CHEST

Aspiration Risk Factors, Microbiology, and Empiric Antibiotics for Patients Hospitalized With Community-Acquired Pneumonia

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BACKGROUND: Aspiration community-acquired pneumonia (ACAP) and community-acquired pneumonia (CAP) in patients with aspiration risk factors (AspRFs) are infections associated with anaerobes, but limited evidence suggests their pathogenic role.

RESEARCH QUESTION: What are the aspiration risk factors, microbiology patterns, and empiric anti-anaerobic use in patients hospitalized with CAP?

STUDY DESIGN AND METHODS: This is a secondary analysis of GLIMP, an international, multicenter, point-prevalence study of adults hospitalized with CAP. Patients were stratified into three groups: (1) ACAP, (2) CAP/AspRF+ (CAP with AspRF), and (3) CAP/AspRF- (CAP without AspRF). Data on demographics, comorbidities, microbiological results, and anti-anaerobic antibiotics were analyzed in all groups. Patients were further stratified in severe and nonsevere CAP groups.

RESULTS: We enrolled 2,606 patients with CAP, of which 193 (7.4%) had ACAP. Risk factors independently associated with ACAP were male, bedridden, underweight, a nursing home resident, and having a history of stroke, dementia, mental illness, and enteral tube feeding. Among non-ACAP patients, 1,709 (70.8%) had CAP/AspRF+ and 704 (29.2%) had CAP/AspRF-. Microbiology patterns including anaerobes were similar between CAP/AspRF-, CAP/AspRF+ and ACAP (0.0% vs 1.03% vs 1.64%). Patients with severe ACAP had higher rates of total gram-negative bacteria (64.3% vs 44.3% vs 33.3%, $P = .021$) and lower rates of total gram-positive bacteria (7.1% vs 38.1% vs 50.0%, $P < .001$) when compared with patients with severe CAP/AspRF+ and severe CAP/AspRF-, respectively. Most patients (>50% in all groups) independent of AspRFs or ACAP received specific or broad-spectrum anti-anaerobic coverage antibiotics.

INTERPRETATION: Hospitalized patients with ACAP or CAP/AspRF+ had similar anaerobic flora compared with patients without aspiration risk factors. Gram-negative bacteria were more prevalent in patients with severe ACAP. Despite having similar microbiological flora between groups, a large proportion of CAP patients received anti-anaerobic antibiotic coverage.

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KEY WORDS: anaerobic; aspiration; bacteria; pneumonia; risk factors

ABBREVIATIONS: ACAP = aspiration community-acquired pneumonia; AspRF = aspiration risk factors; ATS/IDSA = American Thoracic Society and Infectious Diseases Society of America; CAP = community-acquired pneumonia; GLIMP = global initiative for methicillin-resistant staphylococcus aureus pneumonia; GNB = Gram-negative bacteria

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Take-home Points

Study Question: Aspiration risk factors, microbiology patterns, and empiric anti-anaerobic use in patients hospitalized with CAP is not well defined.

Results: Hospitalized patients with ACAP or CAP/AspRF+ had similar anaerobic flora compared to patients without aspiration risk factors. However, a large proportion of CAP patients received anti-anaerobic antibiotic coverage. Severe ACAP patients have a higher prevalence of GNB in comparison with other groups.

Interpretation: According with new 2019 ATS/IDSA CAP guidelines, our results do not support the routine use of anti-anaerobic antibiotic coverage in ACAP or CAP/AspRF+ which is currently over-prescribed in clinical practice.

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Aspiration is common among all age groups, with a higher prevalence in the elderly.[1,2] An estimated 45% of the population aspirates while sleeping without any consequences.[3] Chronicity, frequency, volume of aspirated contents, and adequacy of host defenses may increase the risk of aspiration community-acquired pneumonia (ACAP), which accounts for 10% to 20% of all community-acquired pneumonia (CAP) cases.[4-9] Most of the studies reported in the literature regarding ACAP come from hospitalized patients.[10,11] Hospitalization due to ACAP is associated with high morbidity (Charlson comorbidity index) and high in-hospital and 30-day mortality that is four times higher of non-ACAP patients.[10,11] More than 20 individual risk factors may be linked to ACAP, including impaired swallowing, altered consciousness, impaired cough reflex, and compromised host defenses.[12,13] CAP patients with aspiration or multiple aspiration risk factors (AspRF) represent a therapeutic challenge to clinicians. These patients often receive empiric antibiotic coverage against anaerobes, which are suspected to be the most likely pathogens in ACAP.[14-16]

The 2019 American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) clinical practice guidelines recommend against the use of anti-anaerobic coverage for suspected ACAP, unless abscess or empyema is suspected.[17] Additionally, other authors suggested that patients with ACAP and CAP with AspRF might present a distinct microbiological spectrum compared with patients with CAP without AspRF.[9,18-23] Current studies of patients with ACAP or CAP with AspRF have important limitations, including small sample sizes with historical cohorts (eg, pleuropulmonary conditions), different microbiological techniques, and varying definitions of ACAP. Thus, the true prevalence of anaerobic pathogens in ACAP or CAP with AspRF and the consequential effect on use of empiric anti-anaerobic antibiotic coverage are unknown. Therefore, we sought to assess aspiration risk factors, as well as microbiology and empiric anti-anaerobic antibiotic therapy in patients with ACAP and CAP with AspRF, using a large international cohort of hospitalized patients with CAP.

Methods

This study is a secondary analysis of an international, multicenter, observational, point-prevalence study (Global Initiative for

Methicillin-resistant Staphylococcus aureus Pneumonia [GLIMP]).[24] The GLIMP study enrolled hospitalized patients with CAP from 222 hospitals worldwide during 4 randomly selected days at the investigator's discretion between March and June 2015. Clinicians were encouraged to diagnose and treat patients according to local protocols and standards of care without feedback from the study oversight committee.

The study was designed and conducted in accordance with the amended Declaration of Helsinki and was approved by the institutional review board of the coordinating center located at the University of Texas Health San Antonio (HSC20150184E). Because of the nature of the study, the review board waived the need for receipt of informed consent. All other associated centers were required to follow local, regional, or national ethical regulations. A detailed description of the GLIMP study organization and methodology has been previously published.[24]

Inclusion and Exclusion Criteria

We included all subjects with a clinical diagnosis of CAP in whom bacterial testing was performed. CAP was confirmed by visualization of pulmonary infiltrates by chest imaging (chest radiography, lung ultrasound, or CT) within the first 48 hours or less of admission and the presence of clinical signs, symptoms, or laboratory abnormalities: (a) a new or worsening cough with or without sputum production or purulent respiratory secretions; (b) fever (>37.8°C by rectal or oral temperature) or hypothermia (<36°C by rectal or oral temperature); (c) evidence of systemic inflammation with a leukocyte count >10,000/cm^3 or <4,000/cm^3 or bandemia >10%; increased C-reactive protein level; or increased procalcitonin level.

