The University of Louisville Journal of Respiratory Infections

Volume 2 | Issue 1 Article 10

4-6-2018

Bacteremic Pneumococcal Pneumonia: a Longitudinal Study in 279 Adult Patients from a Single Center

Jorge H. Gentile
Servicio de Infectología, Hospital Santamarina, Tandil, Argentina

Claudia Hernandez
Laboratorio de Microbiología, Hospital Santamarina, Tandil, Argentina

Monica D. Sparo
Servicio de Infectología, Hospital Santamarina, Tandil, Argentina

Edgardo M. Rodriguez
Area de Bioestadística, FCV-UNCPBA

Carolina Ceriani
Area de virología, FCV-UNCPBA, CIVETAN-CONICET

See next page for additional authors

Bacteremic Pneumococcal Pneumonia: a Longitudinal Study in 279 Adult Patients from a Single Center

Cover Page Footnote
Correspondence To: Dr. Jorge Gentile Work Address: Uriburu 950 Tandil CP 7000-Argentina, Work Email: gentilejorgeh@gmail.com Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

Authors
Jorge H. Gentile, Claudia Hernandez, Monica D. Sparo, Edgardo M. Rodriguez, Carolina Ceriani, and Florencia Bruggesser

University of Louisville
Journal of Respiratory Infections

ORIGINAL RESEARCH

Bacteremic Pneumococcal Pneumonia: a Longitudinal Study in 279 Adult Patients from a Single Center

*Jorge Hector Gentile[1], Claudia Hernandez[2], Monica Delfina Sparo[1], Edgardo Mario Rodriguez[3], Carolina Ceriani[4], Florencia Bruggesser[1]

Abstract

Background: Bacteremic pneumococcal pneumonia (BPP) is the most common clinical presentation of invasive pneumococcal disease (IPD). Although it has been extensively studied, there is little knowledge in our region in relation to burden of disease, demographic and outcome features.
Methods: We conducted a prospective, longitudinal, observational study from 1989 to 2015 in adult patients with BPP, in order to deepen our knowledge of the characteristics of this disease in our community hospital in Tandil, Argentina.
Results: 279 patients were included. The mean incidence was 2.8/1000 admissions with a sharp decrease in the last two years, reaching 0.8/1000 admissions. Mean patient age was 60 years. Comorbidities were found in 65% of the cases. Non-respiratory symptoms occurred in 50% of cases. Infiltrates on chest x ray were predominantly unilateral (75%) and lobar (57%). Regarding severity, a low PSI score I-II-II was found in 178 patients (64%), 60 (22%) were admitted to ICU, 40 (14%) required mechanical ventilation, and 21 (8%) developed empyema. Penicillin resistance was not found. Mortality was 18% (49/279), and by a multivariate analysis it was associated with confusion (OR= 5.44), age>80 years (OR =5.72), leukopenia (OR =5.73) and dyspnea (OR=7.87).
Conclusions: In this study of 279 bacteremic pneumococcal pneumonia we reinforce previous knowledge on this disease regarding incidence and clinical features and confirm a considerable an early mortality associated to age and severity of disease at onset. Recent changes in incidence of BPP in adults could be secondary to herd effect of PVC 13 a vaccine that is mandatory in children in our community since 2012.

DOI: 10.18297/jri/vol2/iss1/10
Received Date: February 13, 2018
Accepted Date: March 29, 2018
Website: https://www.louisville.edu/jri
Affiliations:
[1] Servicio de Infectología, Hospital Santamarina, Tandil, Argentina
[2] Laboratorio de Microbiología, Hospital Santamarina, Tandil, Argentina
[3] Area de Bioestadística, FCV-UNCPBA
[4] Area de virología, FCV-UNCPBA, CIVETAN-CONICET

Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is the most common cause of community acquired pneumonia (CAP) in adults accounting for most cases of pneumonia hospitalizations and deaths [1-2]. Bacteremic pneumonia is the most frequent invasive pneumococcal disease (IPD) in adults and remains a major cause of morbidity and mortality despite improvements in medical care [2-3]. From older and recent studies, it is estimated that approximately 20% of patients with pneumococcal pneumonia develop bacteremia [3-4], with a mortality rate ranging between 15-35%.

