Clinical Infectious Diseases

STATE-OF-THE-ART REVIEW

State-of-the-Art Review: Use of Antimicrobials at the End of Life

Daniel Karlin,[1] Christine Pham,[2,3] Daisuke Furukawa,[4] Ishminder Kaur,[5] Emily Martin,[1] Olivia Kates,[6] and Tara Vijayan[2]

[1]Division of General Internal Medicine, Department of Medicine, University of California, Los Angeles, California, USA; [2]Division of Infectious Diseases, Department of Medicine, University of California, Los Angeles, California, USA; [3]Department of Pharmaceutical Services, University of California, Los Angeles, California, USA; [4]Division of Infectious Diseases, Department of Medicine, Stanford University, Palo Alto, California, USA; [5]Division of Infectious Diseases, Department of Pediatrics, University of California, Los Angeles, California, USA; and [6]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Navigating antibiotics at the end of life is a challenge for infectious disease (ID) physicians who remain deeply committed to providing patient-centered care and engaging in shared decision making. ID physicians, who often see patients in both inpatient and outpatient settings and maintain continuity of care for patients with refractory or recurrent infections, are ideally situated to provide guidance that aligns with patients' goals and values. Complex communication skills, including navigating difficult emotions around end-of-life care, can be used to better direct shared decision making and assist with antibiotic stewardship.

Keywords. antibiotic stewardship; end-of-life care; palliative care; hospice.

Navigating the use of antimicrobials at the end of life is a challenge for infectious disease (ID) physicians who remain deeply committed to providing patient-centered care and engaging in shared decision making while also ensuring antimicrobial stewardship. Infectious disease physicians, who often maintain continuity of care for patients with refractory or recurrent infections in both the inpatient and outpatient settings, are ideally situated to provide guidance that aligns with patients' goals and values.

At the end of life, goals of life prolongation and symptom control (comfort) may, at times, be in conflict. Antimicrobials may be aligned with either of these goals. Antimicrobials can temporize refractory infections and potentially prevent sepsis and hospitalization, but at the cost of side effects such as nausea and diarrhea. Antimicrobials can ameliorate some symptoms (such as fever or dysuria) but might complicate or prevent the transition of the dying process to the home environment, where many of these symptoms may be better managed with other treatments such as antipyretics or opioids.

When patients with terminal illnesses present with incurable infections, ID physicians can play an essential role in engaging patients in goals-of-care discussions to ensure that antimicrobial treatments are informed by their prognosis, goals, and priorities. Additionally, understanding and navigating the process of death from an infection, whether it is the primary driver of the disease or secondary to another underlying process such as cancer, is very much within the expertise of the ID physician. The idea of death from an infection may be difficult for patients and non-ID physicians who view infections as curable, but this is a reality that many ID physicians closely understand.

Decisions around antimicrobials in an end-of-life setting may be driven by emotions rather than practical needs [1, 2]. Continuing antimicrobials may provide a sense of hope that an infection complicating the underlying condition (such as cancer) will be reversed, or that treatments for the underlying condition may be offered after an antimicrobial is started. Outlining patients' goals involves masterfully responding to complex and intense emotions experienced by patients, their caregivers, and the healthcare team. Setting realistic expectations, while not diminishing hope and meaning, requires a skill that ID physicians can cultivate with the help of other experts, such as palliative care specialists.

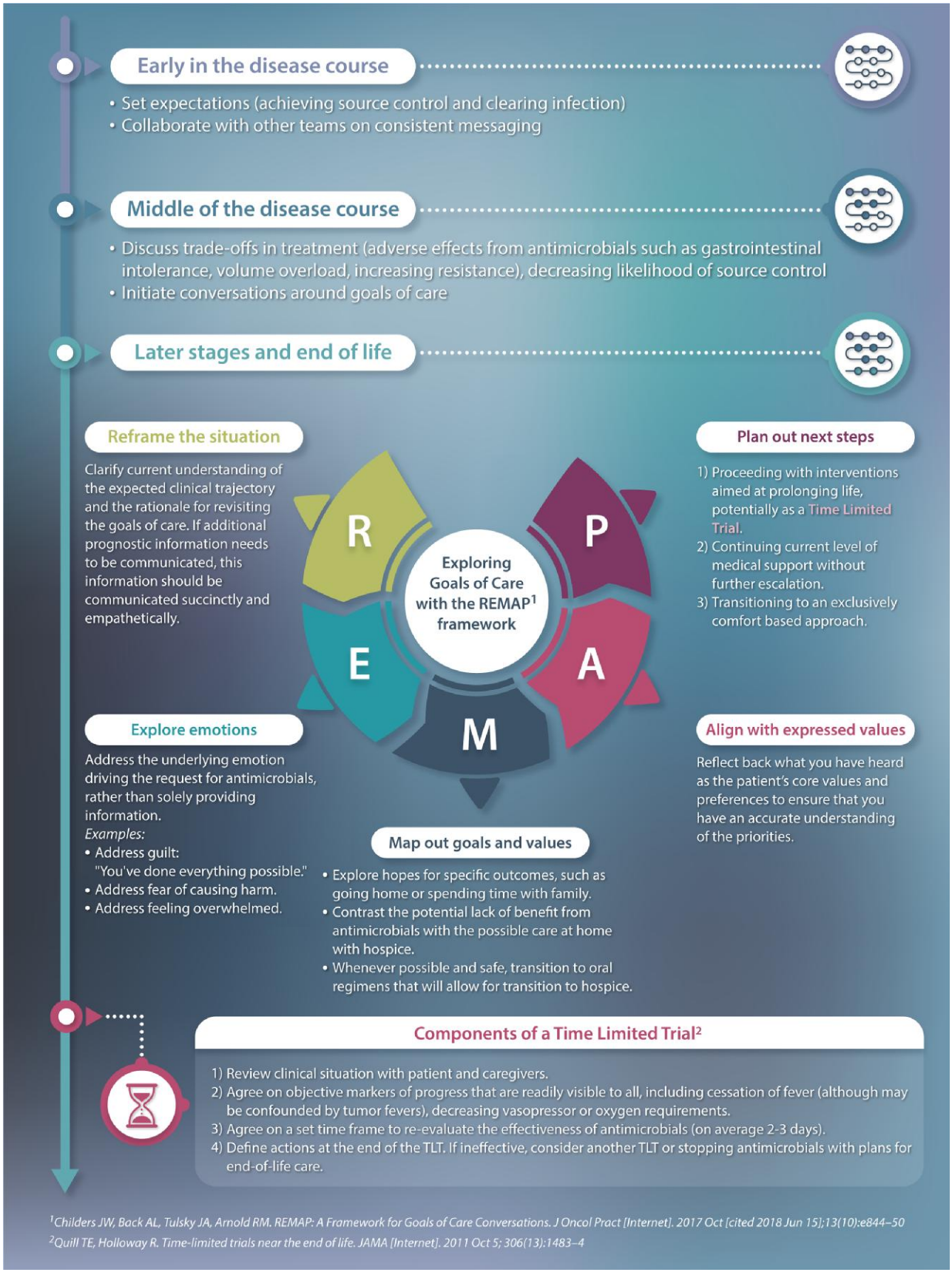
Communication challenges between patients and their various medical teams are at the heart of what we aim to discuss in this paper. Shared decision making involves providing clear, accurate, and unbiased medical evidence about risks and benefits of all reasonable options; understanding a patient's goals and treatment preferences; and integrating this information into a clear clinical recommendation [3]. Here, we describe a common scenario of a patient with a malignant obstruction that results in recurrent abscesses. We outline stepwise changes in the patient's clinical condition, suggest approaches to conversations with the patient and her family, and discuss potential