We excluded patients hospitalized with a diagnosis of hospital-acquired or ventilator-associated pneumonia and immunocompromised patients (eg, hematological malignancies, asplenia, aplastic anemia, neutropenia, HIV/AIDS, active solid tumor or active lung cancer and chemotherapy received in the last 3 months, congenital/genetic immunosuppression, and immunosuppressive therapy due to hematological/solid organ transplantation <6 months before hospital admission).[25]

All site investigators were given verbal and written instructions, as well as study definitions, before subject enrollment. Microbiological samples were collected from the respiratory tract (sputum, pleural fluid, endotracheal aspirate, or BAL) and blood within 24 hours of hospitalization. Diagnostic testing was determined by the attending physician caring for the patient and local microbiological testing protocols.

Specific Definitions

ACAP was defined by the clinician making a clinical diagnosis of presence or absence of aspiration for each patient as indicated in the case report form.[18,26]

Severe CAP was defined as pneumonia in patients requiring any of the following: ICU admission, invasive mechanical ventilation, vasopressors or inotropes during the first 24 hours of hospitalization.

Study Groups

Initially the groups were stratified in ACAP and non-ACAP groups. However, the non-ACAP patients were further stratified into two groups based on the presence (CAP/AspRF+) or absence (CAP/AspRF-) of risk factors for aspiration, resulting in three groups for comparison: (1) ACAP; (2) CAP/AspRF+; and (3) CAP/AspRF-.

Data Collection

Study variables were collected within 7 days of subject enrollment and entered into a web-based application called Research Electronic Data Capture (REDCap) hosted on the University of Texas Health San Antonio server. Subject clinical information was collected within 24 hours of hospitalization and included demographics (age, sex), chronic medical comorbidities (chronic lung, cardiovascular and neurologic diseases, other medical conditions), chronic medications (inhaled corticosteroids, proton-pump inhibitors, statins, glucocorticoids), chronic interventions (enteric tube feeding, hemodialysis, home oxygen therapy, tracheostomy), microbiological testing, antibiotic use, other nonmedical conditions (bedridden, nursing home resident, living in crowded conditions), and pneumonia severity.

Microorganisms considered pathogenic included: *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Acinetobacter baumannii*, other gram-negative bacteria ([GNB], including *Coxiella* species, *Proteus* species, *Serratia* species, *Klebsiella pneumoniae*, *Escherichia coli*, *Moraxella catarrhalis,* and *Enterobacter* species), *Streptococcus pneumoniae*, *Staphylococcus aureus*, other gram-positive cocci (including *Streptococcus pyogenes* and *Streptococcus* species), and anaerobes. Those samples with more than one isolated microorganism were considered as a polymicrobial result. *P aeruginosa*, *H influenzae*, *Acinetobacter* species, and other GNB were grouped in a new category named "total GNB," and *S pneumoniae*, *S aureus,* and other gram-positive bacteria (GPB) in another new category named "total GPB."

Empiric antibiotics initiated within 24 hours of presentation were stratified according to their anti-anaerobic (eg, including *Bacteroides fragilis* group) properties: broad-spectrum anti-anaerobic antibiotics (eg, ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam, meropenem, imipenem, and moxifloxacin), specific anti-anaerobic antibiotics (clindamycin and metronidazole), both (broad-spectrum and specific anti-anaerobic antibiotics), other nonspecific or without anti-anaerobic coverage (including cefotaxime, ceftriaxone, ceftaroline, azithromycin, clarithromycin, vancomycin, linezolid, aztreonam, ceftazidime, cefepime, ciprofloxacin, and levofloxacin).

Statistical Analysis

Continuous variables were expressed as means with SDs or as medians with interquartile ranges, depending on their parametric or nonparametric distribution. Categorical variables were reported as absolute frequencies and percentages. Differences between groups were analyzed using the χ^2 or Fisher exact test for categorical variables, and the analysis of variance, Student *t* test or Mann-Whitney *U* test for continuous variables, respectively. Logistic regression was used to assess independent aspiration risk factors associated with ACAP patients and further stratified the cohort into CAP/AspRF-, CAP/AspRF+, and ACAP. Subgroup analysis was performed by stratifying the patients into severe CAP or nonsevere CAP groups. Individual analyses were performed according to the different anti-anaerobic therapies associated with the different severity groups. ORs and 95% CIs were calculated. Statistical significance was established at $P < .05$. Data were analyzed using the Statistical Package for Social Sciences 24.0 (IBM SPSS Statistics) for Windows.

Results

Demographics and Risk Factors

A total of 2,606 hospitalized CAP patients were included in the study (males, n = 1,510 [58%]; median age, 69 [54-80] years). Among the hospitalized CAP patients, 7.4% (n = 193) had ACAP (Fig 1), which was defined by the clinician making the clinical diagnosis. Patients with ACAP were mainly elderly men with neurologic diseases (stroke, dementia, or mental illness), cirrhosis, proton-pump inhibitor use, enteric tube feeding, home oxygen therapy, tracheostomy, who were bedridden, were admitted from a nursing home, or lived in crowded conditions (Table 1). The presence of at least one AspRF was identified in more than 90% of CAP patients with male sex and age ≥ 65 years being the most prevalent AspRFs (Fig 2). Half of the patients with CAP had at least two of the evaluated AspRFs, with a remarkable overlap among the five AspRF categories, including neurological diseases (stroke, dementia, mental illness), chronic interventions (enteral tube feeding, tracheostomy, oxygen therapy at home, proton-pump inhibitor use), medical and nonmedical conditions (cirrhosis, underweight, nursing home resident, bedridden, living in crowded conditions) and demographic characteristics (elderly and male), respectively (Fig 3A-C). In the multivariate analysis (OR [95% CI]), we identified male sex (1.727 [1.232-2.420]), stroke (1.912 [1.235-2.958]), dementia (2.744 [1.842-4.088]), mental illness (2.011 [1.248-3.241]), being underweight (2.612 [1.457-4.685]), enteral tube feeding (3.767 [1.430-9.924]), bedridden (3.081 [2.128-4.460]), or admission from a nursing home (2.168 [1.427-3.292]) as risk factors independently associated with ACAP (Fig 4). These AspRF were used to perform the study groups, and finally, among those patients with non-ACAP, the distribution of patients was 70.8% (n = 1,709) as CAP/AspRF+ and 29.2% (n = 704) as CAP/AspRF-, respectively (Fig 1).

Microbiology

The pathogens identified from all CAP patients were recovered from sputum samples (58.0%) followed by blood (17.3%), tracheal aspirate (11.9%), BAL (10.7), and pleural fluid (1.5%) and were stratified according to the aspiration risk (e-Tables 1-3). In addition, the pathogens were stratified according to the severity of the disease and are displayed in Figure 5. The denominator of the different groups represents all the patients who had microbiology tests performed (Fig 5A-C) and a specific assessment among patients with culture-positive pneumonia (Fig 5D-F). The proportion of CAP patients with microbiology testing performed who had a pathogen identified as the causative agent were 32% (ACAP), 28% (CAP/AspRF+), and 25% (CAP/AspRF-; Fig 5A).

