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MAJOR ARTICLE

Prophylactic Antimicrobial Therapy for Acute Aspiration Pneumonitis

Vlad Dragan,[1] Yanliang Wei,[1] Marion Elligsen,[2] Alex Kiss,[3] Sandra A. N. Walker,[2,4] and Jerome A. Leis[1,3,5,6]

[1]Department of Medicine, University of Toronto, [2]Department of Pharmacy, Sunnybrook Health Sciences Centre, [3]Sunnybrook Research Institute and Institute of Health Policy, Management and Evaluation, [4]Leslie Dan Faculty of Pharmacy, University of Toronto, [5]Division of Infectious Diseases and General Internal Medicine, Sunnybrook Health Sciences Centre, and [6]Centre for Quality Improvement and Patient Safety, University of Toronto, Ontario, Canada

Background. Prophylactic antimicrobial therapy is frequently prescribed for acute aspiration pneumonitis, with the intent of preventing the development of aspiration pneumonia. However, few clinical studies have examined the benefits and harms of this practice.

Methods. A retrospective cohort study design was used to compare outcomes of patients with aspiration pneumonitis who received prophylactic antimicrobial therapy with those managed with supportive care only during the initial 2 days following macroaspiration. The primary outcome was in-hospital mortality within 30 days. Secondary outcomes included transfer to critical care and antimicrobial therapy received between days 3 and 14 following macroaspiration including escalation of therapy and antibiotic-free days.

Results. Among 1483 patients reviewed, 200 met the case definition for acute aspiration pneumonitis, including 76 (38%) who received prophylactic antimicrobial therapy and 124 (62%) who received supportive management only. After adjusting for patient-level predictors, antimicrobial prophylaxis was not associated with any improvement in mortality (odds ratio, 0.9; 95% confidence interval [CI], 0.4–1.7; $P = .7$). Patients receiving prophylactic antimicrobial therapy were no less likely to require transfer to critical care (5% vs 6%; $P = .7$) and subsequently received more frequent escalation of antibiotic therapy (8% vs 1%; $P = .002$) and fewer antibiotic-free days (7.5 vs 10.9; $P < .0001$).

Conclusions. Prophylactic antimicrobial therapy for patients with acute aspiration pneumonitis does not offer clinical benefit and may generate antibiotic selective pressures that results in the need for escalation of antibiotic therapy among those who develop aspiration pneumonia.

Keywords. aspiration pneumonitis; antimicrobial stewardship; quality improvement.

Aspiration pneumonitis is an acute chemical lung injury caused by inhalation of sterile gastric contents and can progress quickly to respiratory failure [1–3]. Supportive care is the mainstay of treatment for aspiration pneumonitis, with rapid improvement expected within 48 hours of initial insult [4]. One quarter of patients with macroaspiration events that result in pneumonitis will develop secondary bacterial pneumonia in the ensuing 2 to 7 days [3, 4]. Although frequently prescribed, prophylactic antimicrobial therapy at the time of a witnessed or suspected macroaspiration event has not been demonstrated to prevent the development of aspiration pneumonia or to reduce mortality [3–7].

Despite lack of evidence demonstrating benefit, a survey of critical care physicians suggested that 78% routinely prescribe antibiotics for patients at the time of confirmed macroaspiration [5], and a multicenter study of critically ill patients suggested that 87% of patients with a firm diagnosis of aspiration pneumonitis and 97% of those with suspected aspiration receive early antibiotics [6]. This practice exposes patients to potentially unnecessary antibiotics, which may contribute to the development of antimicrobial resistance and adverse events such as *Clostridium difficile* infection [8, 9].

Since antimicrobial therapy for aspiration pneumonitis has not been demonstrated to prevent the subsequent development of pneumonia and may only select for more resistant respiratory pathogens, we hypothesized that this practice is associated with the need for subsequent broader-spectrum antimicrobial therapy following acute aspiration pneumonitis events without improved clinical outcomes. The objective of this study was to determine the potential benefits and harms of antibiotics prescribed for acute aspiration pneumonitis.

METHODS

Study Design and Participants

A retrospective cohort study design was used to compare outcomes of patients with aspiration pneumonitis who received

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Correspondence: J. A. Leis, Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Room B103, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada (jerome.leis@sunnybrook.ca).

