



## Review Article



# Implementation of Antimicrobial Stewardship Programs in End-of-Life Care

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No conflicts of interest.

## ABSTRACT

Many terminal patients at the end-of-life have been receiving antimicrobial therapy despite concerns including futile use, potential lack of efficacy, increased patient burden, excess costs, high risk of adverse effects, and increased antimicrobial resistance. Thus, the implementation of antimicrobial stewardship programs (ASPs) in end-of-life care needs to be discussed. But, the topics of antimicrobial therapy and ASPs have not been addressed in the Life-Sustaining Treatment Decision Act enacted in the Korea in February 2016. Antimicrobial therapy should be included in the decision-making framework for end-of-life care similar to other life-sustaining treatment decisions. If the antimicrobial therapy is legally considered as a life-sustaining treatment which can be withdrawn or withheld in patients at the end-of-life, the feasibility of implementing ASPs among this patient population may improve. Various researches on antimicrobial therapy for patients at the end-of-life need to be conducted and collaborations are required between ASPs professionals and many other concerned parties involved in the legislative process of the Life-Sustaining Treatment Decision Act. This review aims to summarize previous studies on the use of antimicrobials for end-of-life care and reveal important aspects for applying ASPs to this population in Korea.

**Keywords:** Antimicrobial stewardship; Palliative care; Withholding treatment

## INTRODUCTION

In Korea, the Hospice/Palliative Care and Dying Patient's Decisions on Life-Sustaining Treatment Act (Life-Sustaining Treatment Decision Act) was enacted on February 2016 to ensure that the patient's self-determination in the end-of-life care processes is respected [1, 2]. Although cardiopulmonary resuscitation, ventilator therapy, hemodialysis, anti-cancer chemotherapy, extracorporeal life support, transfusion, and inotropic treatments have been included in the decision-making framework for end-of-life care under above-mentioned Act, antimicrobial therapy in this context has rarely been discussed in Korea.

The overuse of antimicrobial agents is a critical problem in healthcare systems, and it is important to emphasize on their judicious use in any scenario. The studies conducted in Korea before enactment of the Life-Sustaining Treatment Decision Act have revealed that 63.8% of cancer patients received antimicrobial therapy until the day they died, and this

therapy was continued for 59.6% of patients after obtaining “do not resuscitate (DNR)” orders [3, 4]. The colonization of multidrug-resistant organisms (MDROs) was common in patients with advanced-stage illness [4, 5]. Although the risks of antimicrobial therapy should not be overlooked even in terminally ill patients, antimicrobial use may be considered as relatively less aggressive or invasive than other potentially life-sustaining treatments mentioned above [6-8].

Antimicrobial stewardship has been defined as “coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of an optimal antimicrobial regimen including dosing, duration of therapy, and route of administration” [9]. Its objective is to improve patient outcome, optimize resource utilization, and reduce antimicrobial resistance. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America suggest that antimicrobial stewardship programs (ASPs) for terminally ill patients provide support to clinical care providers in the decision-making process for antimicrobial therapy [10]. However, given the medical complexity of patients at the end-of-life and difficulty in applying ASPs to such a population, it is understandable that to date, no specific ASPs have been implemented for them. The recognition of this issue is increasing on an international level, and Korea also needs to discuss it at this point when the Life-sustaining Treatment Decision Act is enforced.

This review aims to summarize the previous researches on the use of antimicrobial agents for end-of-life care and to reveal important aspects of ASP application to this population in Korea.

## LIFE-SUSTAINING TREATMENT DECISION ACT

Following the Boramae Hospital case in 1997 and the ruling on old lady Kim's case in 2009, the need for legislation on life-sustaining treatment decisions has been raised [11]. A consensus guideline for the withdrawal of life-sustaining treatments endorsed by Korean Medical Association, Korean Academy of Medical Science, and Korean Hospital Association, was published on October 13, 2009 [12]. After detailed discussions among concerned parties, the Life-Sustaining Treatment Decision Act was enacted on February 2016 and fully implemented on February 2018 after a trial period [13]. The purpose of this Act is to prescribe matters necessary for hospice and palliative care and life-sustaining treatment for patients at the end of life (such as the determination to terminate); such life-sustaining treatment and its implementation thereof helps protect the dignity and value of human beings by assuring the best interests of patients and by respecting their self-determination [1].

