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Original Article

Use of antimicrobial agents in actively dying inpatients after suspension of life-sustaining treatments: Suggestion for antimicrobial stewardship

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Abstract *Background:* The role of antimicrobial treatment in end-of-life care has been controversial, whether antibiotics have beneficial effects on comfort and prolonged survival or long-term harmful effects on increasing antimicrobial resistance. We assessed the use of antimicrobial agents and factors associated with de-escalation in inpatients who suspended life-sustaining treatments (SLST) and immediately died.
Methods: We included 1296 (74.7%) inpatients who died within 7 days after SLST out of 1734 patients who consented to SLST on their own or family's initiative following a decision by two physicians, observing the "Life-sustaining Treatment Decision Act" between January 2020 and December 2020 at two teaching hospitals. De-escalation was defined as changing to narrower spectrum anti-bacterial drugs or stopping $\geq$ one antibiotic of combined treatment.
Results: 90.6% of total patients received anti-bacterial agents, particularly a combination treatment in 60.1% and use of $\geq$ three drugs in 18.2% of them. Antifungal and antiviral drugs were administered to 12.6% and 3.3% of the patients on SLST, respectively. Antibacterial and antifungal agents were withdrawn in only 8.3% and 1.3% of the patients after SLST, respectively. Anti-bacterial de-escalation was performed in 17.0% of patients, but 43.6% of them received more or broad-spectrum antibiotics after SLST. In multivariate regression, longer hospital stays before SLST, initiation of SLST in the intensive care unit, and cardiovascular diseases were independently associated with anti-bacterial de-escalation after SLST.

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Conclusions: The intervention for substantial antibiotic use in patients on SLST should be carefully considered as antimicrobial stewardship after decision by the will of the patient and proxy.
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Nomenclature

AMR	Antimicrobial resistance
ASPs	Antimicrobial stewardship programs
CI	Confidence intervals
CVD	Cardiovascular diseases
DDD	Defined daily dose
DOT	Duration of therapy
EOL	End-of-life
ER	Emergency room
ICU	Intensive care unit
IQR	Interquartile range
IUs	international units
LST	Life-sustaining treatments
MDROs	Multi-drug resistant pathogenic organisms
POLST	Physician Orders for Life-Sustaining Treatment
RR	Relative risk
SLST	Suspended life-sustaining treatments
TMP-SMX	trimethoprim-sulfamethoxazole
WHO	World Health Organization

Introduction

Currently, physicians are faced with the challenge of treating and controlling multidrug- or pandrug-resistant bacteria as well as fungi or viruses with resistance against principal agents in the era of a lack of development of new antimicrobial drugs and growing immunosuppressive patients or aging population.[1–6] They are frequently conflicted between empirical and anticipative broad-spectrum antibiotic treatment to prevent the development and deterioration of severe infectious diseases or preservation of antibiotics to reduce antimicrobial resistance (AMR) in clinical practice.[7,8] Thus, appropriate implementation of antimicrobial stewardship programs (ASPs) to cope with the global threat of AMR by decreasing inappropriate and unreasonable antimicrobial use is required.[9–14]

The role of antimicrobial treatment in near end-of-life (EOL) or hospice care of terminally ill patients has been controversial, especially in terms of whether antibiotics in suspected infections could have beneficial effects on prolonged survival and whether patient comfort or excessive use could have harmful effects on long-term public hazards by increasing AMR in community and hospital settings.[15–23] Most of these studies from patients with advanced cancer or dementia did not reveal the seemingly overwhelming benefits of antibiotic treatment that could exceed the potential concern for AMR.[15–18,22,23] However, previous reports in homes or nursing homes or long-term care facilities on EOL care defined the duration of EOL or hospice care as relatively mid-to-long term, until several months.[22–26] Consequently, it remains unclear how antibiotic prescriptions, including anti-bacterial, anti-fungal, and anti-viral agents, are administered in terminally ill patients who are in a state of the imminent death and formally withdraw all of intensive and palliative treatments for comfort or delaying death in hospital.[27]

