ISSN 0025-7680

ORIGINAL ARTICLE MEDICINA (Buenos Aires) 2003; 63: 9-14

ADULT BACTEREMIC PNEUMOCOCCAL PNEUMONIA ACQUIRED IN THE COMMUNITY

A PROSPECTIVE STUDY ON 101 PATIENTS

JORGE H. GENTILE[1], MONICA D. SPARO[1], MARIA E. MERCAPIDE[1], CARLOS M LUNA[2]

[1] *Servicio de Infectología, Laboratorio de Microbiología, Hospital R. Santamarina, Tandil;* [2] *División Neumonología, Hospital de Clínicas José de San Martín, Facultad de Medicina, Universidad de Buenos Aires*

Abstract Our objective was to describe incidence, clinical, radiographic and microbiological features of bacteremic pneumococcal pneumonia (BPP) in our environment. A total of 101 patients (7 were treated as outpatients), older than 18 years of age suffering BPP were prospectively evaluated. The incidence was 2.8 cases per 1000 admissions, 50 were males, mean age was 59.9 years (19-97), mortality was 11.8%. Eighty three percent of fatalities occurred within 3 days of admission. Mortality rate increased with advancing age. Fever, cough and chest pain were the commonest presenting symptoms and 44% of patients had extrapulmonary manifestations. Cigarette smoking, chronic obstructive lung disease, alcoholism and congestive heart failure (CHF) were the commonest underlying conditions. CHF was more frequent in non-survivors (p = 0.002). A lobar pattern at chest radiograph predominated in survivors and a diffuse pattern in non-survivors (p = 0.007). Pleural effusion (20.7%), empyema (7.9%) and respiratory failure (7.9%) were the main complications. Underlying diseases were present in 100% of non-survivors (p = 0.03). Ninety four percent of patients were treated with beta-lactam antibiotics. *Streptococcus pneumoniae* was isolated from sputum in 6 cases. Three out of 101 *S. pneumoniae* isolates recovered from blood samples (one from each patient) presented organisms resistant to penicillin. We observed an incidence of BPP that is similar to the observed in other countries. There are clinical and radiographic differences between survivors and non-survivors. Penicillin-resistant *S. pneumoniae* is still an unusual problem in our area.

Key words: bacteremic pneumococcal pneumonia, community acquired pneumonia, *Streptococcus pneumoniae*

Resumen ***Neumonía neumocóccica bacteriémica de la comunidad. Un estudio prospectivo en 101 pacientes.*** Se evaluaron en forma prospectiva 101 pacientes ³ 18 años admitidos al hospital con diagnóstico de NNB. El objetivo fue conocer la incidencia y describir las características de la enfermedad, así como la susceptibilidad antibiótica de cepas invasivas de *Streptococcus pneumoniae*. Se halló una incidencia de 2.8 casos/1000 admisiones; 50 fueron varones. La edad media fue de 59.9 años (19-97). Los síntomas principales fueron fiebre, tos y dolor torácico, el 44% consultó por síntomas extrapulmonares. Las comorbilidades más frecuentes fueron tabaquismo, EPOC; alcoholismo e insuficiencia cardíaca. En los sobrevivientes predominó el infiltrado lobar, y en los fallecidos el difuso p=0.007. La insuficiencia cardíaca fue más frecuente en fallecidos (p= 0.002) Se detectaron las siguientes complicaciones: derrame pleural (20.7%), empiema (7.9%), insuficiencia respiratoria (7.9%). La mortalidad fue del 11.8%, ocurriendo el 83% de los decesos dentro de las primeras 72 h de la admisión;100% de los fallecidos padecía otras enfermedades agregadas; 94 pacientes se trataron con ATB betalactámicos; 7 pacientes se trataron en forma ambulatoria. Se aisló *S. pneumoniae* de esputo en 6 casos. De 101 aislamientos de *S. pneumoniae* recuperados de hemocultivo (uno de cada paciente), 3 presentaban resistencia a penicilina. Concluimos que la NNB tiene una incidencia similar en nuestro medio a la de otros países. Existen diferencias clínicas y radiológicas entre sobrevivientes y fallecidos. La resistencia antibiótica del *S. pneumoniae* es poco frecuente en nuestro medio.