Some terms such as terminal patients, patients at the end stage of life, life-sustaining treatment, and hospice/palliative care have been defined in the Act [1, 2]. Terminal patients are defined as having a condition in which despite active treatment, there is no possibility of a fundamental recovery and are expected to die within months owing to gradual deterioration of symptoms [2]. Patients at the end stage of life are defined as those with a condition in which revitalization or recovery is not possible despite treatment, with rapid worsening of symptoms [2]. Life-sustaining treatment refers to medical treatment by cardiopulmonary resuscitation, hemodialysis, anti-cancer chemotherapy, mechanical ventilation, extracorporeal life support, blood transfusion, inotropic treatments, and other medical procedures that are not implemented or need to be discontinued based on the medical decision of the physician-in-charge to ensure the best interests of the patient at the end stage of life; these treatments

are known to merely extend the duration of the end stage of life without providing any curative effects [1]. Hospice/palliative care refers to medical care provided to a terminal patient or patient at the end stage of life and his or her family for the purpose of comprehensively evaluating and providing treatment (including pain and symptom relief) in physical, psychosocial, and spiritual domains [2]. According to this Act, the medical practice for pain relief as well as nutrient, water, and simple oxygen supply should be implemented or should not be discontinued [1]. According to this Act, approximately, 46,400 patients have withheld or withdrawn life-sustaining treatment from March 2018 to April 2019 [14].

Life-sustaining treatment was divided into general and special types in the 2009 consensus guidelines for the withdrawal of life-sustaining treatments [12]. General life-sustaining treatment was defined as a treatment essential for sustaining life but does not require specialized medical knowledge, medical skills, or special equipment [12]. They include tube feeding, water and oxygen supply, maintaining body temperature, helping with defecation and urination, administering painkillers, preventing pressure sores, and primary antimicrobial therapy [12]. Special life-sustaining treatment was defined as a treatment that requires highly specialized medical knowledge, medical skills, and special devices to maintain life [12]. They include cardiopulmonary resuscitation, mechanical ventilation, hemodialysis, organ transplantation, anti-cancer chemotherapy, and advanced antimicrobial therapy [12]. The guideline did not provide any further explanation or discussion regarding primary or advanced antimicrobial therapy and did not consider antimicrobial stewardship. The topic of antimicrobial therapy has not been addressed in the process of legislation on life-sustaining treatment decisions and has consequently not been included in the Life-Sustaining Treatment Decision Act.

## RESEARCH ON ANTIMICROBIAL USE AT THE END-OF-LIFE

So far, only two studies have been conducted on this subject in Korea [3, 4]. Oh et al. retrospectively reviewed 141 patients with terminal stage cancer who were admitted for symptom control only and who eventually died between March 2003 and April 2004 [3]. They reported a high rate (80.1%) of infection and a high frequency (84.4%) of antimicrobial prescription during the last month of life and revealed that 63.8% of patients received antimicrobials until the day of their death [3]. Fever was controlled in 48% of patients, organisms were eradicated in 31% of patients, symptomatic improvement was achieved in 15.1% of patients, and leukocytosis and C-reactive protein level improved in 17% and 29% of patients, respectively [3]. Kwak et al. retrospectively compared antibiotic prescription and the burden of antimicrobial resistance between 303 deceased patients and the same number of surviving patients in general internal medicine wards at four acute care hospitals between January and June 2013 [4]. Antimicrobial therapy was more common in patients who died than in those who survived (87.5% vs. 65.7%,  $P < 0.001$ ), and it was continued in 59.6% of diseased patients even after DNR orders were obtained [4]. Antimicrobials were used for longer durations and MDROs were more prevalent in deceased patients than in surviving patients [13 vs. 7 days ( $P < 0.001$ ); 25.7% vs. 10.6% ( $P < 0.001$ ), respectively] [4]; moreover, third-generation cephalosporins were the most commonly prescribed antibiotics in both patient groups (43.9% and 39.3%, respectively) [4].

Among 260 adult hospitalized patients with an advanced-stage illness in Japan, 136 (52.3%) received antimicrobial therapy in the last 14 days of their life; of the latter, only 31 (22.8%)

achieved symptom relief using antimicrobial therapy [15]. The overall antimicrobial use in the last 14 days of life was 421.9 days of therapy per 1,000 patient days [15]. A retrospective review on antimicrobial use in 137 Australian patients who died in a hospital at Queensland in 2015 revealed that 62.7% received antimicrobial therapy at the end-of-life, and that the most commonly prescribed antimicrobial agent was piperacillin/tazobactam (41.9%) while the most common site of infection was the lungs (32.8%) [16]. Among 86 patients who received antimicrobial therapy, 33.7% received antimicrobials after treatment futility had been documented and 96.5% received their antimicrobials intravenously [16]. A Korean study on changes in life-sustaining treatment in terminally ill cancer patients after signing a DNR order in 2013 revealed that 89.2% of patients received antimicrobials after a DNR order was decided [17]. Nearly 90% of hospitalized patients with advanced cancer, 42% of nursing home residents with advanced dementia, and approximately one-quarter of hospice recipients, for whom the intended goal of care was to provide comfort, receive antimicrobials at the end-of-life [6].