The prevalence of anaerobes isolated from respiratory samples in all patients with microbiology testing performed was similar between ACAP, CAP/AspRF+, and CAP/AspRF- groups (0.5% vs 0.3% vs 0.0%, $P = .27$ [Fig 5A]). ACAP compared with CAP/AspRF+ or CAP/

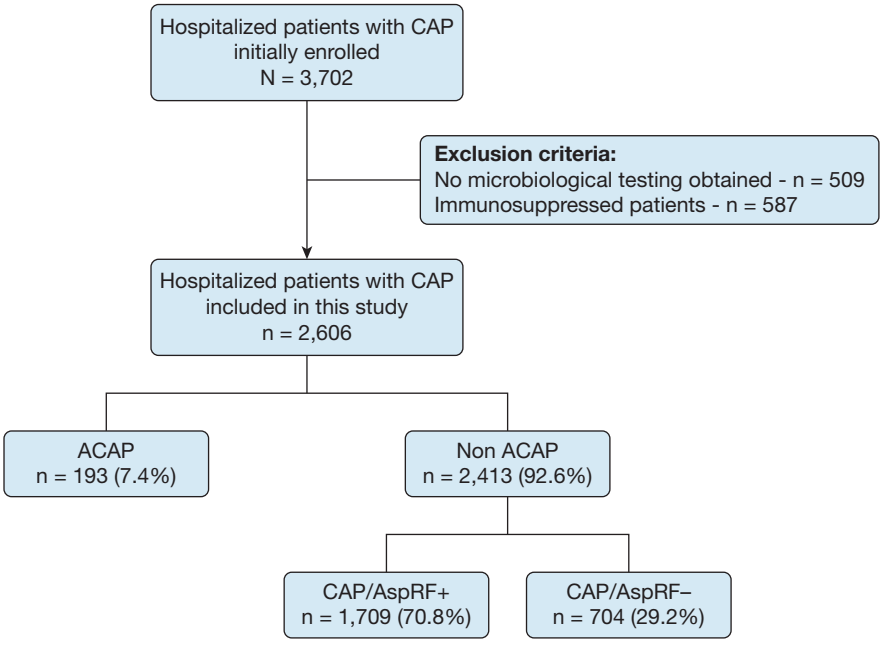

Figure 1 – *Flow chart of patients hospitalized with community-acquired pneumonia included in the study. ACAP = aspiration community-acquired pneumonia; AspRF = aspiration risk factors; CAP = community-acquired pneumonia.*

TABLE 1] Characteristics of Hospitalized CAP Patients by Aspiration Status

Characteristics	Aspiration N = 193	Nonaspiration N = 2,413	*P* Value
Demographics			
Age, y	76 (61-85)	68 (53-80)	<.001
Sex, male	130 (67.4)	1,380 (57.2)	.006
Chronic medical comorbidities			
Chronic lung diseases			
Asthma	9 (4.7)	199 (8.2)	.077
Bronchiectasis	11 (5.7)	132 (5.5)	.893
COPD	44 (22.8)	655 (27.1)	.190
OSA	11 (5.7)	102 (4.2)	.334
Interstitial lung diseases	6 (3.1)	59 (2.4)	.569
Cardiovascular diseases			
Coronary artery disease	42 (21.8)	407 (16.9)	.083
Heart failure	34 (17.6)	323 (13.4)	.100
Hypertension	83 (43.0)	1,136 (47.1)	.275
Neurologic diseases			
Stroke	39 (20.2)	171 (7.1)	<.001
Dementia	73 (37.8)	226 (9.4)	<.001
Mental illness	30 (15.5)	155 (6.4)	<.001
Other medical conditions			
Liver disease	10 (5.2)	83 (3.4)	.209
Cirrhosis	8 (4.1)	37 (1.5)	.007
Chronic renal failure	22 (11.4)	243 (10.1)	.557
Diabetes mellitus	34 (17.6)	543 (22.5)	.116
Alcoholism	17 (8.8)	210 (8.7)	.960
Current or former smoker	63 (32.6)	839 (34.8)	.550
Underweight	19 (9.8)	95 (3.9)	<.001
Obese	27 (14.0)	418 (17.3)	.236
Chronic medications			
Inhaled corticosteroids use	32 (16.6)	434 (18.0)	.624
Proton-pump inhibitor use	72 (37.3)	652 (27)	.002
Statins use	44 (22.8)	532 (22.0)	.809
Glucocorticoid use	13 (6.7)	136 (5.6)	.527
Chronic interventions			
Enteral tube feeding	13 (6.7)	20 (0.8)	<.001
Hemodialysis	1 (0.5)	33 (1.4)	.317
Home oxygen therapy	20 (10.4)	156 (6.5)	.038
Tracheostomy	6 (3.1)	29 (1.2)	.027
Other nonmedical conditions			
Bedridden	75 (38.9)	233 (9.7)	<.001
Nursing home resident	51 (26.4)	173 (7.2)	<.001
Living in crowded conditions	26 (13.5)	548 (22.7)	.003
Pneumonia severity			
Severe CAP	71 (36.8)	734 (30.4)	.065

Data expressed as frequencies and percentages [No. (%)] or medians and interquartile ranges (IQR or 25th-75th percentile).

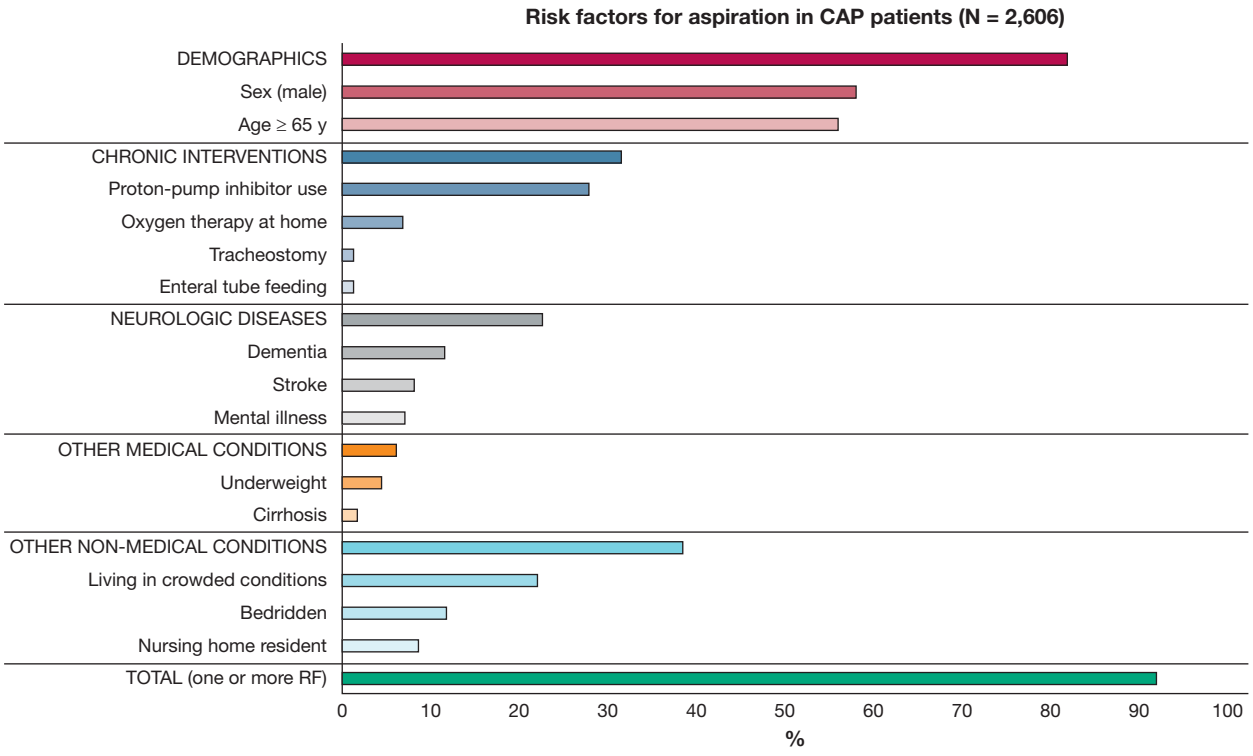

Figure 2 – *Prevalence of risk factors for aspiration in hospitalized CAP patients classified by categories (demographics, chronic interventions, neurologic diseases, medical conditions, nonmedical conditions). First row in every category shows the prevalence of at least one risk factor described below. RF = risk factors. See Figure 1 legend for expansion of other abbreviations.*