Palabras clave: neumonía neumocóccica bacteriémica, neumonía adquirida en la comunidad, *Streptococcus pneumoniae*

Bacteremic pneumococcal pneumonia (BPP) remains an important cause of fatal community acquired pneumonia (CAP)[1]. *Streptococcus pneumoniae* is responsible of 15 to 50% of CAP cases[2]. The ratio of nonbacteremic to BPP has been recognized to be about 4:1[3]. Since the beginning of the antibiotic era the mortality rate of BPP has remained between 20 and 40%[4]. More than 50% or the cases of *S. pneumoniae* bacteremia occurred among elderly people, so that most of the studies coincided that the mortality rate is age-dependent[5,6]. An increase in the incidence of BPP over time is expected, especially because of an increase in the age of the population and of an incidence of some predisposing conditions such as AIDS. Increasing number of reports of isolation of *S.*

Received: 1-VIII-2002 Accepted: 17-X-2002

Postal address: Dr. Jorge H. Gentile, Uriburu 950, 7000 Tandil, Argentina
Fax: (54-11) 2293-424626 e-mail: jorgeg@poraire.net.ar

pneumoniae resistant to penicillin and other antimicrobials have renewed concerns about pneumococcal disease. In our country the higher reported rate of penicillin resistance for *S. pneumoniae* is about 30%, with a wide range depending on the area[7,8]. There are few data concerning pneumococcal invasive disease in Latin America. The lack of regional data may be one potential factor contributing to the limited use of anti-pneumococcal vaccine in the population at risk for pneumococcal diseases as occur in others sites[6]. With the aim of describing the incidence, clinical findings, radiographic features and microbiology of BPP in our area we performed the present study.

Patients and Methods

Between January 1995 and December 2000, we prospectively studied all adults over age 17 who came to the Hospital R. Santamarina, Tandil, Argentina, with a clinical diagnosis of CAP. This institution is a 120 bed public community hospital that serves as a primary care hospital in a city with a population of 100 000 inhabitants. All patients suffering BPP were identified, enrolled and followed-up.

Diagnosis of pneumonia was considered in patients presenting a new infiltrate at the chest radiograph and acutely presenting clinical findings including: fever > 37.8 °C axillary, cough, expectoration, pleuritic chest pain, dyspnea, abdominal pain and mental confusion.

Bacteremia was diagnosed when *Streptococcus pneumoniae* was isolated from at least one of the blood cultures obtained on entry to every patient with CAP, independently of its severity. The figures of incidence were calculated for hospitalized patients based on hospital admission rate.

General information and definitions: Information collected upon entry included: age, sex, place of residence, travels, duration of illness before visit to the hospital presenting symptoms and signs, diagnostic criteria for pneumonia, prior antimicrobial therapy for any indication, past medical history (especially underlying conditions such as diabetes, renal failure, congestive heart failure, chronic lung disease, neurologic disease, malignancy, HIV status, alcoholism and current smoking history). Infiltrates on chest radiograph were categorized according to the presenting pattern (air space pneumonia, interstitial, bronchopneumonia, pleural effusion) and extension (number of lobes involved, bilateral involvement). Empyema was considered if pus or bacteria were founded in pleural fluid. Hypotension was defined as systolic arterial tension lower than 90mm Hg. Consolidation was considered as the presence of dull percussion sounds and bronchial breath sounds at clinical examination. The PORT prediction rule was used to calculate the pneumonia severity index (PSI) that has been described to estimate the severity of disease at admission[9].

Outcome: Follow-up was extended for 30 days after the diagnosis. We sought on a group of severe specific complications, namely: pleural effusion, admission in the ICU, use of mechanical ventilation and development of meningitis. Fatal outcome was assessed regarding type of care (ambulatory, general ward or ICU), antimicrobials used, complications and need for mechanical ventilation.

