Aspiration risk factors, microbiology and empiric antibiotics for patients hospitalized with community-acquired pneumonia

Judith Marin-Corral, MD, PhD, Sergi Pascual-Guardia, MD, PhD, Amati Francesco, MD, Stefano Aliberti, MD, Joan R. Masclans, MD, PhD, Nilam Soni, MD, MSc, Alejandro Rodriguez, MD, PhD, Oriol Sibila, MD, PhD, Francisco Sanz, MD, PhD, Giovanni Sotgiu, MD, PhD, Antonio Anzueto, MD, Katerina Dimakou, MD, PhD, Roberta Petrino, MD, Ewoudt van de Garde, PharmD, PhD, Marcos I. Restrepo, MD, MSc, PhD, GLIMP investigators

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Running title: Aspiration pneumonia and risk factors for aspiration

Judith Marin-Corral, MD, PhD[1,2], Sergi Pascual-Guardia, MD, PhD[2,3,4], Amati Francesco, MD[5], Stefano Aliberti, MD[5], Joan R. Masclans, MD, PhD[1,6], Nilam Soni, MD, MSc[2,7], Alejandro Rodriguez, MD, PhD[4,8], Oriol Sibila, MD, PhD[4,9], Francisco Sanz, MD, PhD[10], Giovanni Sotgiu, MD, PhD[11], Antonio Anzueto, MD[2,7], Katerina Dimakou, MD, PhD[12], Roberta Petrino, MD[13], Ewoudt van de Garde, PharmD, PhD[14], Marcos I.Restrepo, MD, MSc, PhD[2,7] and GLIMP investigators*

1 Critical Care Department, Hospital del Mar, Barcelona, Spain. Critical Illness Research Group (GREPAC), Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain.
2 Division of Pulmonary Diseases & Critical Care Medicine, University of Texas Health San Antonio, San Antonio, TX, USA.
3 Respiratory Department, Hospital del Mar, IMIM, Barcelona, Spain.
4 Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Spain.
5 Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Respiratory Unit and Cystic Fibrosis Adult Center, Milan, Italy and University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy.
6 Department of Medicine. Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.
7 Section of Pulmonary & Critical Care Medicine, South Texas Veterans Health Care System, San Antonio, TX, USA.
8 Critical Care Medicine, Hospital Universitari Joan XXIII and Rovira & Virgili University, Tarragona, Spain.
9 Department of Pulmonary Medicine, Hospital Clínic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) and University of Barcelona, Barcelona, Spain.
10 Pulmonology Department, Consorci Hospital General Universitari de Valencia, Valencia, Spain.
11 Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, 07100 Sassari, Italy.
12 5th Department of Pulmonary Medicine, Sotiria Chest Diseases Hospital, Athens, Greece.
13 Emergency Department, S. Andrea Hospital, Vercelli, Italy.
14 Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands.
*GLIMP investigators (full list at the end of the manuscript)

Corresponding Author: Marcos I. Restrepo, MD, MSc, PhD; South Texas Veterans Health Care System ALMD - 7400 Merton Minter Boulevard - San Antonio Texas, 78229; Email: restrepom@uthscsa.edu.

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Abbreviations list:

ACAP: Aspiration community-acquired pneumonia

CAP: community-acquired pneumonia

ICU: intensive care unit

AspRF: aspiration risk factors

ATS/IDSA: American Thoracic Society and Infectious Diseases Society of America

GLIMP: global initiative for methicillin-resistant staphylococcus aureus pneumonia

HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome

CAP/AspRF+: community-acquired pneumonia with aspiration risk factors

CAP/AspRF-: community-acquired pneumonia without aspiration risk factors

REDCap: research Electronic Data Capture

UTHSCSA: University of Texas Health Science Center at San Antonio

GNB: Gram-negative bacteria

GPB: Gram-positive bacteria

spp: species

e.g.: *exempli gratia*, for example

SD: standard deviation

IR, 25-75%: interquartile range

OR: odds ratio

CI: 95% confidence intervals

vs: versus

Abstract

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 non-severe 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=0.021) and lower rates of total Gram-positive bacteria (7.1% vs. 38.1% vs. 50.0%, p<0.001) when compared to patients with severe CAP/AspRF+ and severe CAP/AspRF-, respectively. The majority of the 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 to 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.

Introduction

Aspiration is common among all age groups, with a higher prevalence in the elderly (1,2). It is estimated that 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) that accounts for 10-20% of all community-acquired pneumonia (CAP) cases (4-9). The majority 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 than 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 ACAP and CAP patients with AspRF might present a distinct microbiological spectrum compared to CAP patients 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 (e.g., 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 CAP subjects from 222 hospitals worldwide during four 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 (UTHSA, San Antonio, TX, USA, number HSC20150184E). Due to 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 computed tomography) within the first <48 hours of admission and the presence of clinical signs, symptoms, or laboratory abnormalities: a) a new or worsening cough with or without sputum production and/or purulent respiratory secretions; b) fever (>37.8ºC by rectal or oral temperature) or hypothermia (<36ºC 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 (e.g., 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 bronchoalveolar lavage) 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 community-acquired pneumonia 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 to include 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 UTHSA server. Subject clinical information was collected within 24 hours of hospitalization and included demographics (age, gender), 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 usage, other non-medical 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 spp.*, *Proteus spp.*, *Serratia spp.*, *Klebsiella pneumoniae*, *Escherichia coli*, *Moraxella catarrhalis* and *Enterobacter spp.*), *Streptococcus pneumoniae*, *Staphylococcus aureus*, other Gram-positive cocci (including *Streptococcus pyogenes* and *Streptococcus spp.*) and anaerobes. Those samples with more than one isolated microorganism were considered as a polymicrobial result. *P. aeruginosa*, *H. influenzae*, *Acinetobacter* spp. and other GNB were grouped in a new category named “total GNB” and *S. pneumoniae*, *S. aureus* and other GPB in another new category named “total GPB”.

Empiric antibiotics initiated within 24 hours of presentation were stratified according to their anti-anaerobic (e.g. including *Bacteroides fragilis* group) properties: broad-spectrum anti-anaerobic antibiotics (e.g. 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 non-specific 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 standard deviations (SD) or as medians with interquartile ranges (IR) depending on their parametric or non-parametric distribution. Categorical variables were reported as absolute frequencies and percentages. Differences between groups were analyzed using the chi-squared or Fisher's exact test for categorical variables, and the ANOVA, Student's 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 stratifying the patients into severe CAP or non-severe CAP groups. Individual analyses were performed according to the different anti-anaerobic therapies associated with the different severity groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was established at a p-value <0.05. Data were analyzed using the Statistical Package for Social Sciences 24.0 (IBM® SPSS Statistics®, Chicago, IL, USA) 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 (Figure 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, 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 gender and age ≥65 years being the most prevalent AspRFs (Figure 2). Half of the patients with CAP had at least 2 of the evaluated AspRFs with a remarkable overlap among the 5 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 non-medical conditions (cirrhosis, underweight, nursing home resident, bedridden, living in crowded conditions) and demographic characteristics (elderly and male), respectively (Figure 3A, 3B and 3C). In the multivariate analysis (Odds ratio [95% Confidence interval]) we identified male gender [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 (Figure 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 (Figure 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%), bronchoalveolar lavage (10.7) and pleural fluid (1.5%) and were stratified according to the aspiration risk (e-Table 1-3). In addition, the pathogens were stratified according to the severity of the disease and displayed in Figure 5. The denominator of the different groups represents all the patients who had microbiology tests performed (Figures 5A-C) and a specific assessment among patients with culture positive pneumonia (Figures 5D-F). The

proportion of CAP patients with microbiology testing performed who had a pathogen identified as the etiology agent were 32% (ACAP), 28% (CAP/AspRF+), and 25% (CAP/AspRF-), respectively (Figure 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=0.27 [Figure 5A]). ACAP compared with CAP/AspRF+ or CAP/AspRF- had higher rates of other GNB (7.8% vs. 5.4% vs. 3.6%, p=0.04 [Figure 5A]). Patients with non-severe CAP had similar microbiology patterns among the three groups (Figure 5B). In contrast, severe CAP patients categorized as ACAP versus CAP/AspRF+ or CAP/AspRF- had higher rates of *P. aeruginosa* (11.3% vs. 3.8% vs. 3.9%; p=0.015) and other GNB (12.7% vs. 8.7% vs. 2.9%; p=0.007), but lower rates of *S. pneumoniae* (1.4% vs. 5.9% vs. 9.7%; p=0.032), respectively (Figure 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=0.33 [Figure 5D]). ACAP patients had lower rates of *S. pneumoniae* (16.4% vs. 25.6% vs. 33.3%, p=0.023 [Figure 5D]). Again, patients with non-severe CAP had similar microbiology patterns among the three groups (Figure 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=0.024) and other GNB (32.1% vs. 23.7% vs. 9.1%; p=0.014), but lower rates of *S. pneumoniae* (3.6% vs. 16.0% vs. 30.3%; p=0.004), respectively (Figure 5F). Patients with severe ACAP had higher rates of total GNB (64.3% vs. 44.3% vs. 33.3%, p=0.021) and lower rates of total GPB (7.1% vs. 38.1% vs. 50.0%, p<0.001) when compared to patients with severe CAP/AspRF+ and severe CAP/AspRF-, respectively.

