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Risk Factors for the Development of Acute Lung Injury in Patients with Infectious Pneumonia

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Abstract

Introduction: While pneumonia has been identified as the single most common risk factor for acute lung injury (ALI) we have a limited knowledge as to why some patients with pneumonia develop ALI and others do not. The objective of this study was to determine frequency, risk factors and outcome of ALI in patients with infectious pneumonia.

Methods: A retrospective cohort study of adult patients with microbiologically positive pneumonia, hospitalized at two Mayo Clinic Rochester hospitals between January 1st 2005 and December 31st 2007. In a subsequent nested-case control analysis we evaluated the differences in pre-hospital and intra-hospital exposures between patients with and without ALI/ARDS matched by specific pathogen, isolation site, gender and closest age in a 1:1 manner.

Results: Study included 596 patients, 365 (61.2%) were men. The median age was 65 (IQR, 53-75) years. 171 patients (28.7%) were diagnosed with ALI. The occurrence of ALI was less frequent in bacterial (n=99/412, 24%) compared to viral (n=19/55, 35%), fungal (n=39/95,41%) and mixed isolates pneumonias (n=14/34, 41%, p=0.002). After adjusting for baseline severity of illness and comorbidities, patients who developed ALI had a markedly increased risk of hospital death (OR_{adj} 9.7; 95%CI, 6.0-15.9). In a nested case-control study, presence of shock (OR 8.9, 95%CI 2.8-45.9), inappropriate initial antimicrobial treatment (OR 3.2, 95%CI 1.3-8.5) and transfusions (OR 4.8, 95% CI 1.5-19.6) independently predicted ALI development.

Conclusions: The development of ALI among patients hospitalized with infectious pneumonia varied among pulmonary pathogens and was associated with increased mortality. Inappropriate initial antimicrobial treatment and transfusion predict the development of ALI independent of pathogen.

Introduction

Despite recent improvements in supportive treatment, acute lung injury (ALI) remains a devastating syndrome, with pneumonia as the most common predisposing condition [1]. Although recent data demonstrated temporal improvement in survival, the mortality in ALI patients still remains high [2][3].

Since therapeutic options are limited and the majority of intervention strategies are focused on supportive treatment, emphasis has been placed on identifying patients who are at higher risk for ALI [4, 5]. Patients with ALI represent a heterogeneous group of patients with regards to predisposing conditions [6] that differ in pathophysiological changes [7, 8], clinical and radiological [9] characteristics as well as treatment options [10, 11], but the data on specific risk factors in subsets of patients according to predisposing causes are limited. While sepsis, particularly pulmonary in origin, is the most common underlying risk factor for ALI, only a small proportion of hospitalized patients with pneumonia develop the complication (<10%) [4]. Defining risk factors associated with the development of ALI in patients with infectious pneumonia is challenging because virulence factors of different pathogens have been implicated in causing lung damage [12, 13]. In patients with pneumonia, the relationship between ALI and specific pathogens has been mainly described in case series and case reports of ARDS in patients with *Legionella,* certain types of viral and fungal pneumonia suggesting that some pathogens are particularly prone to induce lung injury. A recent study of critically ill patients demonstrated that pulmonary infection was associated with a higher risk of developing ARDS as compared to infections at non-pulmonary sites [14].

Systematic data regarding occurrence, risk factors and outcome of ALI/ARDS in patients with infectious pneumonia are lacking.

The objective of the present study is to determine the frequency and outcome of ALI in a retrospective cohort of hospitalized patients with microbiology proven pneumonia and identify pre-hospital and hospital exposures that may predict the development of ALI independent of pathogen.

Materials and methods

We used validated queries of Mayo Clinic electronic medical record database (Mayo Clinic Life Sciences System) [15, 16] to identify consecutive patients with microbiologically positive pneumonia who were hospitalized at the two Mayo Clinic Rochester hospitals between January 1, 2005 and December 31, 2007. The Institutional Review Board approved the study protocol and waived the need for informed consent in this observational study. To be included in the study, patients had to be at least 18 years of age and have a diagnosis of pneumonia with identified pathogens according to the *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* (ICD codes 480.0-480.8, 481-482.89, 483-484.8, 487.0, 114.0, 115.5, 116.0 and 136.3). If a patient had more than one episode that met inclusion criteria, only the first episode was included. Electronic medical records including portable digital chest radiographs and microbiology reports were independently reviewed in order to confirm the diagnosis of pneumonia and pathogen isolation. Pneumonia was defined as a new or progressive infiltrate as seen on a chest radiograph or CT scan along with a high clinical suspicion of

pneumonia defined with at least one of the following: fever (>38°C or >100.4°F), leukopenia (<4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm3), altered mental status with no other recognized cause (for adults >70 years old) and at least two of the following: (1) new onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, (2) new onset or worsening cough, or dyspnea, or tachypnea, (3) rales or bronchial breath sounds, and (4) worsening gas exchange, increased oxygen requirements, or increased ventilation demand [17, 18]. The onset of pneumonia (the time of diagnosis of pneumonia) was defined by the first recorded time of any criterion when the above criteria were met.

