

Guidance for Safe and Appropriate Use of Antibiotics in Hospice Using a Collaborative Decision Support Tool

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Infections often impact care of hospice patients; however, limited guidance exists for end-of-life infection management. Regardless of patient prognosis, appropriate antibiotic use is necessary for maintaining quality of life. Antibiotics may be associated with serious adverse events, posing safety risks to patients that should be factored into the appropriateness determination. Fluoroguinolone antibiotics are prescribed frequently in hospice. There are 8 fluoroquinolone drug safety warnings regarding risk for serious adverse events communicated by the US Food and Drug Administration. A retrospective chart review at a hospice pharmacy services provider identified decedents who used a fluoroquinolone during a 1-month period. Charts were evaluated for the presence of risk factors for serious adverse events, including advanced age (86.0%), orders for multiple QTc prolongation risk medications (51.5%), hypertension (64.1%), and concomitant corticosteroids (22.9%). Findings demonstrate notable risk with the use of at least 1 class of antibiotics in a hospice population. STAMPS is a hospice decision support tool, developed to guide symptom-driven antibiotic use that incorporates safety assessment and individual goals of care into infection management planning. The tool can also serve as a framework for patient-centered communications about appropriate antibiotic use in hospice between providers, patients, and families.

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KEY WORDS

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BACKGROUND

The patient's decision to elect hospice care presents a unique opportunity for health care providers, patients, and caregivers to have an open dialogue on how to weave the hospice philosophy into the individual's plan of care. Among the important topics for discussion is the role of medications in symptom management at end of life. Health care specialists trained in end-of-life (EOL) care, the hospice



interdisciplinary team, especially nurses and pharmacists, are well-suited to provide education to patients and caregivers about the therapeutic benefit versus risk of various medication classes, including antibiotics.

As goals shift from curative to quality of life and comfort, the role of antibiotics should be clearly defined and documented in each patient's plan of care. Incorporating discussions related to antibiotic use in EOL care during advance care planning, rather than at the time of suspected infection identification, is preferred.¹ The potential for harm may be elevated in patients receiving empiric antibiotic therapy in the absence of routine laboratory monitoring, including renal and hepatic function. Factors such as prognosis, swallowing ability, perfusion to the site of infection, and route of administration should be integrated into care planning in advance of the need for antibiotic therapy and documented within the patient's medical record. With decline in health status, clinicians may prescribe antibiotics with the intent of palliating distressing or painful symptoms rather than for life-prolonging benefit or curative intent. This palliative approach must be clearly differentiated to both patient and caregiver to ensure realistic expectations are established. Literature suggests that upward of 38% of hospice patients receive interventions from which they are unlikely to experience benefit underscoring the importance of patient and caregiver education on the intent of antibiotic use and the extent of benefit or harm anticipated as a result of antibiotic use.²⁻⁴

In the setting of very limited prognosis, the importance of discussing deprescribing of nonessential medications with patients and caregivers cannot be overemphasized. In a 2016 retrospective study by Merel and colleagues,⁵ between 15% and 20% of patients continued to receive antimicrobial agents between 24 and 96 hours after EOL comfort care orders were introduced. Analysis of data from the 2007 National Home and Hospice Care Survey estimated that up to 27% of hospice patients received an antibiotic during the last 7 days of life, most without a documented infectious diagnosis.⁶ Additionally, nursing home residents receiving EOL care for advanced dementia are commonly prescribed antimicrobials during the last 2 weeks of life.^{1,7} Cheng and colleagues⁸ found that acute care interventions persisted for patients with hematologicbased cancers into their last week of life, with more than 90% of patients receiving antibiotics during this time. Global concerns related to the inappropriate overuse of antimicrobials and escalating rates of antibiotic resistance led to enhanced safeguards being implemented by the Centers for Medicare & Medicaid Services.^{9,10} Inappropriate antibiotic use elevates the potential for harm from adverse events and drug-drug interactions, increases antimicrobial resistance, and contributes to increased burden without benefit. Collectively, results from these studies demonstrate the continued need for clinical research, training, and hospice-based tools that provide guidance on assessing for appropriate use of antibiotics in end of life. Fluoroquinolones are one class of antibiotics that have the potential for an increase in harm due to associated risk of adverse events.

