

ORIGINAL ARTICLE

Anaerobic antibiotic usage for pneumonia in the medical intensive care unit

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Background and objective: Pneumonia is a common admitting diagnosis in the intensive care unit (ICU). When aspiration is suspected, antibiotics to cover anaerobes are frequently used, but in the absence of clear risk factors, current guidelines have questioned their role. It is unknown how frequently these guidelines are followed.

Methods: We conducted a single-centre observational study on practice patterns of anaerobic antibiotic use in consecutive patients admitted to the ICU with aspiration pneumonia (Asp), community-acquired pneumonia (CAP) and healthcare-associated pneumonia (HCAP).

Results: A total of 192 patients were studied (Asp: 20, HCAP: 107, CAP: 65). Overall, 59 patients received anaerobic antibiotics (Asp: 90%, HCAP: 28%, CAP 17%) but a significant proportion of these patients did not meet criteria to receive them. Inappropriate anaerobic antibiotic use was 12/20 for Asp, 27/107 for HCAP and 9/65 for CAP. Mortality probability model III at zero hours (MPM0) score and a diagnosis of Asp were predictors of receiving inappropriate anaerobic antibiotics. Receiving inappropriate anaerobic antibiotics was associated with a longer ICU length of stay (LOS; 7 days (interquartile range (IQR): 7–21) vs 4 days (IQR:2–9), $P = 0.017$).

Conclusion: For patients in the ICU admitted with pneumonia, there is a high occurrence of inappropriately prescribed anaerobic antibiotics, the use of which was associated with a longer ICU LOS.

Clinical trial registration: NCT03046082 at ClinicalTrials.gov

Key words: anaerobic antibiotics, antibiotic stewardship, aspiration, pneumonia.

Abbreviations: Abx, antibiotics; Asp, aspiration pneumonia; CAP, community-acquired pneumonia; GI, gingival index; HCAP, healthcare-associated pneumonia; ICU, intensive care unit;

SUMMARY AT A GLANCE

For patients with pneumonia, current guidelines recommend narrow criteria as justification for prescribing anaerobic antibiotics. We found a significant proportion of patients with pneumonia who received anaerobic antibiotics without clear indications, and that there was an increased intensive care unit (ICU) length of stay associated with such use.

IDSA, Infectious Diseases Society of America; IQR, interquartile range; LOS, length of stay; MPM0, mortality probability model III at zero hours; VAP, ventilator-associated pneumonia.

INTRODUCTION

Aspiration pneumonia (Asp) develops after the inhalation of colonized oropharyngeal material.¹ Bacteriological studies of Asp in the early 1970s found that anaerobic organisms were predominantly isolated from the respiratory specimens.² On the basis of these studies, antibiotics with activity against anaerobic organisms became the standard of care for patients with Asp.¹ However, there were two potential limitations of these studies. First, the microbiological specimens were obtained late in the course of the illness after the development of necrotizing pneumonia or empyema, such that these isolates may have represented superinfection with anaerobic organisms. Second, the tracheal sampling was contaminated with oropharyngeal flora of less virulent anaerobic bacteria rather than true pulmonary pathogens.^{3–5} More recent studies using protected specimen brushes to avoid oropharyngeal flora contamination found no anaerobic organisms,^{6,7} suggesting that anaerobic antibiotic agents might be dispensable in the absence of severe periodontal disease, putrid sputum, necrotizing pneumonia or lung abscess formation. Moreover, the role of anaerobic bacteria in aspiration syndrome has been overemphasized in clinical practice.⁸ According to current Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines, anaerobic coverage for community-acquired pneumonia (CAP) is indicated only in those patients with gingivitis and a risk for loss of consciousness as seen with seizure disorders, alcohol abuse or

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Received 13 February 2017; invited to revise 14 April 2017; revised 20 April 2017; accepted 20 April 2017 (Associate Editor: James Chalmers).

oesophageal motility disorders⁹ and are not specifically recommended in patients with healthcare-associated pneumonia (HCAP) in the absence of these risk factors.¹⁰

The risks associated with inappropriate antibiotic use are well known and include adverse drug reactions, emergence of resistant pathogens and cost.¹¹ However, the frequency of anaerobic antibiotic use for pneumonia in the absence of evidence-based indications has not been well studied. This study was designed to identify the frequency of inappropriate anaerobic antibiotic use for critically ill patients with pneumonia who lack identifiable risk factors for anaerobic infection. Additionally, we sought to identify the factors that influence the decision to prescribe anaerobic antibiotics inappropriately and the potential impact of such prescribing practices.