Microbiological etiology

Patients were included if there had been recovery of one or more respiratory pathogens from: a) an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, transthoracic aspirate or surgical lung biopsy specimen); b) positive serology defined as elevated IgM antibodies or fourfold increases in IgG antibody titers; c) positive urinary antigen test; d) positive PCR; e) semi-quantitative cultures of a lower respiratory tract sample (endotracheal aspirate, bronchoalveolar lavage-BAL, or protected specimen brush); f) expectorated sputum culture.

We identified ALI patients with a validated electronic syndrome surveillance tool (ALI “sniffer”) that was developed for early recognition of patients meeting inclusion criteria for ARDS-net trials. The negative predictive value 99.6% (95% CI 99.3–99.8) of the electronic alert had been determined in a previous study against the gold standard of prospective assessment by trained intensivist researchers, blinded to the ALI electronic alert. The details of the ALI electronic alert have been previously published [16]. All

patients with a positive ALI "sniffer" were reassessed and ALI diagnosed by an independent review of portable chest radiographs, arterial blood gases and hemodynamic parameters based on American/European consensus conference definition [19]. For adequate interpretation of radiologic studies in the diagnosis of ALI, the abstractors reviewed a structured ALI tutorial prior to study onset. Interrater reliability for diagnosing ALI was assessed in previous studies (kappa value of 0.8)[20].The timing of ARDS was determined by the first recorded time of either criterion when both criteria (PaO2/FIO2, bilateral infiltrates) were met.

To identify the risk factors for ALI development, in a subsequent nested case-control study, patients who developed ALI more than 6 hours after pneumonia onset were matched to patients at risk who did not develop ALI based on specific pathogen, isolation site, gender and closest age in a 1:1 matching. If an appropriate control was not found for a specific pathogen, matching was for the same genus, family and finally pathogen group (G-, G+, atypical bacteria, viruses and fungi). Patients with coinfections were matched to appropriate controls in same fashion (all pathogens were matched). Since preliminary data suggested increased risk of ALI among P. jirovecii pneumonia, these cases were matched to specific pathogen regardless of coinfection. The matching was conservative to provide as perfect as possible matches. Among 171 cases of ALI, 118 were diagnosed with ALI more than 6 hours after pneumonia onset of whom 112 were matched according to above criteria. We extracted data from the pre-existing hospital electronic database which included integrated microbiological and susceptibility results, vital signs as well as laboratory parameters, comorbidities, and use of medications. Risk factors were compared between patients who developed ALI and

matched controls. For quality assurance, we performed random checks of electronic database entries. Standard definitions were used for shock [21], inappropriate antimicrobial treatment [22]; and transfusions [23]. We used Pneumonia severity index (PSI) [24] to assess baseline severity of illness and Charlson score [25] as a measure of comorbidities. Arterial oxygen saturation measured by pulse oximetry (SpO2) was recorded if there was a delay in obtaining arterial blood gas analysis and SpO2/FIO2 ratio was used to substitute PaO2/FIO2 ratio (SpO2/FIO2<315 corresponds to PaO2/FIO2<300)[26]. To assure similar exposure time to possible risk factors between cases and controls the exposure time for each control was matched to the exposure time of the corresponding case. That means data on possible intra-hospital exposures of cases were collected from onset of pneumonia to onset of ALI while in controls data were tabulated for the same number of hours subsequent to onset of pneumonia.

We excluded patients with pneumonectomy and ventilatory associated pneumonia (VAP). VAP patients were excluded to eliminate the possibility of including patients with pneumonia complicating ALI and limit effect-cause bias. Patients with potentially contaminated blood culture (bacteremia cases with a single positive blood culture of coagulase negative staphylococci) were also excluded from the analysis.

Statistical analysis

Continuous variables were compared using the Student's t-test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. The Chi square or Fisher's exact tests were used to compare categorical variables. In a retrospective cohort of pneumonia patients the association between

pathogens and ALI occurrence, and ALI and hospital mortality was assessed in univariate followed by multivariate logistic regression analysis, after adjusting for baseline severity of illness. In a subsequent nested case-control study of 112 ALI cases and 112 matched controls, paired parametric and nonparametric testing were used as appropriate, followed by a conditional logistic regression to investigate the relationship between ALI and specific baseline characteristics and in-hospital exposures. Selection of the variables for conditional logistic regression model was done considering both clinical plausibility, and statistical criteria (significance, colinearity and inter-action). All p values of <0.05 were considered to indicate statistical significance. SAS statistical software (SAS version 9; SAS Institute, Inc., Cary, NC) was used for statistical analysis.