Severe and non-severe ACAP

Among patients with culture positive CAP, 40% (n=288) were stratified as severe CAP and 60% (n=434) as non-severe CAP (Figure 5D-F). Severe vs. non-severe ACAP had a larger proportion of patients with GNB (64.3% vs. 30.3%; p=0.007) and anaerobes (4% vs. 0.0%; p=0.274), but a lower proportion of patients with Gram-positive cocci (7.1% vs. 57.6%; p<0.001) (Figure 6). These group differences in the severe ACAP were driven mainly by the increased prevalence of *P. aeruginosa* (28.6% vs. 6.1%; p=0.018), and the low prevalence of *S. aureus* (3.6% vs. 21.2%; p=0.042) and *S. pneumoniae* (3.6% vs. 27.3%; p=0.013) in the severe ACAP group (Figure 5E and 5F).

Antibiotics against anaerobes for CAP

More than half of the patients with CAP in the three study groups received anti-anaerobic antibiotic coverage (Figure 7A). A larger proportion of ACAP patients (72.5%) received anti-anaerobic coverage (specific or broad spectrum antibiotics) compared to CAP/AspRF+ (53.4%) and CAP/AspRF- (49.8%) patients (p<0.001) (Figure 7A). This difference was greater in the severe CAP (80.3% vs. 61.6% vs. 62.1%, p=0.008) vs. non-severe CAP group (68.0% vs. 49.7% vs. 44.8%, p<0.001), respectively (Figure 7B and 7C). Specific anti-anaerobic coverage with metronidazole (9.3%, 2.7%, and 1.4%; p<0.001) or clindamycin (6.2%, 1.5%, and 3%, p=0.002) were also more frequently prescribed to patients with ACAP when compared to CAP/AspRF+ and CAP/AspRF- patients (Figure 7A). Additionally, specific anti-anaerobic coverage was more frequently seen in patients with severe and non-severe ACAP versus other groups (Figure 7B and 7C).

Discussion

The key findings of this study are: 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 whether risk factors for aspiration are present or not; 3) microbiology differs among patients with severe ACAP compared to non-severe 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 around 10% (5-7). However, other observational studies tend to report higher rates of aspiration pneumonia (23-30%) with one study 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 literature, though 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 revealed 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 1960-1980's and 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 (e.g., collection of samples, use of anaerobic culture techniques, etc.), and patient-related factors (e.g., 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 ACAP patients compared with CAP/AspRF+ and CAP/AspRF- patients (32,34,37-39), mainly among those with severe ACAP versus non-severe ACAP. Consequently, a higher prevalence of *P. aeruginosa* and *Enterobacteriaceae* (other GNB) was seen in severe ACAP patients. As the oral cavity is considered the principal source of pathogens responsible for aspiration pneumonia, our results suggest a shift in the oral flora of severe ACAP patients (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.

As discussed above and according to the 2019 ATS/IDSA CAP guidelines, healthcare providers are recommended to avoid using empiric anti-anaerobic antibiotic coverage in ACAP patients (17). Despite this recommendation, our results showed the inappropriate use of anti-anaerobic antibiotic coverage with clindamycin and metronidazole in 16% of ACAP patients. 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 about 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 is 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 multidrug resistant organisms,

adverse drugs reactions, and higher costs (48). Moreover, some first- and third-generation cephalosporins are active against prevalent oropharyngeal anaerobes, such as *Bacteroides oralis* group, *Peptococcus* or *Peptostreptococcus*. However, ceftriaxone and ceftaroline have limited sensitivity against *Prevotella* spp. In addition, *Bacteroides spp*, particularly *B. fragilis* group, that is relevant in patients with intra-abdominal infections, is usually resistant to recommended CAP antibiotics (49). Our results suggest the changing epidemiology and microbiology of ACAP should promote more judicious use of antibiotics in order to appropriately cover the most likely pathogens. Therefore, it is important to avoid overuse of antibiotics 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).

The present study has important limitations. ACAP clinical diagnosis is considered a heterogeneous process that is not standard in clinical practice and not based on a reproducible definition. Due to geographical diversity, study design characteristics, differences in healthcare 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 the other series and due to 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, culture techniques, might have also contributed to underestimation of anaerobes. Furthermore, evidence of aspiration or dysphagia was not measured by an objective swallowing study as 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. Severe CAP patients 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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Guarantor: Marcos I. Restrepo, MD, MSc, PhD; takes full responsibility for the content of the manuscript, including the data and analysis.

Author's contributions: JMC, SPG, SA, NJS and MIR wrote and edited the manuscript. JMC, SPG, FA and MIR designed the study and performed statistical analysis. SA, NJS, AR, OS, FS, GS, AA, KD, RP, EVG and MIR enrolled patients. JMC, SPG, FA, SA, JRM, NJS, AR, OS, FS, GS, AA, KD, RP, EVG and MIR contributed intellectually. All authors read and approved the last version of the manuscript.

References

1.- Marik PE, Kaplan D. Aspiration pneumonia and dysphagia in the elderly. *Chest* 2003; 124(1): 328-36.

2.- Kozlow JH, Berenholtz SM, Garret E. Epidemiology and impact of aspiration pneumonia in patients undergoing surgery in Maryland, 1999-2000. *Critical Care Med* 2003; 31(7):1930-37.

3.- Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. *Am J Med* 1978; 64:564-8.

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;152:1309-15.

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):879-85.

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):436-42.

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. *Expert Rev Clin Pharmacol* 2019: 12(10):991-1002.

14.- Bartlett JG, Gorbach SL and 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; 73:1097-102.

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; 126:1575-82.

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; 5:329-32.

23.- McDonald D, Ackermenn G, Khailova L et al. Extreme dysbiosis of the microbiome in critical illness. *mSphere* 2016; 1(4). Pii: 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):575-82.

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):1057–65.

30.- Mandell, L, Barlett J, Dowell S, File T, Musher D and Whitney C. Update of Practice Guidelines for the Management of Community-Acquired Pneumonia in Immunocompetent Adults. *Clin infect Dis* 2003; 37:1405-33.

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(Supp 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 and Careau P. The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study. *Chest* 1999; 115:178-83.

35.- Tokuyasu H, Harada T, Watanabe E et al. Effectiveness of meropenem for treatment of aspiration pneumonia in elderly patients. *Inter 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 in 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 acutestroke and suspected dysphagia. *J Oral Rehabil* 2019. In press.

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; 90:1398-404.

49.- Brook I, Wexler HM, Goldstein EJ. Antianaerobic antimicrobials: spectrum and susceptibility testing. *Clin Microbiol Rev* 2013; 26(3):526-546.

Take home points

- Sentence related to study question: Aspiration risk factors, microbiology patterns, and empiric anti-anaerobic use in patients hospitalized with CAP is not well defined.

- Sentence related to results: Hospitalized patients with ACAP or CAP/AspRF+ had similar anaerobic flora compared to patients without aspiration risk factors. Although that, 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 overprescribed in clinical practice.