The "Act on Decisions on Life-sustaining Treatment for Patients at the End of Life" was enforced in August 2017, and the life-sustaining treatments (LSTs) decision system was carried out in February 2018 in South Korea. The "Life-sustaining Treatment Decision Act" aims to ensure the patient's best interests as well as protection of human dignity and worth by respecting the patient's self-determination of LSTs in the process of dying.[28–30] This Act allows the halting of LSTs, which prolong EOL care without therapeutic goals in actively dying patients, following the decision of physicians and voluntary consent of patients or their families according to the predefined process.[28,30] We presumed that antimicrobial treatments, particularly the combination of broad-spectrum antibacterial or recently introduced antifungal drugs, in patients on suspension of LSTs (SLST), may not be medically meaningful or helpful during a short hospital course. If this recognition does not violate moral and ethical issues, attention and practice could be considered as additional components or measures of ASPs to decrease the emergence of AMR and selection pressure of multi-drug resistant pathogenic organisms (MDROs) in addition to expenditure. We assessed the prescription of antimicrobial agents and the contributing factors associated with discreet use in terminally ill patients who withdrew LSTs and immediately died in countries with a high burden of MDROs.[31,32]

Methods

Study design and data collection

We retrieved all inpatients (n = 1734) who consented to SLST on their own or family's initiative following the decision of two physicians according to the below decision processes, observing the "Act on Decisions on Life-sustaining Treatment for Patients at the End of Life," between January 2020 and December 2020 from a query-based relational database management system at Yonsei University Severance Hospital and Gangnam Severance Hospital in Seoul, South Korea. We included 1296 inpatients who died within 7 days after implementation of SLST to

assess the pattern and factors contributing to de-escalation/stopping of antimicrobial treatments in patients judged to be near death among those who were terminally ill, but not in mid-to long-term hospice care for advanced or terminal illness.

We collected the subclass, dose, and duration for all antibacterial, antifungal, and antiviral agents for systemic use before and after implantation of SLST until death. The antimicrobial agents included prophylactic or pre-emptive therapy and treatments for suspected or confirmed infections. The preceding causes of death were categorized into nine groups: (1) infectious diseases without chronic comorbidities, (2) cardiovascular diseases (CVD) (sudden cardiac arrest from unknown origin, ischemic heart diseases, congestive heart failure, cardiomyopathy, and aortic dissection) (3) solid cancers, (4) central nervous system diseases except brain tumors (intracranial hemorrhage, stroke, advanced dementia, Alzheimer's disease, and Parkinson's diseases), (5) hematologic malignancies with or without hematopoietic stem cell transplantation, (6) solid organ transplant status, (7) acute or chronic liver diseases (uncompensated liver cirrhosis and fulminant hepatic failure), (8) chronic renal diseases on dialysis, and (9) chronic lung diseases (idiopathic pulmonary fibrosis, interstitial lung disease, destroyed lung, pneumoconiosis, and chronic pulmonary obstructive disease). This study was approved the Institutional Review Board at Yonsei University Medical Center and the requirement for informed consent was waived for anonymous medical data (IRB No.: 3-2021-0326).

Decision and implementation processes for suspension of life-sustaining treatments

The patients were judged to be near death by one attending physician and one specialist in the Medical Institution Ethics Committee. The two doctors prepared the "Physician Orders for Life-Sustaining Treatment" (POLST) and elucidated the dying process to the patient and family. Then, the physicians checked an "Advance Directive for LST" previously written by the patient in the web-based life-sustaining medical information processing system (https://intra.lst.go.kr). If the patient did not register an advanced directive, but consented to SLST, the patient prepared the "Life-sustaining Medical Plain" document with the attending physician. When an "Advance Directive for LST" could not be verified in the web system and the patient could not express his/her own intention by medical deterioration, the two physicians obtained statements from at least two family members aged $\geq$19 years. If the patient's intention could not be ascertained or inferred, and an "Advance Directive for LST" or "Life-Sustaining Medical Plain" could not be verified from unconscious patients, the two physicians checked that the decision for SLST was agreed upon by all the patients' family members aged $\geq$19 years. Then, the family members drew up the "Confirmation of the Patient's Intention to Suspension of LST" or "Confirmation of the Person with Parental Authority and the Patient's Family for the Decision to Suspend LST". Accordingly, the two physicians finally prepared the "Implementation of Decision of Suspend LST" (Supplementary Fig. 1). Intravenous hydration, nutritional support, pain relief, and simple oxygen supply were maintained even after the implementation of suspension of LSTs. The "life-sustaining medical institution ethics committee" in our hospitals organized and supervised the LST decision system and process. The director of the medical institution notified the head of the "Korean National Life-Sustaining Medical Institution" of the results.[28—30]

Definitions

The Korean "Life-sustaining Treatment Decision Act" defines the following terms: (1) "actively dying patient" - patient whose symptoms is worsened rapidly with no possibility of recovery or revitalization despite aggressive treatments irrelevant to the diseases, and patients who are expected to die within days or weeks, or who begin to show signs of imminent death (2) "LSTs" - cardiovascular resuscitation, mechanical ventilation, hemodialysis including continuous renal replacement therapy, anticancer chemotherapy, and procedures that only extends the duration of the EOL process without any therapeutic effects including transfusion, extracorporeal life supports, such as extracorporeal membrane oxygenation and cardiopulmonary bypass, vasopressor or inotropic use, as well as any treatments that are medically determined not to be performed or discontinued by the attending physician to ensure the best interests of the patient.[28,30,33,34]

