**Appendix for Antimicrobial prescribing in patients with advanced stage illness in the antimicrobial stewardship era**

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Appendix 1. The definition of an advanced stage of illnesses

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| Type of illness | Definition | Reference |
| End-stage cardiovascular disease | NYHA classification III and/or objective evidence of severe cardiac dysfunction. | Metra, et al. |
| End-stage pulmonary disease including advanced COPD and severe pulmonary disease (non-COPD) | Advanced COPD is defined as GOLD classification III with or without long-term oxygen therapy.  Severe pulmonary disease (non-COPD) is defined as the group of non-neoplastic lung diseases chronically limiting patient's activity of daily living or a significant pulmonary disease requiring long-term oxygen therapy. | Marciniuk, et al.  Janssen, et al. |
| End-stage renal disease | Estimated GFR<15ml/min/1.73m2 with or without dialysis | Andrassy, et al. |
| End-stage liver disease | Child-Pugh score >12 or MELD score >21 | Salpeter, et al. |
| Advanced dementia | Stage 7 on the Global Deterioration Scale | Reisberg, et al. |
| Advanced malignancy | Cancer that has metastasized and cannot be cured or controlled with treatment. | National Cancer Institute |

**NOTE.**  NYHA, New York Heart Association; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Obstructive Lung Disease; GFR, estimate glomerular filtration rate; MELD, Modeling for End Stage Liver Disease

Appendix 2. Characteristics of patients with an advanced stage of illness (n=260)

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| Characteristics | n (%) |
| **Demographics** |  |
| Age, median (range)  <65  65-80  >80 | 73 (31-99)  54 (20.8)  170 (65.4)  36 (13.8) |
| Male gender | 166 (63.8) |
| Marital status  Married  Unmarried  Divorced  Unknown | 214 (82.3)  20 (7.7)  8 (3.1)  18 (6.9) |
| Primary care giver  Spouse  Children  Parents  Other  None | 134 (51.5)  77 (29.6)  15 (5.8)  32 (12.3)  2 (0.8) |
| Residential status prior to admission  Home  Long term care facilities  Acute care hospital | 234 (90.0)  17 (6.5)  9 (3.5) |
| **Present comorbidities / Past medical history** |  |
| Diabetes mellitus | 70 (26.9) |
| Congestive heart failure | 34 (13.1) |
| Cerebrovascular diseases | 14 (5.4) |
| Chronic lung diseases | 45 (17.3) |
| Peptic ulcer diseases | 15 (5.8) |
| Chronic liver diseases | 63 (24.2) |
| Connective tissue diseases | 11 (4.2) |
| Dementia | 11 (4.2) |
| Malignancies (both past history and active malignancies) | 203 (78.1) |
| Human immunodeficiency virus infection | 0 (0) |
| Daily use of home oxygen therapy prior to the index hospitalization | 24 (9.2) |
| End stage renal disease being on hemodialysis prior to the index hospitalization | 15 (5.8) |
| Charlson comorbidity index score, median, (interquartile range)  ≥ 6  1-5 | 6 (5-8)  192 (73.8)  68 (26.2) |
| **Primary advanced stage of illnesses** |  |
| End-stage malignancies  End-stage cardiovascular diseases  End-stage pulmonary diseases  End-stage renal diseases  End-stage liver diseases  Advanced dementia | 192 (73.8)  22 (8.5)  16 (6.2)  17 (6.5)  12 (4.6)  1 (0.4) |
| Presence of secondary advanced stage of illnesses | 40 (15.4) |
| **Secondary advanced illnesses (n=40)** |  |
| End-stage malignancies  End-stage cardiovascular diseases  End-stage pulmonary diseases  End-stage renal diseases  End-stage liver diseases  Advanced dementia | 2 (0.8)  5 (1.9)  14 (5.4)  9 (3.5)  9 (3.5)  1 (0.4) |
| **Antimicrobial use** |  |
| Antimicrobial agents given in the last 14 days of life | 136 (52.3) |
| History of antimicrobial use prior to the last 14 days of life during  index hospitalization | 101 (38.8) |
| **Escalation of medical care in the last 14 days of life** |  |
| Central venous catheter placement | 58 (22.3) |
| Arterial line placement for blood pressure monitoring | 21 (8.1) |
| Vasopressor | 37 (14.2) |
| Intubation | 14 (5.4) |
| Ventilatory support (both mechanical ventilation and NPPV) | 30 (11.5) |
| Platelet transfusion | 27 (10.4) |
| Red blood cell transfusion | 51 (19.6) |
| Enteral nutrition | 27 (10.4) |
| Total parenteral nutrition | 24 (9.2) |
| Urinary catheter placement | 196 (75.4) |
| **Escalation of palliative care in the last 14 days of life** |  |
| Antidepressant use as a palliative | 19 (7.3) |
| Anxiolytics use as a palliative | 35 (13.5) |
| Antipyretics use as a palliative | 200 (76.9) |
| Analgesics use including narcotics use as a palliative | 170 (65.4) |
| Psychiatric liaison as a palliative | 33 (12.7) |
| Palliative care consultation | 53 (20.4) |
| **Other details of final hospitalization** |  |
| Transition to supportive care (comfort measure) as the primary treatment status  documented in the medical chart prior to the last 14 days of life | 67 (25.8) |
| Duration of the index hospitalization, median, (interquartile range) | 18 (9-31) |
| Time between the date of admission and the date of latest clinical deterioration,  median (interquartile range) | 13 (6-27) |
| Presence of “do not resuscitate (DNR)” order prior to the last 14 days of life | 64 (24.6) |

