ERJ Express. Published on July 11, 2013 as doi: 10.1183/09031936.00050413

ARTICLE TITLE:

Risk factors for respiratory failure in pneumococcal pneumonia. The importance of pneumococcal serotypes.

Running title: Respiratory failure in pneumococcal pneumonia.

Brief Summary:

We conducted a study to describe factors associated with respiratory failure in a cohort of 1258 patients with invasive pneumococcal pneumonia. Older age, comorbid conditions and also serotypes 3, 19A and 19F are the main determinants of this respiratory complication.

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ABSTRACT

Pneumococcal serotypes are one of the main determinants of pneumococcal disease severity, however there are scarce data about their implication in respiratory failure.

We conducted an observational study of adults hospitalized with invasive pneumococcal pneumonia to describe the host- and pathogen-related factors associated with respiratory failure.

Of 1258 adults with invasive pneumococcal disease, 615 (48.9%) had respiratory failure at presentation. Patients with respiratory failure were older (62.1 vs. 55.4, p<.001) and had a greater proportion of co-morbid conditions. They also had a greater proportion of septic shock (41.7% vs. 6.1%, p<.001), required more often ICU admission (38.4% vs. 4.2%, p<.001) and had a higher mortality (25.5% vs. 3.5%, p<.001). After adjustment, independent risk factors for respiratory failure were: age > 50 years (OR 1.63; 95% CI, 1.15-2.3), chronic lung disease (OR 1.54; 95% CI, 1.1-2.15), chronic heart disease (OR 1.49; 95% CI, 1.01-2.22) infection caused by serotypes 3 (OR 1.97; 95% CI, 1.23-3.16), 19A (OR 2.34; 95% CI, 1.14-4.42) and 19F (OR 3.55; 95% CI, 1.22-10.28).

In conclusion, respiratory failure is a frequent complication of pneumococcal pneumonia and causes high morbidity and mortality. Pneumococcal serotypes 3, 19A and 19F are the main risk factors for this complication.

INTRODUCTION

Streptococcus pneumoniae is the leading cause of pneumonia worldwide. Despite the improvements in different medical aspects and critical care of patients mortality still remains unacceptably high (1). Different factors related to the severity and mortality of pneumococcal disease have been described. Some of them are host-related such as extremes of age, comorbidities or immunosuppressive conditions and it is well known that they all are associated with an increased susceptibility to pneumococcal disease and also to a higher severity of the illness (2-4).

Nowadays there is increasing evidence that organism-related factors play also a key role in the clinical course of the disease. The capsular polysaccharide is probably the major virulence determinant of *Streptococcus pneumoniae*, protecting him from phagocytosis (5). At present, more than 90 pneumococcal serotypes have been described on the basis of differences in the antigenic characteristics of capsular polysaccharides. Experimental studies in animal models have shown that pneumococcal serotypes differ in properties such as resistance to phagocytosis, ability to penetrate into tissues and capacity to activate the inflammatory response (5,6). Different studies have explored the relationship between serotypes and clinical presentation of pneumococcal disease and associations with the severity of the illness and mortality have been demonstrated (4,7,8-10).

The clinical spectrum of pneumococcal pneumonia is wide, from almost an asymptomatic disease in some cases to a devastating illness complicated with respiratory failure and septic shock in others. Septic shock is one of the most important factors influencing prognosis of patients with pneumococcal pneumonia. Interestingly, recent reports have suggested that infection caused by serotype 3 and 19A are independent risk factors for this complication (10,11). Respiratory failure is also an important and severe complication of pneumococcal pneumonia that causes high morbidity and mortality. However, there are scarce data available about the host and pathogen-related factors associated with this complication. We hypothesize that specific serotypes could also play a role in the development of respiratory failure in patients with pneumococcal pneumonia.

The aim of our study is to analyze possible risk factors associated to the development of respiratory failure in adult patients with invasive pneumococcal pneumonia (IPP). We also aimed to investigate the role of any specific serotype in this severe complication.

MATERIALS AND METHODS

Study population and setting.

