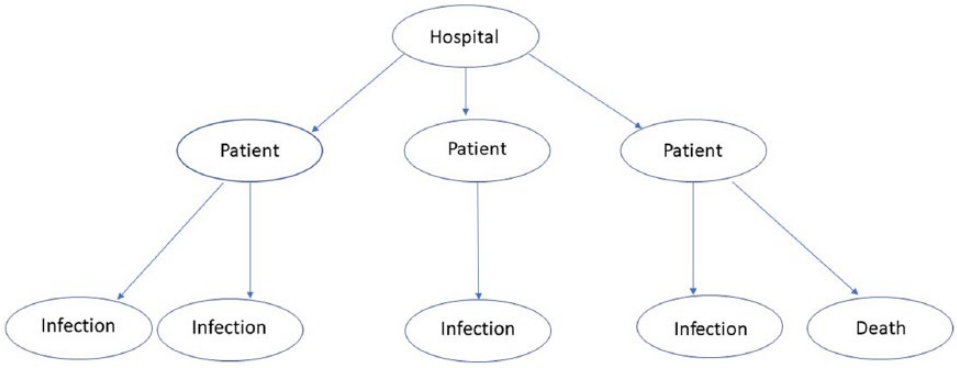

Figure 3. Multilevel design where patients are clustered within a hospital and infections are clusters within a patient.

Longitudinal analytic approaches

Trials with older participants with serious illness face analytic challenges. These include that the follow-up length is likely to differ due to participants' characteristics (e.g. severity of illness, goals of care, time until death). In this trial design, we expect a different number of observations per participant dependent upon the number of infections and the timing between infections will vary. For example, the outcome measure of symptom relief during each infection episode and whether or not antimicrobials were used would be a repeated outcome, observed for each infection episode. Analytically, each participant is a cluster as they may have repeated infections nested within them, each with potentially a different value for the outcome measure. For example, the first infection may not have had symptom relief, but the second and third infections did have symptom relief.

As Figure 2 shows, several potential outcomes, each participant's outcomes may be 'joined' by a shared random effect. Modeling these potentially correlated outcomes separately may fail to extract shared information regarding a treatment effect, possibly leading to biased estimation.[55] As we are not considering either death or admission to hospice as a censoring event, but an outcome potentially aligned with the goals of care, semicompeting risk models do not apply.[56] Thus, one option is modeling these outcomes simultaneously with a shared random effect (i.e. a joint model). A joint model of recurrent hospitalizations and death estimating the participant-level association has been demonstrated.[57] Previously, Fieuws and Verbeke modeled more than two outcomes jointly using a pairwise modeling approach, where joint models for all pairs of outcomes were fit, and on overall intervention, effect was estimated over all the pairs.[58] Notably, in this joint generalized linear mixed modeling approach, the shared random intercept represents unobserved factors underlying a participant's predisposition to experiencing a pair of outcomes, while a scalar multiplier that quantifies the effects of unobserved factors with the second outcome in a pair.[59]

Just as we conceptualize the participant as a cluster with repeated infections, cluster randomization at the hospital-level can be modeled through a random effect (Figure 3). For example, patients in the same hospital will be exposed to similar protocols, environmental factors, and if in the intervention arm, team members engaged. Models that ignore hospital-level clustering effects tend to overestimate the variance of the patient-level cluster. Consequently, there would be an upward biased variance of the participant-level cluster as it includes both unobserved factors from the participant and hospital.[60] Thus, it is important to account for the effect of different levels of clustering in the nested models to avoid misinterpretation of variances. Hierarchical models can account for either multiple levels of clustering (e.g. hospital-level and participant-level clustering) with either fixed or random effects.[61] Random-effect models should be considered when there are other sources of variation (i.e. unmeasured hospital or participant factors) that should be accounted for at each level of the hierarchy. In cluster randomized designs, randomization may not balance all of the higher level (hospital) observed and unobserved factors; hence, using the appropriate model may address these sources of variation (Figure 3).

We plan on estimating an overall intervention effect and not components of the health literacy intervention that may be provided as a result of the triggers described above. This is because each participant randomized to the intervention arm will start with similar health literacy components but may later vary in what is received in response to their infection, goals of care, and underlying illness course. Additionally, each participant's goals of care may update at any time. In such a vulnerable population, patient care is of utmost importance and designs are needed to assess interventions without burdening terminally ill patients.

Conclusion

Informed use of antimicrobials at the end of life is based on weighing the harms of benefits and aligning these with the goals of care. In order for patients and their families to make informed decisions, they need to obtain, process, and understand basic health information and treatment choices, in all aspects of health literacy. Trial results remain the strongest metric of an intervention but are complicated when working with vulnerable populations, such as older adults with terminal cancer. Novel designs and analyses that support the care process, have limited burden, capture sources of variation at various levels, and are responsive to the course of illness have much promise.

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Conflict of interest statement

The authors declare that there is no conflict of interest. Dr Juthani-Mehta served as a consultant to Iterum Therapeutics.

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