***GLIMP INVESTIGATORS**

We would like to thank the following study contributors for their valuable collaboration:

Argentina: Patricia Karina Aruj, Department of Internal Medicine, University Hospital Alfredo Lanari, Buenos Aires, Argentina; Silvia Attorri, Hospital Luis Lago maggiore, Mendoza, Argentina; Enrique Barimboim, Hospital Central de Mendoza, Argentina; Juan Pablo Caeiro and María I. Garzón, Hospital Privado Universitario, Córdoba, Argentina; Victor Hugo Cambursano, V.H. Dr Cazaux A. Servicio de Neumologia, Hospital Rawson, Córdoba, Argentina; Adrian Ceccato, Hospital Nacional Prof Alejandro Posadas, Argentina; Julio Chertcoff, Florencia Lascar and Fernando Di Tulio, Critical Care Unit and Respiratory Medicine, Buenos Aires British Hospital, Buenos Aires, Argentina; Ariel Cordon Díaz, Hospital General Alvear, Ciudad, Mendoza, Argentina; Lautaro de Vedia, Respiratory Intensive Care Unit, Hospital Muñiz, Buenos Aires, Argentina; Maria Cristina Ganaha, Infectious Diseases Ward, Hospital Interzonal General de Agudos "Vicente Lopez y Planes" from General Rodriguez, Buenos Aires, Argentina; Sandra Lambert, Hospital El Cruce - Alta Complejidad en Red, Argentina; Gustavo Lopardo, Hospital Bernardo Houssay, Vicente López, Argentina; Carlos M. Luna, Pulmonary Medicine Division, Department of Medicine, Hospital de Clínicas, Universidad de Buenos Aires, Argentina; Alessio Gerardo Malberti, Hospital Nuestra Señora del Carmen, Argentina; Nora Morcillo and Silvina Tartara, Hospital Zonal Especializado de Agudos y Crónicos Dr. Antonio A. Cetrangolo, Argentina; Claudia Pensotti, Infectious Diseases and Infection Control Department, Buenos Aires, Clinica Privada Monte Grande, Argentina; Betiana Pereyra, Hospital San Roque, Córdoba, Argentina; Pablo Gustavo Scapellato, Infectious Diseases Department, Hospital D.F. Santojanni, Argentina; Juan Pablo Stagnaro, HZGA Mi Pueblo, Florencio Varela, Argentina. **Australia:** Sonali Shah, Department of General medicine, Austin hospital, Heidelberg, Australia. **Austria:** Felix Lötsch and Florian Thalhammer, Division of Infectious Diseases and Tropical Medicine, Department of Medicine I, Medical University of Vienna, Austria. **Belgium:** Kurt Anseeuw, ZNA Campus Stuivenberg,

Antwerp, Belgium; Camille A. Francois, Anesthesia and critical care department, Erasme university hospital, Brussels, Belgium; Eva Van Braeckel, Department of Respiratory Medicine, Ghent University Hospital, Belgium; Jean Louis Vincent, Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium. **Benin:** Marcel Zannou Djimon, Jules Bashi and Roger Dodo, Centre Hospitalier Universitaire HKM of Cotonou, Benin. **Brazil:** Simone Aranha Nouér, Federal University of Rio de Janeiro, Brazil. **Bulgaria:** Peter Chipev and Milena Encheva, Clinic of Pulmonary Diseases, Military Medical Academy, Sofia, Bulgaria; Darina Miteva, UMHAT "St. Marina", Varna, Bulgaria; Diana Petkova, University Hospital Varna, Bulgaria. **Cameroon:** Adamou Dodo Balkissou, Yaounde Jamot Hospital, Yaounde, Cameroon; Eric Walter Pefura Yone, Département de Médecine Interne, University of Yaounde, Yaoundé, Cameroon; Bertrand Hugo Mbatchou Ngahane, Douala General Hospital, Douala, Cameroon. **China:** Ning Shen, Respiratory Medicine, Peking University Third Hospital, Beijing, China; Jin-fu Xu, Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University, China. **Colombia:** Carlos Andres Bustamante Rico and Ricardo Buitrago, Clinica Shaio, Bogota, Colombia; Fernando Jose Pereira Paternina, Las Americas Clinic, Medellin, Colombia. **Congo:** Jean-Marie Kayembe Ntumba, Cliniques Universitaires de Kinshasa, DR Congo. **Croatia:** Vesna Vladic Carevic, Interne Medicine, Dubrovnik, Croatia; Marko Jakopovic, Medical School, University of Zagreb, Department for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia; Mateja Jankovic, University Hospital Center Zagreb, Department for Respiratory Diseases, Zagreb, Croatia; Zinka Matkovic, University Hospital Dubrava, Zagreb, Croatia; Ivan Mitrecic, Karlovac general hospital, Karlovac, Croatia. **Denmark:** Marie-Laure Bouchy Jacobsson, Emergency Department in North Zealand´s Hospital – Hillerød, Denmark; Anette Bro Christensen, Department of Anaethesiology, Viborg Region Hospital, Denmark; Uffe Christian Heitmann Bødtger, Department of Pulmonology, Naestved Hospital, Denmark; Christian Niels Meyer,

Department of Internal Medicine, Roskilde Hospital, Copenhagen University Hospital, Roskilde, Denmark; Andreas Vestergaard Jensen, Gertrud Baunbæk-knudsen, Pelle Trier Petersen and Stine Andersen, Department of Lung- and Infectious Diseases, Nordsjællands Hospital-Hillerød, Denmark. **Egypt:** Ibrahim El-Said Abd El-Wahhab, Thoracic Medicine, Faculty of Medicine - Mansoura University, Egypt; Nesreen Elsayed Morsy, Pulmonary, Critical Care and Sleep Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt; Hanaa Shafiek, Chest diseases department, Faculty of Medicine, Alexandria University, Egypt; Eman Sobh, Chest Diseases Department, Al-Azhar University, Cairo, Egypt. **Ethiopia:** Kedir Abdella Abdulsemed, Department of Medical Laboratory Science and Pathology, College of Health sciences, Mycobacteriology Research Centre, Institute of Biotechnology Research, Jimma University, Jimma, Ethiopia. **France:** Fabrice Bertrand, Critical care Unit, Robert Ballanger Hospital, Aulnay sous Bois, France; Christian Brun-Buisson, Univ Hospital Henri Mondor, 94000 Créteil, France; Etienne de Montmollin, Intensive care unit, Hôpital Delafontaine, Centre hospitalier de Saint-Denis, Saint-Denis, France; Muriel Fartoukh, Unité de réanimation médico-chirurgicale, Pôle Thorax Voies aériennes, Hôpital Tenon, Groupe Hospitalier Est Parisien, France; Jonathan Messika, Publique-Hôpital de Paris, Service de Réanimation Médico-chirurgicale, Hôpital Louis Mourier, Colombes, France, and Université Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, Paris, France; Pierre Tattevin, Infectious Diseases &ICU, Pontchaillou University Hospital, Rennes, France; Abdo Khoury, Department of Emergency Medicine & Critical Care, University of Franche - Comté, Medical Center, France. **Gambia:** Bernard Ebruke, Medical Research Council Unit, Gambia. **Germany:** Michael Dreher, Department of Cardiology, Pneumology, Vascular Medicine and Intensive Care Medicine, University Hospital Aachen, Aachen, Germany; Martin Kolditz, Division of Pulmonology, Medical Department I, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany; Matthias Meisinger, Klinikum Niederlausitz GmbH, Klinik für Innere Medizin und Intensivmedizin, Senftenberg, Germany; Mathias

W. Pletz and Stefan Hagel, Center for Infectious Diseases and Infection Control, Jena University Hospital, Germany; Jan Rupp, Department of Molecular and Infectious Diseases, University of Lübeck, Lübeck, Germany; Tom Schaberg, Zentrum für Pneumologie, Agaplesion Diakonieklinikum Rotenburg, Germany; Marc Spielmanns, Internal Medicine Department, Pulmonary rehabilitation and Department of Health, School of Medicine, University Witten-Herdecke, St.Remigius-Hospital, Leverkusen, Germany; Petra Creutz and Norton Suttorp, Department of Infectious Disease and Respiratory Medicine, Charité - University Medicine, Berlin, Germany. **Ghana**: Beatrice Siaw-Lartey, Komfo-Anokye Teaching Hospital, Kumasi, Ghana. **Greece**: Dimosthenis Papapetrou, Medical Group of Athens (Paleo Faliro Clinic), Athens, Greece; Evdoxia Tsigou and Dimitrios Ampazis, Agioi Anargiroi Hospital, Kifissia, Athens, Greece; Evangelos Kaimakamis, Intensive Care Unit, “G. Papanikolaou” General Hospital of Thessaloniki, Greece. **India**: Mohit Bhatia, S.S. Hospital IMS BHU Varanasi, India; Raja Dhar, Fortis Hospitals, Kolkata, India; George D’Souza, Department of Pulmonary Medicine, St. John's Medical College Hospital, Bangalore, India, 560034; Rajiv Garg, Department of Respiratory Medicine, King George's Medical University UP, Lucknow, India; Parvaiz A Koul, Department of Internal & Pulmonary Medicine, SheriKashmir Institute of Medical Sciences, Srinagar, India; PA Mahesh and BS Jayaraj, Department of Pulmonary Medicine, JSS Medical College, JSS University, Mysore, India; Kiran Vishnu Narayan, Pulmonary Medicine, Government Medical College Kozhikode, Kerala, India; Hirennappa B Udnur and Shashi Bhaskara Krishnamurthy, Columbia Asia Hospital, Hebbal, Bengaluru, Karnataka, India; Surya Kant, Department of Respiratory Medicine, King George's Medical University, Chowk, Lucknow 226003, Uttar Pradesh, India; Rajesh Swarnakar, Getwell Hospital & Research Institute, Dhantoli, Nagpur, India; Sneha Limaye and Sundeep Salvi, on behalf of the Respiratory Research Network of India (RRNI) from the Chest Research Foundation in Pune, India. **Iran**: Keihan Golshani, Isfahan University of Medical Sciences; Iran. **Ireland**: Vera M Keatings, Letterkenny General Hospital, Co. Donegal, Ireland; Ignacio