The anti-bacterial drugs (J01), antifungal drugs (J02AA, J02AC, J02AX), and antiviral drugs (J05AB and J05AH) were defined and classified by the Anatomical Therapeutic Chemical codes of the World Health Organization (WHO).[35] We excluded antivirals for the treatment of hepatitis B and C viruses, and human immunodeficiency virus-1 infections.

The grams or international units (IUs) of antimicrobial agents were converted into the defined daily dose (DDD) according to the DDD index 2021 assigned by the WHO Collaborating Centre for Drug Statistics Methodology.[35,36] The antibiotic usage between the initiation of SLST and death was expressed as the duration of therapy (DOT) per 1000 patient-days, defined as the total number of days that any antimicrobial agent was administered irrespective of the number or strength of dosage, and total utilization in DDDs (total grams or IUs of use/DDD) per 1000 patient-days.[36,37] Antimicrobial de-escalation was defined as alteration of another antimicrobial agent with a narrower spectrum or stopping $\geq$ one component of combined antibiotic treatment.[38,39] We defined community- and hospital-acquired pneumonia as newly developed pulmonary infiltration and clinical signs or laboratory results for systemic infection.[40]

Statistical analyses

Data are expressed as number (percentage) or median (interquartile range [IQR]) or mean $\pm$ standard deviation (SD). The paired sample McNemar's test was performed to compare the change in antimicrobial agents in the same patient just before and after SLST. Univariate and multivariate logistic regression analyses were expressed as unadjusted and adjusted relative risk (RR) and 95% confidence intervals (CIs), respectively. For regression analyses, we

changed the continuous variables into categorical variables using their mean values. We included the co-variables that were significantly different between the two groups from the univariate analysis in the final multivariate regression model. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS (version 25.0; IBM SPSS Statistics, Armonk, North Castle, NY, USA), and cumulative frequencies were visualized using GraphPad Prism (version 8.0; San Diego, CA, USA).

Results

Clinical characteristics of patients with suspension of LST

There were no withdrawals or non-compliance cases for SLST. The 74.7% (1296/1734) of all patients who agreed to discontinue LSTs for one year died within seven days after implementation of SLST (Supplementary Fig. 2 and Supplementary Table 1). The mean (SD) age of the included patients (n = 1296) was 67.6 (11.3) years and 59.7% of them were male. The median number of days from admission to implementation of SLST was 9 (IQR, 3—22) and SLST in half (52.9%) of the patients was initiated within 10 days (Supplementary Fig. 2). Solid cancer (60.8%) was the most common preceding cause of death, followed by infectious diseases (10.1%) and CVD (8.2%). The median survival after SLST was 2 (IQR, 1—4) days, and 47.9% of the patients died within 1 day of SLST (Supplementary Fig. 2). The SLST in two-thirds of the patients was officially registered in the general ward or emergency room (ER).

Using pattern of antimicrobial agents in patients with suspension of LST

Forty-five (3.5%) patients did not receive anti-bacterial therapy during the total admission period before and after SLST, and anti-bacterial agents were stopped in only 8.3% of the patients (108 of 1251 after exclusion of 45 patients without anti-bacterial therapy during admission) after SLST. After SLST, 90.6% of the patients who agreed to withdraw LSTs were taking anti-bacterial agents, particularly combined drugs (60.1%). The administration of antibacterial agents was more frequent after SLST than immediately before SLST (90.6% vs. 82.3%, $p < 0.001$). Although the frequency of anti-bacterial monotherapy did not differ between before and after SLST ($p = 0.102$), the combination treatment with antibacterial agents was carried out at a significantly higher rate post SLST implementation (60.1% vs. 46.5%, $p < 0.001$). The combination of $\geq$ three drugs (18.2% vs. 8.6%, $p < 0.001$), but not two drugs (41.9% vs. 37.9%, $p = 0.273$), was more commonly administered to patients after SLST (Table 1). The combination of carbapenem, quinolone, and glycopeptide showed the largest increase after SLST (from 3.7% to 7.9%), followed by the combination of piperacillin/tazobactam, quinolone, and glycopeptide (from 2.2% to 5.3%) (Table 1).