Fluoroquinolone Use and Safety Risks in Hospice Patients

In hospice, infections involving the urinary tract, respiratory tract, and skin are common indications for antibiotic therapy.^{11,12} For these and other infections, treatment guidelines detail fluoroquinolone antibiotics among agents that may be considered. In select indications, limited guidance also exists for empiric use of fluoroquinolones.¹³⁻¹⁵ Since their approval by the FDA in the 1980s, fluoroquinolones have been used frequently across inpatient, outpatient, and long-term care treatment settings to combat bacterial infections. In 2011, approximately 23.1 million patients were dispensed a prescription for an oral fluoroquinolone, and approximately 3.8 million patients were billed for an injectable fluoroquinolone product in the hospital setting.¹⁶ The prevalence of fluoroquinolone use in hospice is not clearly defined. In a study of advanced dementia patients in a nursing home, 95% of proxies for patients receiving antibiotics stated a primary goal of comfort, whereas 39.8% of suspected infections were treated with a fluoroquinolone. Furthermore, fluoroquinolones and third- and fourth-generation cephalosporins were most commonly associated with subsequent colonization of multidrug-resistant organisms for these patients.¹⁷

Bacterial resistance and antibiotic-associated adverse effects, along with growing evidence for toxicity, elevate the concerns related to widespread fluoroquinolone prescribing. Since 2004, the FDA has released 8 drug safety communications regarding the risk for serious adverse events associated with various fluoroquinolones.16,18-22 All members of a patient's health care team share responsibility for safe medication use. Effective communication between disciplines, especially pharmacists, nurses, and prescribers, is key.^{23,24} Pharmacists can advise prescribers and nurses about potential toxicities related to the use of fluoroquinolones to appropriately assess use and monitor for adverse effects. A summary of safety warnings is presented in Table 1. In an effort to minimize toxicity risks for all patients, the FDA issued a Boxed Warning for appropriate use of fluoroquinolones: avoid use to treat acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections, when other treatment options are available.²¹ Additionally, a recent retrospective review revealed an association between central nervous system stimulant use (methylphenidate, mixed amphetamine salts) with cardiac symptoms such as tachycardia, palpitations, and syncope when used concomitantly with fluoroquinolones.²⁵ Although less

TABLE 1 Flu	oroquinolone FDA Medication Safety Warnings Timeline	
August 2004	t 2004 Peripheral neuropathy risk identified; added to <i>Warnings and Precautions</i> ¹⁶	
July 2008	Boxed Warning added for increased risk of tendinitis and tendon rupture ¹⁹	
February 2011	Boxed Warning added for risk of worsening symptoms of myasthenia gravis ¹⁹	
August 2013	Update of drug labels and medication guides required to better describe the serious adverse effect of peripheral neuropathy. Warning that fluoroquinolone-related nerve damage may have rapid onset and may be permanent ¹⁶	
May 2016	Advisory issued: serious adverse effects generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections with other treatment options; reserve use for those without alternative treatment options for these conditions ¹⁸	
July 2016	Labeling changes added to include association with disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system (eg, neuropathy, confusion, hallucinations). <i>Boxed Warning</i> updated for tendinitis, tendon rupture and worsening of myasthenia gravis to stress the potential for disabling and potentially permanent adverse effects ²⁰	
July 2018	Warning issued regarding the potential for significant hypoglycemia and increased mental health adverse effects in patients. Strengthened warnings required in the prescribing information due to reports of this adverse event ²¹	
December 2018	Warning added for increased occurrence of rare ruptures or tears of the aorta; may be associated with aortic dissections or a rupture of an aortic aneurysm. Advised that fluoroquinolones should not be used in patients at an increased risk, including patients with history of blockages or aneurysms of aorta or other blood vessels, patients with high blood pressure, patients with genetic disorders that involve blood vessel changes, and the elderly, unless there are no other treatment options ²²	

common than other antidepressants, methylphenidate can be used to treat depression and fatigue in advanced illness.²⁶ With this in mind, fluoroquinolone utilization was reviewed using the pharmacy claims database of a national pharmacy benefits services provider to evaluate safety risks that may be commonly present in hospice patients.