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prophylactic antimicrobial therapy with those managed with supportive care only during the initial 2 days following macroaspiration. The source cohort consisted of all patients aged >18 years admitted to the acute care Bayview campus of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada, who met the case definition for aspiration pneumonitis between 1 January 2010 and 9 June 2016. Study approval was obtained from the Research Ethics Board of Sunnybrook Health Sciences Centre. The need for individual consent was waived.

Case Definition

Patients with acute aspiration pneumonitis were identified by searching the database of our hospital's electronic patient record (EPR) for all chest radiographs with the word "aspiration" in the clinical history. Chart review was performed by 2 independent abstractors (V. D. and Y. W.). Patients aged >18 years were included if they had a macroaspiration event confirmed by clinical documentation (eg, witnessed vomiting, choking on food) and a chest radiograph demonstrating a new radiologic infiltrate. Only patients who were non-mechanically ventilated and admitted to an acute care unit at the time of aspiration were included. Patients already receiving antimicrobial therapy on the day of an aspiration event or already intubated prior to acute aspiration were excluded. Interrater reliability of reviewers was determined based on a random sample of 40 charts (Kappa = 0.8; 95% confidence interval [CI], 0.6–1). Both reviewers were blinded to prophylactic antimicrobial exposure, which was extracted from a separate database and matched to the patient cohort following case identification and abstraction of clinical outcomes (Figure 1).

Prophylactic Antimicrobial Exposure

Patient antimicrobial exposures were extracted from the Stewardship Program Integrating Resource Information Technology database, which contains all hospital antimicrobial prescriptions at Sunnybrook Health Sciences Centre [10]. For study purposes, we defined prophylactic antimicrobial exposure as receipt of any antimicrobial agent that would provide coverage for respiratory bacterial pathogens newly initiated within the acute aspiration pneumonitis time window, including piperacillin/tazobactam, ertapenem, meropenem, ceftriaxone, moxifloxacin, levofloxacin, amoxicillin/clavulanate, and cefuroxime. This time window was defined as the initial 2 days following the documented macroaspiration. Patients who did not receive any of the aforementioned antibiotics within 2 days of the acute macroaspiration event were considered not to have received antimicrobial prophylaxis and classified as managed with supportive care only.

Patient Characteristics

Patient age, sex, admitting service (critical care, surgery, medicine), comorbidities, validated risk factors for aspiration, peak serum white blood cell count, diet modification, and change in oxygen requirements or modality within 2 days of an aspiration

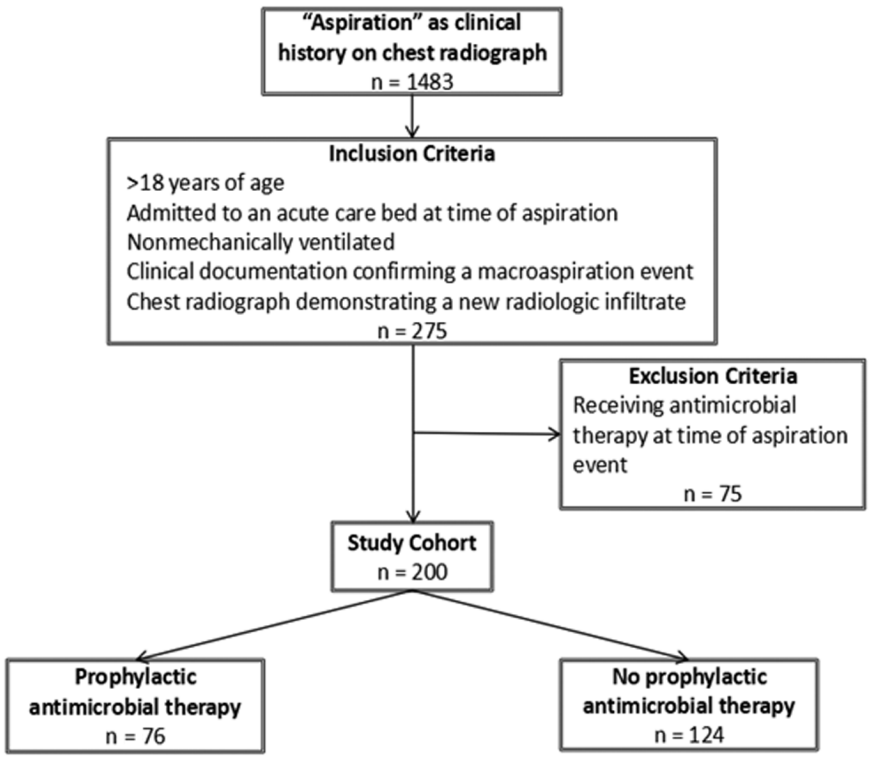

Figure 1. Study design flow diagram.