## SPECIAL CONSIDERATIONS FOR ANTIMICROBIAL STEWARDSHIP PROGRAMS IN END-OF-LIFE CARE

### 1. Goals of antimicrobial therapy

The general goal of antimicrobial therapy is to increase patient's survival and cure infectious diseases. Because antimicrobial agents are unable to alter the progression of underlying diseases or rather sometimes can prolong suffering in patients at the end-of-life, the goal of prolonging life should be weighed against the risk of prolonging suffering [18]. Thus, the goal of antimicrobial therapy shifts from improving survival to symptom control with a shift in the goal of care from cure to palliation [19]. The goal of antimicrobial therapy for terminal patients at an early stage can include symptom control and improvement in survival while maintaining the quality of life. The goal of antimicrobial therapy for terminal patients at the end-of-life is achieving an improvement in symptoms. Antimicrobial agents led to symptomatic relief in only 33% of patients with advanced cancer during the last several weeks of life and in an even smaller proportion of patients (9.2%) during their last week of life [20]. Although symptom improvement was hardly observed when antimicrobial agents were administered during the last week of life, antimicrobial use was common among patients with advanced cancer even after transitioning to comfort care [21]. The risks and burdens of antimicrobial therapy should be carefully examined when comfort is the intended goal of care [21].

### 2. Potential harms of antimicrobial therapy

Polypharmacy is common in terminally ill patients owing to multiple comorbidities and increase adverse drug reactions, drug interactions, and costs. These potential risks are weighted when antimicrobial agents are administered. In addition, intravenous antimicrobial therapy, which is commonly performed using intravenous devices in acute in-hospital care settings, is associated with the risks of phlebitis, local skin, and soft tissue infections as well as secondary bacteremia [18]. *Clostridioides difficile* infection, which is common and often recurrent, is another important potential harm associated with antimicrobial use [22]. Antimicrobial use in end-of-life care is considered as a risk factor for MDRO colonization that adds psychological burden through infection control measures including patient isolation and contact precautions which conflict with the goals of palliative care [5, 19, 23]. When antimicrobial therapy against infections caused by MRDOs is indicated according to the discussions for goals of care, the available treatment options are often limited, invasive,

expensive, or associated with adverse effects that distress patients and their families [19]. All these potential harms of antimicrobial therapy can make the quality of life poor or shorten the survival duration in terminally ill patients with multiple comorbidities.

### 3. Difficulty in diagnosing infections

The diagnosis of infection in a palliative patient is difficult. Common indicators for infections such as fever, leukocytosis, and elevated acute phase protein level are not always present in patients who have multiple comorbidities and are taking medications that obscures an infection. In addition, many end-of-life patients with cognitive impairment have difficulty in exposing their symptoms. On the contrary, fever, leukocytosis, and elevated acute phase proteins are present in non-infectious conditions such as malignancy. Medications as well as malignancy and pulmonary embolism/deep vein thrombosis can cause fever occasionally. Procalcitonin plays a role in the diagnosis of infections in cancer patients [24].

### 4. Perceptions of physician regarding antimicrobial use

A cross-sectional study on attending physicians and fellows with appointments at either the University of Pennsylvania or Children's Hospital of Philadelphia conducted in 2017 revealed that approximately half of the physicians believed that antimicrobial use in end-of-life care contributes to antimicrobial resistance and approximately 30% of physicians intended to continue antimicrobial administration for the patients even after care-giving was deemed medically futile or when comfort was elected to be the main goal of care [25]. Nearly one-fifth of pediatricians intended to continue antimicrobial therapy for hospice patients whose death was imminent compared to few adult physicians (2.7%;  $P < 0.001$ ) [25]. The reasons why the physicians may continue antimicrobials at the end of life includes meeting family expectations, wanting to avoid the perception of "giving up," uncertainty about prognosis, and reducing patient pain or discomfort [25]. A meta-analysis that investigated symptom improvement with antimicrobial therapy in end-of-life patients revealed marked variability, *i.e.*, 60 – 92% of patients with urinary tract infections and 0 – 53% with respiratory infections showed an improvement [26]. Despite the lack of compelling evidence, many physicians may continue antimicrobial therapy to relieve patient symptoms because they perceive adverse consequences to be at a relatively low frequency [25]. However, the relationship between antimicrobial administration and quality of life improvement remains controversial [27]. A survey conducted in Korea in 2014 to explore opinions about end-of-life discussions among oncologists and residents revealed that antimicrobial therapy for end-of-life care was discussed only by approximately 17% of the respondents [28].