The antifungal and antiviral agents were administered in 12.6% and 3.3% of patients, respectively, after SLST. These frequencies were not different compared to the time immediately before SLST ($p = 0.678$ and 0.791, respectively). The antifungal and antiviral drugs were discontinued in only 17 (1.3%) and two (0.2%) patients after SLST, respectively (Table 2).

Factors related to the de-escalation of antibacterial agents after suspension of LST

The de-escalation of anti-bacterial therapy after implementation of SLST was performed in 17.0% (213 of 1251) of the patients. In contrast, 545 (43.6%) patients received a greater number of and/or broad-spectrum anti-bacterial agents after SLST compared to that before SLST. The duration between admission and the implementation of SLST was significantly longer in patients who received the anti-bacterial de-escalation than in those who did not (median days: 14 vs. 9, >10 days: 59.2% vs. 45.7% and unadjusted RR [95% CI], 1.7 [1.3—2.3], $p < 0.001$). However, the duration from SLST to death was significantly shorter in patients with de-escalation (median days: 0 vs. 2, 1 day: 85.8% vs. 39.9% and 0.1 [0.1—0.2], $p < 0.001$). The anti-bacterial de-escalation rate was significantly lower in patients who died due to solid cancers than in those with other causes of death (13.4% vs. 22.6%, 0.5 [0.4—0.7], $p < 0.001$). In contrast, patients with CVD had a significantly higher de-escalation frequency than those with other causes of death (39.4% vs. 15.1%, 3.7 [2.4—5.6], $p < 0.001$). Other causes of death, age, sex, pneumonia, and C-reactive protein levels at the initiation of SLST were not different between patients with and without anti-bacterial de-escalation. Anti-bacterial de-escalation was more commonly practiced when the decision process for SLST was performed in the intensive care unit (ICU) rather than the general ward or ER (29.6% vs. 10.8%, 3.5 [2.6—4.7], $p < 0.001$) (Table 2).

In the multivariate logistic regression analysis, location of the withdrawal process of LST (ICU vs. non-ICU: adjusted RR [95% CI], 2.8 [2.0—3.9], $p = 0.001$), CVD as the cause of death (yes vs. no: 2.1 [1.3—3.4], $p = 0.004$), and longer duration between admission and implementation of SLST (>10 vs. $\leq$10 days: 1.4 [1.1—2.0], $p = 0.021$) were independent factors significantly associated with the de-escalation of anti-bacterial agents after SLST (Table 3).

Usage of antimicrobial agents after implementation of suspension of LST

The DOT of all anti-bacterial agents (excluding narrow-spectrum antibiotics of 1st- and 2nd-cephalosporins, clindamycin, linezolid, macrolides, monobactam, penicillins except piperacillin/tazobactam, and tetracyclines) administrated until death after SLST was 1.8 per 1000 patient-days (range: 1.7—25.3, each 1.7 for piperacillin/tazobactam and fluoroquinolones, and 2.2 and 1.5 for carbapenems and glycopeptides, respectively). The DOT of total anti-fungal and anti-viral agents was 5.2 and 21.1 per 1000 patient-days, respectively. The total DDD of TMP-SMX (73.7 per 1000 patient-days) was the largest, followed by metronidazole (21.5), polymyxin E (13.5), and 3rd-generation cephalosporin with anti-pseudomonal activity (14.6) (Table 4).

Table 1 Antimicrobial agents which were being administered just before implementation of suspension of life-sustaining treatment and during implementation until death.