event were extracted from the EPR. Charlson comorbidity index (CCI) was calculated for each patient [11]. Validated risk factors for aspiration included dysphagia, acute/subacute stroke, enteral feeding, seizure disorder, central nervous system disease including Parkinson's disease, multiple sclerosis, space-occupying lesion, nasopharyngeal carcinoma, prior history of aspiration, peritoneal dialysis or ascites, immobility due to fracture, and tracheostomy [3, 4, 12–14].

Study Outcomes

The primary outcome was in-hospital mortality within 30 days of the acute macroaspiration event. This outcome was defined as any death within the index hospital stay and occurring within 30 days of admission. We elected to use this outcome rather than in-hospital mortality because any in-hospital death occurring after 30 days would involve very prolonged hospital stays and may involve deaths from causes unrelated to the aspiration episode and subsequent development of pneumonia.

Secondary outcomes included transfer to critical care, and antimicrobial therapy received including escalation of therapy and antibiotic-free days between days 3 and 14 following the acute aspiration event. This time period was specifically selected based on the expected development of pneumonia following an episode of acute aspiration pneumonitis while excluding the 2 initial days following the acute macroaspiration event. Antibiotic-free days were defined as the number of days between day 3 and 14 following the index acute macroaspiration event that a patient did not receive any antibiotic [15]. Escalation of antimicrobial therapy was defined as switching antimicrobial class to one with a higher spectrum level as defined by the following predetermined scale: level 1, cefuroxime oral formulation; level 2, levofloxacin oral formulation, moxifloxacin oral formulation; level 3, ceftriaxone, levofloxacin intravenous formulation, moxifloxacin intravenous formulation; level 4, ertapenem and piperacillin/tazobactam; and level 5, meropenem. After identifying antibiotic escalation therapy, cases were reviewed again to confirm the clinical indication for this change in antimicrobial therapy.

Statistical Analyses

Descriptive statistics were calculated for all variables of interest. Continuous measures were summarized using means and standard deviations or median and interquartile range if they did not pass the test for normality. Categorical measures were summarized using counts and percentages.

Predictors of 30-day mortality were assessed using bivariate analysis for the following variables: age, sex, admitting service, CCI, aspiration risk factors, diet, and change in oxygen requirement at the time of aspiration. Odds ratios (ORs) and their associated 95% CIs were provided. Prior to multivariable modeling, the predictors of interest were assessed for multicollinearity (tolerance statistic <0.4). All tolerance values were >0.4. Predictors significantly associated with mortality ($P < .05$) were included in the multivariable logistic regression model to assess the impact of antimicrobial prophylaxis on the primary outcome. ORs, 95% CIs, and P values were reported.

Sensitivity analyses were performed on our primary and secondary outcomes: in-hospital mortality and total antimicrobial therapy exposure. In-hospital deaths were restricted to those occurring between post-aspiration day 3 and 30 to minimize the effect of differences in the severity of the initial aspiration event. Analysis of antibiotic-free days was restricted to post-aspiration days 8 to 14 to exclude any effect of extended prophylactic antimicrobial therapy to 7 days, which would be standard treatment duration for pneumonia sometimes prescribed for patients with acute aspiration pneumonitis.

RESULTS

Inpatient Cohort

Among 1483 patients reviewed, 200 met the case definition for aspiration pneumonitis and were not receiving any antibiotics at the time of the aspiration event. Among these patients, 76 (38%) received prophylactic antimicrobial therapy and 124 (62%) received supportive management only. Prophylactic antimicrobial therapy included ceftriaxone (n = 35, 46%), piperacillin/tazobactam (n = 20, 26%), moxifloxacin or levofloxacin (n = 7, 9%), meropenem (n = 4, 5%), amoxicillin/clavulanate (n = 2, 3%), or combination (n = 8, 11%). Median duration of prophylactic antimicrobial exposure was 3.2 days (interquartile range, 1.9 – 6.0 days)

Patient baseline characteristics of both patient cohorts are summarized in Table 1. There were significantly more females among those receiving prophylactic antimicrobial therapy (51% vs 35%, $P = .02$), but the cohorts were otherwise similar with notably no statistically significant differences in CCI or proportion with risk factors for aspiration.