Patients were enrolled as part of an ongoing observational study initiated in 1996 of all adults (aged ≥ 18 years) hospitalized with IPP in two teaching hospitals from Catalonia, Spain (Hospital Universitari Vall d'Hebron and Hospital Universitari Parc Tauli). In both hospitals, all microbiological strains isolated in sterile samples are collected systematically. When *S. pneumoniae* is isolated from a sterile sample, patient is included in the study and all the clinical and evolutive data are collected prospectively. The study was approved by the Ethics Board of the participating centers. Informed consent was waived due to the observational nature of the study.

Study variables and data collection.

From each patient the following variables were recorded: (1) sociodemographic and temporal data (age, gender, period of influenza epidemic, current tobacco smoking, long-term alcohol abuse and vaccination status with the 23-valent polysaccharide vaccine [PPV-23]); (2) underlying diseases (chronic lung disease, chronic heart disease, liver disease, cerebrovascular disease, diabetes and renal insufficiency); (3) immunosuppressive conditions (human immunodeficiency virus [HIV] infection, hematological cancer, solid cancer, solid organ or stem cell transplantation and current immunosuppressive therapy); (4) variables related to respiratory status (respiratory failure, need of mechanical ventilation and chest radiograph pattern); (5) other variables related to clinical presentation and outcome (septic shock, intensive care unit [ICU]admission, suppurative lung complications, length of hospital stay, mortality and Pneumonia Severity Index [PSI]); (6) antimicrobial therapy and (7) microbiological data (serotype and antibiotic susceptibility).

Definitions

IPP was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid cultures (10). Respiratory failure was defined as an oxygen saturation of <90% on room air or pressure of oxygen in arterial blood to fraction of inspired oxygen ratio (Pa02/FiO2) <250 (12). Mechanical ventilation was defined as any period of mechanically assisted ventilation via an endotracheal or nasotracheal tube. The radiographic examinations were done by radiologists as routine examinations, and the extent of infiltrates was classified as lobar, bilobar or multilobar, and uni or bilateral. For the purpose of this study we analyzed the presence of these variables at the moment of presentation in the Emergency Department.

An episode was considered in the epidemic period if it was diagnosed during the weeks of flu epidemic of each year. The influenza epidemic was defined as a weekly incidence >100 cases/100,000 inhabitants in Catalonia, and information was obtained from the Catalan Public Health System (13).

Smoking status was considered when a patient had smoked >10 cigarettes per day for at least 1 year, and alcoholism when a patient had consumed >80 g of alcohol daily for at least 1 year preceding the study. Chronic lung disease was defined on the basis of clinical, radiological and/or functional tests and included chronic obstructive pulmonary disease, severe asthma and interstitial lung disease. Septic shock was considered when vasoactive drugs were necessary to obtain appropriate arterial pressure values after fluid replacement. A patient was considered pneumococcal vaccinated if the PPV-23 had been ever administered before admission, according to the hospital and primary healthcare centre records.

Microbiological procedures

S. pneumoniae strains were identified by Gram staining, optochin susceptibility testing, bile solubility testing and latex agglutination testing. Antimicrobial susceptibility was determinated using the microdilution method in accordance with Clinical and Laboratory Standards Institute procedures (14). For the purpose of this study we classified pneumococcal isolates according the non-meningitis breakpoints: penicillin susceptible (MIC ≤ 2 μg/mL) or cefotaxime susceptible (MIC ≤ 1 μg/mL). Serotypes were performed by Quellung reaction and/or dot-blot assay at the Spanish Reference Laboratory for Pneumococci (Instituto de Salud Carlos III, Majadahonda, Spain).

Statistical analysis

We estimated attributable risk of respiratory failure due to any specific serotype as the difference of rate between the specific serotype and serotype 8. We have decided to choose this serotype as the reference group because it represents a frequent serotype in our study and had a similar distribution in the risk of respiratory failure in the univariate analysis between the two groups (OR≈1).