Antimicrobial agents	Total patients (N = 1296)		
	Just before LST suspension	From LST suspension to death	*p*-value[a]
Anti-bacterial			
No	230 (17.7)	122 (9.4)	<0.001
Yes	1066 (82.3)	1174 (90.6)	
Monotherapy	463 (35.7)	395 (30.5)	0.102
Piperacillin/tazobactam	196 (15.1)	189 (14.6)	
1st-generation cephalosporins	9 (0.7)	7 (0.5)	
2nd-generation cephalosporins	5 (0.4)	3 (0.2)	
3rd-generation cephalosporins	79 (6.1)	61 (4.7)	
Without anti-pseudomonal activity	46 (3.5)	38 (2.9)	
With anti-pseudomonal activity	33 (2.6)	23 (1.8)	
4th-generation cephalosporins	30 (2.3)	25 (1.9)	
Carbapenems	69 (5.3)	70 (5.4)	
Quinolones	30 (2.3)	11 (0.8)	
Glycopeptides	4 (0.3)	8 (0.6)	
Tigecycline	2 (0.2)	1 (0.1)	
Polymyxin E	2 (0.2)	5 (0.4)	
Others[b]	37 (2.9)	15 (1.2)	
Combination therapy	603 (46.5)	779 (60.1)	<0.001
Two agents	491 (37.9)	543 (41.9)	0.273
Piperacillin/tazobactam + glycopeptides	72 (5.6)	73 (5.6)	
Piperacillin/tazobactam + quinolones	154 (11.9)	155 (12.0)	
Anti-pseudomonal 3rd-cephalosporins + glycopeptides	9 (0.7)	2 (0.2)	
Anti-pseudomonal 3rd-cephalosporins + quinolones	5 (0.4)	8 (0.6)	
4th-cephalosporins + glycopeptides	20 (1.5)	19 (1.5)	
4th-cephalosporins + quinolones	16 (1.2)	15 (1.2)	
Carbapenems + glycopeptides	128 (9.9)	186 (14.4)	
Carbapenems + quinolones	20 (1.5)	30 (2.3)	
Polymyxin E + glycopeptides	5 (0.4)	3 (0.2)	
Polymyxin E + carbapenems	13 (1.0)	18 (1.4)	
Others	49 (3.8)	34 (2.6)	
≥3 agents	112 (8.6)	236 (18.2)	<0.001
Piperacillin/tazobactam + quinolones + glycopeptides	28 (2.2)	69 (5.3)	
Anti-pseudomonal 3rd-cephalosporins + quinolones + glycopeptides	1 (0.1)	2 (0.2)	
4th-cephalosporins + quinolones + glycopeptides	6 (0.5)	2 (0.2)	
Carbapenems + quinolones + glycopeptides	48 (3.7)	102 (7.9)	
Carbapenems + polymyxin E + glycopeptides	16 (1.2)	16 (1.2)	
Carbapenems + quinolones + glycopeptide + polymyxin E	3 (0.2)	29 (2.2)	
Others	10 (0.8)	16 (1.2)	
Anti-fungal			
No	1116 (86.1)	1133 (87.4)	0.678
Yes	180 (13.9)	163 (12.6)	
Monotherapy	174 (13.4)	155 (12.0)	
Fluconazole	90 (6.9)	78 (6.0)	
Amphotericin-B deoxycholate	4 (0.3)	3 (0.2)	
Liposomal amphotericin-B	18 (1.4)	20 (1.5)	
Voriconazole	24 (1.9)	21 (1.6)	
Caspofungin	38 (2.9)	33 (2.5)	
Combination therapy	6 (0.5)	8 (0.6)	
Liposomal amphotericin-B + fluconazole	1 (0.1)	1 (0.1)	
Liposomal amphotericin-B + caspofungin	1 (0.1)	0 (0)	
Fluconazole + caspofungin	4 (0.3)	5 (0.4)	
Voriconazole + caspofungin	1 (0.1)	2 (0.2)	

(*continued on next page*)

Table 1 (*continued*)

Antimicrobial agents	Total patients (N = 1296)		
	Just before LST suspension	From LST suspension to death	*p*-value[a]
Anti-viral			
No	1255 (96.8)	1253 (96.7)	0.791
Yes	41 (3.2)	43 (3.3)	
Acyclovir	11 (0.8)	8 (0.6)	
Ganciclovir	28 (2.2)	32 (2.5)	
Valganciclovir	2 (0.2)	1 (0.1)	
Ribavirin	0 (0)	1 (0.1)	
Oseltamivir	0 (0)	1 (0.1)	

[a] Paired sample McNemar test.
[b] Include amoxacillin/clavulinic acid, ampicillin/sulbactam, nafcillin, macrolides, tetracyclines and trimethoprim-sulfamethoxazole.

Table 2 Comparison of clinical characteristics between patients who were received the de-escalation treatment for anti-bacterial agents and not received the de-escalation after suspension of life-sustaining treatment.