This retrospective chart review studied decedents with pharmacy claims for fluoroquinolones during January 2019. Demographics and claims data were collected with respect to the FDA safety communication alerts including primary hospice diagnosis, presence of cardiac disease or hypertension medications, concomitant corticosteroid or

TABLE 2 Application of STAMPS Collaborative Decision Support Tool to Determine Patient Specific Antibiotic Appropriateness for End-of-Life Symptom Management			
	STAMPS: A Hospice Decision Support Tool for Antibiotic Use		
	Description		
S	Symptom assessment	 When infection is suspected, determine symptoms impacting comfort or quality of life If asymptomatic or symptoms do not significantly impair comfort/quality of life, no antibiotic is indicated 	
Т	Targets/goals of therapy	• Review specific goals for infection and symptom management with the patient and caregiver	
А	Alternative treatment options	• Based on patient-specific goals, determine what other nonantibiotic treatment options exist and compare expected outcomes	
Μ	Medication factors	 Review drug allergies, drug interactions, anticipated adverse effects/risks Assess swallowing function and other factors affecting antibiotic selection and administration 	
Ρ	Prognosis	• Evaluate estimated prognosis versus necessary treatment duration and anticipated time to symptom resolution	
S	Stewardship	 Avoid bug-drug, infection-drug, or patient-drug mismatch If antibiotic therapy is chosen, ensure the use of a correct drug, dose, route of administration, and therapy duration 	





FIGURE 1. Infection management in palliative care and hospice, implementing STAMPS for determining antibiotic appropriateness at end of life. Adapted with permission from Datta et al. ²⁶

QTc-prolonging medication use, sex, and fluoroquinolone claims within 14 days of death. Nearly 15% (n = 10 719) of decedents had at least 1 antibiotic claim during the review period (average age, 80.1 years). Fluoroquinolones comprised 24.4% of claims (n = 4651), the largest percentage of all antibiotic claims. Fluoroquinolones prescriptions were predominantly ciprofloxacin (51.4%) and levofloxacin (48.6%). More than 24% of patients filled the fluoroquinolone within 14 days of date of death. The top 5 hospice diagnoses in the study population were cardiac (21.4%), dementia (21.3%), pulmonary (18.3%), cancer (15.6%), and stroke (8.7%). Known QTc prolongation risk factors identified in the study population included female patients (60.2%), age older than 65 years (86.0%), and use of multiple QTc risk medications (51.5%). Additional FDA fluoroquinolone risk factors present were hypertension (64.1%) and concomitant corticosteroid use (22.9%).

Because of the complex care needs in EOL patient populations, the toxicities and safety warnings associated with fluoroquinolones should carry significant weight. Notably, renal function, drug-drug interactions, and chronic comorbid conditions must be thoroughly evaluated when selecting antibiotics, as well as dosing and determining treatment duration. In hospice care, where comfort is prioritized, the burdens associated with medication-related adverse events must be weighed against potential benefit. Fluoroquinolones are associated with peripheral neuropathy, tendinitis, and central nervous system adverse events risking a substantial impact on patient quality of life. Further, fluoroquinolones may disrupt glycemic regulation and increase the risk for hypoglycemia in all patients, whereas those with comorbid cardiovascular disease have an increased risk of an aortic tear or rupture secondary to fluoroquinolone exposure. For hospice patients considering antibiotic therapy, the potential risks of fluoroquinolone use must be considered in the context of other available palliative modalities such as comfort-based nonpharmacologic and nonantibiotic symptom management strategies.

Hospice Antibiotic Decision Support Tool: STAMPS

There is limited guidance for infection management and antibiotic use in EOL care. A proposed algorithm for antimicrobial use in end of life emphasizes the importance of establishing symptom relief benefit primarily over the survival benefit, as care shifts to palliation of disease.² In contrast, others suggest antimicrobial avoidance should be considered when full comfort or hospice care is established (ie, no prolongation of life).^{27,28} However, literature describes the potential for hospice patients to achieve symptom relief from antibiotics particularly in the setting of urinary tract infections, less so for respiratory tract and bloodstream infections.¹¹ Burden versus benefit will vary by patient and can be affected by changes in condition, locations of care, caregiver support, infection type or severity, and available antibiotic options. Navigating the decision to pursue versus avoid antibiotics can be difficult for clinicians, and involving patients and caregivers may add additional layers of complexity.

