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Title

Antimicrobial prescription in patients dying from Chronic Obstructive Pulmonary Disease

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Introduction
Despite rising antimicrobial resistance, treatment guidelines for COPD exacerbations are frequently ignored. Patients with terminal conditions are often prescribed antimicrobials despite the goal of care to reduce burdensome treatments. The appropriateness of antimicrobials in patients dying from an exacerbation of COPD is unknown.

Aim
To review antimicrobial prescription at the time of death in patients who died from COPD.

Methods
A retrospective medical record audit was performed for 475 patients who died over twelve years (2004-2015). Patients were analysed within three groups: Group 1 – pneumonia on chest radiograph, Group 2 – acute infective exacerbation of COPD (AECOPD) +/- raised inflammatory markers (WCC, CRP) and Group 3 – non-infective AECOPD.

Results
221 patients died from COPD. Median age: 80 years and 136 (60%) were male. Median respiratory function: FEV1 0.8L (41.0%), FVC 2.0L (74.0%) and DLco 8 (40.5%). 109 (49.3%) patients used home oxygen and 156 (70.6%) were ex-smokers.

90.5% of patients received antimicrobials. In Groups 1, 2 and 3, 68 (94.4%), 108 (92.3%) and 24 (75.0%) received antimicrobials, respectively. Guideline concordant therapy occurred in 31.7% of patients (Group 1 79.2%, Group 2 4.3%, Group 3 25.0%). 60.2% of patients received ceftriaxone and 44.8% received azithromycin. Median duration of therapy was four days and 27.1% received antimicrobials at the time of death.

Conclusion
Antimicrobials are overprescribed and non-guideline antimicrobials are overused in patients who die from COPD. Further education of medical staff, regular medication reviews and the use of disease severity scores or clinical pathways may improve antimicrobial stewardship.

ANTIMICROBIAL PRESCRIPTION IN PATIENTS DYING FROM CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction

The rising prevalence of antimicrobial resistance, commonly due to uncontrolled antimicrobial use, has been recognised as an urgent global health priority (1). Infections with resistant microbial organisms are associated with prolonged hospitalisations and increased medical investigations, financial costs, mortality and morbidity (2).

Chronic obstructive pulmonary disease (COPD) is characterised by persistent symptoms, fixed airflow obstruction, parenchymal lung destruction and a variable number of exacerbations (3). A COPD exacerbation may be caused by an infectious or non-infectious precipitant. While 50% of patients will culture a bacterial organism during an exacerbation, not all bacteria are pathogenic; 30% of stable COPD patients culture bacterial organisms when well, and thus are colonised (4).

Australian COPD Guidelines (5,6) recommend that in the absence of radiographic pneumonia, antimicrobial therapy (i.e. oral amoxycillin or doxycycline for 5 to 7 days duration) should be reserved for patients presenting with a significant change in symptoms suggesting an acute infection. The presence of two or more 'cardinal symptoms' of increased dyspnea, sputum volume and sputum purulence have been shown to predict the presence of bacteria in sputum and therefore which patients may respond to antimicrobial therapy to treat the exacerbation, in addition to bronchodilators and glucocorticoids (7,8). A summary of national guidelines for the antimicrobial treatment of COPD exacerbations (without radiological evidence of pneumonia) and community-acquired pneumonia is provided in Table 1.

However, adherence to guidelines by general practitioners and hospital specialists appears to be poor, as nearly 90% of patients who experience an acute exacerbation of COPD in both settings are prescribed antimicrobials and up to 85% of agents are prescribed to patients who do not report a significant change in cardinal symptoms (9-11). In addition, guideline

recommendations regarding the route and number of antimicrobials are frequently disregarded, as half of all inpatients receive at least two antimicrobials and 45% receive intravenous therapy (11).

Infections are common at the end of life. Nearly half of patients with advanced dementia, 90% percent of hospitalised patients with end-stage cancer, and over a quarter of patients in hospices are commenced on antimicrobials in the final two weeks of life (12-14). Despite the documented goal of care being to optimise symptom palliation and reduce burdensome interventions or treatments, antimicrobials are continued into the terminal phase (last few days of life) in more than one third of cancer patients (12).

As almost three quarters of Australian COPD patients die in hospital (15), we hypothesised that these patients may receive more antimicrobials in a bid to do everything to preserve life, compared with those patients who survive exacerbations. Accordingly, this study aimed to examine antimicrobial prescription to patients who died in a tertiary hospital with an exacerbation of COPD.