To identify the risk factors for respiratory failure, need of mechanical ventilation and chest radiograph pattern we compared dichotomous variables using a chi-square test and continuous variables using a T-test. To exclude variables with high co-linearity from the multivariate analysis, those significantly associated in the univariate analysis were assessed for bivariate correlation. We excluded from further analysis significantly correlated variables ($p < 0.001$). Clinical significant variables and those with a p value < 0.1 in the univariate analysis were entered as covariates into a forward stepwise logistic regression analysis for respiratory failure, need of mechanical ventilation and chest radiograph pattern. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. The fit of the model was tested using the Hosmer-Lemeshow goodness of fit test. Analyses were conducted using the statistical software package SPSS, version 15.0 (SPSS, Inc).

RESULTS

Patient characteristics.

Over the study period, 1258 consecutive adults with IPP were diagnosed, 615 of them (48.9%) had respiratory failure at admission. Clinical features and demographic characteristics of the patients are shown in table 1.

Patients with respiratory failure were significantly older and had a greater proportion of comorbid conditions. Patients were also more likely to have received prior pneumococcal vaccine than patients without respiratory failure (24.1% vs. 17.1%, p=.015). Regarding the severity of illness, patients with respiratory failure were more likely to have a bilateral pneumonia with multilobar involvement. As expected they needed more frequently mechanical ventilation. They also had a greater proportion of septic shock and required more often ICU admission than patients without respiratory failure. The case-fatality rate was significantly greater (25.5% vs. 3.5%, p<.001). In contrast the proportion of suppurative complications was similar in both groups.

Serotype distribution and antibiotic susceptibility.

Overall 1029 (81.8%) pneumococcal strains were available for serotyping. The most frequent serotypes are shown in figure 1. Pneumococcal serotypes most commonly associated with respiratory failure were serotype 3, 19A and 19F (respiratory failure developed in 65.8% of infections by serotype 3, in 65.5% by serotype 19A and in 81.5% by serotype 19F). The excess of risk of respiratory failure attributable were 20.4% (95% CI, 4.6 to 35.1) for serotype 3, 20.1% (95% CI, 1.7 to 36.6) for serotype 19A and 36% (95% CI, 16.3 to 55.7) for serotype 19F. Serotypes 3 and 19A were also the most frequently isolated in patients with bilateral infiltrates and in those who needed of mechanical ventilation. In contrast, serotype 1 was less frequently isolated in cases of respiratory failure with a risk attributable of -15.4% (95% CI, -30.6 to -0.6). Regarding antibiotic susceptibility, no differences in the rate of resistance to penicillin and cephalosporin were found between both groups.

Multivariate analysis of risk factors.

The results of the multivariate analysis are shown in tables 2 and 3. After adjustment by age, co-morbidities and pneumococcal vaccine status, independent risk factors for respiratory failure were: age > 50 years (OR 1.63), chronic lung disease (OR 1.54), chronic heart disease (OR 1.49), infection caused by serotype 3 (OR 1.97), serotype 19A (OR 2.34) and serotype 19F (OR 3.55) [Hosmer-Lemeshow p=0.96]. Pneumococcal pneumonia caused by serotype 1 showed a trend to be a protective factor. In the multivariate analysis we did not find independent associations between respiratory failure and previous pneumococcal vaccination. Because patients with underling chronic lung disease may have chronic respiratory insufficiency, we excluded these patients from the analysis in a second model obtaining similar results.

To assess the impact of pneumococcal serotypes in young patients, we analyzed the subgroup of patients ≤ 50 years. After adjustment, the only independent factors associated with respiratory failure were heavy alcohol consumption (OR 2.26), and infections caused by serotype 19A (OR 4.32), and serotype 19F (OR 9.82) [Hosmer-Lemeshow p=0.94].

Multivariate analysis also found that age > 50 years (OR 1.5), serotype 3 (OR 2.69) and serotype 19A (OR 2.75) were independent risk factors for bilateral infiltrates in the radiological pattern [Hosmer-Lemeshow p=0.86]. In the same way, smoking (OR 1.99) and infections caused by serotype 3 (OR 2.97), serotype 19A (OR 2.43) and serotype 19F (OR 3.3) were identified as independent determinants of the need of mechanical ventilation [Hosmer-Lemeshow p=0.84].

DISCUSSION

The results of this large observational study of hospitalized adults with IPP support the hypothesis that specific pneumococcal serotypes play a key role in the development of respiratory failure in patients with pneumococcal pneumonia. This observation has particular interest in the era of conjugate vaccines, because of the continuous replacement of serotypes. In our study, serotypes 3, 19A and 19F were found

to be the main risk factors for respiratory failure, bilateral radiograph involvement and need of mechanical ventilation.