Characteristics	Total (N = 1296)	De-escalation of anti-bacterial agents after suspension of LSTs[a]			
		Yes (N = 213)	No (N = 1038)	Unadjusted RR (95% CI)	*p*-value
Age, years	67.6 ± 13.9	68.1 ± 14.5	67.5 ± 13.7		
<65	555 (42.8)	84 (39.4)	449 (43.3)	Ref.	0.305
≥65	741 (57.2)	129 (60.6)	589 (56.7)	1.17 (0.87–1.58)	
Sex					
Male	774 (59.7)	124 (58.2)	627 (60.4)	Ref.	0.553
Female	522 (40.3)	89 (41.8)	411 (39.6)	0.91 (0.68–1.23)	
Duration from admission to suspension of LST	9 (3–22)	14 (5–26)	9 (2–22)		
≤10 days	685 (52.9)	87 (40.8)	564 (54.3)	Ref.	<0.001
>10 days	611 (47.1)	126 (59.2)	474 (45.7)	1.72 (1.28–2.32)	
Duration from suspension of LST to death	2 (1–4)	0 (0–1)	2 (1–4)		
≤1 day	621 (47.9)	183 (85.9)	414 (39.9)	Ref.	<0.001
>1 day	675 (52.1)	30 (14.1)	624 (60.1)	0.11 (0.07–0.16)	
Preceding cause of death					
Solid cancers					
No	508 (39.2)	111 (22.6)	381 (77.4)	Ref.	<0.001
Yes	788 (60.8)	102 (13.4)	657 (86.6)	0.53 (0.40–0.72)	
Hematologic malignancies[b]					
No	1210 (93.4)	197 (16.9)	969 (83.1)	Ref.	0.648
Yes	86 (6.6)	16 (18.8)	69 (81.2)	1.14 (0.65–2.01)	
Infectious diseases					
No	1165 (89.9)	195 (17.4)	926 (82.6)	Ref.	0.309
Yes	131 (10.1)	18 (13.8)	112 (86.2)	0.76 (0.45–1.29)	
CVD					
No	1190 (91.8)	174 (15.1)	978 (84.9)	Ref.	<0.001
Yes	106 (8.2)	39 (39.4)	60 (60.6)	3.65 (2.37–5.64)	
CNS diseases					
No	1228 (94.8)	201 (16.9)	987 (83.1)	Ref.	0.662
Yes	68 (5.2)	12 (19.0)	51 (81.0)	1.16 (0.61–2.21)	
Chronic liver diseases					
No	1277 (98.5)	209 (17.0)	1023 (83.0)	Ref.	0.639
Yes	19 (1.5)	4 (21.1)	15 (78.9)	1.31 (0.43–3.97)	
Chronic renal diseases					
No	1268 (97.8)	209 (17.1)	1015 (82.9)	Ref.	0.758
Yes	28 (2.2)	4 (14.8)	23 (85.2)	0.85 (0.29–2.47)	

Table 2 (*continued*)

Characteristics	Total (N = 1296)	De-escalation of anti-bacterial agents after suspension of LSTs[a]			
		Yes (N = 213)	No (N = 1038)	Unadjusted RR (95% CI)	*p*-value
Chronic lung diseases					
No	1255 (96.8)	203 (16.8)	1007 (83.2)	Ref.	0.206
Yes	41 (3.2)	10 (24.4)	31 (75.6)	1.60 (0.77–3.32)	
SOT					
No	1274 (98.3)	206 (16.8)	1023 (83.2)	Ref.	0.070
Yes	22 (1.7)	7 (31.8)	15 (68.2)	2.32 (0.93–5.76)	
Location at suspension process of LST					
General ward or ER	870 (67.1)	90 (10.8)	745 (89.2)	Ref.	<0.001
ICU	426 (32.9)	123 (29.6)	293 (70.4)	3.48 (2.57–4.71)	
Pneumonia[c]					
No	986 (76.1)	154 (16.3)	788 (83.7)	Ref.	0.266
Yes	310 (23.9)	59 (19.1)	250 (80.9)	1.21 (0.87–1.68)	
C-reactive protein (mg/L)[c]	122.2 ± 98.8	117.3 ± 99.0	124.5 ± 99.1		
<100	656 (50.6)	114 (53.5)	515 (49.6)	Ref.	0.287
≥100	640 (49.4)	99 (46.5)	523 (50.4)	0.85 (0.63–1.15)	
WBC count (X 10^3/mm^3)[c]	15.1 ± 12.8	16.1 ± 12.7	15.1 ± 13.0		
<12	618 (47.7)	94 (44.1)	492 (47.4)	Ref.	0.407
≥12	678 (52.3)	119 (55.9)	546 (52.6)	1.13 (0.84–1.53)	

[a] We excluded 45 patients who did not receive anti-bacterial therapy before and after suspension of LST during the total admission period.
[b] We included patients who underwent HSCT.
[c] Initiation of LST suspension.
Data are expressed as number (percentage) or mean ± standard deviation or median (interquartile range).
Abbreviations: CNS, central nervous system; CVD, cardiovascular disease, ER, emergency room; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LST, life-sustaining treatment; Ref., reference; RR, relative risk; SOT, solid organ transplantation; WBC, white blood cell.

Table 3 Clinical factors in relation to the de-escalation of anti-bacterial agents after suspension of life-sustaining treatment.