More than 50% of *S. pneumoniae* bacteremia cases occur in elderly patients and most studies show increased pneumococcal-related deaths in this population [1-3-5]. Variations between reported fatality rates might be explained by differences between studied populations including demographic factors, underlying health conditions, severity of illness at the time of admission, and bacterial factors. Also, geographical and temporal situations should be considered. On the other hand, drug resistance does not appear to contribute to mortality or ICU admission rates [5].

Despite the fact that BPP is a frequent and severe disease, there is minimal information regarding BPP in our city. We report here the result of 26-year prospective study in patients with BPP treated in our hospital, to assess local disease incidence, clinical, radiographic and microbiological features, as well as to evaluate factors related to mortality.

Methods

Study Design and Study Population

This was a longitudinal, prospective observational study of adult patients with BPP evaluated at the Santamarina Hospital in the city of Tandil. The hospital is a 130-bed primary care community hospital. Tandil is a city with a population of 130,000 inhabitants located in the province of Buenos Aires, Argentina.

Inclusion/exclusion criteria

Inclusion criteria: Patients 18 years or older with BPP that were assisted in the emergency room and admitted to the hospital or

*Correspondence To: Dr. Jorge Gentile
Work Address: Uriburu 950 Tandil CP 7000-Argentina,
Work Email: gentilejorgeh@gmail.com

treated in ambulatory setting between 1989 and 2015.
Exclusion criteria: having been hospitalized in the last 30 days, or presented with any other evidence suggestive of nosocomial pneumonia, severe immunosuppression such in transplantation, AIDS or receiving chemotherapy or other immunosuppressive drugs.

Study definitions/variables
Pneumonia was defined as the presence of a new infiltrate on chest radiograph plus two or more of the following clinical manifestations including: fever (axillary temperature >37.8°C), cough, production of purulent sputum, pleuritic chest pain and dyspnoea. BPP was defined as a diagnosis of pneumonia with one or more positive blood cultures for *S. pneumoniae*.

Identification of patients with BPP: one of the authors of this manuscript, (CH or JG), or a resident, reviewed admissions to the hospital daily, including holidays. The laboratory informed as soon as possible, when *S. pneumoniae* was isolated from blood culture. Data of chart was reviewed and a form was completed within 48-72h of admission. All patients were questioned, examined and followed exclusively by the authors. (JG or CH). When a patient with criteria of BPP was not admitted and sent home we strived to contact him in order to assist and include him in the study.

Hospital based incidence was calculated dividing number of BPP/adult patients admitted annually to the hospital x 1000. Seasonal distribution was registered. Population incidence, was calculated during the period 2010- 2015, adding to our series of patients with BPP admitted to the other two centres of the city, and considering population variations in the period.

The following variables were recorded on admission directly from the subject, or from documentation in chart or interview with relatives: age, sex, duration of illness before consult, underlying chronic conditions such as diabetes, chronic renal failure, congestive heart failure, chronic lung disease, neurologic disease, malignancies, HIV infection, alcoholism, hepatic disease, smoking, prior antimicrobial therapy as well as clinical signs and symptoms. Living in nursing home or homelessness was registered too.

Patients with dull percussion and bronchial breathing sounds on auscultation were considered as having clinical consolidation. Hypotension was defined as systolic arterial tension below 90mmHg. Abdominal pain, vomiting, hypotension, and confusion were considered nonpulmonary symptoms.

Classical pneumococcal infection was considered if patients had all four of the following features: fever, pleuritic chest pain, lobar consolidation on chest X ray and leucocytosis. Pleural fluid examination was performed in all patients with pleural effusion. Empyema was considered when macroscopic pus or bacteria were identified in pleural fluid.

History of pneumococcal vaccination was recorded in all cases and considered positive in patients who had received at least a single dose of 23-valent pneumococcal polysaccharide vaccine within the last 5 years. On admission, patients were stratified into risk classes I to V based on Pneumonia Severity Index (PSI) score [6].