Martin-Loeches, Multidisciplinary Intensive Care Research Organization (MICRO), St James's University Hospital, Trinity Centre for Health Sciences Dublin, Ireland. **Israel**: Yasmin Maor, Infectious Disease Unit, Affiliated to Tel Aviv University, Wolfson Medical Center, Holon, Israel; Jacob Strahilevitz, Department of Clinical Microbiology & Infectious Diseases, Hadassah-Hebrew University, Jerusalem, Israel. **Italy**: Paola Faverio, Cardio-Thoracic-Vascular Department, University of Milan Bicocca, Respiratory Unit, San Gerardo Hospital, ASST di Monza, Monza, Italy, Salvatore Battaglia, University of Palermo, Pneumologia DiBiMIS, Palermo, Italy; Maria Carrabba, Internal Medicine Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122, Milano, Italy; Piero Ceriana, Pulmonary rehabilitation, IRCCS Fondazione Maugeri, 27100, Pavia, Italy; Marco Confalonieri, Department of Pulmunology, University Hospital, Trieste, Italy; Antonella d'Arminio Monforte, Department of Health Sciences, Clinic of Infectious Disease, San Paolo Hospital, University of Milan, Italy; Bruno Del Prato, Interventional Pneumology, Hospital Antonio Cardarelli, Naples, Italy; Marino De Rosa, UOC Pneumologia P.O. San Filippo Neri ASL RM E Roma, Italy; Riccardo Fantini, Respiratory Diseases clinic, Policlinico di Modena, 41124 Modena, Italy; Giuseppe Fiorentino, UOC Fisiopatologia e Riabilitazione Respiratoria AO Ospedali dei Colli PO Monaldi, Italy; Maria Antonia Gammino, Pulmonary Medicine Unit, San Martino Hospital, ASL 5 Oristano, Sardegna, Italy; Francesco Menzella, Department of Cardiac-Thoracic-Vascular and Intensive Care Medicine, Pneumology Unit, IRCCS-Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Giuseppe Milani, Azienda Ospedaliera Sant Anna di Como, Presidio Ospedale S. Anna Nuovo, Unità Operativa di Pneumologia, Como, Italy; Stefano Nava, Alma Mater University of Bologna, DIMES, Respiratory and Critical Care Unit Sant'Orsola Malpighi Hospital, Italy; Gerardo Palmiero, Respiratory Unit, Versilia Hospital, Azienda USL 12 Viareggio, Lido di Camaiore, Lucca, Italy; Barbra Gabrielli, Emergency Medicine Unit, S. Andrea Hospital, Vercelli, Italy; Paolo Rossi, Internal Medicine Department, Azienda Ospedaliero-

Universitaria S. Maria della Misericordia, Udine, Italy; Claudio Sorino, Pulmonology Unit, A.O. Sant'Anna di Como, Italy; Gundi Steinhilber, Spedali Civili Brescia, U.O. Pneumologia e Fisiopatologia Respiratoria, Brescia, Italy; Alessandro Zanforlin, ULSS 18 Rovigo, Ospedale San Luca, 45027 Trecenta (RO), Italy; Fabio Franzetti, Manuela Carugati, Manuela Morosi and Elisa Monge, Department of Biomedical and Clinical Sciences, Division of Infectious Diseases, Luigi Sacco Hospital, Università degli Studi di Milano, Milan, Italy; Mauro Carone, Fondazione Salvatore Maugeri, IRCCS, Cassano Murge, Italy; Vincenzo Patella, Allergology and Clinical Immunology Unit, Department of Medical Sciences, Battipaglia Hospital, Battipaglia, Salerno, Italy; Simone Scarlata, Geriatrics, Unit of Respiratory Pathophysiology and Thoracic Endoscopy, Campus Bio Medico University and Teaching Hospital, Rome, Italy; Andrea Comel, UO Pneumologia, Ospedale Pederzoli, Peschiera del Garda, Italy. **Japan**: Kiyoyasu Kurahashi, Yokohama City University Medical Center, Japan. **Lebanon**: Zeina Aoun Bacha, Medicine school, St Joseph University, Beyrouth, Lebanon. **Mexico**: Daniel Barajas Ugalde, National Institute of Respiratory Diseases, Mexico; Omar Ceballos Zuñiga, Hospital General de Mexicali, Mexicali, Baja California, Mexico; José F Villegas, Hospital Universitario Monterrey, n. l. México CP 64030. **Montenegro:** Milic Medenica, Department for tuberculosis, Hospital for Lung disease and Tuberculosis Brezovik, Niksic, Montenegro. **Nepal**: Deebya Raj Mihsra, Internal Medicine, BP Koirala Institute of Health Sciences, Nepal; Poojan Shrestha, Oxford University Clinical Research Unit, Patan Hospital, Nepal; **New Zealand**: Elliott Ridgeon, Medical Research Institute of New Zealand; **Nigeria**: Babatunde Ishola Awokola, Department of Family Medicine & Primary Care, Lily Hospitals Limited, Warri, Nigeria; Ogonna N.O. Nwankwo, University of Calabar Teaching Hospital, Calabar, Nigeria; Adefuye Bolanle Olufunlola, Olabisi Onabanjo University teaching hospital, Sagamu, Ogun State, Nigeria; Segaolu Olumide, Department of Medicine (Pulmonary Unit), University College Hospital, Ibadan, Nigeria; Kingsley N. Ukwaja, Department of Medicine, Federal Teaching Hospital Abakaliki, Ebonyi State, Nigeria; **Pakistan**:

Muhammad Irfan, Section of Pulmonary and Critical Care Medicine, Department of Medicine, Aga Khan University, Karachi-74800, Pakistan; **Poland**: Lukasz Minarowski, Department of Lung Diseases and Tuberculosis, Medical University of Bialystok, Poland; Skoczyński Szymon, Department of Pneumology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Institute of Occupational Medicine and Environmental Health, Sosnowiec, Poland; **Portugal**: Felipe Froes, Hospital Pulido Valente - CHLN, Lisboa, Portugal; Pedro Leuschner, Centro Hospitalar do Porto, Porto, Portugal; Mariana Meireles, Cláudia Ferrão, Pedro Leuschner and João Neves, Serviço de Medicina, Centro Hospitalar do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal; Sofia B Ravara, Faculty of Health Sciences, University of Beira Interior; Cova da Beira Hospital Center, 6200-251 Covilhã, Portugal; **Republic of Moldova**: Victoria Brocovschii, Department of Pneumology & Allergology, State University of Medicine and Pharmacy "Nicolae Testemitanu" Republic of Moldova; Chesov Ion, Clinic of Anesthesia and Intensive Care "Valeriu Ghrerg", Institute of Emergency Medicine, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Republic of Moldova; Doina Rusu, SMFU "N.Testemitanu", Chisinau, Republic of Moldova; Cristina Toma, Department of Pneumology & Allergology, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Republic of Moldova; **Romania**: Daniela Chirita, Hospital Sfantul Stefan, Bucharest, Romania; Carmen Mihaela Dorobat, Universitatea de Medicină şi Farmacie “Gr. T. Popa” I a ş i Facultatea de Medicină Stomatologică, Spitalul Clinic de Boli Infecţioase “Sfânta Parascheva” I a ş i str. Octav Botez, nr. 2, 700116, Iaşi, Romania; **Russia**: Alexei Birkun, Department of Anesthesiology, Critical Care and Emergency Medicine, Medical Academy named after S. I. Georgievsky, Russian Federation; Anna Kaluzhenina, Volgograd State Medical University, Russia. **Saudi Arabia**: Abdullah Almotairi, King Fahad medical City (KFMC), Riyadh, KSA; Zakeya Abdulbaqi Ali Bukhary, College of Medicine, Taibah University, Medina, KSA; Jameela Edathodu, Al Faisal University, King Faisal Specialist Hospital, Riyadh, KSA;