Received 12 May 2023; editorial decision 15 September 2023; published online 1 February 2024

Correspondence: D. Karlin, Division of General Internal Medicine, Department of Medicine, University of California, Ronald Reagan UCLA Medical Center, 757 Westwood Plaza, Ste. 7501, Los Angeles, CA 90095 (dkarlin@mednet.ucla.edu).

Clinical Infectious Diseases® 2024;78(3):e27–e36

https://doi.org/10.1093/cid/ciad735



ethical conflicts affecting the ID physician, including antimicrobial stewardship [4].

PART 1. EARLY CONVERSATIONS AND SETTING EXPECTATIONS

A 67-year-old woman with newly diagnosed unresectable cholangiocarcinoma begins chemotherapy. She subsequently develops fever, loss of appetite, and right upper quadrant abdominal pain, resulting in a hospital admission. She is started on piperacillin-tazobactam. A computed tomography scan reveals several rim-enhancing fluid collections in her liver. A percutaneous biliary drain is placed, and fluid from this procedure grows Enterobacter cloacae *complex. Her oncology team is preparing to discharge her home.*

As integral members of the patient's care team, ID clinicians are well positioned to recognize that this clinical presentation warrants expectation setting and the potential involvement of palliative care clinicians in the care team [5].

Definitive drainage, which may allow for shorter courses of antibiotics [6, 7], is seldom possible with malignant obstructions. The unresectable nature of the patient's obstructive malignancy portends a clinical course of recurrent, prolonged, and polymicrobial infections involving increasingly drug-resistant organisms with progressively fewer anti-infective options. Even as ID physicians start to set expectations for the current infection and introduce concepts of home intravenous antibiotics versus oral antibiotics, we should be mindful of anticipated recurrences and complications. This warrants a discussion of long-term care goals. Clinicians should ensure that the patient understands that this infection is not a transient event, but rather a manifestation of their underlying disease that may periodically recur or may become "incurable."

Clear, direct communication should be used when delivering this news. "This infection happened because of the blockage caused by the cancer. I'm concerned that even if we manage to control the infection this time, the infection may keep coming back because the blockage will still be there. We can use our best antibiotics to treat the infection when it recurs, but it may become the limiting factor for your overall health, just as much as the cancer itself." This information should be discussed with the patient's oncologist and other primary clinicians, to promote consistent messaging.

Several ID syndromes present similar dilemmas across different primary disease processes, including obstructive uropathy in pelvic malignancies and post-obstructive pneumonia in thoracic malignancies. Treatment of infections is complicated in these cases, either because source control is not feasible when the obstructive malignancy cannot be resected or because diversion devices, such as nephrostomy tubes or biliary stents, can also become infected [8]. The lack of a definitive solution must be communicated in a manner that reflects the likelihood of a prolonged and recurrent course.

It is important during discussions regarding source control to use language that does not blame other team members. For example, "the location and large size of the tumor means it can't be removed without causing serious damage to the surrounding organs" is a nonjudgmental statement of fact, rather than "we know that we need to relieve the obstruction so the infection can be drained/treated, but the surgeons are unwilling to operate on the tumor because they are afraid of its size and location." Professionalism, particularly with respect to collaboration and support for other team members, is essential in these discussions.

When source control cannot be achieved, patients may be prescribed prolonged courses of intravenous antimicrobials or long-term "suppressive" oral antimicrobials. In rare cases, suppressive antimicrobials may allow a more definitive procedure, such as resection or radiation, to take place with fewer complications. In other situations, the practice of prolonging treatment or assigning indefinite antimicrobial durations can be seen by the primary clinical teams, patients, and their families as a "low-risk intervention" that provides insurance against future episodes of sepsis that could lead to hospitalization or death. The ID physician should be aware of these common anxieties when setting expectations with patients, families, and fellow clinicians. Plans for treatment duration and for ongoing monitoring after stopping antimicrobials should all be clarified to build confidence in the treatment plan. Treatment duration may be either predetermined (by guidelines or clinical experience) or based on specific indicators (such as symptoms, biomarkers, or surveillance imaging).