METHODS

Study design, setting and population

A single-centre prospective cohort study was performed among adult patients (age ≥ 18) admitted to the medical intensive care unit (ICU) of an urban-based tertiary care teaching hospital, from 4 January 2016 to 4 May 2016 with a primary diagnosis of pneumonia. The medical ICU consists of five separate services, each of which have a primary/admitting team consisting of internal medicine residents, a pulmonary/critical care fellow and a board-certified pulmonary attending staff.

The clinical diagnosis of pneumonia was made by the primary team, as documented in the patient's chart. The attending staff rounded after the patient had been admitted with antibiotics prescribed, typically the next day, and had the opportunity to change the antibiotic regimen if they felt this was appropriate. Pneumonia type was categorized by the primary team as HCAP, CAP or Asp. Cases of ventilator-associated pneumonia (VAP) were categorized as HCAP. The antibiotics prescribed by the primary team were also recorded. During the study period, choice of antibiotics usually included both vancomycin and cefepime for HCAP, ceftriaxone and azithromycin for CAP and the addition of metronidazole or clindamycin when anaerobic coverage was desired. Antibiotics that broadly covered both aerobic and anaerobic microbes (i.e. piperacillin/tazobactam or ampicillin/sulbactam) were excluded from the study as there would be difficulty in ascertaining whether the rationale for these antibiotics included treating anaerobic organisms.

The research team independently assessed all patients to determine if they met the criteria for Asp coverage as detailed in the ATS guidelines.⁹ So as not to influence the clinical decision-making process, the primary team was not aware that their diagnoses and antibiotic choices were being monitored. Anaerobic antibiotic use was considered appropriate if any of the following criteria were met: (i) poor periodontal condition, defined as a gingival index (GI) score of ≥ 2 performed within 24 h of ICU admission (Fig. 1);¹² (ii) loss of consciousness from alcohol/drug overdose or after seizure or witnessed aspiration, as documented in the history and physical; (iii) high risk for chronic aspiration

Criteria for the gingival index system

0 = Normal gingiva

1 = Mild inflammation — slight change in colour, slight oedema. *No bleeding on probing*

2 = Moderate inflammation — redness, oedema and glazing. *Bleeding on probing*

3 = Severe inflammation — marked redness and edema. Ulceration; *tendency to spontaneously bleed*

Figure 1 Gingival index scoring system.

such as oesophageal motility disorders or chronic tracheostomy or (iv) radiological evidence of abscess or necrotizing pneumonia.^{6,7}

To evaluate microbiology of sputum samples, the first sputum samples were evaluated. For intubated patients, samples were obtained via tracheal aspirate or bronchoalveolar lavage. Expectored sputum was obtained from those patients who were not intubated.

Statistical analysis

All analyses were performed with STATA software, version 12.0 (Stata Corp, College Station, TX USA). Continuous variables were compared using the Student's *t*-test or the Kruskal-Wallis rank-sum test in cases of non-normally distributed variables and expressed, respectively, as means \pm SD or median and interquartile range (IQR). Categorical variables were expressed as percentages and analysed using a chi-square test.

To determine independent risk factors for inappropriate anaerobic antibiotic use, univariate logistic regression was used to test the following factors: age, BMI, Charlson co-morbidity index, risk of mortality based on mortality probability model III at zero hours (MPM0) score¹³ and clinically diagnosed pneumonia type. All variables with $P < 0.05$ were kept in the model. For continuous variables, we evaluated the data based on groups to see if risk was linear. We also wanted to assess whether the use of inappropriate antibiotics was associated with either a prolonged ICU length of stay (LOS) among survivors or in-hospital mortality. To do this, multivariate linear regression was used to evaluate ICU LOS and logistic regression was used to evaluate mortality risk. In all of these analyses, the following factors were assessed to see if they might confound the relationship: age, BMI, Charlson co-morbidity index, risk of mortality based on MPM0 score and clinically diagnosed pneumonia type. Due to the fact that it was not normally distributed, ICU LOS was transformed using the square root.