Results

Figure 1 shows the flow of study participants. The cohort included 596 patients, 365 (61.2%) were men. The median age was 65 (interquartile range [IQR], 53-75) years. The etiology of pneumonia was mostly bacterial (n=412, 69%), followed by fungal (n= 95, 16%), viral (n=55, 9%), and mixed pathogens (n=34, 6%). Co-infections were present in 131 cases (22%). The pathogens were most commonly isolated from sputum 206 (28.2%), tracheal aspirate 151 (20.6%), bronchoalveolar lavage (BAL) fluid 126 (17.3%), blood 92 (12.6%), and bronchial washings 46 (6.3%).

Baseline characteristics of patients are presented in Table 1. One hundred and seventy-one patients (28.7%) were diagnosed with ALI. ALI less commonly occurred in patients with community-acquired pneumonia (CAP) (n=61, 21.8%) compared to those

with healthcare-associated (HCAP) (n=53, 31.6%, p=0.02) and hospital-acquired pneumonias (HAP) (n=57, 38.5%, p<0.001). Among 448 patients who had evidence of pneumonia at the time of hospital admission, 43 (9.6%) presented with ALI on admission of whom 21 (49%) were transferred from another hospital; in the remainder, the median time to development of ALI was 2 (IQR 1-3) days.

The occurrence of ALI was less frequent in bacterial pneumonias (n=99/412, 24%) compared to viral (n=19/55, 35%), fungal (n=39/95, 41%) and mixed isolates pneumonias (n=14/34, 41 %) (p=0.002). Figure 2 displays the frequency of ALI according to the most common pathogens. Similar results were obtained when coinfections were excluded from the analysis. When the analysis was restricted to bacteremic patients, Gram-positive and Gram-negative bacterial infections had a similar frequency of ALI (20 vs. 15%, p=0.75). All patients diagnosed with respiratory syncytial virus (RSV) pneumonia (4/4) developed ALI. Pneumonia due do *Pneumocystis jiroveci* and *Blastomyces* species was associated with increased risks of ALI when compared to *S. pneumoniae*, the most common cause of pneumonia, in both univariate (OR 3.35, 95% CI 1.5-7.61, OR 4.41, 95% CI 1.1-19.4, respectively) and multivariate analyses (OR 3.8, 95% CI 1.65-8.93, OR 5.6, 95% CI 1.3-26.2, respectively), after adjusting for baseline severity of illness (pneumonia severity index). Patients who developed ALI had a markedly increased risk of hospital death in both univariate (OR_{adj} 9.2; 95% CI, 5.8-14.8) and multivariate analysis after adjusting for baseline severity of illness and comorbidities (Charlson score) (OR_{adj} 9.7; 95% CI, 6.0-15.9).

The association between previously proposed risk factors for the development of ALI was examined in 112 patients who had no ALI at the time pneumonia was diagnosed

who were matched by specific pathogen, age and gender. The characteristics of ALI cases and controls are presented in Table 2. Patient groups were similar in terms of comorbidities expressed as cumulative Charlson score. No difference was found in frequency of diabetes between cases and controls. Patients who developed ALI were more likely to present with bilateral infiltrates. Fifty-one patients (45.5%) that presented with unilateral infiltrate later progressed to ALI. ALI cases had lower SaO2/FiO2 at the baseline and higher baseline pneumonia severity index. Most of patients with RSV and PCP infections were immunosuppressed (30/32). The median time to any antibiotic administration was similar in cases and controls but inappropriate initial antimicrobial treatment was associated with increased risk of ALI (Table 2). The transfusion of fresh frozen plasma, platelets and red blood cells were all associated with ALI development.

When adjusted for baseline imbalances (shock, SpO2/FiO2, type of pneumonia) in a conditional logistic regression analysis inappropriate antimicrobial treatment (OR 3.2, 95%CI 1.3-8.5) and transfusions (OR 4.8, 95% CI 1.5-19.6) were independently associated with the development of ALI (Table 3). The results were similar after adjustment for PSI (as a composite measure of baseline severity of illness) (Table 4).

Patients who developed ALI were more likely to be mechanically ventilated, had longer hospital length of stay and a markedly increased risk of hospital death (Additional file 1). In a post-hoc analysis we explored the association between the prehospital use of certain medications (statins, ACE-inhibitors and antiplatelet drugs) that were found to modify development of ALI in previous studies. When adjusted for adequate antibiotics, transfusion and PSI in conditional logistic regression analysis, the use of statin was associated with a decreased risk of ALI (OR 0.36, 95% CI 0.14-0.92).