PART 2. MANAGING SIDE EFFECTS FROM ANTIMICROBIALS

The patient is discharged home with cefepime but develops distressing anasarca. At a follow-up visit with her ID physician, she is switched to oral trimethoprim-sulfamethoxazole but develops severe nausea and vomiting, leading to a subsequent readmission for dehydration. During this hospitalization her biliary drain is replaced, and 2 additional drains inserted. Cultures from these drains grow drug-resistant Escherichia coli. *Due to resistance and intolerance, the ID team identifies no appropriate oral antibiotic options. She is discharged with ertapenem, with a plan for close follow-up in the clinic.*

Over the next several months. antibiotics are stopped intermittently due to ongoing side effects, but she continues to have hospitalizations with recurrent abscesses. Consultants from gastroenterology, interventional radiology, and general surgery agree that definitive source control is not possible.

Antibiotic use in this context is rarely static. The infection may have been perceived as a single entity that can be reliably treated the same way with each recurrence. At this juncture, clinicians should address toxicities (including volume overload

Table 1. Using REMAP in Early and Late Goals-of-Care Conversations

Steps	Key Points	Phrasing in Early Conversations	Phrasing in Late Conversations
Reframe	Clarify current understanding of the expected clinical trajectory and the rationale for revisiting the goals of care. If additional prognostic information needs to be communicated, this information should be communicated succinctly and empathetically.	"What is your understanding of the current status of the infection? How has the treatment been working?"	"What has the ICU team shared with you about how you're doing?" "What are the latest updates that you've heard about your condition?"
	Acknowledge the change in clinical status and the need to revisit goals of care.	"Unfortunately, the infection is getting harder to treat, and we will never be able to get rid of it. I'm worried that this will be what affects your life the most going forward."	"We're in a different place now. Our treatments are no longer helping in the way that we hoped, and I'm worried we're approaching the end."
Expect Emotion	Acknowledge and respond to emotional responses, whether verbal or nonverbal. Addressing these emotional responses with empathy is a critical step in eliciting patients' goals and values and establishing a plan of care that best aligns with those goals.	"I can see how hard this is to hear." "You've done so much work just to get to this point."	"Anyone would feel saddened by this situation right now. I wish I had better news for you."
Map Out Patient Goals	Outline priorities expressed by the patient and family. It may be necessary to note that no immediate decisions are required.	"Can you tell me what feels most important to you as we continue treating your illness and managing your infection? What should we prioritize?"	"Knowing that we are approaching the end, what should we prioritize the most right now?"
	If patients are unable to name priorities, provide examples of what other patients choose.	"Some patients favor doing the most aggressive treatment to slow down or suppress an infection, regardless of the effect on comfort. Others want to prioritize reducing side effects, even if it isn't the strongest medication for treating the infection. Can we talk about your priorities so I can be sure we're following a path that matches your wishes?"	"Some patients tell me that they want to maximize their time at home in their final days, while others want to be certain they've exhausted all reasonable attempts to prolong their life. Do any of these ring true for you?"
	Probe into simple or one-word answers to extract more detail that helps in understanding a patient's specific goals.	"Tell me more about what worries you about side effects. What situations should we avoid?"	"You mentioned wanting time with family. What might that look like right now?" "When you spoke about being at home, what are you hoping for your time at home to be like?"
Align with Goals	Reflect back on what you have heard as the patient's core values and preferences to ensure that you have an accurate understanding of the priorities. You can incorporate any pertinent emotions as well, such as ambivalence or fear, that you have observed.	"I'm hearing that you truly prioritize your level of comfort above all and want to ensure that we keep that in mind when we order treatments." "It sounds like you're worried about the infection getting rapidly worse. Let's make sure we are thoughtful about using the best ways to treat this."	"It sounds like having some time to focus on saying goodbye is most important to you. I think your whole medical team wants to help you achieve that."
Propose a Plan	Provide a clear recommendation based upon the communicated goals and priorities. Asking for permission prior to communicating your recommendation may increase the likelihood that the patient or family is ready to hear and integrate additional information.	"Let's make sure that we use antibiotic regimens that are most tolerable for you in the future. I'll make sure that my colleagues are aware of this if you come back to the hospital."	"Based on what you've shared is most important to your partner, may I share what I think would best help you achieve that?" "Knowing that the most important part is to be at home, let's do everything we can to make that happen in a safe, comfortable way. I want to make sure that we focus on comfort in treating these infections, and I'd like to share how we can adapt our treatments to do that."
	In earlier conversations, this may be an opportunity to provide an anticipatory recommendation for a later situation.	"There may come a point where treating this infection with more and more procedures and antibiotics may lengthen your life, but would force that additional time to only be in a hospital setting, away from your family. Knowing how important their presence and your comfort is to you, when that time comes, we should talk about changing our approach to the infection."	"I remember we talked about this some weeks ago. I think now we are at the point where more procedures and antibiotics would mean that you spend your final days in the hospital. Should we talk about options that could help you be comfortable and close to your family instead?

Data from reference [11].

Abbreviations: ICU, intensive care unit; REMAP, Reframe, Expect Emotion, Map Out Patient Goals, Align with Goals, Propose a Plan.

[9]), emergence of drug resistance, and escalating spectrum of antibiotic activity to lay the groundwork for anticipated progression or complications. Ultimately, the goal of antibiotics becomes to control the infection rather than cure it [10]. When the diminishing probability of definitive source control and cure becomes apparent, goals-of-care conversations should address this.