Laboratory
Leukocytosis was considered when white blood cells were more than 12,000/ml and leukopenia when WBC <4,000/ml

Microbiological Testing
S. pneumoniae was identified using standard microbiology procedures. One set of blood cultures were collected from each patient at entry, which is considered standard of care for patients with CAP admitted to the hospital.

Conventional broth culture using nutritionally enriched media was used until 1997, after which fully automated, continuous blood culture monitoring equipment (BacT/ALERT® 3D BioMérieux, Inc. 100 Rodolphe Street, Durham, NC) became available. High quality sputum specimens (containing <10 squamous epithelial cells and >25 Polymorph Nuclear cells per low power field) were processed for bacterial diagnosis. Briefly, sputum was homogenized in 1.2 ml of sterile saline, spread onto a glass slide, air dried and heat fixed. Strains were identified based on Gram stains and morphology: gram-positive cocci found in singles, in pairs or in short chains were indicative of pneumococci infection. Sputum samples were inoculated on blood agar and chocolate agar plates and incubated at 35°C with 5-10% CO_2 for 72 hours. All *S. pneumoniae* isolates were tested for penicillin susceptibility by diffusion, using 1 µg oxacillin disks and by broth micro-dilution test. Isolates were also screened for susceptibility to erythromycin, tetracycline, and levofloxacin using disk diffusion method. In addition, minimum inhibitory concentration (MIC) tests were used to determine susceptibility to erythromycin, extended spectrum cephalosporins, fluoroquinolones, tetracycline, trimethoprim sulfametoxazol, clindamycin, cefuroxime and vancomycin, in accordance to Clinical and Laboratory Standards Institute (CLSI, 2012) established guidelines [7].

Radiology
Images on chest radiograph were classified by one of the investigators (JG) according to pattern (lobar consolidation, interstitial infiltrate, bronchopneumonia, pleural effusion) and extension (number of lobes affected, bilateral involvement)

Outcome
Patient were followed for 30 days after diagnosis, and complications were recorded, namely: pleural effusion, empyema, admission to ICU and need of mechanical ventilation. Overall case fatality rate was defined as death due to any cause within 30 days of hospitalization. Overall case fatality rate was defined as death due to any cause within 30 days of hospitalization.

Statistical Analysis
Qualitative variables are presented as the mean and range(min-max), while categorical variables are presented as frequency and percent. Contingency tables were used to measure associations with calculation of the chi-squared or Fisher's exact test, and odds ratio (OR) were estimated. Multiple logistic regression analyses was performed to evaluate those factors found to be significant by univariate analysis and previously hypothesized to affect mortality. Two-tailed p-values are reported, with statistical significance when $p<0.05$. SAS V9.3 statistical software was used for calculations (SAS, Institute Inc. Cary, NC, USA).

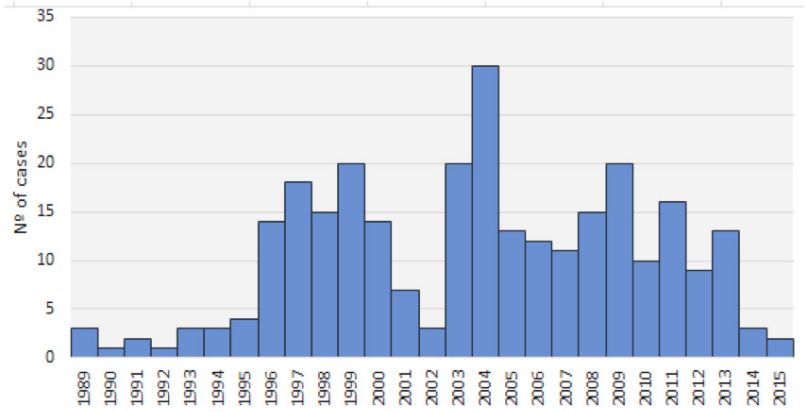

Figure 1 Number of cases of BPP between 1989-2015 (n=279)

Results

Epidemiology: 279 patients were included. Distribution of cases showed a sporadic pattern along the study ranging from 3 to 30 cases per year **Figure 1**. A decrease of 50% was observed in the last two years of the study. Hospital-based incidence of BPP was 2.1 cases/1,000 admissions and population-based incidence was 11.8 per 100,000 person-years (95% CI, 11.65-12.01), while 38% of episodes occurred in winter. The mean time from onset of illness to hospital admission was 2.9 days (1.15).