Amal Fathy, Pulmonary and respiratory critical care Medicine, Mansoura University Egypt, Affiliate at Taibah University, KSA; Abdullah Mushira Abdulaziz Enani and Nazik Eltayeb Mohamed, Infectious Diseases Section, Medical Specialties Department, King Fahad Medical City, Riyadh, KSA; Jawed Ulhadi Memon, Pulmonology Division, Department of Internal Medicine, King Fahad Hospital, Hofuf, Al Ahasa, 31982, KSA; Abdelhaleem Bella, Dammam University-Saudi Arabia and King Fahad Hospital, KSA. **Serbia**: Nada Bogdanović, Pulmonary department of KHC Dr.Dragiša Mišović, Belgrade, Serbia; Branislava Milenkovic, Clinic for Pulmonary Diseases, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; Dragica Pesut, University of Belgrade School of Medicine, Teaching Hospital of Pulmonology, Clinical Centre of Serbia, Belgrade, Serbia. **Spain**: Luis Borderìas, Respiratory and Sleep Unit, Hospital San Jorge, Huesca, Spain; Noel Manuel Bordon Garcia, Barcelona Policlínic and Moises Broggi Hospital at sant Joan Despí, Spain; Hugo Cabello Alarcón, Sant Hospital Seu de Urgell, Catalonia, Spain; Catia Cilloniz and Antoni Torres, Department of Pneumology, Institut Clinic del Tórax, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB), Spain; Vicens Diaz-Brito and Xavier Casas, Infectious diseases Unit and Pneumology Service, Parc Sanitari Sant Joan de Deu, Sant Boi, Barcelona, Spain; Alicia Encabo González, Hospital Complex of Pontevedra, Spain; Maria Luisa Fernández-Almira, Medicina Interna, Hospital Universitario Central de Asturias, Spain; Miguel Gallego, Department of Respiratory Medicine, Hospital de Sabadell, Institut Universitari Parc Taulí-UAB, Sabadell, Spain. CIBER de Enfermedades Respiratorias, CIBERES, Bunyola, Spain; Inmaculada Gaspar-GarcÍa, Department of Respiratory Medicine, Hospital Costa del Sol, Marbella, Málaga, Spain; Juan González del Castillo, Emergency Department, Hospital Universitario Clínico San Carlos, Madrid, Spain; Patricia Javaloyes Victoria, Hospital General Universitario de Alicante, Alicante, Spain; Elena Laserna Martínez, Hospital Mollet, Barcelona, Spain; Rosa Malo de Molina, University Hospital Puerta de Hierro

Majadahonda, Madrid; Pedro J Marcos, Servicio de Neumología, Complejo Hospitalario Universitario de A Coruña (CHUAC), INIBIC, Sergas, Universidade de A Coruña (UDC), Spain; Rosario Menéndez, Pneumology Service, Universitary and Polytechnic Hospital La Fe, Valencia, Spain; Ana Pando-Sandoval, Hospital Universitario Central de Asturias. Area de Gestion Clinica de Pulmon. Servicio de Neumologia, Oviedo, Spain; Cristina Prat Aymerich, Alicia Lacoma de la Torre and Ignasi García-Olivé, Microbiology Department and Pneumology Department, Hospital Universitari Germans Trias i Pujol, Institut d'Investigació Germans Trias i Pujol, Badalona, Spain. Universitat Autònoma de Barcelona. CIBER Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Spain; Jordi Rello and Silvia Moyano, Critical Care Department, Hospital Vall d'Hebron, Barcelona, Spain; Ana Rodrigo-Troyano, Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Barcelona, Spain; Jordi Solé-Violán, Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain; Ane Uranga, Pulmology Department, Hospital of Galdakao-Usansolo, Spain; Job FM van Boven, Hospital Universitari Son Espases, Palma de Mallorca, Spain; Ester Vendrell Torra and Jordi Almirall Pujol, Intensive Care Medicine, Hospital de Mataró, Spain. **South Africa**: Charles Feldman, Division of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa. **South Korea**: Ho Kee Yum, Inje Univ. Seoul Paik Hospital, South Korea. **Togo**: Arnauld Attannon Fiogbe, Pulmonology and Infectious Diseases Service/University hospital of Sylvanus Olympio, Lomé, Togo. **Tunisia**: Ferdaous Yangui, Department of Pneumology, Hospital of Internal Forces Security (I.F.S), Marsa, Tunis, Tunisia. **Turkey**: Semra Bilaceroglu, Izmir Dr. Suat Seren Training and Research Hospital for Thoracic Medicine and Surgery, Izmir, Turkey; Levent Dalar, Pulmonary Medicine, Istanbul Bilim University, Istanbul, Turkey; Ufuk Yilmaz, Suat Seren Chest Disease and Surgery Training and Research Hospital, İzmir, Turkey. **Ukraine**: Artemii Bogomolov, Vinnitsa National Pirogov Memorial

Medical University, Vinnitsa regional antituberculosis hospital, Vinnitsa, Ukraine. **United Arab Emirates**: Naheed Elahi, Dubai Hospital, U.A.E. **United Kingdom**: Devesh J Dhasmana, Victoria Hospital, Kirkcaldy, NHS Fife, UK; Andrew Feneley, Rhiannon Ions, Julie Skeemer and Gerrit Woltmann, University Hospitals of Leicester NHS Trust and University of Leicester, Leicester, UK; Adam T Hill, Royal Infirmary and University of Edinburgh, UK; Banu Rudran, The Royal London Hospital, Barts Health Trust, London, UK; Silvia Ruiz-Buitrago and Marion Campbell, Hairmyres Hospital, Eaglesham Road, East Kilbride, G75 8RG, UK; Paul Whitaker, Department of Respiratory Medicine, St James's Hospital, Leeds, LS9 7TF, UK; Alexander Youzguin, Southport and Ormskirk Hospitals NHS Trust, UK; Anika Singanayagam, Imperial College Healthcare NHS Trust, London, UK. Hancock C, Respiratory Infection Group, Royal Liverpool and Broadgreen University Hospital Trust, Liverpool, United Kingdom. **United States of America**: David Villafuerte, Division of Pulmonary Diseases & Critical Care Medicine, South Texas Veterans Health Care System, San Antonio, TX, USA, Karen S Allen, University of Oklahoma Health Sciences Center, USA; Veronica Brito, Texas A&M Health Science Center, Division of Pulmonary, Critical Care and Sleep Medicine Baylor Scott & White Health, USA; Jessica Dietz, Fargo VA Health Care System, Fargo, North Dakota, USA; Claire E. Dysart and Susan M. Kellie, Clement J. Zablocki VA Medical Center, 5000 W. National Ave Milwaukee, WI 53295, USA, Division of Infectious Diseases, University of New Mexico School of Medicine, Raymond G. Murphy VA Medical Center, 1501 San Pedro SE Albuquerque, NM87108, USA; Ricardo A Franco-Sadud and Garnet Meier, Division of Hospital Medicine, Cook County Hospital, Chicago, USA; Mina Gaga, 7th Resp. Med. Dept and Asthma Center, Athens Chest Hospital, USA; Thomas L. Holland and Stephen P. Bergin, Department of Medicine, Duke University Medical Center and School of Medicine, Duke Clinical Research Institute, USA; Fayez Kheir, Department of Pulmonary Diseases, Critical Care & Environmental Medicine, Tulane University Health Sciences Center, New Orleans, LA, USA; Mark Landmeier, Division of Pulmonary and Critical Care

Medicine, Northwestern Memorial Hospital, Chicago, IL 60611, USA; Manuel Lois, John Peter Smith Hospital, Fort Worth, TX, 76104, USA; Girish B Nair, Interstitial Lung Disease Program and Pulmonary Rehabilitation, SUNY Stony Brook Winthrop University Hospital, Mineola, NY 115501, USA; Hemali Patel, Department of Medicine, Division of General Internal Medicine, Hospital Medicine Group, University of Colorado, USA; Katherine Reyes, Henry Ford Hospital, Detroit, IL, USA; William Rodriguez-Cintron, Pulmonary/Critical Care Medicine VA Caribbean Healthcare System, USA; Shigeki Saito, Tulane University, New Orleans, USA; Julio Noda, Cecilia I. Hinojosa, Stephanie M. Levine, Luis F. Reyes, Luis F. Angel and Antonio Anzueto, Divisions of Hospital Medicine & Pulmonary/Critical Care Medicine, South Texas Veterans Health Care System, University of Texas Health Science Center San Antonio, San Antonio, TX, USA; K. Scott Whitlow, John Hipskind, Kunal Sukhija and Vicken Totten, Kaweah Delta Health Care District, Department of Emergency Medicine, Visalia, CA, USA; Richard G. Wunderink and Ray D. Shah, Northwestern University Feinberg School of Medicine, Chicago, IL, USA. **Zambia**: Kondwelani John Mateyo, Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia. **Other investigators**: Lorena Noriega; Ezequiel Alvarado; Mohamed Aman; Lucía Labra.