Methods

A retrospective medical record audit was performed of four hundred and seventy-five consecutive patients who died at The Royal Melbourne Hospital (Australia) over twelve years between 1st January 2004 and 31st December 2015, with COPD listed in one of the first five diagnoses at death. The cohort was limited to include only patients with a confirmed diagnosis of COPD (by spirometry or radiological investigations) and who died as a consequence of COPD, and not from co-morbidities such as cancer or heart failure.

Patients were identified from the hospital mortality database by searching for patients with a diagnosis of emphysema or COPD (ICD codes: J43-44) listed in diagnosis 1-5. Patients with a diagnosis of asthma were included (ICD code J45) in the initial search to ensure no deaths

were misattributed to asthma. On reviewing the medical files all asthma deaths were excluded.

Paper clinical records and electronic, administrative and clinical databases (including pathology and radiology databases) were examined to determine the use and duration of therapeutic treatments including antimicrobials during the final admission in which death occurred. Data collected included demographic information and pre-admission disease severity (lung function testing, use of domiciliary oxygen and inferred Modified Medical Research Council (mMRC) breathlessness score). Whilst nearly all patients had spirometry which confirmed obstruction performed at some point after their diagnosis of COPD, only lung function tests results performed within two years prior to death were included.

Information regarding the duration of admission, presence of cardinal symptoms on presentation (for patients without radiological evidence of pneumonia), inflammatory markers including white cell count (WCC) and C-reactive protein (CRP) on admission, microbiology, radiology results and antimicrobial use were also collected. Single dose antimicrobial/s given in the emergency department (ED) were excluded.

Included patients were divided into three groups. Group 1 consisted of patients with pneumonia, based on the radiologist's report of the chest radiograph. Group 2 consisted of patients with an infective acute exacerbation of COPD (AECOPD), defined as two or more cardinal symptoms of respiratory infection (increased sputum purulence, increased sputum volume and increased breathlessness), and/or with elevated inflammatory markers (WCC>11.0 and/or CRP>30), but who did not have radiological evidence of pneumonia. Group 3 consisted of patents with a non-infective AECOPD, who did not have elevated inflammatory markers or symptoms of acute infection. Antibiotic prescription for patients in each group was compared with Australian Therapeutic Guidelines' recommendations (5, 16). Ethics approval for this study was granted by the Melbourne Health Research office.

Statistical analysis

Patient demographics are reported descriptively, using counts and frequencies. Median values are reported for variables with significant distribution skew. Student's paired t test was used to compare means from continuous variables. Categorical variables were compared using the chi-squared test or Fisher's exact test used when indicated, with univariate logistic regression used to further explore positive associations. Statistical analyses were performed using IBM SPSS Statistics version 24, with a p-value of less than 0.05 indicating statistical significance.

Results

Patient characteristics

Of four hundred and seventy-five patients, 221 who died from COPD were included. Two hundred and forty died primarily from a cause other than COPD and fourteen had missing medical files. On admission, 72 patients (32.6%) had pneumonia (Group 1), 117 (52.9%) had an infective AECOPD (Group 2) and 32 (14.5%) had a non-infective AECOPD. Based on calculated admission CURB-65 scores (17), 70 patients in Group 1 had severe pneumonia and two patients had moderate (non-severe) pneumonia.

The study population was elderly with mean age of 80 years and patients had pre-existing severe breathlessness and severe lung function impairment (Table 2). The patients with pneumonia (Group 1) had significantly fewer admissions to hospital in the previous year compared to patients in Group 3 who were admitted with a non-infective AECOPD (p=0.002).

Approximately two thirds of patients (n=134, 60.6%) were admitted under a general medical unit, with one quarter (n=61, 27.6%) admitted under respiratory medicine and the remainder under other medical units, including 9 (4.1%) patients admitted directly under palliative care.

There was a non-significant trend to more patients in Group 1 (8.3%) being intubated compared to Group 2 (1.7%) and Group 3 (1.7%) patients. Over half of all patients (54.8%) received acute non-invasive ventilation (NIV) during admission, with similar rates of NIV use across the three groups.