AspRF- had higher rates of other GNB (7.8% vs 5.4% vs 3.6%, $P = .04$ [Fig 5A]). Patients with nonsevere CAP had similar microbiology patterns among the three groups (Fig 5B). In contrast, patients with severe CAP categorized as ACAP vs CAP/AspRF+ or CAP/AspRF- had higher rates of *P aeruginosa* (11.3% vs 3.8% vs 3.9%; $P = .015$) and other GNB (12.7% vs 8.7% vs 2.9%; $P = .007$), but lower rates of *S pneumoniae* (1.4% vs 5.9% vs 9.7%; $P = .032$), respectively (Fig 5C).

Among culture-positive pneumonia patients, the prevalence of anaerobes isolated from respiratory samples was also similar between ACAP, CAP/AspRF+, and CAP/AspRF- groups (1.6% vs 1.0% vs 0.0%; $P = .33$ [Fig 5D]). Patients with ACAP had lower rates of *S pneumoniae* (16.4% vs 25.6% vs 33.3%; $P = .023$ [Fig 5D]). Again, patients with nonsevere CAP had similar microbiology patterns among the three groups (Fig 5E). Similarly to microbiology testing performed, patients with severe ACAP in the culture-positive pneumonia group analysis had higher rates of *P aeruginosa* (28.6% vs 10.3% vs 12.1%; $P = .024$) and other GNB (32.1% vs 23.7% vs 9.1%; $P = .014$), but lower rates of *S pneumoniae* (3.6% vs 16.0% vs 30.3%; $P = .004$), respectively (Fig 5F). Patients with severe ACAP had higher rates of total GNB (64.3% vs 44.3% vs 33.3%; $P = .021$) and lower rates of total GPB (7.1% vs 38.1% vs 50.0%; $P < .001$) when compared with patients with severe CAP/AspRF+ and severe CAP/AspRF-, respectively.

Severe and Nonsevere ACAP

Among patients with culture-positive CAP, 40% (n = 288) were stratified as severe CAP and 60% (n = 434) as nonsevere CAP (Fig 5D-F). Severe vs nonsevere ACAP had a larger proportion of patients with GNB (64.3% vs 30.3%; $P = .007$) and anaerobes (4% vs 0.0%; $P = .274$), but a lower proportion of patients with gram-positive cocci (7.1% vs 57.6%; $P < .001$) (Fig 6). These group differences in the severe ACAP were driven mainly by the increased prevalence of *P aeruginosa* (28.6% vs 6.1%; $P = .018$), and the low prevalence of *S aureus* (3.6% vs 21.2%; $P = .042$) and *S pneumoniae* (3.6% vs 27.3%; $P = .013$) in the severe ACAP group (Fig 5E, F).

Antibiotics Against Anaerobes for CAP

More than half of the patients with CAP in the three study groups received anti-anaerobic antibiotic coverage

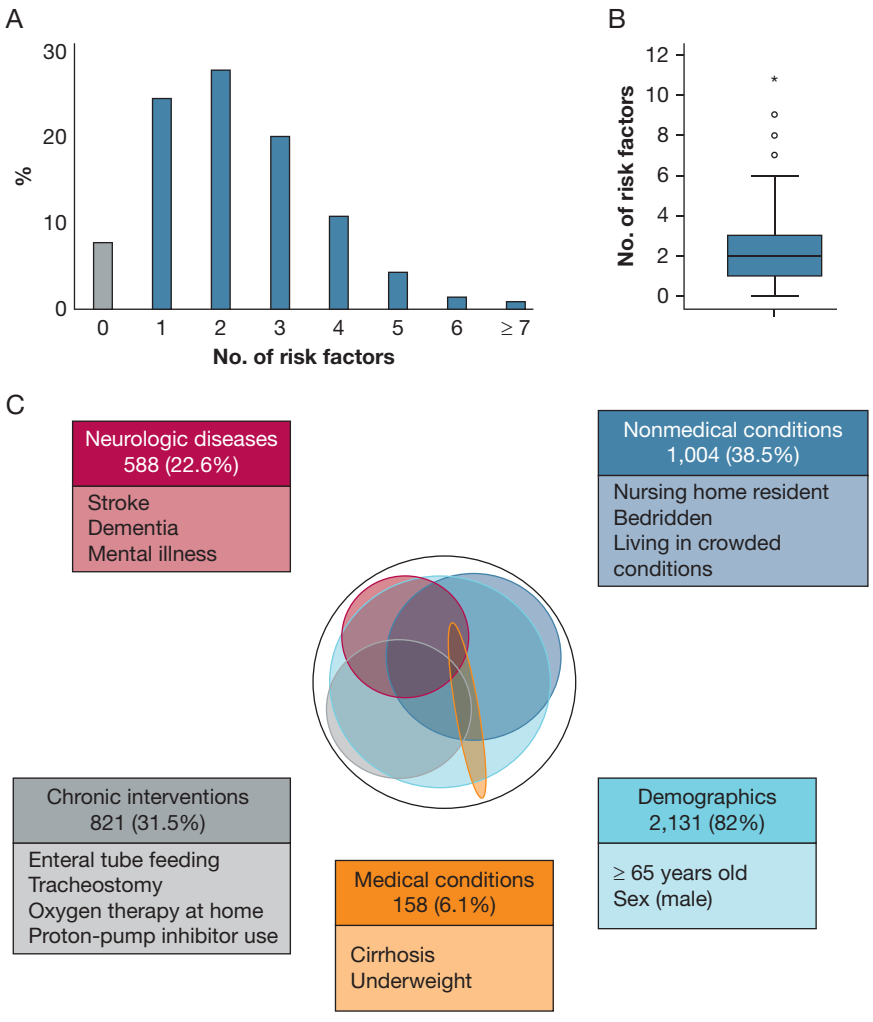

Figure 3 – *Characteristics of aspiration risk factors in hospitalized CAP. A, Distribution of the number of aspiration risk factors for patients with CAP; B, Box plot representing the distribution of number of aspiration risk factors among CAP patients; C, Graphic representation of the different aspiration risk factors that overlap among hospitalized CAP patients. See Figure 1 legend for expansion of other abbreviations.*

(Fig 7A). A larger proportion of ACAP patients (72.5%) received anti-anaerobic coverage (specific or broad-spectrum antibiotics) compared with CAP/AspRF+ (53.4%) and CAP/AspRF- (49.8%) patients ($P < .001$) (Fig 7A). This difference was greater in the severe CAP (80.3% vs 61.6% vs 62.1%; $P = .008$) vs nonsevere CAP group (68.0% vs 49.7% vs 44.8%; $P < .001$), respectively (Fig 7B, C). Specific anti-anaerobic coverage with metronidazole (9.3%, 2.7%, and 1.4%; $P < .001$) or clindamycin (6.2%, 1.5%, and 3%; $P = .002$) were also more frequently prescribed to patients with ACAP when compared to patients with CAP/AspRF+ and CAP/AspRF- (Fig 7A). Additionally, specific anti-anaerobic coverage was more frequently seen in patients with severe and nonsevere ACAP vs other groups (Fig 7B, C).