Microbiology: Two sets of blood cultures were collected from each patient at entry. Conventional broth culture system using nutritionally enriched media were used during 1997, then the fully automated continuously monitoring blood culture system (*Bactec 9250, Becton-Dickinson*) became available and was used. High quality sputum specimens (defined when both < 10 epithelial cells and > 25 PMNs per low power field were present), were submitted for bacterial cultures and processed as follows: sputum was homogenized with 1-2 ml of sterile saline, then it was placed on a glass slide, air dried, heat fixed and stained by the Gram technique. Gram-positive cocci found singly, in pairs or in short chains were indicative of pneumococci. A loopfull of sputum was streaked on the surface of a blood agar infusion and chocolate agar medium and incubated at 35 °C with 5-10% CO_2 for 72 h. In all isolates susceptibility to penicillin was tested by using 1microgram oxacillin disk and dilution method by broth microdilution; testing for erythromycin was done by minimum inhibitory capacity (MIC) test and disk diffusion methods. MIC method was used for the susceptibility to extended spectrum cephalosporins, fluoroquinolones, tetracycline, cotrimoxazole, clindamycin, cefuroxime and vancomycin.

Data processing and analysis: Data were reviewed and then entered into a database and subjected to standard verification procedures. Results are expressed as mean ± SD. Data were analyzed using commercially available packages (Primers for Biostatistics, Mc Graw Hill Inc, New York, NY; and SPSS, SPSS Inc, Chicago, IL). Chi-square or Fisher exact tests were used for comparisons. Findings potentially related with death were studied by an univariate approach using chi-square test. Significance level was set at a p value < 0.05.

Results

One hundred and one episodes of BPP identified in 101 patients, were enrolled in the study. This resulted in an incidence of 2.8 cases for 1000 admissions, and 17 cases/100 000 persons year. Median age was 61, mean 59.9 ± 18.3, range 19-97 years. Fifty patients were male and 51 female, no patient had received anti-pneumococcal vaccine.

Clinical and radiographic presentation: The mean time period from onset of disease to admission was 3.3 ± 2.2, range 1-15 days. Fever, cough and chest pain were the most common presenting symptoms. Non respiratory symptoms occurred in 44% (Table 1). Fever was more frequent in survivors (p = 0.037) while dyspnea was more frequent in non-survivors (p = 0.027). The classic association of fever, chest pain, leukocytosis, and lobar pattern on chest radiography was present only in 21 patients (20.8%), all of them survived. The most common signs were crackles, 73/101 (72.2%), consolidation, 33/101 (32.6%), and hypotension, 27/101 (26.7%). Seventy six patients (75.2%) had one or more underlying condition. Underlying conditions were more common among non-survivors than among survivors (p = 0.035). Two underlying conditions were present in 45% of patients and three in 12.8%. Among this patients with BPP, 25% had the antecedent of a previous episode of pneumonia (Table 2). Considering the radiographic presentation most of patients had unilateral (76%) and lobar patterns (63.3%).

TABLE 1.– Presenting symptoms of adult patients with bacteremic pneumococcal pneumonia (BPP)

Presenting symptoms	Survivors N=89 n	(%)	Deaths N=12 n	(%)	All patients N=101 n	(%)	p value *
Fever	76	(85.3)	7	(58.3)	83	(82.1)	p=0.03
Cough	51	(57.4)	7	(58.3)	58	(57.4)	
Chest pain	42	(47.1)	2	(16.6)	44	(43.5)	
Disnea	34	(38.2)	9	(75.0)	43	(42.5)	p=0.02
Sputum production	33	(37.0)	4	(33.3)	37	(36.6)	
Abdominal pain	21	(23.6)	1	(8.3)	22	(21.7)	
Mental confusion	17	(19.0)	5	(41.6)	22	(21.7)	

**Only significant differences for p values are shown*

TABLE 2.– Underlying conditions in adult patients with bacteremic pneumococcal pneumonia*

Underlying condition	Survivors n=89 n	%	Non-survivors n=12 n	%	All patients N=101 n	%	p value ‡
Smoking	23	(25.8)	2	(16.6)	25	(24.7)	
COPD †	17	(19.1)	4	(33.3)	21	(20.7)	
Alcoholism and /or cirrhosis	17	(19.1)	2	(16.6)	19	(18.8)	
Congestive heart failure	12	(13.4)	5	(41.6)	17	(16.8)	0.028
Diabetes	11	(12.3)	1	(8.33)	12	(11.8)	
Malignancy	6	(6.7)	2	(16.6)	8	(7.9)	
Neurologic diseases	5	(5.6)	2	(16.6)	7	(6.9)	
Renal insufficiency	4	(4.5)	0	(0)	4	(5.0)	
HIV	0	(0)	2	(16.6)	2	(2.0)	
Only one	26	(29.2)	6	(50)	32		
Two or more	29	(32.6)	6	(50)	35		

**Many patients had more than 1 underlying condition*
‡ Only significant p values are shown
† Chronic obstructive pulmonary disease

Lobar pattern was more frequent in survivors (p=0.0077), while the significantly more frequent presentations observed in n non-survivors were diffuse (p = 0.0077) and bilateral patterns (p= 0.0210).