Two patients, the only individuals who had received antipneumococcal vaccine, both with humoral immunodeficiency multiple myeloma and hypogammaglobulinemia, had recurrent episodes of BPP.

The main demographic, comorbidities, clinical findings, radiographic, laboratory, severity and outcome features of patients are showed in **Table 1A and Table1B**.

Table 1A Main characteristics of study population. Differences between survivors and mortalities by univariate analysis.

	Study Population	Survivors	Mortalities	Pvalue
Total number of patients	279	230	49	
Demographics				
Mean age	59.7 SD+18.42			
18-50	76(27.24)	70(92.1)	6(7.89)	
50-65	81(29.03)	68(83.9)	13(16)	
65-80	83(29.74)	69(83.1)	14(16.8)	
>80	39(13.9)	23(58.9)	16(41)	<0.0001
Males/females	177			
Females	102			
Comorbidities				
One or more	180(64.5)	144 (62.61)	36(73.47)	0.1491
Cigarette smoking	75(26.8)	64(27.83)	11(22.45)	0.44
COPD	51(18.09)	13(5.65)	38(77.55)	0.0998
CHF	47(16.85)	15(6.52)	32(65.31)	0.0046
Alcoholism	44(15.77)	5(2.17)	39(79.59)	0.2390
Diabetes	28(10.04)	3(1.30)	25(51.02)	0.4353*
Liver disease	21(7.53)	4(1.74)	17(34.69)	0.0771*
Malignancy	20(7.17)	5(2.17)	15(30.61)	0.3635*
Neurologic disease	19(6.91)	5(2.17)	14(28.57)	0.3451*
Renal failure	9(3.23)	3(1.30)	6(12.24)	0.1970*
HIV infection	5(1.79)	4(1.73)	1(2.04)	
Physical Examination				
Fever	212(75.99)	186(80.8)	26(53)	<0.0001
Cough	158(56.63)	139(60.4)	19(38.7)	0.005
Dyspnoea	140(50.8)	98(42.6)	42(85.7)	0.0001
Chest pain	114(40.86)	106(46)	8(16.3)	0.0001
Consolidation	105(37.6)	94(40.8)	11(22.4)	0.01
Expectoration	79(28.32)	70(30.4)	9(18.3)	0.08
Hypotension	79(28.3)	56(24.3)	23(46.9)	0.0015
Confusion	55(19.7)	34(14.7)	21(42.8)	<0.0001
Abdominal Symptoms	59(17.9)	43(24.7)	7(14.2)	0.26
Non-pulmonary Symptoms	139(50)	108(47)	31(43)	0.0131

Fisher Exact test*
COPD-Chronic obstructive pulmonary disease CHF-Congestive heart failure PSI-Pneumonia severity index

Table 1B Patient characteristics of study population. Differences between survivors and mortalities by univariate analysis.

	Study Population	Survivors	Moratlities	Pvalue
Total number of patients	279	230	49	
Radiographic findings				
Unilateral infiltrate	209(74.91)	178(77.39)	31(63.26)	0.0384
Bilateral infiltrate	56(24.35)	40(17.39)	16(41.02)	0.0154
Lobar	160(57.34)	143(62.17)	17(34.69)	0.0006
Diffuse	102(36.55)	76(33.04)	26(53.06)	0.0057
Pleural effusion	49(17.56)	40(17.39)	9(18.36)	0.8705
Laboratory				
Mean Hematocrit	37.7(16-59)			
White blood cells	16800 (900-44700)	17276	13247	
Leukocytosis	177(63.44)	156(67.82)	21(42.85)	0.0010
Leukopenia	28(10.03)	14(6.08)	14(28.57)	<0.0001
Severity				
PSI Score I	47 (16.84)			
PSI Score II	71(25.44)			
PSI Score III	60(21.5)			
PSI Score IV	94(33.69)			
PSI Score V	7(2.5)			
PSI Score I-II-III	178(63.7)	167(72.6)	11(22.4)	<0.0001
PSI Score IV+V	101(36.2)	52(22.60)	38(77.55)	<0.0001
Complications				
ICU admission	60(21.50)	32(13.9)	28(57.14)	<0.0001
Mechanical Ventilation	40(14.33)	14(6.08)	26(53.06)	<0.001
Empyema	21(7.52)	18(7.82)	3(6.12)	0.707

The classic association of fever, chest pain, leukocytosis and lobar consolidation was present in 35 patients (14%), all of whom survived.