Discussion

The key findings of this study are that (1) aspiration risk factors are frequently found and overlap with each other in hospitalized patients with CAP; (2) microbiology is similar among patients with CAP regardless of whether risk factors for aspiration are present; (3) microbiology differs among patients with severe ACAP compared with nonsevere ACAP and non-ACAP, mainly driven by a higher prevalence of GNB; and (4) antibiotics with specific activity against anaerobes are overused in clinical practice and are not supported by a higher prevalence of anaerobes in ACAP or CAP/AspRF+.

Aspiration at the time of hospitalization was identified in 7% of our CAP patients, similar to prior observational studies that reported a prevalence of approximately 10%.[5-7] However, other observational studies tend to report higher rates of aspiration pneumonia (23%-30%), with one study's rates as high as 47%.[4,8,9] These differences could be explained by differences in clinical definitions and diagnostic criteria for ACAP based on confirmation or suspicion of aspiration. Our clinical definition was consistent with previously published

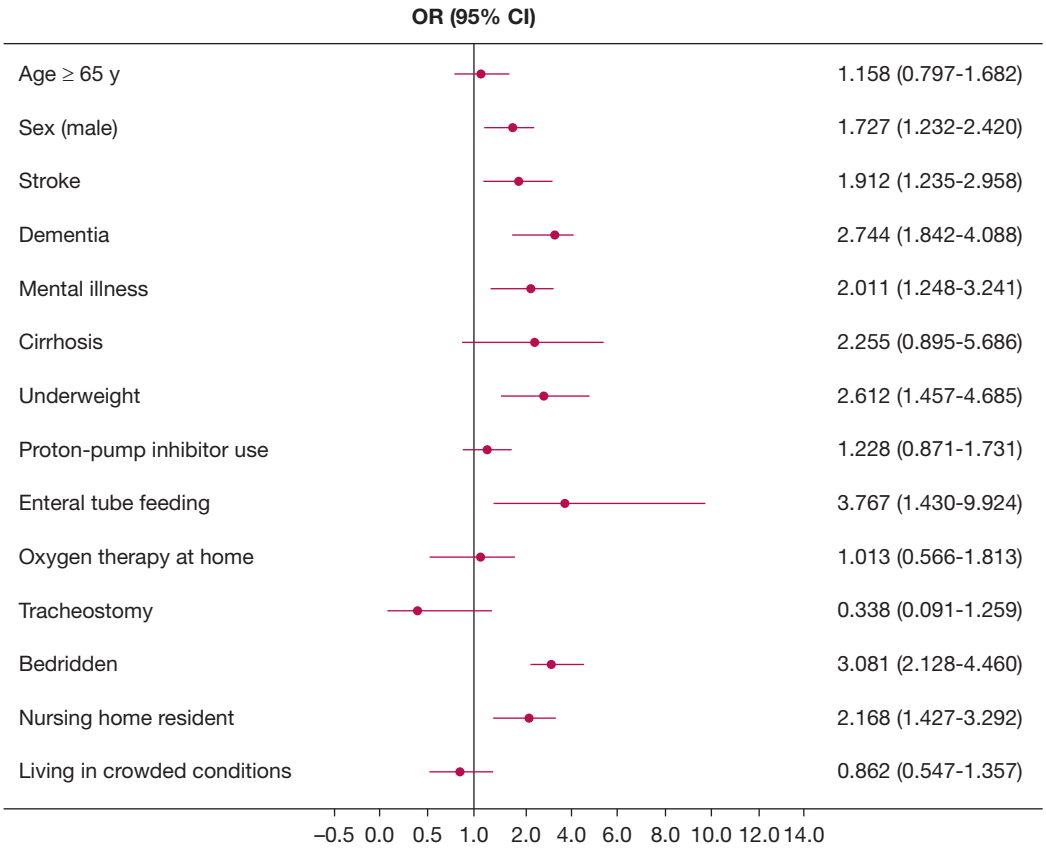

Figure 4 – *Multivariate analysis of independently associated risk factors related to aspiration in patients hospitalized with CAP. See Figure 1 legend for expansion of other abbreviations.*

literature, although we stratified non-ACAP patients according to AspRFs as observed in clinical practice.[4,9,10,13,15,19-23,26-28] The large proportion of patients with AspRFs (>90%) was higher than initially expected. Our results showed that being male, bedridden, underweight, a nursing home resident, and having a history of stroke, dementia, mental illness, and enteral tube feeding were independently associated with aspiration; the novelty of these findings are the significant overlap between these AspRFs.[12,13,28,29] The importance of stratifying ACAP and CAP/AspRF+ is supported by a detailed understanding of the microbiological variability associated with aspiration.

Based on studies from the 1960s through the 1980s, prior clinical practice guidelines suggested that anaerobic bacteria were the predominant pathogens in ACAP.[14-16,30,31] In contrast, our results showed that specific anaerobic flora were not the predominant pathogens among ACAP or CAP/AspRF+ patients. This difference might be explained by a shift in demographics, diseases (cavitary lung or pleuropulmonary diseases), laboratory techniques (eg, collection of samples, use of anaerobic culture techniques, and so forth), and patient-related factors (eg, prior administration of antibiotics and host factors). However, studies over the past two decades have suggested a trend toward lower rates of specific anaerobes in patients with CAP.[10,32-36] In addition, we found a higher prevalence of GNB among patients with ACAP compared with patients with CAP/AspRF+ and CAP/AspRF-,[32,34,37-39] mainly among those with severe ACAP vs nonsevere ACAP. Consequently, a higher prevalence of *P aeruginosa* and *Enterobacteriaceae* (other GNB) was seen in patients with severe ACAP. Because the oral cavity is considered the principal source of pathogens responsible for aspiration pneumonia, our results suggest a shift in the oral flora of patients with severe ACAP.[12,40,41] Microbiology data from patients with other comorbid conditions suggested that *P aeruginosa*, *K pneumoniae*, and *E coli* were frequently isolated from oral samples.[40,42] These results should alert clinicians of the need to appropriately cover against GNB in severe ACAP, especially if risk factors for *Pseudomonas* are present.