On admission, 61 (52.1%) Group 2 patients had two or more cardinal symptoms consistent with an infection exacerbation, compared to none of the patients in Group 3 ($p<0.0001$). Group 2 patients reported increased sputum purulence (n=48, 41.0%) or increased sputum volume (n=59, 50.4%) commonly, however none of the Group 3 patients reported either symptom ($p<0.001$). However, in both groups patients reported increased dyspnea on admission, although rates were higher in Group 2 than Group 3 (80.3% v 53.1%, p=0.0029)

Sputum culture results

Pathogenic bacteria were cultured in the sputum of 75 patients (33.9%), with this occurring more commonly in Group 1 patients, and significantly more in Group 2 (p=0.0072) as compared with Group 3 patients (Table 3). Commonly cultured bacteria included *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Haemophilus influenzae* and *Stenotrophomonas maltophilia.* While resistance to first line antimicrobial therapy was present in one third of organisms (25 patients), antimicrobial therapy was changed because of resistance in only nine patients (4.1%).

Antimicrobial therapy

Antimicrobials were prescribed to 200 (90.5%) patients (Table 4), with the prescription frequency being similar for Group 1 (94.4%) and Group 2 (92.3%), but significantly lower for Group 3 patients with non-infective AECOPD (75.0%, p=0.011). The majority of patients (176, 79.6%) across all groups received intravenous antimicrobial therapy. However, this occurred more frequently in Group 1 patients (90.3%) as compared to Group 2 (77.8%, p=0.031) or Group 3 (62.5%, p=0.002).

Prescribed antimicrobial therapy was concordant with guidelines in approximately one third of patients (n=70, 31.7%), however, significantly fewer patients in Group 2 (4.2%, p<0.0001) and Group 3 (25.0%, p=0.0002) received guideline concordant therapy compared with Group 1 (79.2%).

Of the 151 (68.3%) patients who received discordant antimicrobial therapy, the reasons included: intravenous route when oral indicated (n=111, 73.5%), oral route when intravenous indicated (n=2, 1.3%), dual therapy when monotherapy recommended (n=108, 77.1%), no symptoms of acute infection (n=24, 17.1%), non-guideline oral antimicrobial (13, 8.6%), non guideline intravenous antimicrobial (10, 6.6%) and no antimicrobial prescribed when antimicrobials were indicated (n=15, 9.9%). Ceftriaxone was the most frequently prescribed antimicrobial, in 60.2% of the cohort, and nearly one half (n=99, 44.8%) of patients received azithromycin (Table 4). Thirty patients (13.6%) received agents with activity against *P.aeruginosa*. Of these, only six patients had cultured *P.aeruginosa* in the 12 months prior to their final admission.

Of patients in Groups 2 and 3, only 12 patients (8.1%) were referred to specialist palliative care services prior to their terminal hospital admission. These patients were more likely to receive guideline-concordant therapy (p=0.016, OR 5.2, 95%CI=1.4-20.0) as compared with the rest of the cohort. Patients who required NIV or intubation were more likely to receive discordant antimicrobial treatment (p=0.020, OR 3.8, 95%CI=1.2-11.5).

No significant associations were found between discordant antimicrobial therapy and any other patient, disease or admission characteristics (age, preadmission functional status; lung function impairment; admission WCC, CRP, ABG pH or PaCO2, admitting team, inpatient involvement of palliative care unit, inpatient consultation by the respiratory unit, sputum culture organism, or significant antimicrobial resistance in sputum).

Duration and withdrawal of antimicrobials

The median duration of antimicrobial use was four days (IQR 2-8 days) and 53 patients (24.0%) received antimicrobials for longer than seven days. Antimicrobials were withdrawn prior to death in 140 patients, leaving 60 (27.1%) patients who died whilst receiving antimicrobials. Thirty-four (15.4%) patients continued to receive antimicrobials at the time of death despite having a goal of care to provide comfort only.

Healthcare costs

The cost of individual antimicrobials ranged widely, from $0.24 per day for oral doxycycline to $39.90 per day for intravenous azithromycin. The cost of prescribed antimicrobials in patients who received guideline discordant therapy totaled $11,780. Azithromycin, benzylpenicillin and moxifloxacin accounted for 59.3%, 11.1% and 9.6% of total cost, respectively.

Discussion

In this novel study of antimicrobial use in patients who die from COPD exacerbations, most patents received discordant antimicrobial therapy, with the highest rates seen in patients who did not have radiological evidence of pneumonia or symptoms suggesting acute infection. In the majority of cases, antimicrobials were ceased prior to death.