As ID physicians continue to frame the discussion around an expected disease course, it is important to state that, even though the infection is not an independent disease process from the underlying disease, it may be the infection that leads to death. Although not yet imminently dying, patients will often endure clinical episodes that challenge their expressed goals or create conflict between their priorities.

In the above case, drug intolerance and the emergence of resistant pathogens cause the patient to switch away from simpler antibiotic regimens to more complex ones. As treating these infections creates escalating demands for the patient, the ID physician is well positioned to further explore goals of care as they pertain to the current clinical situation, using the REMAP (Reframe, Expect Emotion, Map Out Patient Goals, Align with Goals, Propose a Plan) framework (Table 1). Emotional challenges pertaining to these discussions are further explored below.

PART 3. INTENSIVE CARE: EXPLORING END-OF-LIFE WISHES

The patient becomes confused and drowsy at home and is readmitted for acute kidney injury and fluid-refractory hypotension. She is transferred to the intensive care unit (ICU) for pressor support and management of septic shock. The ICU team starts meropenem and vancomycin empirically. Blood cultures grow Candida *species, and the ID team recommends adding caspofungin. Per the oncology team, chemotherapy is on hold until candidemia is appropriately treated and unlikely to be continued due to her physical deconditioning and comorbidities. Palliative care is consulted, and the family agrees to transition to home with hospice care if the patient is stable for discharge. They request to continue the same antimicrobials while on hospice.*

With an estimated 1 out of 7 ICU patients needing palliative care consultation [12], ICU admissions are another access point for ID clinicians to address palliative care issues. Even if they survive, critically ill patients can experience a significant decline in functional status that persists months to years after discharge [13–15], thereby further impacting their clinical trajectory. In the continuum of care from inpatient to outpatient, ID clinicians are optimally positioned to navigate palliative care conversations with patients and their families who are trying to manage the aftermath of their critical illness, particularly if it was precipitated by their recurrent or refractory infection.

As patients approach the end of life, the benefits of antimicrobial therapy become less clear [10, 16], and the decision to initiate and/or continue antimicrobials should be centered on the current goals of care. Patients' goals and priorities frequently evolve throughout the course of a terminal illness, and it is important to re-engage patients and families in discussions about the benefits and burdens of antimicrobial therapy, particularly when continuing these treatments may come at the cost of other attainable goals, such as spending one's final days at home. Essential to these conversations is a shared understanding of the patient's prognosis and expected risks and benefits of continued therapy. When patients or families express a desire to "continue antibiotics," ID physicians can navigate this request by connecting it to a patient-centered goal, such as prolonging life, avoiding re-hospitalization, or alleviating symptoms.

FORMULATING AN ACCEPTABLE END-OF-LIFE PLAN

In the setting of end-of-life care, it can be helpful to present general care pathways, such as (1) proceeding with interventions aimed at prolonging life to the greatest extent possible; (2) continuing the current level of medical support without further escalating treatments in the setting of clinical decline; and (3) transitioning to an exclusively comfort-focused approach, adding treatments to promote comfort and discontinuing interventions that do not directly contribute to comfort. It is important to frame the advantages and disadvantages of each pathway with respect to the patient's values and priorities. For example, if the priority is to die at home, surrounded by friends and family, then it is important to explain each pathway with respect to the likelihood of achieving that goal.

In this case example, the family has communicated the goal of bringing the patient home with hospice care, yet also wants to continue the current level of antimicrobial therapy. However, since multiple intravenous antimicrobials will complicate discharge planning, the family and patient may miss the window in which it is safe to transition home with hospice care.

Instead of framing treatments as a list of equivalent options, it is important for the clinician to listen to the family's concerns, identify and attend to the emotions underlying those concerns, and then use clinical expertise to recommend the medical interventions that are likely to achieve the desired goals. Table 1 summarizes using a similar approach between "middle" and "late" goals-of-care conversations to identify patients' values and priorities [11].

PROPOSING A TIME-LIMITED TRIAL

When providers, patients, and caregivers are considering invasive interventions in the setting of a poor or uncertain prognosis, a time-limited trial (TLT) may offer a means of allowing for potential benefit while reducing the exposure to toxicity or harm [17]. Time-limited trial have been demonstrated to reduce aggressive interventions in the ICU setting as well as ICU length of stay [16].

A TLT of antimicrobials may help satisfy patients and caregivers who want to exhaust all interventions even with a low chance of benefit, while reducing the likelihood of inappropriate continuation of antimicrobials at the end of life and providing valuable prognostic information. Patients with sepsis in the setting of advanced cancer who do not clinically respond to antimicrobials in the first days of treatment have a dramatically worse prognosis for survival (5 days vs 142 days in nonresponders and good responders, respectively [18]). Key components of a TLT are outlined in Box.

Box: Key Components of a Time-Limited Trial

1. Review the clinical situation with patient and caregivers.
2. Agree on objective markers that would indicate progress or improvement. Ideally, identify signs that would be readily visible to the family and unlikely to be confounded by other treatments or by time (eg, cessation of fevers, decreasing vasopressor or oxygen requirements).
3. Agree on a set time frame to re-evaluate the effectiveness of antimicrobials. We recommend 2–3 days in the setting of bacterial or fungal sepsis, although shorter or longer time frames can be used based on the clinical situation and the need for a rapid decision.
4. Define actions at the end of the TLT, based on effectiveness. If ineffective, this should include negotiating another TLT or withdrawing antimicrobials, with plans for possible end-of-life care.

Abbreviation: TLT, time-limited trial.

As always, the success of TLTs is dependent on the level of trust and rapport between patients, caregivers, and clinicians. Maintaining this trust and managing complex emotions are integral communication skills described further below.