Study Outcomes

During the aspiration pneumonitis time window, 34 (17%; 95% CI, 12%–22%) of the total patient cohort required transfer to critical care and 9 (4%; 95% CI, 2%–8%) died. Patients who were transferred to critical care or died within this aspiration pneumonitis time window were more likely to have received antimicrobial prophylaxis (OR, 2.6; 95%, CI, 1.3–5.1; $P < .01$).

The unadjusted and adjusted study outcomes are summarized in Table 2. Unadjusted 30-day in-hospital mortality was similar between patients receiving prophylactic antimicrobial therapy (25%; 95% CI, 17%–36%) and patients receiving supportive care only (25%; 95% CI, 18%–33%; $P = 1$). Between days 3 and 14 following the acute aspiration pneumonitis episode, patients who received antimicrobial prophylaxis were no less likely to require transfer to critical care (5% vs 6%; $P = .7$). These patients subsequently had lower average antibiotic-free days compared with those managed with supportive care only (7.5 vs 10.9; $P < .0001$). Similarly, escalation of antibiotic therapy

Table 1. Hospitalized Patients With Acute Aspiration Pneumonitis Managed With or Without Prophylactic Antimicrobial Therapy

Characteristic	Prophylactic Antimicrobial Therapy (%) (n = 76)	Supportive Care Only (%) (n = 124)
Age, year		
Median (interquartile range)	83(72–90)	81(66–86)
Sex		
Male	37 (49)	81 (65)
Female	39 (51)	43 (35)
Admitting service		
Critical care	16 (21.1)	20 (16.1)
Surgery	17 (22.4)	36 (29.1)
Medicine	43 (56.5)	68 (54.8)
Comorbidity		
Prior myocardial infarction	17 (22)	27 (22)
Congestive heart failure	18 (24)	24 (19)
Peripheral vascular disease	13 (17)	19 (15)
Cerebral vascular disease	17 (22)	20 (16)
Dementia	20 (26)	23 (18)
Chronic pulmonary disease	15 (20)	17 (14)
Connective tissue disease	0 (0)	0 (0)
Peptic ulcer disease	8 (10)	14 (11)
Mild liver disease	5 (7)	7 (6)
Moderate to severe liver disease	1 (1)	6 (5)
Diabetes without end-organ damage	12 (16)	16 (13)
Diabetes with end-organ damage	8 (10)	6 (5)
Hemiplegia	10 (13)	6 (5)
Moderate to severe renal disease	7 (9)	14 (11)
Solid tumor without metastasis	10 (13)	19 (15)
Solid tumor with metastasis	6 (8)	19 (15)
Leukemia	2 (3)	0 (0)
Lymphoma	3 (4)	3 (2)
AIDS	0 (0)	0 (0)
Charlson comorbidity index, mean	3.2	3.2
Risk factors for aspiration[a]	64 (84)	97 (78)
Dysphagia	31 (41)	43 (35)
Acute or subacute stroke	13 (17)	20 (16)
Delirium or altered level of consciousness	42 (55)	60 (48)
Enteral feeding	28 (37)	38 (31)
Seizure disorder	8 (10)	10 (8)
Central nervous system diseases[b]	23 (30)	36 (29)
Nasopharyngeal carcinoma	4 (5)	7 (6)
Prior history of aspiration	25 (33)	39 (31)
Peritoneal dialysis or ascites	2 (2)	10 (8)
Immobility due to fracture	8 (10)	16 (13)
Tracheostomy	8 (10)	10 (8)
Modified diet[c]	53 (70)	84 (68)
Change in oxygen requirement or modality[d]	52 (68)	69 (56)

[a]Proportion of patients with at least 1risk factor for aspiration present.

[b]Including Parkinson's disease, multiple sclerosis, or any space-occupying disease.

[c]Modified diet includes nil per os, dysphagia diet, and presence of enteral feeding.