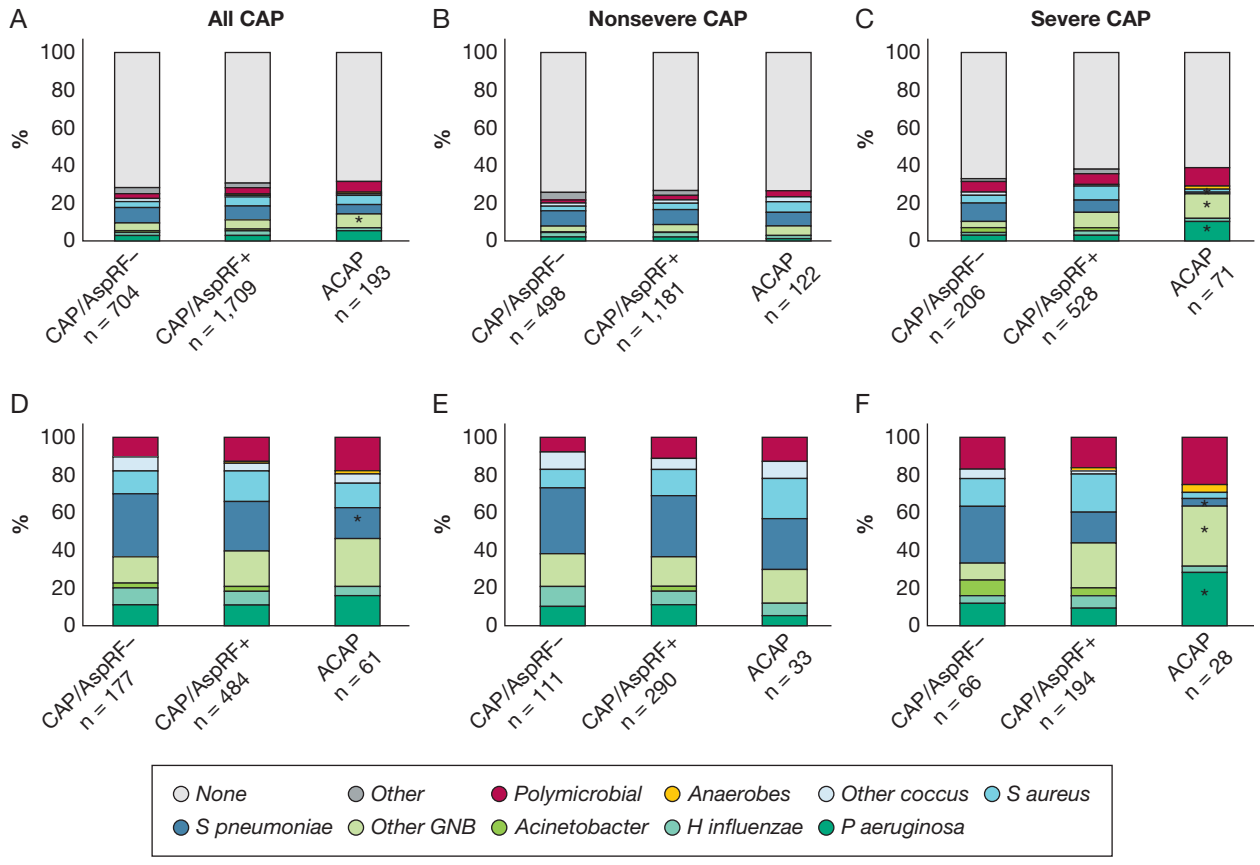

Figure 5 – - *Prevalence of microbiological results in the study groups in all patients with microbiological testing performed (A-C) and among patients with culture-positive pneumonia (D, E) in all included patients (A, D) and stratified depending on the severity of the disease (B, C, and E, F). See Figure 1 legend for expansion of other abbreviations. *P < .05, differences between CAP/AspRF-, CAP/AspRF+, and ACAP by χ^2 in the indicated microbiological groups.*

As discussed previously and according to the 2019 ATS/IDSA CAP guidelines, health care providers are encouraged to avoid using empiric anti-anaerobic antibiotic coverage in patients with ACAP.[17] Despite this recommendation, our results showed the inappropriate use of anti-anaerobic antibiotic coverage with clindamycin and metronidazole in 16% of patients with ACAP. Overused anti-anaerobic antibiotic coverage has been reported in a small cohort of ICU patients with pneumonia.[43] Surprisingly, specific anti-anaerobic antibiotics were administered in approximately 5% of CAP patients without any AspRFs. Metronidazole is the most commonly prescribed specific anti-anaerobic antibiotic that has limited efficacy in anaerobic pulmonary infections but does have potential adverse effects.[44-46] Metronidazole should be reserved for infections caused by the *Bacteroides fragilis* group, particularly when the infection originated below the diaphragm.[47] The overuse of broad-spectrum antibiotics with anti-anaerobic activity is a challenge for antimicrobial stewardship programs. The benefit of covering GNB does not imply the need to cover anaerobes, and de-escalation and specific therapy against the most likely pathogens should be implemented as soon as possible. Overuse and inappropriate administration of broad-spectrum antibiotics can be associated with *C difficile* infection, development of multi-drug-resistant organisms, adverse drugs reactions, and higher costs.[48] Moreover, some first- and third-generation cephalosporins are active against prevalent oropharyngeal anaerobes, such as the *Bacteroides oralis* group, *Peptococcus* or *Peptostreptococcus*. However, ceftriaxone and ceftaroline have limited sensitivity against *Prevotella* species. In addition, *Bacteroides* species, particularly the *B fragilis* group, which is relevant in patients with intraabdominal infections, is usually resistant to recommended CAP antibiotics.[49] Our results suggest that the changing epidemiology and microbiology of ACAP should promote more judicious use of antibiotics to appropriately cover the most likely pathogens. Therefore, avoiding overuse of antibiotics