Discussion

The results of this study suggest that ALI is common in hospitalized pneumonia patients with positive microbiological diagnosis. In addition, patients with bacterial pneumonia had lower rates of ALI compared to fungal, viral and mixed infections. When controlled for age, gender and specific pathogen, independent predictors of ALI in pneumonia patients are baseline severity of illness, inappropriate initial antimicrobial treatment and transfusion.

ALI rates in our study were higher compared to a previous study of hospitalized patients with clinically defined pneumonia by Ferguson and colleagues (10%) [4]. This could be due to the inclusion , in our study, of only patients with a high clinical suspicion of pneumonia and identified isolates which has been described in less than 50% of hospitalized patients with pneumonia [27]. In addition, most of our patients had an infectious agent isolated from lower respiratory tract secretions indicating that this population probably represents a group of more severely ill patients. Recent report of infection-related ARDS in patients with sepsis, pneumonia and bacteremia yielded results similar to ours [14].

In our study, the main causes of pneumonia were *S.aureus* (with high percentage of MRSA), *S.pneumoniae and P. aeruginosa*. Similar results were obtained by Kollef et al [28]. Among most common pathogens no difference in rates of ALI was found. We observed higher proportion of ALI occurrence in patients with less common infections due to fungal and viral respiratory pathogens. The higher rate of ALI among these pathogen groups likely relates to *P. jiroveci*, and specific endemic fungi, including

Blastomyces species and viral infections (RSV, cytomegalovirus). Possible explanations for this higher risk include delayed antimicrobial treatment as these pathogens are often not treated with initial empiric antimicrobial coverage, as well as baseline characteristics of the patients since these infections more commonly occur in those who are immunocompromised. Progression to ALI is likely a result of complex interaction of patient immune status and specific pathogen [29]. On the other hand, when adjusted for specific pathogen, immunosupression did not influence progression to ALI. However, these results must be interpreted with caution since matching by specific pathogen is similar to matching by immune status or other baseline risk factors for these pathogens, that precludes analyzing the significance of these risk factors for developing ALI. Unfortunately, our study design does not allow further assessment of independent effects of pathogen on risk for ALI development. Although there are numerous reports of *Legionella* pneumonia-induced ARDS, our study failed to confirm increased risk of ALI in these patients. It is possible that early initiation of empirical antimicrobial coverage for atypical bacteria as proposed in current pneumonia guidelines has reduced this devastating complication in patients with *Legionella* pneumonia. We observed no case of ALI in the course of pneumonia caused by other "atypical" bacteria.

Several studies have shown that ALI is rarely present at the time of hospitalization and usually develops in hours to days following hospital admission [4, 30]. The evolution of ALI could be influenced by both baseline characteristics of the patients (first hit) as well as a variety of intra-hospital exposures (second hit) [31]. Certain pre-hospital exposures (alcohol, smoking) [32, 33], medical errors (delayed shock resuscitation, delayed antibiotic treatment) [30] and iatrogenic exposures (plasma

transfusion from alloimmunized donors, gastric aspiration, certain chemotherapeutic drugs) [23, 34, 35] have all been associated with development of ALI in hospitalized patients. Similar to other studies [35] we observed higher baseline severity of illness among ALI cases. Considering baseline characteristics, patients with ALI were more often smokers, although statistical difference was not reached. This could be due to a fact that we used patients' history to obtain information on smoking. In a recent study by Hsieh [36] serum and urine nicotine metabolites identified considerably more active smokers than did smoking history. Active and passive cigarette smoking was found to be associated with ALI after severe blunt trauma, when biomarker of tobacco smoking was used to assess smoking history [37]. Unlike several other studies [32, 38] the history of alcohol abuse did not influence risk of ALI. In addition, while majority of studies implicated diabetes to have a protective role [39, 40], no difference in number of diabetics was found between the cases and controls in our study.

The highest percentage of ALI was found among patients with healthcare-associated pneumonia (HCAP) and hospital-acquired pneumonia (HAP), suggesting that health-care related exposures could have contributed to the development of ALI. When matched for age, gender and pathogen characteristics, and adjusted for baseline severity of illness, the major interventions that were associated with an increased risk of ALI were transfusions and inappropriate initial antimicrobial therapy. Previous studies demonstrated increased risk of ALI in patients with delayed treatment of infection [30]. The time of antibiotic initiation did not influence ALI development in our study as most patients received antibiotics in the emergency department or immediately following admission, however ALI was associated with inappropriate initial antimicrobial therapy.