Patients presenting with COPD exacerbations present a number of clinical challenges. Breathlessness frequently occurs in stable disease, during COPD exacerbations and from other causes, and therefore is not helpful alone in determining significant changes in disease state (18). As infection is the most treatable cause for breathlessness and antimicrobials may be lifesaving, perhaps it is not surprising that many patients continue to receive antimicrobials in the absence of clinical, pathological or radiological evidence of infection. Additionally, the course of COPD exacerbations is difficult to predict: while respiratory failure is the

commonest cause of mortality in COPD (19) and up to 10% of patients with hypercapnic respiratory failure will die during their admission (20), many patients seemingly in extremis will have a rapid clinical response to treatments such as non-invasive ventilation. Unfortunately, clinicians have been shown to be poor discriminators of the outcomes of COPD exacerbations (21).

Challenges in determining the aetiology and clinical course of a COPD exacerbation may go some way to explain the low rates of compliance with antimicrobial guidelines documented in previous studies (9-11). *Fanning et al* showed that in a cohort of Australian inpatients who survived an exacerbation of COPD, the rate of discordant antimicrobial prescription was 87.5%. Similarly, in our study of patients who die from COPD and do not have pneumonia, discordant prescription occurred in 91.3% of cases. Variation in the baseline functional status and the severity of exacerbations may explain the minor difference in results; we note that our cohort on average was older, had higher rates of home 02 prescription, lower FEV1 results and required NIV treatment more frequently.

However, tools are available to assist clinicians in discriminating patients who are likely to survive admission from those likely to deteriorate. The Dyspoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) score is a simple to perform, validated predictor of in-hospital mortality in COPD exacerbations, superior to other prognostic tools such as CURB-65, and equivalent to the APACHE II score (22). The median time to death in patients with the highest DECAF scores (5 or 6 out of 6) is two days. The use of validated mortality prediction tools such as DECAF may facilitate early implementation of palliative treatments and review of antimicrobials in patients with high scores on admission.

As less than a third of COPD exacerbations are caused by bacteria (4), clinicians must remain vigilant regarding appropriate antimicrobial prescription as there is potential to cause harm by

excessive antimicrobial use. Adverse events related to antimicrobial use occur in 20% of patients (23) and unnecessary antimicrobial prescription is contributing to increasing rates of antimicrobial resistance. Current data from Australian hospitals (24) shows that while penicillin-resistant *S.pneumoniae* remains rare, resistance in *Enterobacteriaceae* (including *K.pneumoniae*, *H.influenzae*) via acquired B-lactamase production is now present in at least half of human-isolated strains. In public hospitals, resistance to piperacillin-tazobactam is present in over 10% of *P.aeruginosa* isolates, with similar rates seen for other first line agents. The rates of resistance in *S.pneumoniae* and *Enterobacteriaceae* in our cohort (0%, 50% respectively) is consistent with contemporary data, while as many as 57% of *P.aeruginosa* isolates in our study demonstrated resistance to first line antimicrobials. This should be of particular worry to clinicians given that multidrug resistant *P.aeruginosa* quadruples inpatient mortality (25), and cross-transmission of resistant *P.aeruginosa* serotypes has been documented between patients in tertiary hospitals (26).

We found that ceftriaxone-based antimicrobial regimes were employed most frequently, being used in over two thirds of patients with pneumonia and over half of patients with infective exacerbations of COPD. In the prospective, multi-centre Australian Community Acquired Pneumonia Study (27), in which 25% of patients had COPD, penicillin-based regimes were more common than ceftriaxone-based (56% v 37% respectively) with ceftriaxone more commonly used in patients with severe pneumonia. In the single centre study by *Fanning* et al, 43% received penicillin- or ampicillin- based regimes and only 13% received ceftriaxone. However, we note that the mortality rate was significantly lower in both these studies (5.6% and 0%, respectively).

The higher rate of ceftriaxone use in our study may be in part due to the increased severity of clinical presentation, including much higher rates of NIV usage. Patients in our cohort requiring NIV were more likely to receive discordant antimicrobial therapy, and while a Cochrane review (28) has shown that antimicrobials may reduce mortality and length of

hospital stay in patients in ICU, this recommendation has not been upheld in local guidelines (5,6). While reduced consciousness may influence the route of antimicrobial treatment in some patients, only three patients in our study were intubated and thus unconscious on admission. In addition, antimicrobial allergies may have affected prescription, however this is unlikely to have significantly affected our results as the incidence of dual allergy to penicillin and tetracycline is extremely low (29).