This study was approved with waiver of informed consent by the Institutional Review Board of Henry Ford Hospital, Detroit, Michigan (IRB No. 10229). This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

RESULTS

Cohort and encounter characteristics

During the study period, 242 patients admitted to the ICU with a primary diagnosis of pneumonia were screened (Fig. 2). Twenty-two patients were excluded because they were on anaerobic antibiotics for refractory septic shock or gastrointestinal infection including *Clostridium difficile* colitis. Twenty-eight were excluded

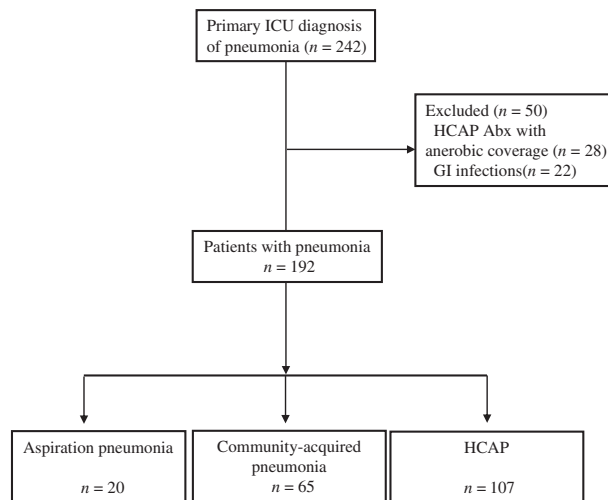


Figure 2 Cohort study flow diagram. Abx, antibiotics; GI, gastrointestinal; HCAP, healthcare-associated pneumonia; ICU, intensive care unit.

due to the use of piperacillin/tazobactam or ampicillin/sulbactam. The remaining 192 patients had a diagnosis of Asp (20 (10%)), CAP (65 (34%)) or HCAP (107 (56%)). Characteristics of the study population are shown in Table 1. There were no differences between groups in age, race, BMI or co-morbidities, but the predicted mortality score (MPM0) was significantly higher in the aspiration group.

Prescribing pattern of anaerobic antibiotics

As expected, most patients (90%) with a clinical diagnosis of Asp received anaerobic antibiotics (18/20). However, a significant proportion of patients with CAP and HCAP also received anaerobic antibiotics (17% and 28%, respectively) (Table 1). Regardless of pneumonia type, 180 patients did not meet the criteria for anaerobic antibiotic coverage as defined in the methodology, 48 (26.7%) of whom were nonetheless prescribed anaerobic antibiotics (Table 2). Over half of the patients with HCAP who received anaerobic antibiotics received them inappropriately. Moreover, of the patients with Asp who received anaerobic antibiotics, one-fourth of them did not meet the criteria for appropriate anaerobic antibiotic use. Overall, of the 48 patients who received inappropriate anaerobic antibiotics, only 6 (12.5%) had these antibiotics discontinued the next day by the attending staff, while anaerobic antibiotics were continued in the remaining 42 patients (87.5%) ($P = 0.002$).

Significant predictors for inappropriate anaerobic antibiotic use included an MPM0 score ≥ 75 th percentile (OR: 2.22 (95% CI: 1.08–4.63); $P = 0.031$) and patients with a clinical diagnosis of Asp (OR: 21.51 (95% CI: 4.52–102.24); $P < 0.001$) (Table 3). As expected, MPM0 score was a significant predictor of mortality (OR: 12.08 (95% CI: 3.06–47.72); $P < 0.001$), but after controlling for severity of illness, inappropriate antibiotic use was not (OR: 1.43 (95% CI: 0.59–3.51); $P = 0.43$) (Table 4).

Table 1 Baseline demographic and clinical characteristics of patients by type of pneumonia

	Community-acquired pneumonia (n = 65)	Healthcare-associated pneumonia (n = 107)	Aspiration pneumonia (n = 20)
Median age (IQR)	61 (45–68)	63 (51–71)	58 (52–69)
Male	34 (52%)	58 (54%)	12 (60%)
Race			
Black	33 (51%)	41 (38%)	8 (40%)
Caucasian	21 (32%)	51 (48%)	9 (45%)
Arabic	2 (3%)	5 (5%)	0 (0%)
Hispanic	0 (0%)	3 (3%)	0 (0%)
Other/unknown	9 (14%)	7 (6.5%)	3 (15%)
Median BMI (IQR)	27 (22–35)	27 (24–34)	26 (22–31)
Charlson co-morbidity index	2 (1–3)	3 (2–5)	3 (1–4)
MPM0 (IQR)	8.1% (3.8–23.4)	29.2% (7.6–55.0)	44.1% (23.9–82.1)

IQR, interquartile range; MPM0, mortality probability model III at zero hours.