Non-pulmonary symptoms as abdominal pain, confusion and hypotension were present in 50% of cases. In 3 cases there was associated meningitis, and in one case purulent pericarditis.

Antibiotic treatment: Ninety five percent of BPP cases admitted to the hospital received monotherapy and 5% combined therapy. Fifteen patients were managed as outpatients, and treated with oral antibiotics as amoxicillin, clarithromycin, and fluoroquinolones, or intramuscular ceftriaxone. βeta-lactam antibiotics (cefotaxime, ceftriaxone, ampicillin, ampi/sulbactam) were used in 93% of patients.

Mortality: 49 patients died, resulting in an overall mortality rate of 16.7%: 27 deaths (55%) occurred within the first 3 days of hospitalization. Mean time elapsed between hospital admission and death was 5.2 days (median time 3 days) and there was an increment of death with age. Factors found to be significantly associated with mortality in univariate analyses were: age >80 years, dyspnea, hypotension, confusion, nonpulmonary symptoms, bilateral and diffuse infiltrates on chest radiograph, leukopenia, and high PSI score. Conversely, fever, chest pain and lobar infiltrates were significant predictors of survival. Multivariate analysis is shown in **Table 2**.

Table 2 Multivariate analysis of variables potentially associated with mortality

Factor	OR	(95% CI)	P
Fever	0.292	(0.13-0.66)	0.0033
Chest pain	0.3619	(0.13-0.95)	0.04
Age of >80 years	4.03	(1.55-10.49)	0.0042
Confusion	5.43	(2.24-13.19)	0.0002
Leukopenia	6.27	(2.24-18.38)	0.0008
Dyspnea	8.58	(3.20-23.04)	<0.0001

Microbiology: All pneumococcal strains were found to be susceptible to penicillin (MIC=0.006-2 μg/ml) and ceftriaxone (MIC =0.012 to 0.019 μg/ml). Percentages of resistance to other antibiotics were: erythromycin 8.1% (MIC =0.064 – 256 μg/ml), clindamycin 6.4% (MIC= 0.024-128 μg/ml), doxycycline 6.9% (MIC=0.5-64.0 μg/ml). Resistance rate to fluoroquinolones (levofloxacin) remained low 2.8% (MIC=0.38-8.00 μg/ml). Only 4 patients had S. pneumoniae isolated simultaneously in sputum and blood. One case of BPP and simultaneous pulmonary tuberculosis was detected.

Discussion

In this study of 279 patients with bacteremic pneumococcal pneumonia we confirm a considerable early mortality associated to increased age and increased severity of disease at time of presentation.

Overall annual rate of BPP in this study population was 11.8 cases/100,000 person-years, which is in agreement with other published results [8-10]. The reduction in the last two years could be secondary to herd effect of PVC 13, a vaccine that is mandatory in children in our city since 2012. The average age of 60 years found for the patients in our study is comparable to the mean age in other studies (range between 52 and 64 years old)[5,8,11].

Regarding underlying conditions and in agreement with previous published results, cigarette smoking, was the most prevalent risk factor, followed by chronic obstructive lung disease and congestive heart failure [10,12,13]. In fact, current cigarette smoking was predictive of BPP in one study [8] and was associated to septic shock in another [14].

Interestingly, one third of the patients had no evidence of any predisposing condition for BPP. We believe that this group deserves to be exhaustively evaluated in order to gain knowledge in the prevention of IPD.

Clinical manifestations were similar to those reported in the literature [12,15], except for sputum production which was less frequent: only 30% of the patients with BPP presented this symptom and this fact has been observed by others [16,17]. Isolation of *S. pneumoniae* from sputum specimens was very uncommon in our population. This can be related to early hospital admission or to differences in BPP and non-BPP pathophysiology [18].