Table 1. Characteristics of hospitalized CAP patients by aspiration status.

	Aspiration n = 193	Non Aspiration n = 2,413	p-value
Demographics			
Age, years	76 (61-85)	68 (53-80)	<0.001
Gender, male	130 (67.4)	1,380 (57.2)	0.006
Chronic medical comorbidities			
Chronic lung diseases			
Asthma	9 (4.7)	199 (8.2)	0.077
Bronchiectasis	11 (5.7)	132 (5.5)	0.893
COPD	44 (22.8)	655 (27.1)	0.190
Obstructive sleep apnea	11 (5.7)	102 (4.2)	0.334
Interstitial lung diseases	6 (3.1)	59 (2.4)	0.569
Cardiovascular diseases			
Coronary artery disease	42 (21.8)	407 (16.9)	0.083
Heart failure	34 (17.6)	323 (13.4)	0.100
Hypertension	83 (43.0)	1,136 (47.1)	0.275
Neurologic diseases			
Stroke	39 (20.2)	171 (7.1)	<0.001
Dementia	73 (37.8)	226 (9.4)	<0.001
Mental illness	30 (15.5)	155 (6.4)	<0.001
Other medical conditions			
Liver disease	10 (5.2)	83 (3.4)	0.209
Cirrhosis	8 (4.1)	37 (1.5)	0.007
Chronic renal failure	22 (11.4)	243 (10.1)	0.557
Diabetes mellitus	34 (17.6)	543 (22.5)	0.116
Alcoholism	17 (8.8)	210 (8.7)	0.960
Current or former smoker	63 (32.6)	839 (34.8)	0.550
Underweight	19 (9.8)	95 (3.9)	<0.001
Obese	27 (14.0)	418 (17.3)	0.236
Chronic medications			
Inhaled corticosteroids use	32 (16.6)	434 (18.0)	0.624
Proton-pump inhibitor use	72 (37.3)	652 (27)	0.002
Statins use	44 (22.8)	532 (22.0)	0.809
Glucocorticoid use	13 (6.7)	136 (5.6)	0.527
Chronic interventions			
Enteral tube feeding	13 (6.7)	20 (0.8)	<0.001

Hemodialysis	1 (0.5)	33 (1.4)	0.317
Home oxygen therapy	20 (10.4)	156 (6.5)	0.038
Tracheostomy	6 (3.1)	29 (1.2)	0.027
Other non-medical conditions			
Bedridden	75 (38.9)	233 (9.7)	<0.001
Nursing home resident	51 (26.4)	173 (7.2)	<0.001
Living in crowded conditions	26 (13.5)	548 (22.7)	0.003
Pneumonia severity			
Severe CAP	71 (36.8)	734 (30.4)	0.065

Data expressed as frequencies and percentages [n (%)] or medians and interquartile ranges (IQR or 25th-75th percentile).

Figure 1. Flow chart of patients hospitalized with community acquired pneumonia included in the study.

Footnote Figure 1. ACAP, aspiration community acquired pneumonia; AspRF, aspiration risk factors; CAP, community acquired pneumonia.

Figure 2. Prevalence of risk factors for aspiration in hospitalized CAP patients classified by categories (demographics, chronic interventions, neurologic diseases, medical conditions, non-medical conditions). First row in every category shows the prevalence of almost one risk factor described below.

Footnote Figure 2. CAP, community acquired pneumonia; RF, risk factors.

Figure 3. Characteristics of aspiration risk factors in hospitalized CAP.

Figure 3A- Distribution of the number of aspiration risk factors for patients with CAP; **Figure 3B-** Box plot representing the distribution of number of aspiration risk factors among CAP patients; **Figure 3C-** Graphic representation of the different aspiration risk factors that overlap among hospitalized CAP patients.

Figure 4. Multivariate analysis of independently associated risk factors related to aspiration in patients hospitalized with CAP.

Figure 5. Prevalence of microbiological results in the study groups in all patients with microbiological testing performed (**Figures 5A-C**) and among patients with culture positive pneumonia (**Figures 5D-E**) in all included patients (Figures A and D) and stratified depending on the severity of the disease (Figures B-C and E-F).

Footnote Figure 5. ACAP, aspiration community acquired pneumonia; AspRF, aspiration risk factors; CAP, community acquired pneumonia.

* p<0.05, differences between CAP/AspRF-, CAP/AspRF+ and ACAP by chi-squared in the indicated microbiological groups.

Figure 6. Prevalence of microbiological results in ACAP group and in the severity stratified groups in all patients with microbiological testing performed.

Footnote Figure 6. ACAP, aspiration community acquired pneumonia.

* p<0.05, *** p<0.001, differences between severe and non-severe ACAP by chi-squared in the indicated groups.

Figure 7. Frequency of specific, broad-spectrum or non-specific/non-anti-anaerobic antibiotics among all patients with CAP (**Figure 7A**) and after stratification of non-severe (**Figure 7B**) and severe CAP (**Figure 7C**).

Footnote Figure 7. ACAP, aspiration community acquired pneumonia; AspRF, aspiration risk factors; CAP, community acquired pneumonia.

* p<0.05, *** p<0.001, differences between CAP/AspRF-, CAP/AspRF+ and ACAP by chi-squared in the indicated empirical antibiotic groups.

Table 1. Characteristics of hospitalized CAP patients by aspiration status.