MANAGING COMPLEX EMOTIONS

Conversations regarding serious illness often have forceful emotional subtexts, even when the discussion appears calm and concrete on the surface. Explicit or tacit strong emotions, if unattended, may result in further emotional suffering and strain relationships among clinicians, patients, and caregivers [19, 20]. Yet, physicians frequently fail to address emotional cues. In a study evaluating goals-of-care conversations with oncologists, opportunities for empathic exploration were left unattended nearly 80% of the time [21].

Goals-of-care conversations pertaining to ID concerns are equally likely to include complex emotions that we will explore here. This is not meant to be exhaustive nor scientifically proven, but rather to identify complex emotions that frequently arise and our consensus regarding approaches to better respond to them. We encourage clinicians to listen and observe carefully for the emotional subtext and, if possible, name and intervene on the underlying emotion. Often, this may be the key to moving past obstacles, establishing a trusting patient–clinician relationship, and delivering care that matches goals.

Importantly, all of these emotional cues should be considered through a lens of cultural humility. Different cultures and religions espouse varying ethical obligations to pursue life-prolonging care, perhaps rooted in a sense of filial piety or religious edict. Some groups (including Black and Indigenous Americans) may have personal, community, or historical experiences of mistreatment by the medical system, requiring concerted efforts to earn and preserve trust. Our approach to emotions is not meant to be reductive; at all times, the deeper narrative beyond the surface emotions will hold a richer, more nuanced context that we encourage clinicians to seek out. Nevertheless, working with the most accessible and operative emotions is a readily attainable skill for clinicians and can produce meaningful change in their practice.

Guilt

Refusing or discontinuing treatments may evoke feelings of guilt for patients, caregivers, and treating teams. Despite the lack of cause and effect, families may feel that discontinuing a superfluous antimicrobial at the end of life may hasten the dying process. Patients choosing not to place a percutaneous drain because of concerns about pain may feel guilt for not pursuing every intervention offered, or for prioritizing their own comfort over the expectations of others. When families or patients express feelings that they "can't just give up" or "can't let their family down," this may indicate feelings of guilt.

When antimicrobials are initiated in a dying patient without thoughtful consideration or discussion of the intent of treatment [22], the implicit norm for patients and families is that these antimicrobials should or must be initiated in critical illness, regardless of prognosis, risk, or benefit. Addressing this misperception is often critical to helping patients and families navigate feelings of guilt or failure that may arise when de-escalating antimicrobials. Statements that affirm previous efforts while reframing the focus of care moving forward in the context of achievable goals, such as symptom control and time with family, are likely to provide reassurance and alleviate a sense of guilt.

For example: "I have seen you both work so hard and go through so much just to make it through this illness. You've shown us how strong your relationship is by supporting each other in such difficult times. And it is so clear to me that you want to do the absolute best for each other. Anything less than that would feel wrong, like so many other families have told me. At the same time, I don't want either of you to feel obligated to do treatments that we know won't provide benefit. That's merely putting more pressure on you. Let's keep our

focus on doing things that we can achieve, whether they're medical or personal, that are more important."

"What Would You Do If This Were Your Parent?"

Requests for personal viewpoints, especially when they pertain to a clinician's own family members, can be a source of discomfort. Some clinicians may respond by avoiding the question and refocusing the attention back to the patient. This is not altogether unhelpful; in fact, it presents an opportunity for clinicians to remind caregivers that the expressed goals and values of the patient are of the utmost importance in guiding treatment decisions.

The underlying emotion guiding this question, however, requires a more attentive response. Family members may be feeling overwhelmed by technical information or uncertain as to how to proceed. Frequently, they seek the validation of a clinician. Moreover, they may worry that the clinician is considering the patient from a purely objective, clinical viewpoint (one that may be subject to influences such as cost or protocols) and want to ensure that their loved one is receiving the same quality of care that would be given to the physician's own family member. Such a question can be an invitation for clinicians to provide reassurance to family members struggling with the burden of decision making and affirming that they are making choices that resonate with the patient's goals and values. "I can see how deeply you love your mother and want to be certain you're making the right choices for her. Based on everything you've told me, it's clear that she is having difficulty with the side effects of the antibiotics and may prefer less invasive treatments. If she were family to me, I would try to respect that. Can we talk about what this might look like?"

Indecision and Feeling Overwhelmed

In very rare cases, patients and families may be paralyzed by the burden of decision making, even when goals and values are clearly stated. An overwhelming sense of anxiety or guilt may stymie any attempts to avoid or discontinue unhelpful interventions. Similarly, open-ended questions may be intrinsically too broad or too challenging for a patient or family member to express a coherent response. In some of these cases, palliative paternalism may play a role in assisting patients and families through this process.

Roeland and colleagues [23] define palliative paternalism as "an approach to communication with limited open-ended questions that utilizes well-informed, discrete, concrete options during medical discussions, in order to reduce confusion and suffering by avoiding nonbeneficial care." This is not meant to override patient autonomy but to shift the balance in shared decision making back toward the physician who draws from experience and compassion.

Concrete guidance can be most effective with respect to unhelpful or futile interventions. "We know that your father is coming to the end of his life, regardless of what we do. We know that CPR or starting antibiotics will not change this outcome, and we will not offer them. But we will do our best to ensure that he's comfortable." Such directive statements must be accompanied by compassion and respect, or they will be perceived as cruel. Such directive statements should only be used to relieve the patient and family of emotional suffering and are not appropriate when patients or families are requesting nonfutile aggressive care that is in line with established goals. Differences in medical opinion or unresolved grief are not an indication for coercive care. If palliative paternalism does appear to be appropriate for the situation, we recommend discussing with a palliative care specialist beforehand to craft a compassionate, careful approach, so that directive statements are not perceived as cruel.