Classical presentation with fever, chest pain, leukocytosis and lobar pattern on chest radiograph, although uncommon, showed significant correlation to better outcome.

Almost half of the patients had nonpulmonary symptoms from onset, so it is important to consider hemodynamic, abdominal or neurological manifestations in patients at risk for IPD in order to ensure prompt diagnosis and treatment [19].

As has been previously described most patients with BPP presented marked leukocytosis and neutrophilia. Leukopenia, although less frequent, was significantly related to worst outcome, as others investigators have observed [18,20].

In agreement with already published large series of patients [5,21,22] the presence of bacteremia was not associated with severity of illness, since most patients presented low PSI score (classes I-III). Even though the PSI score was not originally designed as a prognostic tool for BPP, it can be used to define illness severity because, although less specific, it is still more sensitive than other scores for BPP-related risk of death [23]. Surprisingly, patients in the low score risk group had higher than expected mortality rate. These were mainly young individuals, with specific comorbidities not identified by the PSI score such as asthma, COPD; HIV infection, obesity, alcohol and tobacco use. As some experts have reported, mortality within a certain score stratum may differ depending on the patient group [23].

It is possible that pneumococcal disease by itself may differ in previously healthy patients compared to those who present an underlying condition.

Main complications overlapped with those frequently observed in patients with CAP admitted to hospital, namely: ICU stay, presence of pleural effusion, empyema and need for mechanical ventilation [5].

Mortality rate was 17%, similar to the results obtained by others in larger series [5,11,13] and most deaths (55%) occurred within the first 3 days after hospital admission as already has been described [4,5]. In our study, severity of disease at onset was the most important factor associated with death. The presence of severe symptoms such as dyspnea, hypotension or altered mental status, may suggest organ dysfunction, indicating early signs of sepsis. As others have observed, age was found to be an important marker of poor prognosis, mostly in patients over 80 years of age [5,24].

Penicillin resistance is not a problem in our region, so we can continue using βeta-lactams, alone or combined for treatment of BPP.

This study has several limitations. The study was performed in a single center, in a small city then generalizibility of this data may be limited. Since the study was performed during a prolonged period of time, the local pactice for therapy of BPP may have changed and affected the clinical outcomes. In this study *S. pneumoniae* serotyping was not performed.

In conclusion we found that BPP is a common infection with a considerable mortality, mostly after the first days of onset of the disease. Deaths were associated with increased age, increased severity of disease at onset and leukopenia.

We believe that a large-scale collaborative epidemiological study is needed in the region to gain further insight related to circulating pneumococcal strains. This knowledge would allow

us to improve the use of available pneumococcal vaccines. We must not forget that surveillance strategies focusing on BPP, underestimate pneumococcal disease burden and hence the true benefits of pneumococcal immunization in adults.

Funding Source: No financial support.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