Several studies have shown that specific serotypes are associated with different clinical patterns of pneumococcal disease. Brueggemann et al classified pneumococcal serotypes according to their capacity to cause invasive disease. Serotypes 1, 5 and 7F were classified as high invasive serotypes, and they were associated to invasive disease in younger adults, nevertheless they caused infections with low mortality rates. In contrast, serotypes 3, 19F and 23F had a low invasive potential, affecting older patients with co-morbidities and causing higher case-fatality rates (7-10). Specific serotypes have also been related with particular clinical presentations of pneumococcal disease. Thus, after the implementation of the 7-valent conjugate vaccine an increase of suppurative complications were observed associated to the emergence of serotypes 1 and 3 (15,16). In the same way, recent reports have found that septic shock in patients with pneumococcal pneumonia developed more frequently in infections caused by serotypes 3 and 19A (10,11). However, to our knowledge, no previous studies had addressed the relation between pneumococcal serotypes with respiratory failure. In our study we have found that serotypes 3, 19A and 19F were the main independent risk factors for development of respiratory failure, even higher than the risk related to age and comorbidities. These findings are consistent with previous data that associated these serotypes with greatest severity and mortality rates of pneumococcal disease (17,18). Although it was not statistically significant, serotype 1 showed a trend to be a protective factor to develop respiratory failure. The paradox of this serotype with a high capacity to develop invasive illness and empyema in young adults but with a lesser tendency to cause severe illness (6,15,16) could explain why the rates of empyema were similar in both groups.

The pathogenic mechanism to explain why some specific pneumococcal serotypes might cause respiratory failure is unknown. It has been described that heavily encapsulated serotypes could resist better to neutrophil-mediated killing (19) and induce a greater inflammatory response causing a more severe disease (17). In fact, serotypes 3, 19F and 19A that we have identified as the main risk factors of respiratory failure, match with those which have been found to be heavily encapsulated (17). However, it is certain that other serotypes with a thick capsule such as serotype 8 are not associated to a greater risk of respiratory failure, so other factors should be involved.

Recently Sanchez et al found that serotypes differ in the ability to adhere to the respiratory epithelium due to the expression of different adhesins, causing an impact on virulence (20). We hypothesize that the pneumococcus requires both factors, bacterial attachment and resistance to phagocytosis, in order to persist and difficult the bacterial clearance from the alveoli. This phenomenon could facilitate an excessive inflammatory response that finally leads to cellular damage and lung injury.

Other factors of the pneumococci rather than capsular polysaccharides are also implicated in the virulence and may affect disease severity. In this way different studies reveal an association between

the amount of bacterial load of pneumococci and the risk to develop septic shock, the need of mechanical ventilation and the mortality of pneumococcal disease (21,22). The genetic properties of pneumococci might also play a role. The relationship between these factors and the pathogenic basis for these observations is complex and poorly understood.

In addition to pathogen related factors host aspects have also a significant role on the severity of the illness (2-4). As we have found in our study other authors had reported that older age and chronic lung disease were independent risk factors for respiratory failure (23,24). Interestingly it should be noted that the serotypes, and not the underlying disease, were the main risk factors for respiratory failure in the multivariate analysis. This is best exemplified in the group of young adults without co-morbidities in whom the causal serotype became the most determinant factor of outcome. To avoid confusion regarding the role of underlying chronic lung disease in the propensity to cause respiratory failure, we made an analysis excluding these patients obtaining similar results.
Nevertheless, we must keep in mind that this study did not evaluate other host factors that might also influence the risk of developing respiratory failure. Recently, specific genetic polymorphisms have been associated with a poor respiratory outcome in pneumococcal pneumonia (23,25). Therefore, a tendency to a particular presentation of pneumonia might also be genetically determined for the ability of the individual to respond to the infection.