Pneumonia severity index: Mean score of PSI was 86.5 +21.6; in survivors it was 72.1 ± 24.7 and in non-survivors 98.3 +12.2. Grouping the patients according with their PSI score they were classified as group I in 12 cases (11.9%), group II in 31 cases (30.7%), group III in 31 cases (30.7%), group IV in 26 cases (25.7%) and in group V in 1 case (1%). In the 12 non survivors the distribution was group II 1case, group III 3 cases, group IV 7 cases, V 1 case.

Laboratory findings: Hematocrit was 38 ± 7 (range: 18-55%) and white blood cells (WBC) count was 15 297 ± 9193 (range: 1000-47 900/ml). Neutrophilia was common, mean 87 ± 8.9 (range 43-97%). Leukocytosis (>12 000 WBC/ml) was present in 65/101 patients (63.3%). Leukopenia (<4 000 WBC/ml) was detected in 11 patients (10.9%); 5 of them suffered alcoholism (p = 0.031), 2 were HIV positive, one had cancer and three did not have any associated condition.

Complications: Incidence and rates of complications are displayed in Table 2. Pleural effusion was detected in 21 patients (20.7%); 8 of these patients (7.9%) developed empyema, 1 of them died before intervention, 3 required chest tube drainage and the resting 4 did well with only needle aspiration plus antibiotic therapy. Sixteen patients that required admission in the ICU were considered as suffering severe CAP. Eight of these patients with severe CAP progressed to severe respiratory failure and required mechanical ventilation, 5 of them (62.5%) died. Meningitis was diagnosed in 3 patients, one of them (33.3%) deceased.

TABLE 3.– *Findings on chest radiograph of patients with bacteremic pneumococcal pneumonia*

Radiographic finding	Survivors n=89		Non-survivors n=12		Total n=101		p value*
	n	%	n	%	n	%	
Unilateral infiltrate	73	(82)	6	(50)	79	(78.2)	
Bilateral infiltrate	16	(17.9)	6	(50)	22	(21.7)	p=0.0210
Lobar/segmented	61	(68.5)	3	(25)	64	(63.3)	p=0.0077
Diffuse/Bronchoneumonia	28	(31.4)	9	(75)	37	(36.6)	p=0.0077
Pleural effusion	19	(21.3)	2	(16.6)	21	(20.7)	

**Only significant p values are shown*

TABLE 4.– *Fatality rate for adult bacteremic pneumococcal pneumonia*

Age range (y)	Nº of Patients	Mortality n %)
18-44	21	1(4.76)*
45-64	38	5(13.16)*
³ 65	42	6(14.29)*
Total	101	12(11.8)

**Fisher´s Exact test (2 tails) p = 0.62 (non significant)*

Mortality: Twelve patients died resulting in a mortality of 11.8%. Ten (83%) of these deaths happened within the first 3 days of hospitalization. All 12 dying patients had some underlying condition. The mean time from admission to death was 2.4 days (1-5). Six of the 16 patients (37.5%) admitted to the ICU, died. Fatality rate increased with advancing age, no patient younger than 40 years old died, but this did not reach statistical significance (p = 0.62). Congestive heart failure was the more frequent underlying condition in 5/12 patients who died (p = 0.0028).

Treatment: Initial antibiotic therapy was administered intravenously to the 94 hospitalized patients; 64 received ampicillin, 26 cefotaxime and 4 cephalotin. Eight patients had received ATB before admission (1 clarithromycin, 2 cefixime, 3 amoxicillin, 1 azitromicin and 1gentamycin). Seven were treated with combination therapy (1 cephalotin + gentamycin 1, 3 ampicillin + gentamycin, 1 cephalotin + amikacyn, 1 cefotaxime + gentamycin and 1 cefotaxime + clarithromycin. No patient received initial antibiotics to which the isolated pneumococus was resistant. In 6 cases the empiric initial treatment was changed after the isolation of *S. pneumoniae* to reduce the antimicrobial spectrum. Oral antimicrobials were administered to the 7 patients managed as outpatients (2 amoxicillin, 3 clarithromycin and 2 trovafloxacin), all they were younger than 40 years old, had no comorbidities, did not suffered complications and all of them survived.