"Do Everything"

Nearly all clinicians will be confronted by the injunction to "do everything," whether directly from patients and families, relayed by other clinicians ("They want everything done"), or even offered by other clinicians ("Would you like us to do everything possible?"). Such injunctions often prematurely close discussions about the utility or goals of medical care, insulating the individuals making the request from potentially painful discussion about the detailed risks of every possible action, but leaving clinicians feeling obligated to offer every possible intervention, including intubation, vasopressors, and broad-spectrum antibiotics [24].

In some cases, however, the request to "do everything" carries a tacit qualifier: "Do everything you think is reasonable", "do everything so we don't give up too soon", or "do everything while we still come to terms with this shock and grief." To recognize these cases, requests to "do everything" should prompt further probing. Exploratory questions should seek to identify underlying emotions, such as fear of giving up, which can be directly addressed, rather than an exhaustive discussion about the utility of each intervention [25]. A summary of potential meanings for "everything" is provided in Table 2 [25].

Conversational interventions will depend on the underlying emotion. Patients and families who fear abandonment may respond well to reassurances that the ID team will still stay involved to help other teams manage symptoms of infection and restart antimicrobials if they become appropriate. Families struggling with anticipatory grief may require more intensive support from a palliative care clinician or social worker; reintroducing the discussion around antimicrobials might need to be delayed until the most salient feelings subside.

TRANSITIONING TO HOSPICE CARE

Patients in hospice commonly receive antimicrobials [26]; however, the benefits of antimicrobials for symptom relief are

Table 2. Potential Underlying Meanings of "Everything"

Domain	Concept	What "Everything" Might Mean	Questions to Ask	Possible Intervention
Affective	Abandonment	"Don't give up on me."	"What worries you the most?"	"We are with you every step of the way."
	Fear	"Keep trying for me."	"What are you most afraid of?"	"The situation is scary. Let's talk about how we can support you."
	Anxiety	"I don't want to leave my family."	"What does your doctor say about your prospects?"	"When this feels overwhelming, what seems to help most?"
	Depression	"I'm scared of dying."	"What is the hardest part for you?"	"Would it be helpful for you to talk about this with a professional?"
		"I would feel like I'm giving up."	"What are you hoping for?"	"You've come such a long way just to get here."
Cognitive	Incomplete understanding	"I do not really understand how sick I am."	"Can we review what you know about your illness?"	"What are your most important goals?"
	Wanting reassurance that best medical care has been given	"Do everything you think as a doctor is worthwhile."	"What is your understanding of your condition/prognosis?"	"Let's make certain you get everything done that we think can help you with your goals. But I don't want you to get interventions if we know that they won't help you."
	Wanting reassurance that all possible life-prolonging treatment is given	"Don't leave any stone unturned." "I really want every possible treatment that has a chance of helping me live longer." "I will go through anything, regardless of how hard it is."	"What have others told you about what is going on with your illness?" "What have they said the impact of these treatments would be?" "Tell me more about what you mean by everything."	"You want us to do our absolute best to help you live as long as possible. We will take this goal to heart. Can we make sure we discuss what some of those situations might entail, and if that's acceptable to you?"
Spiritual	Vitalism	"I value every moment of life, regardless of the pain and suffering (which has important meaning for me)."	"Does your religion (faith) provide any guidance in these matters?"	"We admire your acceptance. We also don't want to contribute to you suffering unnecessarily."
	Faith in God's will	"I will leave my fate in God's hands; I am hoping for a miracle; only He can decide when it is time to stop."	"How might we know when God thinks it is your time?"	"If we find ourselves in that situation, we might have to recognize that that would be when God is calling you home."
Family	Differing perceptions	"I cannot bear the thought of leaving my children (wife/husband)."	"How is your family handling all of this?"	"Let's find ways to get them additional support."
	Family conflict	"My husband will never let me go."	"Who else is a part of your family or gives you support?"	"Can we include them in the conversation so they can discuss it with you and with your husband?"
	Children or dependents	"My family is only after my money." "I don't want to bother my children with all this."	"Have you made plans for your children (other dependents)?" "Have you discussed who will make decisions for you if you cannot?" "Have you completed a will?"	"Let's make sure everything is arranged for. Have you ever spoken with a social worker about these issues?"

Adapted from Quill et al [25].

not clearly defined. The highest likelihood of benefit appears to be when antibiotics are used to treat pain and dysuria from urinary tract infections (UTIs), suggesting this is an appropriate indication for palliative antibiotics when UTI is accurately diagnosed. A systematic review by Rosenberg and colleagues [27] showed symptomatic relief in as many as 92% of patients diagnosed with UTIs treated with antibiotics. It is also reasonable to believe that, in situations where symptoms are definitively due to an infection such as herpes zoster, *Clostridioides difficile* infections, or mucocutaneous candidiasis, trials of antimicrobials may improve quality of life. In other situations, however, there is no clear evidence to suggest benefit of antimicrobials for symptomatic relief. The systematic review by Rosenberg and colleagues found symptomatic relief from antibiotics in 0% of patients diagnosed with pneumonia, and additional evidence suggests that antibiotics may prolong suffering without relieving any symptoms in patients with pneumonia at the end of life [28]. Non-antimicrobial options for symptom management, such as opiates for air hunger and pain or antipyretics for fevers and rigors, may promote comfort as well as or better than antimicrobials and should be considered. Patients and families should be counseled that symptoms from ongoing infections can be managed effectively by the hospice team, even if antimicrobials are not continued.

Any benefits must be weighed against the potential harms of antimicrobials, in the framework of the patient's own goals.