[d]Change in oxygen requirement or modality defined as change from room air to >4 L nasal prong or change of oxygen delivery device.

occurred more frequently among patients who received antimicrobial prophylaxis (8%, 95% CI, 3%–16% vs 1%, 95% CI, 0%–5%; $P = .002$). Table 3 describes the clinical indication and timing of antibiotic escalations among patients from both study cohorts. All escalations in antibiotics were related to worsening respiratory status and concern for aspiration pneumonia with the exception of 1 patient (number 3).

Multivariate Analysis

Results of bivariate analysis are reported in the Supplementary Table. The following variables were predictive of 30-day mortality: age (OR, 1.04; 95% CI, 1.01–1.07; $P < .05$), CCI (OR, 1.2; 95% CI, 1.05–1.3; $P < .05$), and being admitted to the medicine service as opposed to surgery (OR, 5.2; 95% CI, 1.9–14.1; $P < .05$). After adjusting for these predictors, antimicrobial prophylaxis was not associated with any improvement in mortality (OR, 0.9; 95% CI, 0.4–1.7; $P = .7$).

Sensitivity Analyses

After excluding patients who died within 2 days of macroaspiration, there remained no significant difference in 30-day in-hospital mortality between patients who received prophylactic antimicrobial therapy and those who received supportive care only (22% vs 21%; $P = .9$). Average antibiotic-free days between days 8 and 14 of the aspiration event remained significantly lower among patients who received prophylactic antimicrobial therapy compared with those who received supportive care only (5.9 vs 6.5; $P = .009$).

DISCUSSION

In this single-center retrospective cohort study of patients with acute aspiration pneumonitis, the use of prophylactic antimicrobial therapy was not associated with a reduction in mortality or transfer to critical care compared with patients managed with supportive care only. Conversely, prophylactic antimicrobial therapy was associated with greater frequency of antibiotic escalation and fewer antibiotic-free days up to 2 weeks following the acute aspiration pneumonitis episode.

Supportive care has long been recommended for patients with aspiration pneumonitis based on lack of evidence that antimicrobial therapy could prevent subsequent development of pneumonia, but limited published clinical data are available [4]. In 1976, Bynum and Pierce performed a smaller retrospective study of patients with acute aspiration events and found no difference in mortality between the 37 patients who received prophylactic antimicrobial therapy and the 13 patients managed with supportive care only [1]. One other study of 47 patients with documented aspiration suggested limited effect of prophylactic antimicrobial therapy on mortality [7].

Despite lack of demonstrated benefit, patients with aspiration pneumonitis following macroaspiration frequently receive prophylactic antimicrobial therapy, and this practice is not without potential patient harm [5, 6]. Overuse of antimicrobial therapy is the single most important driver of the emergence of antimicrobial-resistant organisms [8, 16]. We found

Table 2. Clinical Outcomes of Patients With Aspiration Pneumonitis Managed With or Without Prophylactic Antimicrobial Therapy

Outcome	Prophylactic Antimicrobial Therapy (%) n = 76	Supportive Care Only (%) n = 124	*P* Value
Primary outcome			
Unadjusted 30-day in-hospital mortality	19 (25)	31 (25)	1.0
Secondary outcomes (day 3 to 14)			
Transfer to critical care[a]	2 (5)	6 (6)	.7
Mean antibiotic-free days	7.5	10.9	**<.0001**[b]
Escalation of antimicrobial therapy	6 (8)	1 (1)	**.008**[b]
Multivariate analysis[c]			
Primary outcome			
Adjusted 30-day in-hospital mortality	0.85 (0.42–1.74)	…	.7

[a]Excluding patients already in critical care at time of aspiration.

[b]Significant ($P < .05$; in bold) when comparing prophylactic antimicrobial therapy group with supportive care only group.

[c]Multivariable model adjusted for Charlson comorbidity index, admitting service, and age. Supportive care only cohort is reference for multivariate odds ratio (ORs), expressed as ORs and 95% confidence intervals in parenthesis.

that antimicrobial therapy upfront for the management of acute aspiration pneumonitis gives rise to the need for more antibiotics later, frequently with broader spectrum of activity. These findings support our hypothesis that prescribing post-aspiration prophylaxis simply generates antibiotic selective pressures that result in the need for escalation of antimicrobial therapy in the event of development of aspiration pneumonia. Conversely, supportive management of patients with acute aspiration pneumonitis may preserve the use of antimicrobial agents for the development of signs of infective pulmonary process, allowing for shorter targeted antibiotic treatment.