Table 2 Characteristics by anaerobic antibiotic use

	Inappropriate anaerobic antibiotics (n = 48)	Appropriate anaerobic antibiotics (n = 11)	P-value
Asp	12 (25%)	6 (55%)	0.055
HCAP	27 (56.3%)	3 (27.3%)	0.083
CAP	9 (18.8%)	2 (18.2%)	0.965
Charlson co-morbidity index	3 (2–6)	2 (0–3)	0.069
MPM0 (IQR)	43.2 (9.9–70.3)	24.9 (10.3–77.6)	0.0026
ICU LOS, days (IQR)	7 (4–21)	4 (2–9)	0.017

Asp, aspiration pneumonia; CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MPM0, mortality probability model III at zero hours.

Table 3 Predictors of inappropriate anaerobic antibiotic use

	OR (95% CI)	P-value
Asp	21.5 (4.5–102.2)	<0.001
MPM0 (>75%)	2.2 (1.10–4.63)	0.031

Asp, aspiration pneumonia; MPM0, mortality probability model III at zero hours.

Table 4 Predictors of in-hospital mortality

	OR (95% CI)	P-value
Asp	0.38 (0.069–2.08)	0.26
HCAP	3.27 (0.69–15.60)	0.14
MPM0	12.08 (3.06–47.72)	<0.001
Inappropriate Abx	1.43 (0.59–3.51)	0.43
Charlson co-morbidity index	1.06 (0.91–1.25)	0.45

Abx, antibiotics; HCAP, healthcare-associated pneumonia; MPM0, mortality probability model III at zero hours.

Overall, the median ICU LOS was 5 days (IQR: 3–10). There was no significant difference in ICU LOS between the three types of pneumonia diagnoses (Asp: 4 days (IQR: 3–10), HCAP: 5 days (IQR: 3–9) and CAP 4 days (IQR: 2–10), $P = 0.842$). However, patient who inappropriately received anaerobic antibiotics had a significant increase in ICU LOS compared with all other patients who received antibiotics (median: 7 days (IQR: 7–21) vs 4 days (IQR: 2–9), respectively, $P = 0.017$). This outcome remained significant after controlling for potential confounders.

Microbial aetiology

The overall results of microbial aetiology in each pneumonia group are given in Table 5. Regardless of the pneumonia group, Gram-positive bacteria were predominant organisms, but a significant proportion were also Gram-negative bacteria. No anaerobic bacterium was isolated from any of the sputum cultures. In CAP patients group, more than 4% (3/25(4.27%)) of patients grew Methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa* in their sputum cultures and more than 20% percent of the same

group's influenza antigen detection test was positive (16 (22.85%)) during admission.

DISCUSSION

Both the IDSA and ATS guidelines recommend that anaerobic coverage for CAP be limited to those patients with gingivitis or who have a risk for aspiration such as loss of consciousness, seizures, alcohol abuse or oesophageal motility disorders.⁹ In addition, the role of antibiotics with anaerobic coverage in HCAP has been vague and less clear¹⁴ and in these patients guidelines do not specifically recommend their use unless risk factors or history suggest an aspiration event.¹⁰ Our study showed that for patients admitted to a medical ICU of an urban teaching hospital, most of them who received anaerobic antibiotics did not have one of these indications. Indeed, these guidelines were followed only 6% of the time. Surprisingly, only 30% of patients with a diagnosis of Asp met criteria for anaerobic antibiotic use, despite 90% of these patients receiving them. As expected, a very low percent of patients with CAP or HCAP met aspiration criteria, but up to one-third of these patients nonetheless received anaerobic antibiotics.

A number of factors might influence a provider's decision to prescribe anaerobic antibiotics in the absence of a clear indication. Our data suggest that the severity of illness was an independent predictor of the choice to prescribe these antibiotics, even when there was no clear indication to do so. There was a twofold increase in inappropriate anaerobic antibiotic use in those with a predicted mortality score above the 75th percentile. The relationship between antibiotic prescription and severity of illness has been reported by others. Children with respiratory infections were more likely to be prescribed an antibiotic if the clinician perceived the child to be moderately to severely unwell.¹⁵ Williams *et al.* found that the Acute Physiology and Chronic Health Evaluation (APACHE) score was a significant factor affecting the number of antibiotics prescribed in patients.¹⁶ One possible explanation for this phenomenon is that the clinician may add antibiotics if they perceive that the patient is more ill even if there is no justification for their use. We surmise that this effect may be more pronounced when covering for presumed anaerobic bacteria, because these microbes are rarely isolated in the hospital laboratory.