STAMPS is a hospice decision support tool that provides clinicians with a structured process for the evaluation of treatment burden versus benefit, providing a guide to symptom-driven antibiotic use (Table 2). When clinicians, patients with limited prognosis, and their caregivers are faced with an infection, it helps answer the question: "What symptom management strategy should be used to provide comfort to the patient: antibiotic or nonantibiotic?" The STAMPS decision support tool can facilitate conversations about infection management with patients, families, or other clinicians participating in the patient's care,



Upon arrival of the hospice nurse, Mr. M appears fatigued and dyspneic while at rest in his recliner. He has audible wheezing and a deep, productive cough. Mr. M reports pain associated with frequent coughing. The nurse documents his vitals: BP 110/70 mmHg, pulse 98 bpm, respirations 20/min, temperature 99.1°F, pulse oximeter checks for O₂ sats are refused because the results cause increased anxiety for both Mr. M and his wife. The hospice nurse administers a small dose of short-acting morphine oral solution and assists Mr. M with his nebulized albuterol. When reviewing Mr. M's goals of care, his nurse does not find documentation of a discussion about his views on antibiotic use. To help Mr. M and his wife determine the most beneficial symptom management approach for a suspected lower respiratory tract infection, his nurse references the STAMPS tool.

Symptom Assessment and Targets/Goals of Therapy: The nurse identified and documented the signs and symptoms observed, as well as patient and caregiver reported symptoms. Particular emphasis was given to the symptoms most concerning to the patient and his quality of life. With respect to his new pulmonary decline, Mr. M's primary concern is that worsened fatigue and dyspnea would limit his ability to sit on his porch. Mrs. M expressed concern about his cough and the pain evidenced on his face with each inhalation. In addition to improving pain relief, she also expressed concern that he might choke on thickened phlegm. Mr. M is clear that he does not want to return to the hospital and only wants care that can be managed at home.

Alternative Treatment Options: Mr. M was hospitalized three times in the past year and received intravenous (IV) antibiotics for pneumonia during each acute care stay. Mrs. M vividly recalls him receiving IV levofloxacin which caused considerable confusion and agitation. Mrs. M states she is afraid "to ever see him act like that again." The agitation and confusion improved but they would prefer to avoid antibiotics like levofloxacin, because of "bad side effects." Because Mr. M does not want to return to the hospital for IV antibiotics, his nurse provides education that not all antibiotics for pneumonia can be administered orally and about side effects risk with many antibiotics, such as agitation, nausea, and diarrhea.

As an alternative to antibiotics, his nurse assures Mr. M that other medications paired with non-pharmacologic approaches can be used to manage his respiratory symptoms, fatigue, and pain in the home. Taking a pause from their conversation on antibiotic use in hospice, Mr. M's dyspnea and cough are evaluated following morphine and albuterol administration. Mr. M reports some relief and visibly appears more comfortable. The nurse makes sure to explain that choosing a non-antibiotic strategy as a first-line approach does not mean the use of antibiotics cannot be revisited. She explains that if Mr. M's symptoms are not responding to comfort medications or if he changes his mind, the hospice team will revisit this conversation. For now, an oral corticosteroid (prednisone), expectorant (guaifenesin) and a fan best fit his goals of care.

Medication Factors and Prognosis: From his nurse's observation, Mr. M's prognosis may be only weeks. Mr. M states that one of his primary goals in electing hospice was to stay at home and avoid hospitalizations. He also prefers only oral medications. With recent decline in appetite, Mr. M tells his hospice nurse that maintaining his appetite is important to him. He does not want medications that could contribute to nausea or cause diarrhea. He has no known drug allergies. While his ability to swallow tablets and liquids remains intact, it is taking longer to administer medications and reducing pill burden remains a priority. A detailed conversation on possible adverse effects associated with antibiotics was led by Mr. M's hospice nurse and he expressed concern that many agents used to treat pneumonia (e.g. azithromycin, amoxicillinclavulanate, or levofloxacin) are associated with adverse gastrointestinal effects.

Stewardship: Based on the open communication between the hospice nurse, Mr. M, and his wife, non-antibiotic palliative approaches were chosen as a first-line treatment strategy. The care plan was updated to include: 1) prednisone taper for dyspnea and airway inflammation; 2) education on use of as-needed morphine for dyspnea, cough, and pain; 3) education on the use of as-needed lorazepam for anxiety related to dyspnea; 4) guaifenesin twice daily to help thin respiratory secretions; 5) continued use of as-needed nebulized albuterol for wheezing or dyspnea. Mrs. M agreed to place a fan by the recliner to assist with cooling and improve Mr. M's sense of airflow. Mr. M's hospice nurse assures that if Mr. M reconsiders antibiotics, the hospice medical director will be consulted to determine the best options for Mr. M based on diagnosis and goals of care.