Distinguishing aspiration pneumonitis from aspiration pneumonia is not always unambiguous in clinical practice, especially in the absence of a witnessed aspiration event or a patient with several days of preceding cough or dyspnea that may suggest underlying pneumonia. The benefit of antimicrobial therapy in reducing mortality for patients with pneumonia is undisputable, and clinical judgment is required. In our study, we specifically selected patients unlikely to have underlying pneumonia since they all had documented macroaspiration events and were not receiving prior antibiotics. These patients are generally easy to recognize in clinical practice when aspiration is witnessed, resulting in sudden respiratory deterioration without a prior history of respiratory symptoms [5, 6, 17].

Our study has several important strengths. To our knowledge, this is the largest cohort of patients with acute aspiration pneumonitis for whom the clinical utility of prophylactic antimicrobial therapy was assessed. More than 1400 patients were reviewed spanning records from over 6-years to identify this 200-patient cohort. The case definition used allows for easy and consistent identification in clinical practice, as demonstrated by the high interrate reliability between independent clinician abstractors. Furthermore, the abstractors were blinded to the exposure of prophylactic antimicrobial therapy during data collection to exclude potential bias.

Table 3. Description of Antibiotic Escalations Following Initial Management of Acute Aspiration Pneumonitis Episode

Patient Number	Initial Antibiotic Agent	Antibiotic Escalation	Day of Escalation[a]	Indication for Escalation
Prophylactic antimicrobial therapy (n = 6, 8% of cohort)[b]				
1	Ceftriaxone	Piperacillin-tazobactam	3	Persistent oxygen requirements; worsening radiographic consolidation
2	Ceftriaxone	Piperacillin-tazobactam	13	Increased respiratory secretions; worsening radiographic consolidation
3	Moxifloxacin oral	Moxifloxacin intravenous	10	Concern regarding absorption with administration of enteral feeds
4	Amoxicillin/ clavulanate	Piperacillin-tazobactam	3	Increasing oxygen requirements; worsening radiographic consolidation
5	Levofloxacin oral	Levofloxacin intravenous	4	Persistent oxygen requirements; increasing leukocytosis; worsening delirium; unable to take oral medications
6	Ceftriaxone	Meropenem	9	Increasing oxygen requirements; hypotension and fever
Supportive care only (n = 1, 1% of cohort)				
1	Ceftriaxone[c]	Piperacillin-tazobactam[d]	4	Oxygen desaturation; suspected recurrent aspiration

[a]From day of acute macroaspiration event.

[b]All antibiotic escalations prescribed for 3–10 days.

[c]Initiated for treatment of pneumonia following 2 days of supportive care only.

[d]Single dose given and completed 7-day course of ceftriaxone.

Several important limitations should also be noted. First, the observational retrospective nature of our study is subject to confounding variables that may have influenced patient outcomes. Confounding by indication was likely present in that patients with more severe aspiration pneumonitis episodes tended to receive prophylactic antimicrobial therapy. However, no difference in outcomes was noted following multivariate analysis adjusting for measurable confounders, nor following a sensitivity analysis excluding patients with the poorest clinical outcome during the acute aspiration pneumonitis episode. Second, despite the large number of patients reviewed, our study cohort is relatively small and not powered to detect a less than 10% difference in mortality. Third, our study was not designed to evaluate the impact of prophylactic antimicrobial therapy on the development of pneumonia. We instead focused on mortality as a more objective clinical outcome due to the lack of a gold standard to assess pneumonia. Based on our observation that prophylactic antimicrobial therapy was associated with a greater need for subsequent antibiotics, it may be inferred that this therapy was ineffective in preventing pneumonia as suggested in other studies [1, 7]. Finally, our study only included non-mechanically ventilated patients with documented macroaspiration events with acute aspiration pneumonitis and would not apply to patients with silent aspiration or in whom the diagnosis of aspiration pneumonitis is ambiguous.

Prophylactic antimicrobial therapy for patients with acute aspiration pneumonitis does not offer clinical benefit and may generate antibiotic selective pressures that result in the need for escalation of antibiotic therapy among those who develop aspiration pneumonia. Supportive care should remain the mainstay of management of patients with acute aspiration pneumonitis following a macroaspiration event.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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