Table 5 Microbiological aetiology

Organism	Met aspiration Criteria <i>n</i> (%)	Did not meet aspiration criteria (<i>n</i> = 180) [†]	
		No anaerobic antibiotics <i>n</i> (%)	Inappropriate anaerobic antibiotics <i>n</i> (%)
Gram-positive cocci	3 (25)	24 (16.7)	10 (18.9)
Gram-negative bacilli	1 (8.3)	17 (11.8)	7 (13.2)
Other [‡]	1 (8.3)	31 (21.5)	7 (13.2)
All cultures no growth	7 (58.3)	72 (50)	29 (54.7)
Total (<i>n</i>)	12	144	53

[†]Summation greater than the total represented polymicrobial results.

[‡]Other: RSV, rhinovirus, aspergillus, coronavirus, influenza or parainfluenza. RSV, respiratory syncytial virus.

Not surprisingly, the diagnosis of Asp was strongly associated with the use of anaerobic antibiotics, despite the fact that most patients with this diagnosis did not have clear criteria for receiving them. Thus, a major reason for using anaerobic antibiotics inappropriately was the initial diagnosis of Asp. Chart review did not reveal clear reasoning for this diagnosis in patients without a clear indication. Indeed, oftentimes, a clear rationale was not documented in the notes as to how the diagnosis of CAP, HCAP or Asp was determined. Surveys were not done in our study, which may have revealed possible reasons for choosing the diagnosis of pneumonia type. One potential reason was that the choice of antibiotics (and the initial diagnosis of pneumonia type) was initially made by the resident and fellow, rather than the more experienced attending staff. However, this only partly explains the choice for anaerobic antibiotics, as only 12% of the inappropriate anaerobic antibiotics was changed by the attending staff the next day.

Some antibiotics in the penicillin family cover anaerobes and could also be used to cover pneumonia even if the clinician did not suspect anaerobes. For this reason, we excluded piperacillin/tazobactam or ampicillin/sulbactam. At our institution for the study period of this paper, the standard antibiotic regimen for HCAP or VAP was a combination of cefepime and vancomycin. Cefepime has weak anaerobic coverage. Therefore, if clindamycin or metronidazole was not added to the vancomycin and cefepime, we assumed that the clinician was not trying to cover for anaerobes. As we could not determine the clinician's intent to cover anaerobes when prescribing piperacillin/tazobactam or ampicillin/sulbactam, patients receiving these antibiotics were excluded.

In patients without clear risk factors for aspiration, anaerobic organisms are not likely to be of clinical importance.^{6,7} In addition, our data showed that the percent of no growth was similar between those that did and those that did not meet the criteria for Asp and therefore it may have been less likely that anaerobic organisms were the primary microbiological aetiology of pneumonia. Furthermore, there was no difference in the distribution of microbe types even in those patients who met criteria for Asp. The microbiological data indicate that all cultured organisms would be responsive to the standard antibiotics without needing to resort to anaerobic coverage.

The use of inappropriate or unjustified antibiotics is not without consequence. Indiscriminate antibiotic use is associated with resistance,¹⁷ adverse effects^{18,19} and development of secondary infections including *C. difficile*.²⁰ In addition, our study showed that patients with inappropriate anaerobic antibiotic use had significantly higher ICU LOS. This association remained even after controlling for predicted mortality score or co-morbidities, as measured by the Charlson co-morbidity index.

A number of important limitations exist in our study. Our data are not robust enough to determine whether the practice patterns or effect on ICU LOS was related to clindamycin, metronidazole or both. In addition, our study was limited to patients with pneumonia in the ICU. The results may not be applicable in other settings such as general inpatients or in outpatient settings.

Furthermore, this was a single-centre study, so the results may represent local practices that are not generalizable. The criteria used to measure inappropriate anaerobic antibiotic use (witnessed aspiration, evidence of periodontal disease or have a co-morbidity with a high risk for aspiration) was in part based on the GI, which rates gingival disease on a scale of 0–3. There is no consensus regarding the definition of poor dentition in medical literature, so a GI score ≥ 2 was arbitrarily selected as an indicator of poor periodontal condition. It is conceivable that this cut-off score underestimated those patients who received anaerobic antibiotics. Nonetheless, outside of the above risk factors for Asp, there is little evidence to support the use of anaerobic antibiotics.²¹

In conclusion, for patients with pneumonia, there was a high rate of inappropriate use of anaerobic antibiotics that was associated with an increased ICU LOS. Although sicker patients were more likely to have received inappropriate antibiotics, there was no benefit to patients without a clear risk factor for anaerobic infection. Further studies should evaluate the impact of withholding such antibiotics from these patients.

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