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Demographics			
Age, years	76 (61-85)	68 (53-80)	<0.001
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Neurologic diseases			
Stroke	39 (20.2)	171 (7.1)	<0.001
Dementia	73 (37.8)	226 (9.4)	<0.001
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Liver disease	10 (5.2)	83 (3.4)	0.209
Cirrhosis	8 (4.1)	37 (1.5)	0.007
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Chronic medications			
Inhaled corticosteroids use	32 (16.6)	434 (18.0)	0.624
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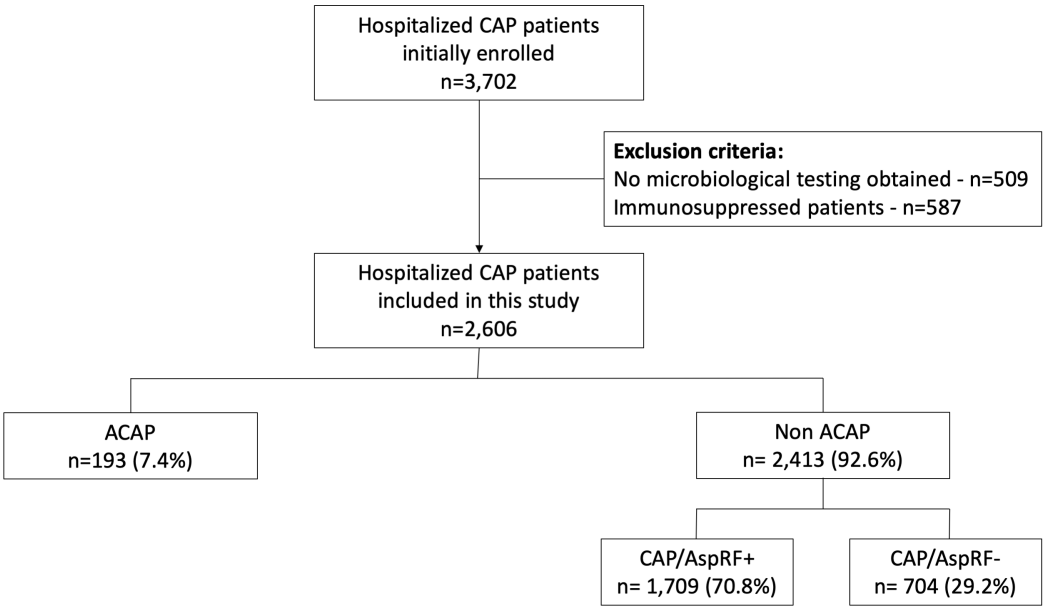
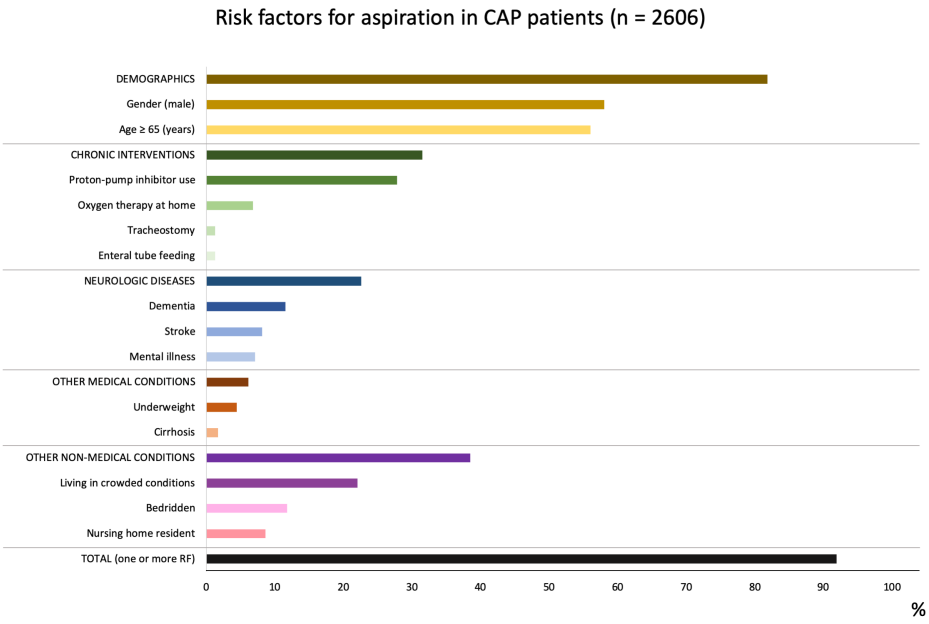
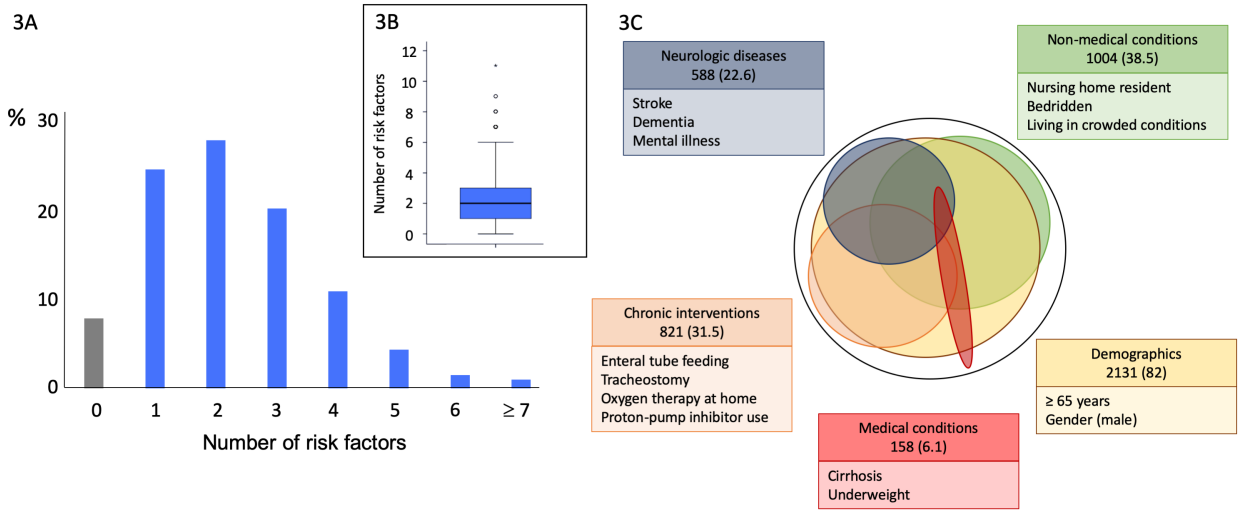
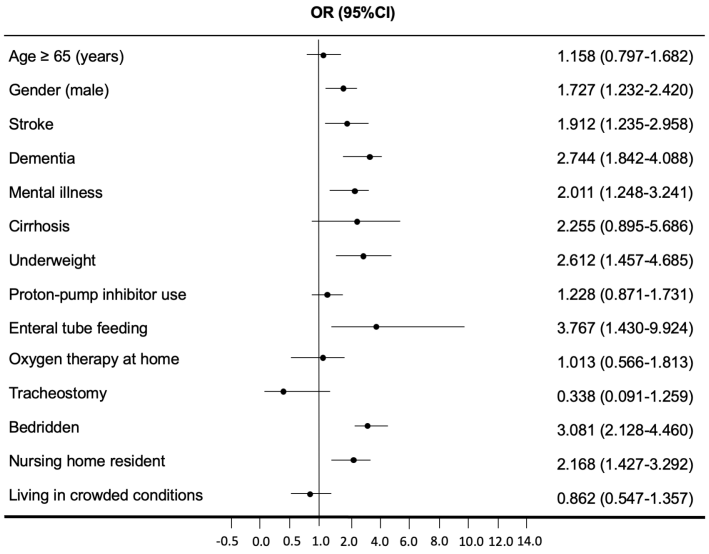
Chronic interventions			
Enteral tube feeding	13 (6.7)	20 (0.8)	<0.001
Hemodialysis	1 (0.5)	33 (1.4)	0.317
Home oxygen therapy	20 (10.4)	156 (6.5)	0.038
Tracheostomy	6 (3.1)	29 (1.2)	0.027
Other non-medical conditions			
Bedridden	75 (38.9)	233 (9.7)	<0.001
Nursing home resident	51 (26.4)	173 (7.2)	<0.001
Living in crowded conditions	26 (13.5)	548 (22.7)	0.003
Pneumonia severity			
Severe CAP	71 (36.8)	734 (30.4)	0.065

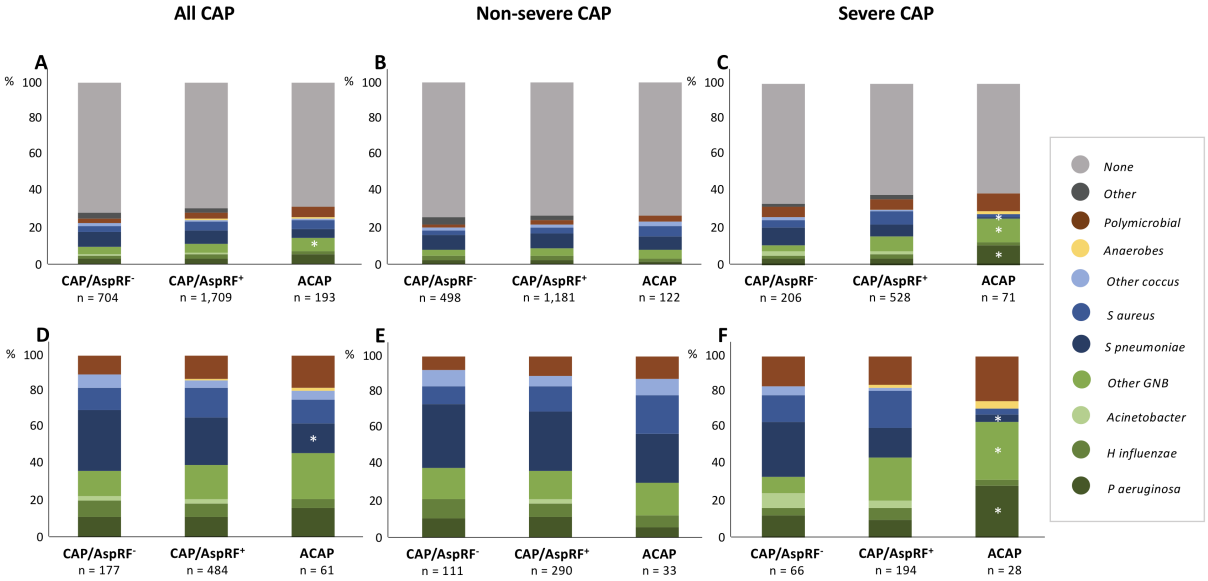
Data expressed as frequencies and percentages [n (%)] or medians and interquartile ranges (IQR or 25th-75th percentile).