The structured approach that STAMPS provides can frame patient-caregiver discussions, empower patient-centered decision-making, and facilitate clinician documentation of patient preferences. In this patient case example, the hospice nurse may use documentation from her conversations with Mr. M and his wife to emphasize his goals of care when discussing future steps. Finally, STAMPS provides a structure for decision-making as factors (e.g. clinical/functional status, symptoms, and prognosis) change during the hospice length of stay.

FIGURE 2. STAMPS: case illustration.



helping them make informed decisions that align with documented goals of care. Finally, when an antibiotic is warranted, based on the individual assessment, STAMPS promotes antimicrobial stewardship by directing prescribers to ensure selection of the correct drug, dosage, route, and duration of therapy. Figure 1 illustrates a treatment approach applying the STAMPS framework to redefine appropriate antibiotic use in end of life.

STAMPS is well-suited for inclusion in the transition-ofcare process. For the hospice patient currently completing a course of antibiotics, STAMPS provides the framework for streamlining therapy and minimizing risks associated with antibiotics while improving patient-centered care during transitions of care. In these settings, when antibiotics are not discontinued, STAMPS may prompt more timely conversion to an oral regimen or ensure duration of antibiotic therapy is no longer than necessary. Use of the STAMPS tool creates an opportunity to ascertain hospitalbased prescriber expectations for the antibiotic course (ie, survival benefit, intended duration, preventive vs curative goals), ultimately assisting hospice clinicians with decision making when those expectations do not align with patient goals of care. Incorporation of the STAMPS clinical decision support tool, during the transition from hospital discharge to hospice admission, can foster a patientcentered team approach to antibiotic decision making while unifying clinical information shared by hospital and hospice providers to patients and their families.

A recent survey of hospital antibiotic stewardship programs (ASPs) gives insight into educational opportunities to promote symptom-driven antibiotic use for EOL patients.²⁹ Less than two-thirds of ASPs reported monitoring antimicrobial use in patients during EOL care and noted that most recommendations involved intravenous antimicrobials, suggesting less support for evaluating oral therapy. Guidance for antimicrobial use in EOL patients was facilitated by only 36% of the ASPs, with 8% reporting formal antibiotic stewardship guidance for comfort care patients. Institutionally, 14% noted availability of EOL guidelines addressing antimicrobial use. Palliative care practitioners were employed by 92% of the hospitals that responded, and only 8% of ASPs reported known antibiotic stewardship education for their palliative care practitioner. Notably, they also identify the need for formal guidelines to assist providers with antibiotic decision making for palliative care and hospice transitions of care.²⁹ The importance of addressing this need is supported by evidence of increased hospital lengths of stay associated with antibiotic use for advanced cancer patients who transition to comfort care.30 The STAMPS tool can serve as a general framework for education and guidelines. Figure 2 provides a case example using the STAMPS tool for hospice patient communication and decision making.

STAMPS places emphasis on interdisciplinary clinicians identifying and communicating the risks, expectations, and appropriateness of therapy in conversations with patients, caregivers, and fellow health care colleagues.

CONCLUSION

Studies have shown that hospice patients are commonly treated with antibiotics.11 Bacterial resistance and antibioticassociated adverse effects are a growing concern for patient safety. Despite warnings of serious and potentially irreversible adverse events, fluoroquinolone antibiotics were shown to be the most commonly prescribed antibiotic at a large hospice pharmacy services provider. To this point, limited guidance exists for infection management and antibiotic use in EOL care. STAMPS is a hospice decision support tool that provides clinicians with a standardized approach to evaluating treatment burden versus benefit, guiding symptom-driven antibiotic use. The STAMPS decision support tool can facilitate conversations between providers, or with patients and families, about infection management, supporting informed decision making that aligns with documented goals of care. Ultimately, STAMPS promotes antimicrobial stewardship by helping further define appropriate antibiotic use in hospice, shaped by symptom management indications, prognosis, and overall quality-of-life goals. Applying a standardized approach to evaluating burden and benefit of antibiotics may lower the occurrence of common and serious antibiotic-associated adverse events in the hospice population and reduce risk of bacterial resistance associated with antibiotic misuse. Future research is needed to determine the feasibility of incorporating STAMPS into the antibiotic-prescribing process for transition of care to hospice.

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