There is also some debate about the beneficial effects of the prior administration of the PPV-23 by improving clinical outcomes in patients with pneumonia. Some studies have observed better clinical outcomes, in patients who had previously received the PPV-23 compared with unvaccinated individuals (26,27). We also observed this beneficial effect on the incidence of septic shock and survival in vaccinated patients with HIV infection who developed an invasive pneumococcal infection (28). Regarding respiratory outcomes, Fisman et al found that prior receipt of pneumococcal vaccine was associated with a decreased risk of respiratory failure in a large cohort of adults with pneumonia (27). In our experience we have not been able to find a benefit of PPV-23 in the risk of respiratory failure. It is possible that the relative low rates of vaccination, the limited number of patients and the confounding factor derived from the fact that patients with increased risk of respiratory complications have a stronger indication to receive the PPV-23, make it difficult to establish this association.

It is known that influenza plays an important role in the incidence of pneumococcal pneumonia (29). Moreover, animal models suggest that previous influenza infection could result in a more severe pneumococcal disease (30). Although we do not have information regarding this viral co-infection in each patient, we analyzed the risk factors of respiratory failure according to the period of flu epidemic. The results suggest that the serotypes continue to be the main risk factor of respiratory failure irrespective of the period of influenza infection.

Some limitations of our study must be pointed out. First, the study included patients with IPP which represent only a proportion of all patients with pneumococcal pneumonia which may cause a possible bias due to the selection of the most invasive serotypes. This therefore makes it difficult to generalize the findings to all cases of pneumococcal pneumonia. Noteworthy, the majority of studies focused in pneumococcal serotypes are performed in patients with invasive disease. Second, it presents data from only two centers, so the results might not translate to other geographical areas where specific serotype distribution could differ. Finally, and despite the adjustment for an important number of covariables, other potential factors that might modulate the clinical presentation of pneumococcal pneumonia such as genetic properties of *S. pneumoniae* strains, genetic characteristics of the host or the effect of other viral co-infections have not been evaluated in our study.

Despite these limitations, we believe that our study have shown important and novel findings about the clinical presentation of invasive pneumococcal pneumonia. We have identified pneumococcal serotypes 3, 19A and 19F as the main determinants of respiratory failure, extensive radiograph involvement and need of mechanical ventilation, after adjusted by age, comorbidities and pneumococcal vaccination. This observation is of particular interest in the era of conjugate vaccines, because of the continuous replacement of serotypes.

ACKNOWLEDGMENTS

Role of authors: J. B. and V. F. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions were as follows:

Study concept and design: J. B., V. F.

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Critical revision of the manuscript for important intellectual content:

J. B., M. L., V. F., J. R., N.L., AM.P., M. P., A. P.

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All authors approved the final version of the manuscript.

Financial support. This work was institutionally supported by the Spanish Network for Research in Infectious Diseases (REIPI), RD06/008 from the Ministry of Science and Innovation, ‘‘Instituto de Salud Carlos III’’ and Centro de Investigación Biomédica en Red (CIBER) de EnfermedadesRespiratorias.

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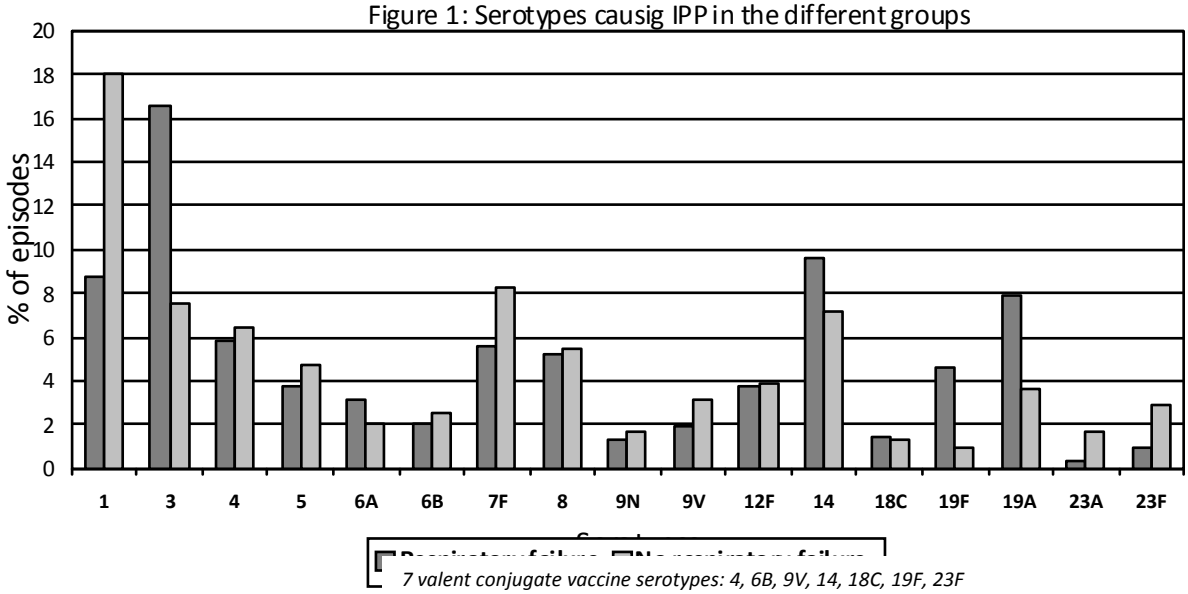
TABLE 1: Basal characteristics, clinical presentation and microbiological data of patients

