**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.