As stated above, if palliation is the goal, antimicrobials may be counterproductive by increasing short-term survival without ameliorating symptoms, thereby only prolonging suffering. For hospitalized patients transitioning to comfort care, we recommend considering stopping antimicrobials prior to discharge as antimicrobials have been shown to increase hospital length of stay, taking away valuable time a patient could be spending with family at home [29].

If antibiotics are being considered for patients transitioning to comfort care or hospice, we recommend careful review for potential drug–drug interactions and prefer oral antimicrobials over intravenous or intramuscular medications. Patients who are unable to take oral antimicrobials due to confusion, lethargy, or inability to eat or drink should be recognized as having a significantly worse prognosis and thus a lower probability of meaningful palliative benefit from antimicrobials. Although not as commonplace as oral "prophylactic and suppressive" antimicrobials, palliative outpatient parenteral antimicrobial therapy (OPAT) is increasingly used for terminally ill patients with incurable infections [30, 31]. Because the primary purpose of OPAT has been to manage curable infections, palliative OPAT has minimal literature on healthcare resource allocation and outcomes, and the target populations who would benefit most from intravenous antimicrobials with death as an anticipated endpoint are unknown [32]. Additional research is needed to inform and facilitate these conversations that surround palliative OPAT.

ANTIMICROBIAL STEWARDSHIP AND THE MORAL DISTRESS OF THE INFECTIOUS DISEASE PHYSICIAN

Ongoing drug shortages, the emergence of multidrug-resistant organisms, and persistently high rates of *C. difficile* infection are among the many systems issues that put pressure on the ID physician to curtail antimicrobial use. Every discussion to clarify a patient's goals and select treatments to promote those goals is aligned with the value placed on individual patient outcomes in antimicrobial stewardship. These conversations may also promote future- and community-oriented goals of stewardship. Some patients' goals may be better promoted without antimicrobials, and some patients and/or their families may even express a preference for limited antimicrobials (eg, TLT, as described above). An advance directive requesting limited antibiotics is associated with decreased antibiotic use in patients with terminal cancer [33]. Having and documenting these conversations, using the tools outlined above, is an antimicrobial stewardship intervention.

Still, some patients, families, or treating teams may choose to use antimicrobials that the ID clinician believes will offer minimal benefit in terms of patient outcomes, but at considerable risk to other goals of stewardship. If stewardship considerations are set aside in deference to these emotional needs, ID clinicians may feel frustrated or disempowered. It is important that any frustration or moral injury be explored and addressed outside of the clinical encounter, preserving the focus on the patient whenever they are in the room.

CONCLUSIONS

Ultimately our patient with metastatic cholangiocarcinoma did not respond to a TLT of caspofungin, so the decision was made to proceed with comfort measures in the ICU. The patient passed away after vasopressors were titrated off. Caspofungin was continued until the day of death. This is not an uncommon scenario; in 1 study, 82% of patients with metastatic solid-organ cancers remained on antimicrobials within 3 days of death [34]. Earlier conversations using the REMAP framework may have resulted in considerations of home hospice and may have obviated the need to abruptly pivot in the ICU when death was clearly imminent.

Although other members of a patient's healthcare team (such as the oncologists or generalists) may be perceived as leading the conversation addressing end-of-life care, ID clinicians can play an integral role in setting expectations and defining goals with patients with terminal illnesses, particularly where recurrent or refractory infections are a part of the disease process.

While a patient-centered approach should be the first priority, we caution that being "patient-centered" does not mean doing every medical intervention the patient requests, but rather aligning the patient's goals with the clinical expertise of the treating team, including the ID physicians. This requires having clarity on what is being expressed by patients and their families, and we have offered some strategies to understand their complex emotions. There are times when it may be appropriate to consider palliative paternalism, relieving the burden of decision making from patients and their families, but this approach should be taken with utmost care and ideally under the guidance of a palliative care specialist.

We acknowledge the power imbalances to which specific groups are particularly vulnerable, including racial and ethnic minorities, when using any of the above approaches to having difficult conversations [35]. Discordant language preferences can add a layer of complexity, even in the presence of translators. Dialects can carry signs and symbols that are difficult to fully translate, and we acknowledge this potential limitation in the iterative process we have described above. We ask that our colleagues take this into account when initiating and moving through these conversations and ensuring that utmost care is taken in framing these conversations in the appropriate cultural context.

In our experience, ongoing collaborative discussions between ID and palliative care teams have allowed for more fruitful conversations with patients at each phase of their evolving condition. Even in the absence of a dedicated palliative care team, ID doctors can set clear expectations based on their clinical experience, allowing for patients to process and plan and

consider TLTs as a strategy at the end of life. The ability to engage our patients in discussions about goals of care can be meaningful even in the face of parallel challenges such as heavy consult burden, diagnostic challenges, and antimicrobial overuse. Furthermore, modeling such care on the use of antimicrobials at the end of life is important for our trainees and formal pedagogy and should be considered as part of the core curriculum. We encourage our ID colleagues, who often can provide consistency in the chaos and uncertainty of a patient's terminal illness in and outside of the hospital setting, to engage earnestly in these impactful conversations.