In patients with pneumonia, inappropriate initial antibiotic treatment noticeably increases the risk of hospital death [41] [42]. The failure to provide adequate antibiotic treatments is more likely in HCAP and HAP as gram negative bacteria and *S. aureus* are major pathogens in these patients [28]. In addition to antimicrobial resistance [41], it seems that patients with HCAP are often not empirically treated for these organisms, resulting in suboptimal antibiotic therapy and increased mortality [43]. Although shock was clearly associated with ALI development, the association of delayed goal-directed resuscitation could not be examined due to a relatively low number of shock patients among controls. The observed association between transfusion and lung injury has been demonstrated in number of studies [40, 44, 45]. The observed association between the use of statins and the decreased risk of ALI is consistent with the recent report by O'Neal et al[46]. Contrary to a previous report in a population-based cohort of non-selected patients at risk of ALI [47], the use of antiplatelet agents in patients with infectious pneumonia was not associated with decreased risk of ALI.

Severe pneumonia is associated with high rates of morbidity and mortality [48-51]. The majority of these studies failed to account for ALI as well as its role in the course of pneumonia and patient outcomes. Our work demonstrated that the development of ALI was independently associated with increased mortality after adjusting for baseline severity of illness and comorbidities. This is particularly important since multiple factors influence ALI development and are potential targets for preventing this devastating syndrome.

Our study has several limitations. First, enrollment was limited to microbiologically proven pneumonia. Since the majority of patients with pneumonia do

not undergo any microbial testing, some patients with pneumonia were excluded and may have biased our study population to more severe cases that underwent such evaluation. Diagnosis of atypical pneumonia is difficult due to fastidious nature of atypical organisms; sensitivity of cultures is low, serological assays are poorly standardized [52], and PCR is not generally available [27]. Because only semi-quantitative analysis of lower respiratory secretions were available, differentiation between microbiologically definite and probable pneumonia was not possible in all patients. On the other hand, since ALI/ARDS has also noninfectious etiologies (aspiration, organizing pneumonia, transfusion induced lung injury [TRALI], acute eosinophilic pneumonia, diffuse alveolar hemorrhage and other interstitial lung diseases), we believe that isolation of a microbiological agent strengthened the diagnosis of infectious pneumonia and prevented the inclusion of non-infectious lung diseases that might have been included using only the clinical definition. Second, since we matched by pathogen we could not properly examine the influence of specific pathogen and immune status on ALI development. It is likely that the results would be different for specific viral (RSV, CMV) or fungal (PCP) pathogens, but limited control data precludes the analysis (since clinicians rarely test immunocompetent patients for these pathogens). Conversely, matching by specific pathogen supports the findings that inappropriate antimicrobial treatment is an independent predictor of ALI and not just a marker of having an atypical pathogen. Third, differentiation between severe bilateral pneumonia and ALI/ARDS may be challenging. Sensitivity and specificity of clinical assessment compared to pathological finding of diffuse alveolar damage (DAD) was found to be poor with the weakest correlation in pneumonia patients [53]. Fourth, we used pneumonia severity index as a composite

measure of baseline severity of illness in all patients. The PSI has been validated in CAP and HCAP but not HAP patients. However, the results were similar when adjusted for baseline imbalances (shock, SpO2/FiO2) instead of PSI. Finally, a limitation of our study is inherent in its retrospective design.

Conclusions

In conclusion, to our knowledge, this is the first study to assess the relationship between ALI and specific respiratory pathogens isolated from patients with pneumonia. The results show that patients with confirmed infectious pneumonia are at a high risk of ALI, especially those with certain types of fungal and viral pneumonias. No difference was found in occurrence of ALI among the most common bacterial pathogens suggesting other possible mechanisms that may promote the development of ALI aside from pathogen characteristics. Potentially modifiable health care delivery factors such as antibiotic therapy and transfusion pose significant risk and provide important targets for ALI prevention.

Key messages

- ALI development is common among hospitalized pneumonia patients with positive microbiology.
- The development of ALI among patients hospitalized with infectious pneumonia varies among pulmonary pathogens and is associated with increased mortality.

- Inappropriate initial antimicrobial treatment and transfusion of blood products are modifiable independent predictors of ALI development in pneumonia patients.