Characteristics	*Pneumococcal pneumonia presenting with respiratory failure (N=615)*	*Pneumococcal pneumonia presenting without respiratory failure (N=643)*	*P value*
Sociodemographic and temporal variables			
Age (years, mean)	*62.13*	*55.42*	*<.001*
Male sex	*66.9% (411)*	*60.4% (388)*	*.019*
Period of influenza epidemic	*24.2% (155)*	*26.3% (169)*	*NS*
Previous pneumococcal vaccination	*24.1% (124)*	*17.1% (96)*	*.015*
Smoking	*56.2% (341)*	*55.3% (349)*	*NS*
Heavy alcohol consumption	*21% (127)*	*16.1% (101)*	*.028*
Underlying disease			
Chronic lung disease	*35.6% (216)*	*22.8% (144)*	*<.001*
Chronic heart disease	*23.1% (140)*	*12.2% (76)*	*<.001*
Cerebrovascular disease	*12.4% (62)*	*6.4% (34)*	*.001*
HIV infection	*15.4% (94)*	*19.4% (124)*	*.063*
Hematologic cancer	*7.5% (46)*	*7.4% (47)*	*NS*
Solid Cancer	*13.8% (84)*	*10.3% (68)*	*.068*
Clinical presentation and outcomes			
Bilateral pneumonia	*34.2% (210)*	*9.8% (63)*	*<.001*
Bilobar o multilobar pneumonia	*58.2% (296)*	*17% (109)*	*<.001*
Septic shock	*41.7% (254)*	*6.1% (39)*	*<.001*
ICU admission	*38.4% (234)*	*4.2% (27)*	*<.001*
PSI ≥ 4 [a]	*87.6% (518)*	*51.4% (216)*	*<.001*
Mechanical ventilation	*26.1% (161)*	*2.3% (15)*	*<.001*
Length of hospital stay (days, mean)	*17.83*	*10.62*	*<.001*
Empyema	*19.5% (120)*	*18.7% (120)*	*NS*
Hospital mortality	*25.5% (155)*	*3.5% (26)*	*<.001*
Microbiological data			
Serotype 1	*8.8% (42)*	*18% (98)*	*<.001*
Serotype 3	*16.5% (79)*	*7.6% (41)*	*<.001*
Serotype 7F	*5.6% (27)*	*8.3% (45)*	*.111*
Serotype 8	*5.2% (25)*	*5.4% (30)*	*.467*
Serotype 19A	*7.9% (38)*	*3.7% (20)*	*.004*
Serotype 19F	*4.6% (22)*	*0.9% (5)*	*<.001*
Serotype 23A	*0.4% (2)*	*1.7% (9)*	*.07*
Serotype 23F	*1% (5)*	*2.9% (16)*	*.045*
Penicillin susceptibility [b]	*97.5% (600)*	*98.5% (633)*	*NS*
Cephalosporin susceptibility [c]	*97.7% (601)*	*97% (624)*	*NS*

[a] *PSI ≥ 4: Indicate a Pneumonia Severity Index ≥ 4 at the moment of admission at the Emergency Department.*
[b] *Includes isolates with MIC ≤ 2 ug/ml.*
[c] *Includes isolates with MIC ≤ 1 ug/ml.*

Figure 1: Serotypes causig IPP in the different groups



7 valent conjugate vaccine serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F

TABLE 2: Multivariate analysis: variables associated to respiratory failure.