References

1. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012 Jan 1;67(1):71-9.
2. Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, O'Brien KL, Andreo F et al.; AGEDD Adult Pneumococcal Burden Study Team. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One. 2013;8(4):e60273. https://doi.org/10.1371/journal.pone.0060273 PMID:23565216
3. Weycker D, Strutton D, Edelsberg J, Sato R, Jackson LA. Clinical and economic burden of pneumococcal disease in older US adults. Vaccine. 2010 Jul;28(31):4955–60. https://doi.org/10.1016/j.vaccine.2010.05.030 PMID:20576535
4. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Annals of internal medicine. 1964 May 1;60(5):759-76.
5. Yu VL, Chiou CC, Feldman C, Ortqvist A, Rello J, Morris AJ et al.; International Pneumococcal Study Group. An international prospective study of pneumococcal bacteremia: correlation with in vitro resistance, antibiotics administered, and clinical outcome. Clin Infect Dis. 2003 Jul;37(2):230–7. https://doi.org/10.1086/377534 PMID:12856216
6. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997 Jan;336(4):243–50. https://doi.org/10.1056/NEJM199701233360402 PMID:8995086
7. CLSI, Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement, in CLSI document M100-S22.2012, Clinical and Laboratory Standards Institute: Wayne, PA
8. Shariatzadeh MR, Huang JQ, Tyrrell GJ, Johnson MM, Marrie TJ. Bacteremic pneumococcal pneumonia: a prospective study in Edmonton and neighboring municipalities. Medicine. 2005 May 1;84(3):147-61.
9. Moroney JF, Fiore AE, Harrison LH, Patterson JE, Farley MM, Jorgensen JH, Phelan M, Facklam RR, Cetron MS, Breiman RF, Kolczak M. Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. Clinical Infectious Diseases. 2001 Sep 15;33(6):797-805.
10. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20-year longitudinal study, 1978–1997. The American journal of medicine. 1999 Jul 26;107(1):34-43.
11. Berjohn CM, Fishman NO, Joffe MM, Edelstein PH, Metlay JP. Treatment and outcomes for patients with bacteremic pneumococcal pneumonia. Medicine. 2008 May 1;87(3):160-6.
12. Musher DM, Alexandraki I, Graviss EA, Yanbeiy N, Eid A, Inderias LA, Phan HM, Solomon E. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. Medicine. 2000 Jul;79(4):210-21.
13. Wagenvoort GH, Sanders EA, de Melker HE, van der Ende A, Vlaminckx BJ, Knol MJ. Long-term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. Vaccine. 2017 Mar 27;35(14):1749-57. https://doi.org/10.1016/j.vaccine.2017.02.037 PMID:28262334
14. García-Vidal C, Ardanuy C, Tubau F, Viasus D, Dorca J, Liñares J et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. Thorax. 2010 Jan;65(1):77–81. https://doi.org/10.1136/thx.2009.123612 PMID:19996337
15. Watanakunakorn C, Bailey TA. Adult Bacteremic Pneumococcal Pneumonia in a Community Teaching Hospital, 1992-1996n: A Detailed Analysis of 108 Cases. Archives of internal medicine. 1997 Sep 22;157(17):1965-71.
16. Brandenburg JA, Marrie TJ, Coley CM, Singer DE, Obrosky DS, Kapoor WN, Fine MJ. Clinical presentation, processes and outcomes of care for patients with pneumococcal pneumonia. Journal of general internal medicine. 2000 Sep 1;15(9):638-46.
17. Palma I, Mosquera R, Demier C, Vay C, Famiglietti A, Luna CM. Impact of bacteremia in a cohort of patients with pneumococcal pneumonia. Jornal Brasileiro de Pneumologia. 2012 Aug; 38 (4): 422-30.
18. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. Clinical infectious diseases. 2004 Jul 15;39(2):165-9.
19. Jover F, Cuadrado JM, Andreu L, Martínez S, Cañizares R, de la Tabla VO, Martin C, Roig P, Merino J. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. European journal of internal medicine. 2008 Jan 1;19(1):15-21.
20. Blot M, Croisier D, Péchinot A, Vagner A, Putot A, Fillion A, Baudouin N, Quenot JP, Charles PE, Bonniaud P, Chavanet P. A leukocyte score to improve clinical outcome predictions in bacteremic pneumococcal pneumonia in adults. InOpen forum infectious diseases 2014 Sep 1 (Vol. 1, No. 2). Oxford University Press.
21. Bordón J, Peyrani P, Brock GN, Blasi F, Rello J, File T et al.; CAPO Study Group. The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. Chest. 2008 Mar;133(3):618–24. https://doi.org/10.1378/chest.07-1322 PMID:18198264
22. Metersky ML, Ma A, Bratzler DW, Houck PM. Predicting bacteremia in patients with community-acquired pneumonia. American journal of respiratory and critical care medicine. 2004 Feb 1;169(3):342-7.
23. Spindler C, Ortqvist A. Prognostic score systems and community-acquired bacteraemic pneumococcal pneumonia. Eur Respir J. 2006 Oct;28(4):816–23. https://doi.org/10.1183/09031936.06.00144605 PMID:16737983
24. Chi RC, Jackson LA, Neuzil KM. Characteristics and Outcomes of Older Adults with Community-Acquired Pneumococcal Bacteremia. Journal of the American Geriatrics Society. 2006 Jan 1;54(1):115-20.