Abbreviations

ALI: Acute lung injury; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body mass index ; CAP: Community-acquired pneumonia; CI: Confidence interval; ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; ICU: Intensive care unit; IQR: Interquartile range; HCAP: Healthcare-associated pneumonia; HAP: Hospital-acquired pneumonia; OR: Odds ratio; PSI: Pneumonia severity index score; TRALI: Transfusion induced lung injury

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study concept and design: MK and OG; **Acquisition of data:** GL, KML, LT, JV, AA, MK; **Analysis and interpretation of data:** MK, GL, OG; **Drafting of the manuscript:** MK and OG; **Critical revision of the manuscript for important intellectual content**: LB, and JR; **Statistical analysis:** AH, GL and MK

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Table 1. Baseline characteristics of the cohort

	N=596
Age, median (IQR)	64.5 (53-75)
Male gender, n (%)	365 (61%)
Pneumonia severity index score, median (IQR)	119 (94-146)
Charlson comorbidity score, median (IQR)	2 (1-4)
Pneumonia type, n (%)	
CAP	280 (47)
HCAP	168 (28)
HAP	148 (25)

Abbreviations: IQR- interquartile range, CAP- community-acquired pneumonia, HCAP- healthcare-associated pneumonia, HAP- hospital-acquired pneumonia

Table 2. Univariate analysis of baseline characteristics and interventions in ALI cases and matched controls

	ALI cases N=112	**Controls N=112**	**Odds ratio**	**P value**
Baseline characteristics				
Age	64.5	62.0	1.00 (0.98-1.03)	0.65
Median (IQR)	(53.5-72.0)	(53.0-71.5)		
Male gender	56 (50)	61 (55)	1.43 (0.68-3.3)	0.52
N (%)				
BMI	26.7 (24.07-	26.4	1.00 (0.99-1.01)	0.48
Median (IQR)	31.05)	(21.9-30.4)		
Ever smoker	66 (59)	52 (46)	1.24 (0.96-1.65)	0.07
N (%)				
Alcohol abuse	13 (12)	9 (8)	1.28 (0.74-1.93)	0.37
N (%)				
Pneumonia type				0.007*
N (%)				
CAP	33 (29.5)	55 (49)	0.32 (0.15-0.63)	
HCAP	33 (29.5)	29 (26)	1.22 (0.66-2.27)	
HAP	46 (41)	28 (25)	2.10 (1.19-3.86)	
Charlson score	3 (2-4)	2 (1-4)	1.0 (0.88-1.14)	0.26
Median (IQR)				
Aspiration N (%)	8 (7.1)	4 (3.6)	1.84(0.63-6.55)	0.25

Diabetes N (%)	25 (22)	33 (29)	0.71(0.39-1.26)	0.24
Immunosuppression N (%)	52 (46.4)	50 (44.6)	1.13 (0.54-2.36)	0.73
Pneumonia severity index score Median (IQR)	115 (92-142)	101 (76-119)	1.02 (1.01-1.03)	<.001*
Shock N (%)	47 (42)	9 (8)	16.3 (5.47-79.04)	<.001*
Respiratory rate Median (IQR)	23 (20-28)	20 (18-24)	1.04 (1.00-1.08)	0.05
SaO2/Fio2 Median (IQR)	236 (107-336)	336 (247-448)	0.995 (0.993-0.997	<.001*
Bilateral infiltrates N (%)	61 (54.5)	31 (38.2)	3.67 (1.92-7.61)	<.001*
Pleural effusion N (%)	23 (20.5)	17 (15.4)	1.34 (0.68-2.69)	0.38
Interventions				
Time to antibiotics (hours), Median (IQR)	0 (0-9)	0 (0-3)	1.00 (0.99-1.02)	0.11
Appropriate initial antimicrobial treatment N (%)	62 (55.4)	85 (75.9)	0.29 (0.13-0.58)	<.001*
Any transfusion	38 (33.9)	15 (13.4)	4.53 (2.08-11.59)	<.001*

N (%)				
Platelets	15 (13.4)	4 (3.6)	6.50 (1.47-59.33)	0.0098*
Red blood cells	31 (27.7)	13 (11.6)	4.0 (1.59-11.96)	0.002*
Fresh frozen plasma	10 (8.9)	1 (0.9)	-	0.008*
Corticosteroids systemic N (%)	48 (42.9)	51 (45.5)	0.89 (0.51-1.55)	0.67
Mechanical ventilation N (%)	95 (85)	24 (21)	29.4 (10.2-141.17)	<.001*
Invasive	80 (71)	19 (17)	18.36 (7.24-66.69)	
Non-invasive	15 (14)	5 (4)	2.83 (1.13-8.25)	

Abbreviations: BMI-Body mass index, IQR- interquartile range, CAP- community-acquired pneumonia, HCAP- healthcare-associated pneumonia, HAP- hospital-acquired pneumonia

Table 3. Conditional regression analysis of ALI risk factors

	OR	**95%CI**
Shock	8.9	2.8-45.9
SpO2/Fio2	0.996	0.993-0.999
Inappropriate initial antimicrobial treatment	3.2	1.3-8.5
Any transfusion	4.8	1.5-19.6
HAP	1.9	0.8-4.5

Abbreviations: HAP- hospital-acquired pneumonia

Table 4. Conditional regression analysis of ALI risk factors

	OR	**95%CI**
PSI	1.01	1.00-1.03
Inappropriate initial antimicrobial treatment	3.1	1.5-7.0
Any transfusion	3.2	1.3-8.8
HAP	1.8	0.9-3.8

Abbreviations: HAP- hospital-acquired pneumonia, PSI- Pneumonia severity index

Figure legends

Figure 1. Study flow diagram

Figure 2. Frequency of ALI among the most commonly isolated pathogens

*Coinfections included

Additional files

Additional file 1

Title: Outcomes of ALI cases and matched controls

Description: Table describing the differences in hospital length of stay, duration of mechanical ventilation and hospital mortality between ALI cases and matched controls.