Variables	Adjusted RR	95% CI	*P*-values
Duration from admission to suspension of LST, >10 days	1.44	1.06∼1.97	0.021
Preceding cause of death			
Solid cancer, yes	0.94	0.66∼1.35	0.744
Cardiovascular diseases, yes	2.08	1.27∼3.41	0.004
Location at suspension process of LST, ICU	2.77	1.97∼3.90	<0.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; LST, life-sustaining treatment; RR, relative risk.

Discussion

The primary treatments that are maintained in terminally ill patients after SLST or near the EOL would be hydration, artificial nutrition, and pharmaceutical management of distress and pain.[41–43] Deciding whether antibiotic therapy should be administered in these situations might be subject to legal pressures and could have conscientious scruples against physicians.[44–47] In addition to ethical inquiry or moral responsibility, our data showed that most patients on the actively dying process after the implementation of SLST according to their own and families' will and the legal framework, received maximal antimicrobial treatment using combined antibacterial agents with broad-spectrum. The antibacterial agents were discontinued and de-escalated in a small proportion of patients who died within 7 days after the implementation of SLST. Conversely, more patients received the new broad-spectrum anti-bacterial drugs and combination therapy with ≥ three agents after SLST compared to before SLST. In addition, antifungal agents and ganciclovir were maintained after SLST. This pattern is compatible with advanced antimicrobial treatments (curative, not palliative) to actively cope with severe infections, including serious pneumonia or sepsis caused by MDROs and fungi.[48,49]

Our study showed that more efforts have been made to reduce the use of anti-bacterial agents in the setting of initiation of SLST after a longer hospital stay and during ICU care. The independent relationship between CVD and anti-bacterial de-escalation may be associated with post-arrest SLST. SLST was implemented after cardiac arrest in 48.7% of the decedents by CVD, and the frequency of de-escalation was significantly higher in post-arrest SLST than in SLST, irrespective of cardiac arrest (36.6% vs. 15.1%, $p < 0.001$). The rates of post-arrest SLST in the deceased due to other diseases were low (data not shown).

Table 4 Usage of antimicrobial agents in actively dying patients who suspended the life-sustaining treatments and died within 7 days after the suspension.

Anti-microbial agents	Number of patients (% of 1296)	DOT		Total DDD[a]
		Total (days)	Per 1000 patient-days	
Anti-bacterial				
Piperacillin/tazobactam	618 (47.7)	1739	1.7	1.5
3rd-generation cephalosporins				
Without anti-pseudomonal activity	68 (5.2)	149	14.2	11.0
With anti-pseudomonal activity	57 (4.4)	188	15.7	14.6
4th-generation cephalosporins	97 (7.5)	285	9.5	8.6
Carbapenems	463 (35.7)	1079	2.2	1.3
Quinolones	426 (32.9)	1028	1.9	2.7
Fluoroquinolones	393 (30.3)	767	1.7	3.1
Aminoglycosides	39 (3.0)	72	25.3	10.0
Metronidazole	41 (3.2)	112	21.3	21.5
TMP-SMX	257 (19.8)	674	4.0	73.7
Polymyxin E	64 (4.9)	110	16.2	13.5
Glycopeptides	540 (41.7)	1139	1.5	1.2
Total[b]	**1045 (80.6)**	**6898**	**1.8**	**6.3**
Anti-fungal				
Amphotericin-B[c]	22 (1.7)	49	45.8	78.3
Fluconazole	89 (6.9)	246	9.7	4.6
Voriconazole	24 (1.9)	58	50.3	17.9
Caspofungin	39 (3.0)	76	24.4	11.7
Total	**163 (12.6)**	**436**	**5.2**	**4.1**
Anti-viral				
Acyclovir	8 (0.6)	12	93.8	8.6
Ganciclovir and valganciclovir	33 (2.5)	84	29.6	5.9
Total	**41 (3.2)**	**100**	**21.1**	**4.3**

[a] Per 1000 patient-days.
[b] Exclude 1st- and 2nd-generation cephalosporins, clindamycin, lincosamides, linezolid, macrolides, monobactam, other penicillins except piperacillin/tazobactam, and tetracyclines.
[c] Include amphotericin-B deoxycholate and liposomal amphotericin-B.
Abbreviations: DDD, the defined daily dose; DOT, duration (day) of therapy; TMP-SMX, trimethoprim-sulfamethoxazole.