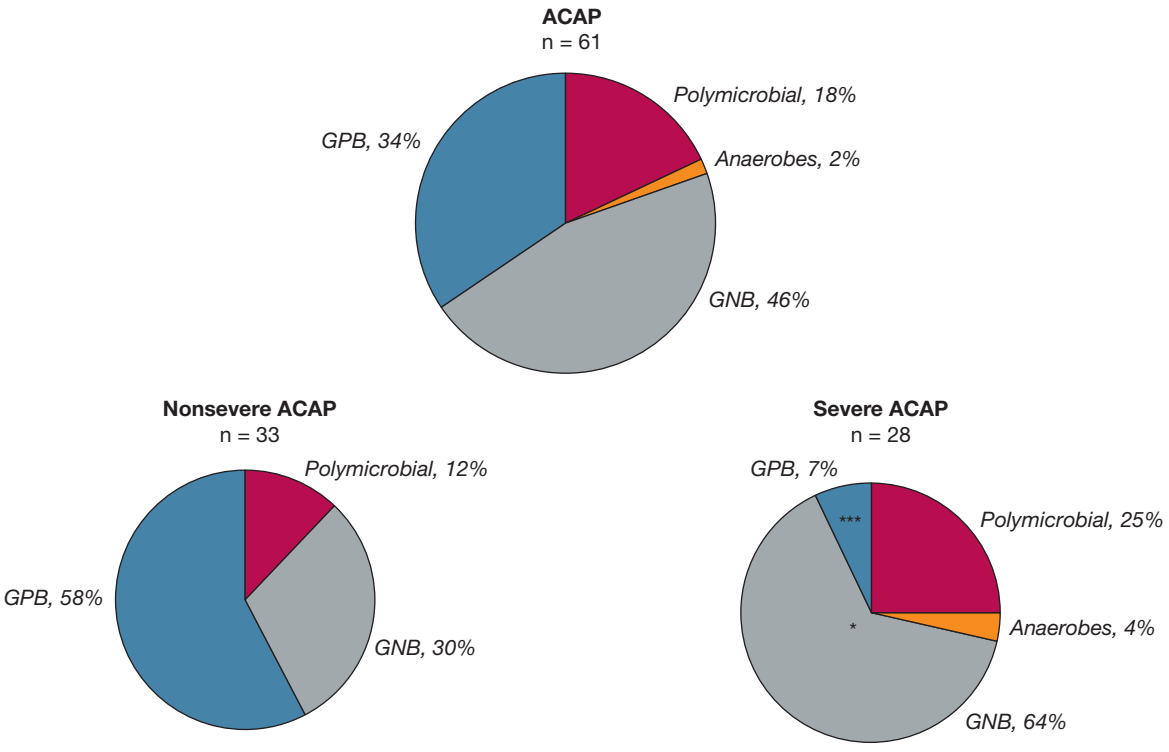

Figure 6 – - *Prevalence of microbiological results in ACAP group and in the severity stratified groups in all patients with microbiological testing performed. See Figure 1 legend for expansion of other abbreviations. *P < .05, ***P < .001, differences between severe and nonsevere ACAP by χ^2 in the indicated groups.*

against anaerobes in patients with CAP despite the presence of AspRFs or aspiration, which is consistent with the most recent ATS/IDSA clinical practice guidelines for CAP,[17] is important.

The current study has important limitations. ACAP clinical diagnosis is considered a heterogeneous process that is not standard in clinical practice and is not based on a reproducible definition. Because of geographical

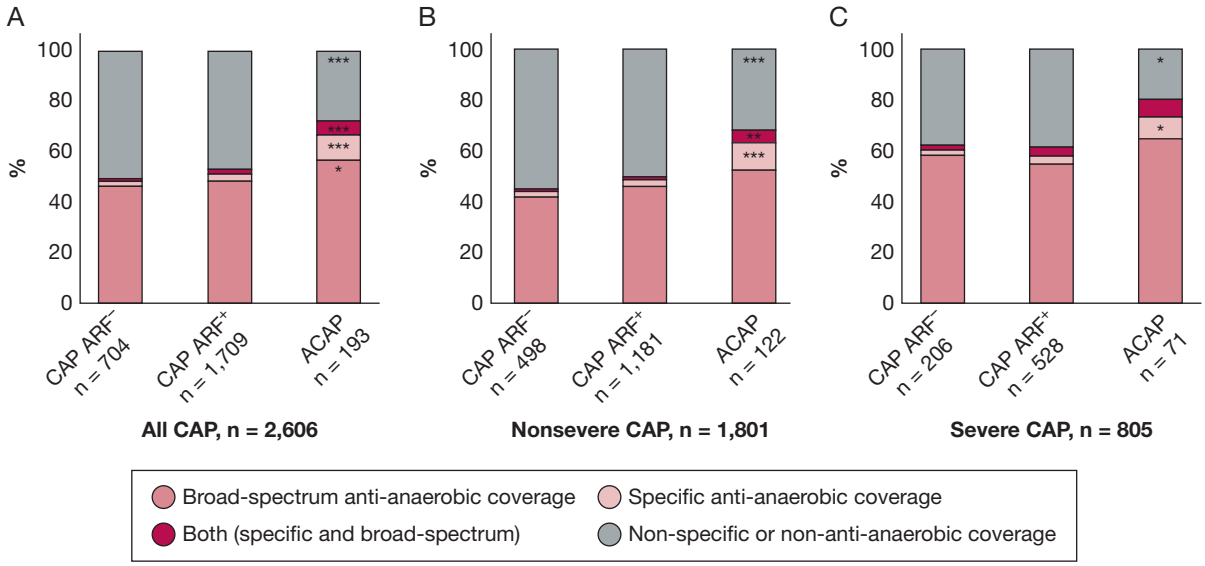

Figure 7 – - *Frequency of specific, broad-spectrum or nonspecific/non-anti-anaerobic antibiotics among all patients with CAP (A) and after stratification of nonsevere (B) and severe CAP (C). See Figure 1 legend for expansion of other abbreviations. *P < .05, ***P < .001, differences between CAP/AspRF-, CAP/AspRF+, and ACAP by χ^2 in the indicated empirical antibiotic groups.*

diversity, study design characteristics, differences in health-care systems and units, the results of this study should be carefully adapted to individual clinical settings. The sample size of patients with ACAP is similar to those of the other series, and because of this, the analysis was constrained to the continental level and not at the country level.[7-9] Microbiological isolation of anaerobic organisms by currently available laboratory techniques is challenging and may have underestimated the true prevalence. Other factors, such as specific sampling methods, sample transport, and culture techniques, might also have contributed to underestimation of anaerobes. Furthermore, evidence of aspiration or dysphagia was not measured by an objective swallowing study, because the patients were already admitted at the time of enrollment. Our study was designed to address the prevalence of microbial pathogens and the utilization of empiric antibiotics at one point in time, but did not include specific anaerobic pathogens or clinical outcomes. However, diverse groups of subjects from 222 hospitals in 54 countries worldwide were enrolled following a pragmatic approach, and the study results suggest clinical practice differences in real-life settings.

Interpretation

In conclusion, this multinational, point prevalence study found that most hospitalized patients with CAP have risk factors for aspiration, but only a small proportion of patients presented with CAP due to aspiration. The microbiological findings of our study do not support the routine use of anti-anaerobic antibiotic coverage, which is currently overprescribed in clinical practice. Patients with severe CAP with aspiration may have higher proportion of GNB, and their empiric coverage should be considered for this high-risk group of patients. Finally, our study supports the recent 2019 ATS/IDSA clinical practice guidelines that suggest not to use antibiotics with anaerobic coverage in patients with CAP, despite presence of risk factors. Future microbiome studies might be able to better clarify the role of anaerobes and other pathogens in health and disease, as in patients hospitalized with CAP.

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References

1. Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. *Chest*. 2003;124(1):328-336.
2. Kozlow JH, Berenholtz SM, Garret E. Epidemiology and impact of aspiration pneumonia in patients undergoing surgery in Maryland, 1999-2000. *Crit Care Med*. 2003;31(7):1930-1937.
3. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med*. 1978;64:564-568.
4. Leroy O, Vandenbussche C, Coffinier C, et al. Community-acquired aspiration pneumonia in intensive care units. *Am J Respir Crit Care Med*. 1997;156:1922-1929.
5. Marrie TJ, Durant H, Yates L, et al. Community-acquired pneumonia requiring hospitalization: 5-year prospective study. *Rev Infect Dis*. 1989;11:586-599.
6. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med*. 1995;152:1309-1315.
7. Shariatzadeh MR, Huang JQ, Marrie TJ, et al. Differences in the features of aspiration pneumonia according to site of acquisition: community or continuing care facility. *J Am Geriatr Soc*. 2006;54(2):296-302.