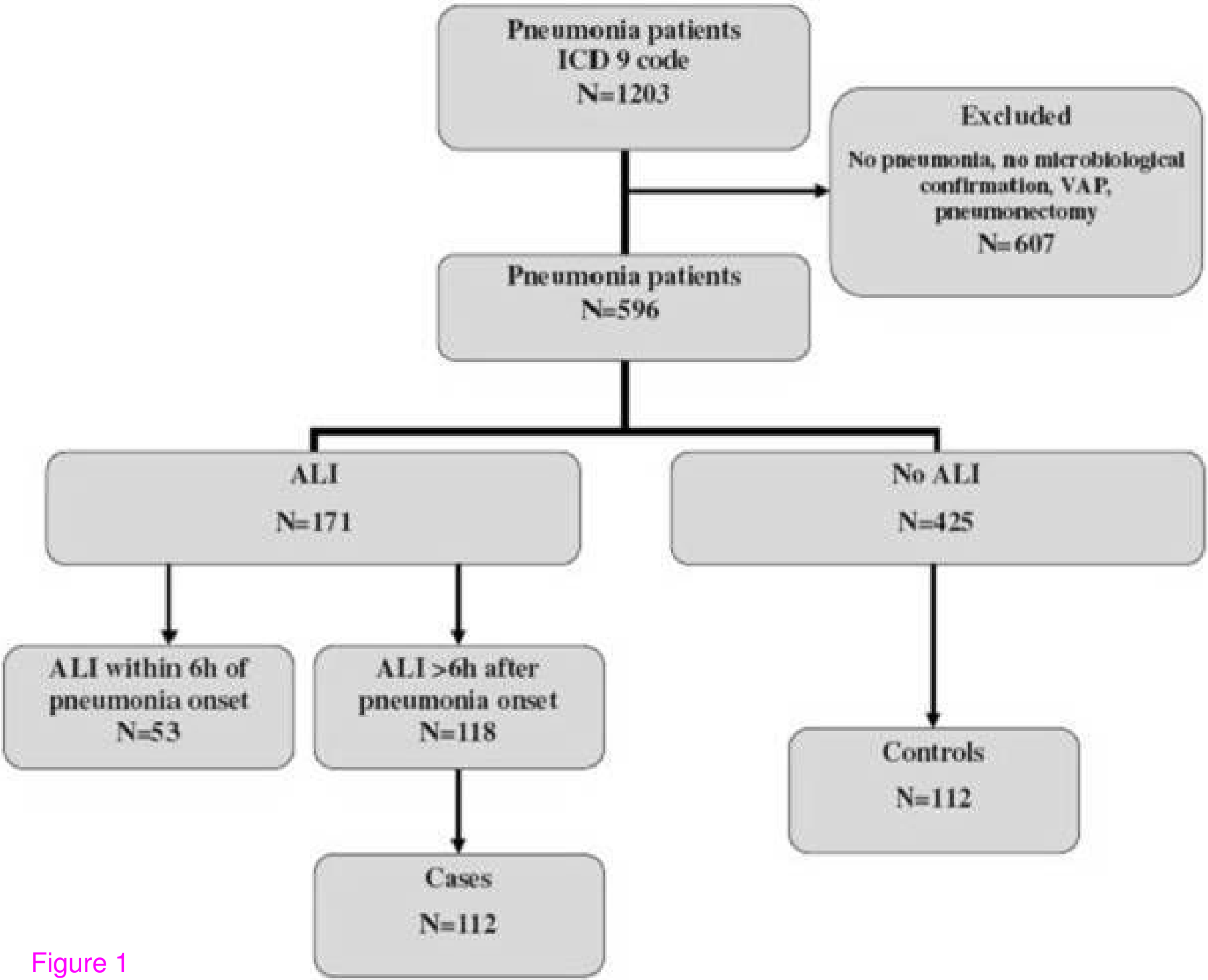
Pneumonia patients
ICD 9 code
N=1203
Excluded
No pneumonia, no microbiological confirmation, VAP, pneumonectomy
N=607
Pneumonia patients
N=596
ALI
N=171
No ALI
N=425
ALI within 6h of pneumonia onset
N=53
ALI >6h after pneumonia onset
N=118
Controls
N=112
Cases
N=112