Note

Potential conflicts of interest. D. F. reports a National Institutes of Health grant (R25 AI 147369), unrelated to this work. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Gengler AM. Emotions and medical decision-making. Soc Psychol Q **2020**; 83: 174–94. https://doi.org/10.1177/019027251987693
2. Childers JW, Bulls H, Arnold R. Beyond the NURSE acronym: the functions of empathy in serious illness conversations. J Pain Symptom Manage **2023**; 65: e375–9.
3. MGH Health Decision Sciences Center. What is shared decision making? Available at: https://mghdecisionsciences.org/about-us-home/shared-decision-making/. Accessed 5 April 2023.
4. Sullivan T. Antibiotics are often used at the end of life, but at what cost? Health Affairs **2018**.
5. Wald-Dickler N, Holtom PD, Phillips MC, et al. Oral is the new IV. Challenging decades of blood and bone infection dogma: a systematic review. Am J Med **2022**; 135:369–379.e1.
6. Montravers P, Tubach F, Lescot T, et al. Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial. Intensive Care Med **2018**; 44:300–10.
7. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med **2015**; 372:1996–2005.
8. Bahu R, Chaftari AM, Hachem RY, et al. Nephrostomy tube related pyelonephritis in patients with cancer: epidemiology, infection rate and risk factors. J Urol **2013**; 189:130–5.
9. Frisbee J, Eric Heidel R, Rasnake MS. Adverse outcomes associated with potentially inappropriate antibiotic use in heart failure admissions. Open Forum Infect Dis **2019**; 6:ofz220.
10. Juthani-Mehta M, Malani PN, Mitchell SL. Antimicrobials at the end of life: an opportunity to improve palliative care and infection management. JAMA **2015**; 314:2017–8.
11. Childers JW, Back AL, Tulsky JA, Arnold RM. REMAP: a framework for goals of care conversations. J Oncol Pract **2017**; 13:e844–50.
12. Hua MS, Li G, Blinderman CD, Wunsch H. Estimates of the need for palliative care consultation across United States intensive care units using a trigger-based model. Am J Respir Crit Care Med **2014**; 189:428–36.
13. Al Khalaf MS, Al Ehnidi FH, Al-Dorzi HM, et al. Determinants of functional status among survivors of severe sepsis and septic shock: one-year follow-up. Ann Thorac Med **2015**; 10:132–6.
14. Ito K, George N, Wilson J, Bowman J, Aaronson E, Ouchi K. Primary palliative care recommendations for critical care clinicians. J Intensive Care **2022**; 10:1–8.
15. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA **2010**; 304: 1787–94.
16. Chang DW, Neville TH, Parrish J, et al. Evaluation of time-limited trials among critically ill patients with advanced medical illnesses and reduction of nonbeneficial ICU treatments. JAMA Intern Med **2021**; 181:786–94.
17. Quill TE, Holloway R. Time-limited trials near the end of life. JAMA **2011**; 306: 1483–4.
18. Thai V, Lau F, Wolch G, Yang J, Quan H, Fassbender K. Impact of infections on the survival of hospitalized advanced cancer patients. J Pain Symptom Manage **2012**; 43:549–57.
19. Pollak KI, Back AL, Tulsky JA. Disseminating effective clinician communication techniques: engaging clinicians to want to learn how to engage patients. Patient Educ Couns **2017**; 100:1951–4.
20. Weiner JS, Roth J. Avoiding iatrogenic harm to patient and family while discussing goals of care near the end of life. J Palliat Med **2006**; 9:451–63.
21. Pollak KI, Arnold RM, Jeffreys AS, et al. Oncologist communication about emotion during visits with patients with advanced cancer. J Clin Oncol **2007**; 25: 5748–52.
22. Mack JW, Smith TJ. Reasons why physicians do not have discussions about poor prognosis, why it matters, and what can be improved. J Clin Oncol **2012**; 30: 2715–7.
23. Roeland E, Cain J, Onderdonk C, Kerr K, Mitchell W, Thornberry K. When open-ended questions don't work: the role of palliative paternalism in difficult medical decisions. J Palliat Med **2014**; 17:415–20.
24. Pantilat SZ. Communicating with seriously ill patients: better words to say. JAMA **2009**; 301:1279–581.
25. Quill TE, Arnold R, Back AL. Discussing treatment preferences with patients who want "everything". Ann Intern Med **2009**; 151:345–9.
26. Servid SA, Noble BN, Fromme EK, Furuno JP. Clinical intentions of antibiotics prescribed upon discharge to hospice care. J Am Geriatr Soc **2018**; 66:565–9.
27. Rosenberg JH, Albrecht JS, Fromme EK, et al. Antimicrobial use for symptom management in patients receiving hospice and palliative care: a systematic review. J Palliat Med **2013**; 16:1568–74.
28. Givens JL, Jones RN, Shaffer ML, Kiely DK, Mitchell SL. Survival and comfort after treatment of pneumonia in advanced dementia. Arch Intern Med **2010**; 170: 1102–7.
29. Datta R, Zhu M, Han L, Allore H, Quagliarello V, Juthani-Mehta M. Increased length of stay associated with antibiotic use in older adults with advanced cancer transitioned to comfort measures. Am J Hosp Palliat Care **2020**; 37:27–33.
30. Hart E, Snape S, Thomson R. Palliative outpatient parenteral antibiotic therapy: a review of 5 years of patient data. JAC Antimicrobial Resist **2020**; 2:dlaa052.
31. Chapman ALN, Patel S, Horner C, et al. Updated good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults and children in the UK. JAC Antimicrob Resist **2019**; 1:dlz026.
32. Durojaiye OC, Jibril I, Kritsotakis EI. Palliative outpatient parenteral antimicrobial therapy (OPAT): a single center experience and systematic scoping review. Clin Infect Pract **2022**; 16:100205.
33. Kates OS, Krantz EM, Lee J, et al. Association of physician orders for life-sustaining treatment with inpatient antimicrobial use at end of life in patients with cancer. Open Forum Infect Dis **2021**; 8:ofab361.
34. Kim J-H, Yoo SH, Keam B, Heo DS. The impact of palliative care consultation on reducing antibiotic overuse in hospitalized patients with terminal cancer at the end of life: a propensity score-weighting study. J Antimicrob Chemother **2022**; 78:302–8.
35. Zisman-Ilani Y, Khaikin S, Savoy ML, et al. Disparities in shared decision-making research and practice: the case for black American patients. Ann Fam Med **2023**; 21:112–8.