It is likely that the choice of antimicrobials used on the ward was also influenced by the initial antimicrobial used in the Emergency Department (ED). *Kiyatkin et al.* showed that in patients treated for a urinary tract infection in ED, over half were treated with inappropriate antimicrobials, the majority of which were continued into the admission (30). We hypothesise that a similar effect may occur in treating COPD exacerbations: antimicrobials are frequently initiated by junior medical staff in ED who may not have a full understanding of current guidelines. Lack of awareness and familiarity with clinical practice guidelines has been repeatedly shown to be the principal barrier to guideline adherence (31). In addition to promoting guideline awareness, regular review of the rationale for antimicrobial choice should occur for all patients throughout their admissions, to ensure that the most appropriate antimicrobial therapy is prescribed.

A systematic review demonstrated that Respiratory physicians were more likely to adhere to guidelines when managing hospitalised patients with COPD exacerbations (31). While we found no difference in the rates of discordant antimicrobial therapy according to treating team, the low numbers of patients admitted under the Respiratory Unit may have influenced our results. Additionally, we found no difference in antimicrobial guideline adherence for patients for whom an opinion regarding the use of NIV was sought from the Respiratory team. Therefore, perhaps respiratory consultations are an underused opportunity, during which the appropriateness of the antimicrobial therapy regimen could also be reviewed,

Focusing on active treatments may distract clinicians from recognising that a patient is dying despite best efforts, and requires good symptom palliation and comfort care. While most antimicrobials were ceased appropriately, a quarter of our cohort continued to receive antimicrobials at the time of death. While clinicians may fail to recognise imminent death, other factors may have contributed: antimicrobials may not have been ceased due to a rapid deterioration in patient condition, or due to the wishes of the patient's family.

Limitations

This was a single-centre, retrospective, medical record audit, in which data collection was dependent on the quality of documentation in medical notes. Similarly, due to poor medical record documentation, it was not possible to collect accurate data regarding oral antimicrobials use prior to hospital admission. The latter may have influenced the choice of antimicrobials used in hospital and warrants further study.

Conclusion

Antimicrobial prescription in patients who die from COPD exacerbations deviates widely from current guidelines, with antimicrobials being both overprescribed and non-guideline antimicrobials being overused. Therefore, greater antimicrobial stewardship is required in hospitals, including in the ED. Additionally, a significant number of patients received antibiotics until the time of death, highlighting the need for improved end-of-life care with less burdensome interventions. Further education of medical staff, regular medication reviews and the use of disease severity scores or clinical pathways may address some of these issues.

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Table 1: Australian guidelines' recommendations for first line antibiotic treatment of COPD exacerbations and community acquired pneumonia

	Therapeutic Guidelines (5, 16)	**COPD-X (6)**
COPD exacerbation	Amoxycillin (M)or doxycycline (M)	Amoxycillin (M)or doxycycline (M)
Community acquired pneumonia		
Moderate (CURB-65 score 0-1)	Benzylpenicillin (iv) plus doxycycline (M)	N/A
Severe (CURB-65 score e2)	Ceftriaxone (iv) plus azithromycin (iv)	N/A
Penicillin hypersensitivity	Moxifloxacin (M)or (iv)	N/A
Suspected or proven *S.aureus* MSSA MRSA	Flucloxacillin (iv) Vancomycin (iv)	N/AN/A N/A
Suspected or proven *P.aeruginosa*	Ceftazidime (iv) or piperacillin-tazobactam (iv) or meropenem (iv)	

COPD- X Chronic Obstructive Pulmonary Disease-X guidelines, (M) oral, (iv) intravenous, CURB-65 Confusion, Urea, Respiratory rate, Blood pressure, Age pneumonia severity score (17), *S.aureus Staphylococcus aureus,* MSSA methicillin-sensitive *S.aureus*, MRSA methicillin-resistant *S.aureus. P.aeruginosa Pseudomonas aeruginosa*, N/A not applicable.