Figure 1

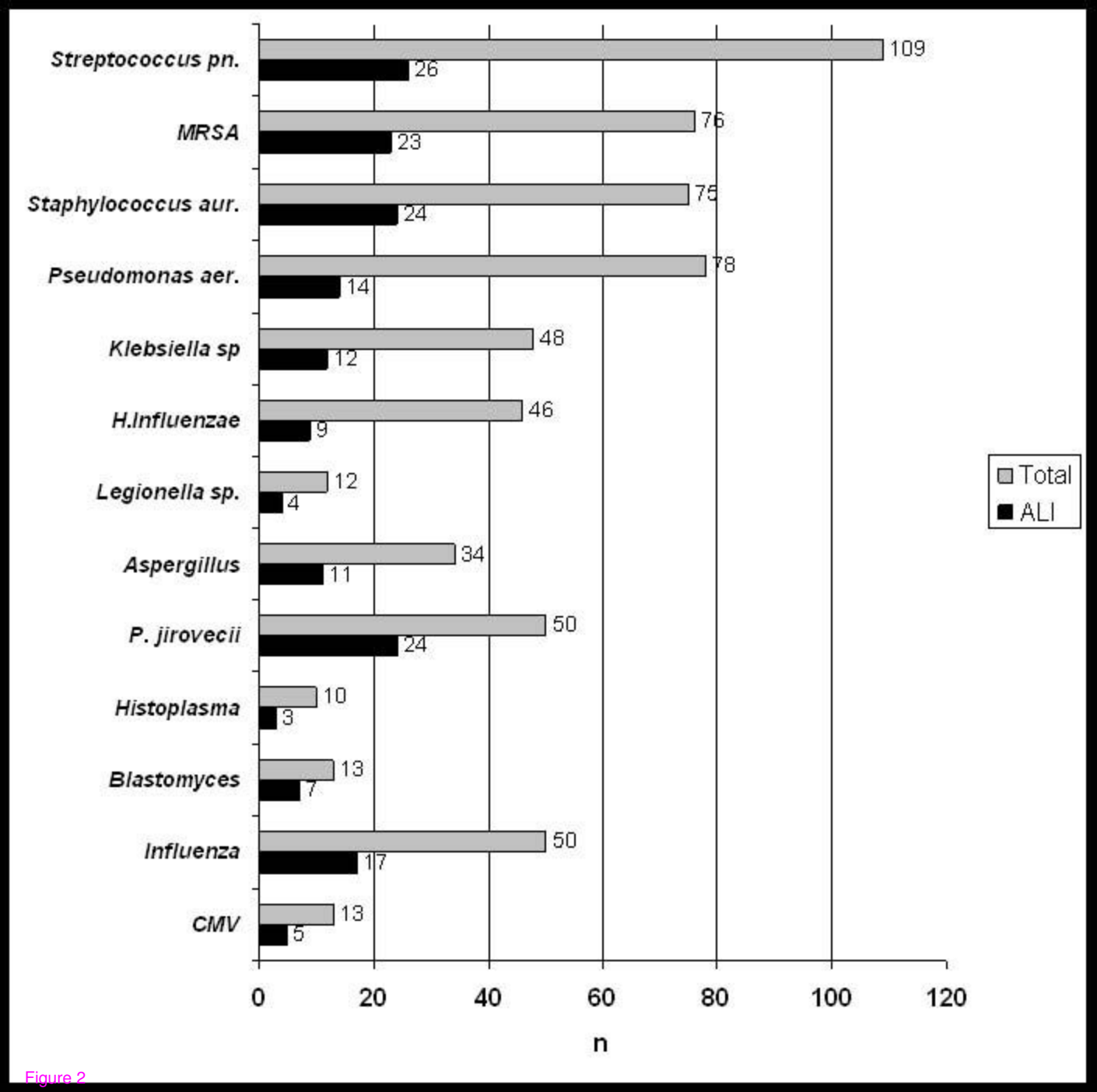
Streptococcus pn.
109
26
MRSA
76
23
Staphylococcus aur.
75
24
Pseudomonas aer.
78
14
Klebsiella sp
48
12
H.Influenzae
46
9
Legionella sp.
12
4
Aspergillus
34
11
P. jirovecii
50
24
Histoplasma
10
3
Blastomyces
13
7
Influenza
50
17
CMV
13
5
Total
ALI
0
20
40
60
80
100
120
n

Figure 2

Additional files provided with this submission:

Additional file 1: Additional files.doc, 27K
http://ccforum.com/imedia/8884438306930264/supp1.doc