**NOTE.** NPPV, non-invasive positive pressure ventilation.

Appendix 3. Use of initial antimicrobial agents in the last 14 days of life

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| Initial antimicrobial therapy (n=136) |  |  |
| **3-drug regimen (n=5)** | **2-drug regimen (n=10)** | **Single drug regimen (n=121)** |
| Vancomycin, cefepime, metronidazole (n=1) | Cefepime, metronidazole (n=2) | Meropenem (n=3) |
| Vancomycin, piperacillin/tazobactam, azithromycin (n=1) | Ceftriaxone, azithromycin (n=2) | Cefepime (n=23) |
| Vancomycin, cefazolin, amphotericin B (n=1) | Piperacillin/tazobactam, TMP/SMX (n=1) | Piperacillin/tazobactam (n=17) |
| Vancomycin, ceftriaxone, azithromycin (n=1) | Piperacillin/tazobactam, ciprofloxacin (n=1) | Ampicillin/sulbactam (n=32) |
| Levofloxacin, fluconazole, Trimethoprim/Sulfamethoxazole (n=1) | Cefepime, azithromycin (n=1) | Fluoroquinolones (n=5) |
|  | Vancomycin, piperacillin/tazobactam (n=1) | 1st generation cephalosporin (n=11) |
|  | Vancomycin, meropenem (n=1) | Cefmetazole (n=5) |
|  | Meropenem, micafungin (n=1) | Ceftriaxone or other 3rd generation cephalosporins (n=12) |
|  |  | Metronidazole (n=1) |
|  |  | Trimethoprim/Sulfamethoxazole (n=9) |
|  |  | Vancomycin (n=1) |
|  |  | Micafungin (n=1) |
|  |  | Amikacin (n=1) |

Appendix 4. Proportion of antimicrobials used for initial therapy by antimicrobial class

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| Antimicrobials | Cases, n=136 (%) |
| Ampicillin/sulbactam | 32 (25.4) |
| Cefepime | 27 (19.9) |
| Piperacillin/tazobactam | 21 (15.4) |
| 3rd generation cephalosporins | 15 (11.0) |
| 1st generation cephalosporin | 12 (8.8) |
| Trimethoprim/Sulfamethoxazole | 11 (8.1) |
| Fluoroquinolones | 7 (5.1) |
| Vancomycin | 7 (5.1) |
| Cefamycin | 5 (3.7) |
| Carbapenems | 5 (3.7) |
| Macrolides | 5 (3.7) |
| Antifungals | 4 (2.9) |
| Metronidazole | 4 (2.9) |
| Aminoglycosides | 1 (0.7) |

**NOTE:** Fifteen (10.9%) patients received a combination therapy.

Appendix 5. Days of therapy per 1,000 patient-days for each antimicrobial class in the last 14 days of life, used for patients with an advanced stage of illnesses

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| Antimicrobials | Days of therapy | Days of therapy per 1,000 patient-days |
| Ampicillin/sulbactam | 212 | 70.7 |
| Cefepime | 227 | 75.7 |
| Piperacillin/tazobactam | 167 | 55.7 |
| 3rd generation cephalosporins | 87 | 29.0 |
| 1st generation cephalosporin | 61 | 20.3 |
| Trimethoprim/Sulfamethoxazole | 95 | 31.7 |
| Fluoroquinolones | 57 | 19.0 |
| Vancomycin | 59 | 19.7 |
| Cefamycin | 63 | 21.0 |
| Carbapenems | 66 | 22.0 |
| Macrolides | 35 | 11.7 |
| Antifungals | 101 | 33.7 |
| Metronidazole | 32 | 10.7 |
| Aminoglycosides | 3 | 1.0 |
| Total | 1265 | 421.9 |

**NOTE.**

A total patient-days for all patients with an advanced stage of illnesses were 2,998.