Table 2: Patients' characteristics

	Group 1 N=72	Group 2 N=117	Group 3 N=32
Age (years)*	78 (±10)	80 (±9)	82 (±9)
Male	50 (69.4%)	68 (58.1%)	18 (56.3%)
Ex-smoker	50 (69.4%)	85 (72.6%)	21 (65.6%)
Current smoker	20 (27.8%)	28 (23.9%)	7 (21.9%)
mMRC score (0-4)**	3 (0-3)	3 (3-4)	3 (3-4)
Home oxygen use	31 (43.1%)	63 (53.8%)	15 (46.9%)
FEV_1 (L) (n=125)	0.9 (40.0%)	0.8 (39.5%)	0.8 (45.0%)
FVC (L) (n=125)	2.1 (73.5%)	2.0 (71.5%)	1.9 (73.0%)
DLco (n=103) (ml/min/mmHg)	8.5 (36.5%)	8.5 (43.0%)	9.5 (40.0%)
>1 admission in past 12 months	15 (20.8%)	40 (34.2%)	17 (53.1%)
Raised WCC	40/71 (56.3%)	61/95 (64.2%)	0
Raised CRP	34/50 (68.0%)	51/69 (73.9%)	0

Data represent counts with frequencies in parentheses, means (*) with standard deviation in parentheses or medians (**) with interquartile range in parentheses. mMRC Modified Medical Research Council, FEV1 forced expiratory volume in 1 second, FVC forced vital capacity, DLco diffusing capacity for carbon monoxide, WCC white cell count, CRP C-reactive protein. FEV1 and FVC are shown with percent predicted in parentheses.

Table 3: Sputum culture results

Positive sputum culture N (%)	**Group 1** 22 (30.6%)	**Group 2** 48 (41.0%)	**Group 3** 5 (15.6%)	**Total** 75 (33.9%)
P. aeruginosa	8 (11.1%)	12 (10.3%)	1 (3.1%)	21 (9.5%)
M. catarrhalis	2 (2.8%)	10 (8.5%)	3 (9.4%)	15 (6.8%)
H. influenzae	2 (2.8%)	6 (5.1%)	0	8 (3.6%)
S. maltophilia	1 (1.4%)	6 (5.1%)	0	7 (3.2%)
K. pneumoniae	3 (4.2%)	3 (2.6%)	0	6 (2.7%)
Acinetobacter spp.	2 (2.8%)	3 (2.6%)	0	5 (2.3%)
S. pneumoniae	2 (2.8%)	2 (1.7%)	0	4 (1.8%)
Other	2 (2.8%)	6 (5.1%)	1 (3.1%)	9 (4.1%)
Resistance in e1 first-line antimicrobial/s	11 (15.3%)	14 (12.0%)	0	25 (11.3%)
Resistance leading to change in antimicrobial	5 (6.9%)	4 (3.4%)	0	9 (4.1%)

Data represent counts with frequencies in parentheses.

Table 4: Antimicrobial therapy

	Group 1 N=72	Group 2 N=117	Group 3 N=32	Total N=221
Antimicrobials prescribed	68 (94.4%)	108 (92.3%)	24 (75.0%)	200 (90.5%)
Number of antimicrobials*	3 (2-3)	2 (2-3)	2 (2-3)	2 (2-3)
Antimicrobial duration, days*	4 (3-7)	5 (2-8)	3 (2-5)	4 (2-8)
Oral antimicrobials only	3 (4.2%)	17 (14.5%)	4 (12.5%)	24 (10.8%)
Oral monotherapy with amoxycillin or doxycyline	1 (1.4%)	5 (4.3%)	2 (6.3%)	8 (3.6%)
Guideline concordant therapy	57 (79.2%)	5 (4.3%)	8 (25%)	70 (31.7%)
Antimicrobial withdrawal				
Withdrawn prior to death	45 (62.5%)	76 (64.9%)	19 (59.4%)	140 (63.3%)
Continued at time of death with palliative goals in place	15 (20.8%)	16 (13.7%)	3 (9.4%)	34 (15.4%)
Initial antimicrobial/s				
Ceftriaxone	52 (72.2%)	66 (56.4%)	15 (46.9%)	133 (60.2%)
Azithromycin	49 (68.1%)	39 (33.3%)	11 (34.4%)	99 (44.8%)
Benzylpenicillin	7 (9.7%)	8 (6.8%)	1 (3.1%)	16 (7.2%)
Doxycycline	4 (5.6%)	21 (17.9%)	4 (12.5%)	29 (13.1%)
Oral macrolide	9 (12.5%)	21 (17.9%)	3 (9.4%)	33 (14.9%)
Oral beta-lactam	4 (5.6%)	24 (20.5%)	7 (21.9%)	35 (15.8%)
Anti-pseudomonal	15 (20.8%)	14 (12.0%)	1 (3.1%)	30 (13.6%)
Other	8 (11.1%)	12 (10.3%)	4 (12.5%)	24 (10.9%)

Data represent counts with frequencies in parentheses or medians (*) with interquartile range in parentheses.