Although some guidelines did not mention the use of antibiotics in EOL settings,[50–53] others recommend the abrupt withdrawal of antimicrobial treatment for patients on SLST in the ICU.[54,55] Downar et al. showed that ICU providers completely agreed with the discontinuation of antibiotic use.[54] Although several guidelines and logical judgments have been implemented, the decision process of SLST and practical performance after SLST showed marked variation across countries, regions, and individualized ICUs worldwide in clinical settings.[56,57] Moreover, a substantial proportion (40–70%) of terminally ill hospitalized patients after SLST are actually treated with antibiotics near the EOL for ≤7 days of life, similar to our findings.[42,58–63]

The process and forms of SLST in South Korea may be similar to the national PLOST in the United States, which include the preferences for the limited antibiotic use, including only comfort measures or full antibiotic use.[64] Several patients (25–56%) requested the comfort-oriented antimicrobial treatment according to PLOST with relatively high concordance.[64,65] However, PLOST does not directly address the withdrawal or non-use of antibiotics, unlike other LSTs (for instance, none for artificial nutrition).[64,66] The Korean official forms for SLSTs also do not include the selection of antibiotics. Moreover, physicians are legally able to record and implement the withdrawal of antimicrobial therapy in other items of LSTs.[28,30] Non-specific expression may have affected the excessive rates of aggressive antibiotic treatment. We found SLST with antibiotic decisions in only few (0.4%) deceased inpatients. Therefore, the responsibility of physicians would have a responsibility to inform them on the futility of continuing antimicrobial agents. And, the use of antibiotics after SLST should be actively and clearly discussed with patients and their families within ethical and legal boundaries.

Importantly, we should consider that the antibiotics are not comfort-oriented therapy and do not have the anticipated therapeutic effect, especially near the EOL situation applied in our study.[67] The potential obstacles of decision-making and practice to stop the antibiotics for patients after SLST and near the EOL[45,68] include the following: (1) The lack of widely accepted recommendation or strategies to guide antimicrobial treatment.[61] (2) The inability to predict the time to death after SLST in terminally-ill patients, where physicians may expect an extended lifespan or survival.[69] However, our data showed that most inpatients died within a short period after fulfillment of SLST.

(3) Resolution of all liability-related issues. (4) Effective communication by the physicians to consider the wishes of the patients or families and dispel any misconceptions toward the use of antibiotics[70]; however, this could be a significant burden on doctors and result in physician burnout.[63] (5) Finally, the lack of precise definitions for various and somewhat confusing medical terms or clinical settings (actively dying process vs. chronic life-limiting illness, EOL, subacute or chronic hospice or palliative cares, forgoing or withdrawal LSTs, SLST, and terminally-ill).[33,34,61,71] It is necessary to understand that the SLST status is a more active expression of intention to discontinue aggressive treatments during EOL than comfort measures, do-not-resuscitate orders, or hospice care at home/long-term facilities.[33] However, Wider-Smith et al. presented the possibility that an appropriately planned intervention could induce the reduction of antimicrobial use in patients near the EOL.[62]

Our first attempt to evaluate the detailed patterns of antimicrobial therapy after SLST has the following strengths: (1) analysis of only patients (largest number of decedents) who died within 7 days after the implementation of SLST, which indicated actively dying process, (2) obligatory fulfillment of withdrawal therapy after SLST within the legal and ethical frameworks, (3) no limitation of underlying diseases preceding the cause of death or ICU care, and (4) first evaluation for the use of anti-fungal and anti-viral agents in SLST. In particular, our study deals with a clinical situation among various EOL settings where the necessity and expected benefits of antibiotics are least likely. However, this study also has some limitations. First, the purpose of antimicrobial therapy could not be clearly distinguished as to whether it was preventive/prophylactic or treatment for presumptive or definite infections. Second, we could not obtain information about the patients' and their families' intentions for antibiotic use owing to the characteristics of our current form in the process of SLST. Third, we did not assess the effect of antibiotic withdrawal or maintenance on psychological comfort and stability during the dying process.

In conclusion, our findings revealed the excessive use of antimicrobial agents in actively dying terminally ill patients with advanced directives and implementation of SLST. Our study suggests that the discontinuation or restricted use of antibiotics in patients undergoing SLST or ordering the limited use of PLOST could be an additional approach for ASPs if all processes are properly discussed as part of DNR (do-not-resuscitate), and agreed upon with informed consent from patients and/or their proxy, because the public health risks or burdens of overused antimicrobial agents to increase AMRs or medical costs would far outweigh the benefits for these patients and their families.

Author contributions

D. K., K. H. L., and S.H.H. designed the study. D.K. and S.H.H. collected and arranged the data and performed statistical analyses. D.K. wrote the original draft, and S.H.H. reviewed and edited the manuscript. S.K. and K. H. L. revised the manuscript. All authors approved the final version of the manuscript.

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Declaration of competing interest

None of the authors have any conflicts of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2022.03.003.