### 5. Attitudes and opinions of patients and family caregivers for end-of-life care discussions

Among 255 American patients who had advanced cancer and had been taking community-based outpatient hospice and palliative care in 2003, a majority of them (79.2%) chose either no antimicrobial therapy (31%) or symptomatic use only (48.2%) [29]. Other studies performed in Taiwan, which has a distinctive culture deeply influenced by Confucianism and Buddhism, have revealed that 45.8% of the patients with terminal cancer expressed their wish to use antimicrobials even in the very terminal stage and 26.4% did not wish to use antimicrobials [7]. The most influential persons were medical professionals [7]. A study on 3,840 Korean individuals (1,242 cancer patients, 1,289 family caregivers, and 303 oncologists) showed that a large majority of individuals supported the withdrawal of futile life-sustaining treatment (87.1 – 94.0%) and use of active pain control (89.0 – 98.4%) [30]. A smaller majority (60.8 – 76.0%) supported withholding of life-sustaining treatment [30]. Another

study on the discussion regarding end-of-life care among Korean elderly patients and their family caregivers through focus group interviews reported a wide range of diverse attitudes and opinions across all study questions and suggested that the end-of-life care discussion should focus upon devising an approach which takes into account the individualized needs of these elderly patients and their family members [31].

### 6. Complexity of antimicrobial stewardship programs

Infection is an important and normal part of dying process for many patients, and thus often cannot (or should not) be “treated” [32]. In a retrospective chart review of all deaths from 1998 to 2000 in an inpatient hospice unit in San Antonio, Texas, pneumonia was found to be present in 79% of patients at autopsy and appeared to be the major cause of death in 44% of patients [33]. Infections and febrile episodes are the most common acute complications experienced by terminally ill patients. It is difficult to distinguish between the normal part of the dying process and the aspects that are either reversible or clinically reasonable to treat. The question of whether to withdraw or withhold antimicrobials at the end-of-life cannot be definitely answered based on scientific evidence. The decisions for antimicrobial therapy at the end-of-life are complicated and multidimensional that includes ambiguity of therapeutic effectiveness, physician perception, quality of life, attitudes and opinions of patients and family caregivers, ethics, and public health.

## FUTURE DIRECTIONS

There are several steps that need to be taken in the future for applying ASPs in end-of-life care in Korea. First, a nationwide survey or research for antimicrobial use in end-of-life care should be performed. The survey should include classes of antimicrobials, measurements for antimicrobial use such as days of therapy or defined daily dose, presence of MDROs, and burden of antimicrobial use and MDROs in end-of-life care. Further researches investigating the indications of antimicrobial therapy, appropriateness of antimicrobial therapy, changes in antimicrobial use after a decision to withdraw or withhold the life-sustaining treatment, perceptions of physicians regarding antimicrobial use, attitudes and opinion of patients and their family caregivers on antimicrobial use, and the factors associated with antimicrobial use in end-of-life care also warranted.

Second, similar to other life-sustaining treatment decisions, antimicrobial therapy should also be included in the decision-making framework for end-of-life care. The professional societies for ASPs may encourage the department in charge of the Life-Sustaining Treatment Decision Act to clarify that antimicrobial therapy is considered as life-sustaining treatment which can be withdrawn or withheld in patients at the end-of-life. Reviewing the legislative process of the Life-Sustaining Treatment Decision Act will prove to be helpful.

Third, the consensus guideline for ASPs applied to end-of-life care need to be established and implemented. A balanced decision for antimicrobial therapy should be made considering the patient's and family's goal of care (life-prolonging or comfort-achieving), the progression of underlying diseases, and the benefits and harms of antimicrobial agents. Antimicrobial therapy may be appropriate when the goal of care is the prolongation of life and underlying diseases are not advanced. However, if the withdrawal or withholding of life-sustaining treatment has already been decided for the end stage of life, antimicrobial therapy is inappropriate and futile. It is expected that the guideline will assist physicians to wisely

decide regarding antimicrobial therapy in the context of end-of-life care and consequently help reduce antimicrobial use and MDRO prevalence. Collaboration with healthcare personnel involved in life-sustaining treatment decision and hospice care will help ensure that ASPs are successfully implemented in the facility.

## CONCLUSIONS

Antimicrobial therapy should be included in the decision-making framework for end-of-life care similar to the other life-sustaining treatment decisions. If the antimicrobial therapy is legally considered as a life-sustaining treatment which can be withdrawn or withheld in patients at the end-of-life, the feasibility of implementing ASPs among this patient population may improve. Various researches on antimicrobial therapy for patients at the end-of-life need to be conducted and collaborations are required between ASPs professionals and many other concerned parties involved in the legislative process of the Life-Sustaining Treatment Decision Act.

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