All adults patients		
Respiratory failure	***OR (95% CI)***	***P value***
Age, > 50 vs. 18-50 years	*1.63 (1.15-2.30)*	*.006*
Chronic lung disease	*1.54 (1.10-2.15)*	*.012*
Chronic heart disease	*1.49 (1.01-2.22)*	*.049*
Serotype 1	*0.63 (0.40-1.01)*	*.054*
Serotype 3	*1.97 (1.23-3.16)*	*.005*
Serotype 19A	*2.24 (1.14-4.42)*	*.020*
Serotype 19F	*3.55 (1.22-10.28)*	*.020*

Adjusted ORs: adjusted for age, sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A, 19F, 23A and 23F) and comorbidities associated with respiratory failure (chronic lung disease, chronic heart disease, cerebrovascular disease, solid cancer and HIV infection).

Adults excluding patients with chronic lung disease		
Respiratory failure	***OR (95% CI)***	***P value***
Age, > 50 vs. 18-50 years	*1.96 (1.37-2.85)*	*<.001*
Serotype 3	*2.52 (1.44-4.4)*	*.001*
Serotype 19A	*2.58 (1.14-5.82)*	*.023*
Serotype 19F	*3.7 (1.08-12.69)*	*.037*

Adjusted ORs: adjusted for age, sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A, 19F, 23A and 23F) and comorbidities associated with respiratory failure (chronic heart disease, cerebrovascular disease, solid cancer and HIV infection).

Patients aged 18-50 years		
Respiratory failure	***OR (95% CI)***	***P value***
Heavy alcohol consumption	*2.26 (1.29-12.25)*	*.010*
Serotype 19A	*4.32 (1.38-13.51)*	*.012*
Serotype 19F	*9.82 (1.06-90.78)*	*.044*

Adjusted ORs: adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A and 19F) and comorbidities associated with respiratory failure (chronic lung disease, cerebrovascular disease and HIV infection).

Patients aged > 50 years		
Respiratory failure	***OR (95% CI)***	***P value***
Chronic lung disease	*1.45 (1.03-2.05)*	*.035*
Chronic heart disease	*1.69 (1.14-2.48)*	*.008*
Serotype 1	*0.53 (0.3-0.93)*	*.026*
Serotype 3	*2.39 (1.45-3.93)*	*<.001*
Serotype 19F	*3.45 (1.11-10.73)*	*.032*

Adjusted ORs: adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A and 19F) and comorbidities associated with respiratory failure (chronic lung disease and cerebrovascular disease).

TABLE 3: Multivariate analysis: variables associated to bilateral infiltrates and mechanical ventilation.

Bilateral infiltrates	***OR (95% CI)***	***P value***
Age, > 50 vs. 18-50 years	*1.5 (1-07-2.1)*	*.018*
Serotype 3	*2.69 (1.74-4.14)*	*<.001*
Serotype 19A	*2.75 (1.55-4.88)*	*.001*

Adjusted ORs: adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 12, 19A and 19F) and comorbidities associated with bilateral infiltrates (solid cancer and HIV infection).

Mechanical ventilation	***OR (95% CI)***	***P value***
Smoking	*1.99 (1.34-2.94)*	*.001*
Solid cancer	*0.42 (0.2-0.87)*	*.019*
Serotype 3	*2.97 (1.84-4.8)*	*.<.001*
Serotype 19A	*2.43 (1.25-4.72)*	*.001*
Serotype 19F	*3.3 (1.32-8.21)*	*.010*

Adjusted ORs: adjusted for sex, smoking, alcohol consumption, previous pneumococcal vaccination, period of influenza epidemic, serotypes (1, 3, 19A, 19F and 23F) and comorbidities associated with mechanical ventilation (solid cancer).