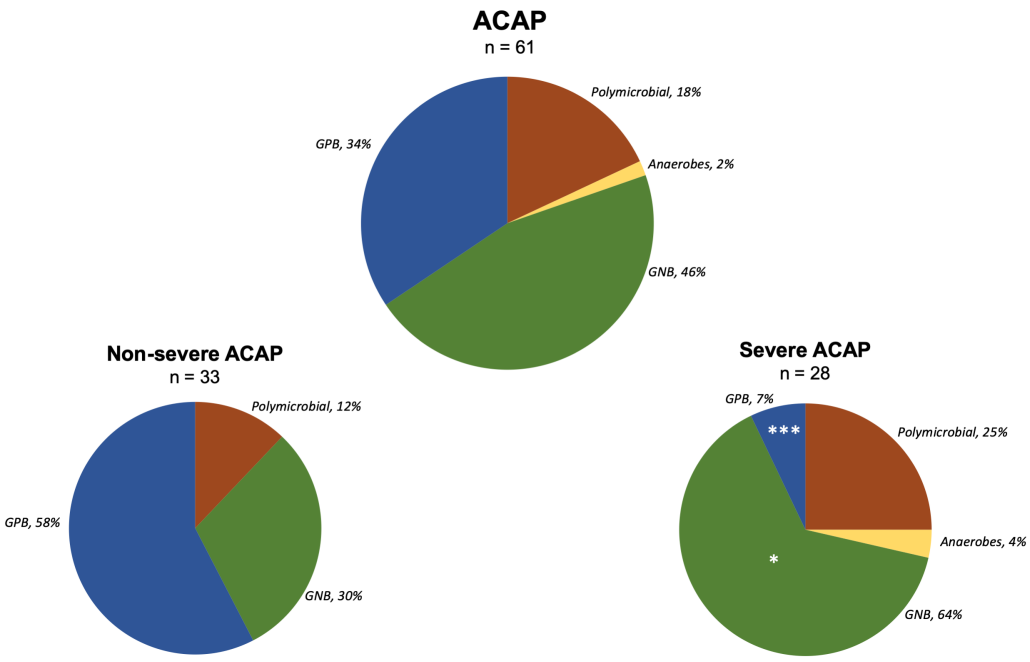


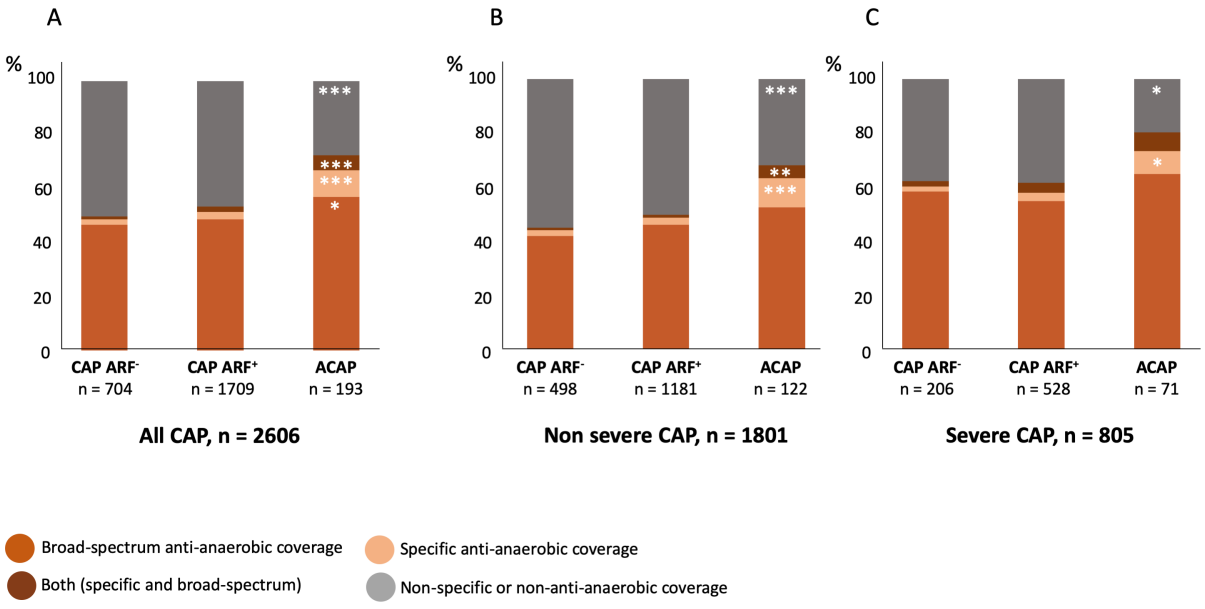



3A
%
30
20
10
0
0
1
2
3
4
5
6
≥ 7
Number of risk factors
3B
Number of risk factors
12
10
8
6
4
2
0
3C
Neurologic diseases
588 (22.6)
Stroke
Dementia
Mental illness
Non-medical conditions
1004 (38.5)
Nursing home resident
Bedridden
Living in crowded conditions
Chronic interventions
821 (31.5)
Enteral tube feeding
Tracheostomy
Oxygen therapy at home
Proton-pump inhibitor use
Demographics
2131 (82)
≥ 65 years
Gender (male)
Medical conditions
158 (6.1)
Cirrhosis
Underweight


OR (95%CI)
Age ≥ 65 (years)
1.158 (0.797-1.682)
Gender (male)
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)
Cirrhosis
2.255 (0.895-5.686)
Underweight
2.612 (1.457-4.685)
Proton-pump inhibitor use
1.228 (0.871-1.731)
Enteral tube feeding
3.767 (1.430-9.924)
Oxygen therapy at home
1.013 (0.566-1.813)
Tracheostomy
0.338 (0.091-1.259)
Bedridden
3.081 (2.128-4.460)
Nursing home resident
2.168 (1.427-3.292)
Living in crowded conditions
0.862 (0.547-1.357)
-0.5 0.0 0.5 1.0 2.0 4.0 6.0 8.0 10.0 12.0 14.0


All CAP
Non-severe CAP
Severe CAP
A
B
C
D
E
F
%
100
80
60
40
20
0
CAP/AspRF-
CAP/AspRF+
ACAP
n = 704
n = 1,709
n = 193
n = 498
n = 1,181
n = 122
n = 206
n = 528
n = 71
n = 177
n = 484
n = 61
n = 111
n = 290
n = 33
n = 66
n = 194
n = 28
None
Other
Polymicrobial
Anaerobes
Other coccus
S aureus
S pneumoniae
Other GNB
Acinetobacter
H influenzae
P aeruginosa


ACAP
n = 61
Polymicrobial, 18%
Anaerobes, 2%
GNB, 46%
GPB, 34%
Non-severe ACAP
n = 33
Polymicrobial, 12%
GPB, 58%
GNB, 30%
Severe ACAP
n = 28
GPB, 7%
***
Polymicrobial, 25%
Anaerobes, 4%
*
GNB, 64%



Abbreviations list:

ACAP: Aspiration community-acquired pneumonia

CAP: community-acquired pneumonia

ICU: intensive care unit

AspRF: aspiration risk factors

ATS/IDSA: American Thoracic Society and Infectious Diseases Society of America

GLIMP: global initiative for methicillin-resistant staphylococcus aureus pneumonia

HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome

CAP/AspRF+: community-acquired pneumonia with aspiration risk factors

CAP/AspRF-: community-acquired pneumonia without aspiration risk factors

REDCap: research Electronic Data Capture

UTHSCSA: University of Texas Health Science Center at San Antonio

GNB: Gram-negative bacteria

GPB: Gram-positive bacteria

spp: species

e.g.: *exempli gratia*, for example

SD: standard deviation

IR, 25-75%: interquartile range

OR: odds ratio

CI: 95% confidence intervals

vs: versus