8. Lauterbach E, Voss F, Gerigk R, Lauterbach M. Bacteriology of aspiration pneumonia in patients with acute coma. *Intern Emerg Med*. 2014;9(8):879-885.
9. Hayashi M, Iwasaki T, Yamazaki Y, et al. Clinical features and outcomes of aspiration pneumonia compared with non-aspiration pneumonia: a retrospective cohort study. *J Infect Chemother*. 2014;20(7):436-442.
10. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. *J Hosp Med*. 2013;8:83-90.
11. Komiya K, Rubin BK, Kadota JI, et al. Prognostic implications of aspiration pneumonia in patients with community acquired pneumonia: a systematic review with metaanalysis. *Sci Rep*. 2016;6:38097.
12. Mandell L, Niederman M. Aspiration pneumonia. *N Engl J Med*. 2019;380:651-663.
13. Rodriguez A, Restrepo MI. New perspectives in aspiration community acquired pneumonia. *Exp Rev Clin Pharmacol*. 2019;12(10):991-1002.
14. Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. *Am J Med*. 1974;56:202-207.
15. Lorber B, Swenson RM. Bacteriology of aspiration pneumonia: a prospective study of community- and hospital-acquired cases. *Ann Intern Med*. 1974;81:329-331.
16. Cesar L, Gonzalez C, Calia FM. Bacteriologic flora of aspiration-induced pulmonary infections. *Arch Intern Med*. 1975;135:711-714.
17. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia: An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67.
18. Taylor J, Fleming G, Singanayagam A, Hill A, Chalmers J. Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. *Am J Med*. 2013;126:995-1001.
19. Akata K, Yatera K, Yamasaki K, et al. The significance of oral streptococci in patients with pneumonia with risk factors for aspiration: the bacterial floral analysis of 16S ribosomal RNA gene using bronchoalveolar lavage fluid. *BMC Pulm Med*. 2016;16(1):79.
20. Kageyama S, Takeshita T, Furuta M, et al. Relationships of variations in the tongue microbiota and pneumonia mortality in nursing home residents. *J Gerontol A Biol Sci Med Sci*. 2018;73:1097-1102.
21. El-Solh AA, Pietrantoni C, Bhat A, et al. Colonization of dental plaques: a reservoir of respiratory pathogens for hospital-acquired pneumonia in institutionalized elders. *Chest*. 2004;126:1575-1582.
22. Leibovitz A, Plotnikov G, Habot B, et al. Saliva secretion and oral flora in prolonged nasogastric tube-feed elderly patients. *Isr Med Assoc J*. 2003;5:329-332.
23. McDonald D, Ackermenn G, Khailova L, et al. Extreme dysbiosis of the microbiome in critical illness. *mSphere*. 2016;(4). e00199-16.
24. Aliberti S, Reyes LF, Faverio P, et al. Global initiative for meticillin-resistant Staphylococcus aureus pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis*. 2016;16(12):1364-1376.
25. Kalil AC, Metersky ML, Klompas M, et al. Executive summary: management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infec Dis*. 2016;63(5):575-582.
26. Lanspa M, Peyrani P, Wiemken T, Wilson E, Ramirez J, Dean N. Characteristics associated with clinician diagnosis of aspiration pneumonia: a descriptive study of afflicted patients and their outcomes. *J Hosp Med*. 2014;10(2): 90-96.
27. Papadopoulos D, Bader I, Gkioxari E, et al. Microbiology and prognosis assessment of hospitalized patients with aspiration pneumonia: a single-center prospective cohort study. *Infez Med*. 2018;26(2):103-114.
28. Neill S, Dean N. Aspiration pneumonia and pneumonitis: a spectrum of infectious/noninfectious diseases affecting the lung. *Curr Opin Infect Dis*. 2019;32: 152157.
29. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax*. 2013;68(11): 1057-1065.
30. Mandell L, Barlett J, Dowell S, File T, Musher D, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis*. 2003;37:1405-1433.
31. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections: full version. *Clin Microbiol Infect*. 2011;17(Suppl 6):E1-E59.
32. Mier L, Dreyfuss D, Darchy B, et al. Is penicillin G an adequate initial treatment for aspiration pneumonia? A prospective evaluation using a protected specimen brush and quantitative cultures. *Intensive Care Med*. 1993;19:279-284.
33. El-Solh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med*. 2003;167: 1650-1654.
34. Marik PE, Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. *Chest*. 1999;115:178-183.
35. Tokuyasu H, Harada T, Watanabe E, et al. Effectiveness of meropenem for treatment of aspiration pneumonia in elderly patients. *Intern Med*. 2009;48:129-135.
36. Bowerman TJ, Zhang J, Waite LM. Antibacterial treatment of aspiration pneumonia in older people: a systematic review. *Clin Interv Aging*. 2018;13:2201-2213.
37. Wei C, Cheng Z, Zhang L, Yang J. Microbiology and prognostic factors of hospital- and community-acquired aspiration pneumonia in respiratory intensive care unit. *Am J Infect Control*. 2013;41(10):880-884.
38. Terpenning M, Taylor GW, Lopatin D, et al. Aspiration pneumonia: dental and oral risk factors in an older veteran population. *J Am Geriatr Soc*. 2001;49: 557-563.
39. Bousbia S, Papazian P, Saux P, et al. Repertoire of intensive care unit pneumonia microbiota. *PLoS One*. 2012;7(2):1-14.
40. Perry SE, Huckabee ML, Tompkins G, Milne T. The association between oral bacteria, the cough reflex and pneumonia in patients with acute stroke and suspected dysphagia. *J Oral Rehabil*. 2020;47(3):386-394.
41. Ohrui T, Tohoku J. Preventive strategies for aspiration pneumonia in elderly disabled persons. *J Exp Med*. 2005;207:3-12.
42. Milns B, Gosney J, Martin MV, Wright AE. Acute stroke predisposes to oral gram-negative bacilli: a cause of aspiration pneumonia? *Gerontology*. 2003;49:173-176.
43. Kioka MJ, Digiovine B, Rezik M, Jennings JH. Anaerobic antibiotic usage for pneumonia in the medical intensive care unit. *Respirology*. 2017;22:1656-1661.
44. Sarna JR, Furtado S, Brownell AKW. Neurologic complications of metronidazole. *Can J Neurol Sci*. 2013;40: 768-776.
45. Kim DW, Park JM, Yoon BW, et al. Metronidazole-induced encephalopathy. *J Neurol Sci*. 2004;224:107-111.
46. Perlino CA. Metronidazole vs clindamycin treatment of anaerobic pulmonary infection: failure of metronidazole therapy. *Arch Intern Med*. 1981;141:1424-1427.
47. Sanders CV, Hanna BJ, Lewis AC. Metronidazole in the treatment of anaerobic infections. *Am Rev Respir Dis*. 1979;120:337-343.
48. Van der Maarel-Wierink CD, Vanobbergen JN, Bronkhorst EM, Schols JM, de Baat C. Meta-analysis of dysphagia and aspiration pneumonia in frail elders. *J Dent Res*. 2011;90:1398-1404.
49. Brook I, Wexler HM, Goldstein EJ. Antianaerobic antimicrobials: spectrum and susceptibility testing. *Clin Microbiol Rev*. 2013;26(3):526-546.