Microbiology: Streptococcus pneumoniae was isolated from all patients in 1 or 2 blood cultures. Only twenty high quality sputum specimens were available for culture, pneumococcus could be isolated from this sputum in 6 patients (5.9%). Additionally, *S. pneumoniae* was isolated from the CSF in 3 patients (2.9%) and from pleural fluid in 4 (3.9%). All strains were susceptible to vancomycin, cefotaxime, cefuroxime, trovafloxacin and levofloxacin. Sixty-eight percent were resistant to sulphametoxazole + trimetroprim, 8% were resistant to eritromycin, 8% to doxyciclin and 7% to clindamycin. Sensitivity to penicillin was reduced, according with oxacillin screening, in 3 strains (3%); in 1 these strain MIC was = 2 µg/ml and in 2 strains it was 0.48-0.96 µg/ml.

Discussion

The incidence of BPP in the literature ranges from 0.8 to 2.3/1000 admissions and 9.1 to 18/100 000 inhabitants[4, 10, 11]. Results in the present study were 2.8/1000 admissions and 17/100 000 inhabitants.

Clinical features were not different from those reported by other authors[2,11], nevertheless, we observed a significant predominance of classic clinical, laboratory and radiographic findings (fever, chest pain, leukocytosis, and lobar pattern) in survivors, and the presence of dyspnea in non-survivors. Non-respiratory findings were commonly observed, almost half the patients (44%) presented symptoms such as abdominal pain, hypotension and confusion at the onset of illness; these findings may sometimes distract the physician's attention and preclude an adequate diagnosis. Hemodynamic, abdominal or neurological findings must been considered in patients at risk of invasive pneumococcal disease in order to speed up the diagnosis and therapy of BPP.

The mean duration of illness previous to hospital admission was 3.3 ± 2.2 (range 1-15) days. This feature together with the low rate of administration of previous antibiotics might be the reason explaining why we had an improved detection of bacteremia in the present study.

Current smoking, COPD, alcoholism and CHF were the most frequently associated conditions. The area where is located our hospital has a low incidence of HIV, this explains why only two patients were recognized as HIV infected. In coincidence with previous publications, non-survivors had more associated conditions than survivors ($p = 0.0348$)[12]. CHF was the only isolated underlying condition significantly associated with increased mortality ($p = 0.028$).

The commonest pattern observed at chest radiograph was lobar consolidation, this pattern was more commonly observed in survivors ($p=0.0077$). Bilateral and diffuse patterns were more common in non-survivors ($p = 0.0210$ and $p = 0.0077$ respectively), this fact has been described in previous publications[10,11].

Leukocytosis was very common, 64% of patients had more than 12 000 WBC/ml. On the other hand, leukopenia was less common, it was found to be associated with alcoholism. This association could be related to the suppression of production of and response to granulocytic colony stimulating factors due to the direct effect of alcohol and acetaldehyde, or be secondary to the pneumococcal bacteremia by the production of sequestration of neutrophils in the lung; this last hypothesis has been demonstrated experimentally in rabbits[11]. We were not able to find any association between leukopenia and mortality as has been suggested in other studies[2, 3, 5].

The mortality rate was 11.8%. The lack of serotype distribution made it difficult to compare the fatality rate with others studies. Despite this, our figures are near the lowest end of several reports[14, 18].

Fatality rate in BPP in the pre-antibiotic era was over 85%[19,20]. During the last decades the case fatality rate ranged from 20 to 40% but it is not clear if Intensive Care Units were useful to improve survival rates[16, 21]. In the present study we failed to demonstrate a significantly higher fatality rate in the older patients despite the finding that there was a trend through an increased mortality rate as the patient's age increased[13, 14].

Ten of the 12 fatalities occurred during the first 72 hours after the admission of BPP; this is a well-known event that has been described in the pre-antibiotic era[10]. There is not adequate explanation for this early high mortality rate in BPP that is not modified by an early adequate antimicrobial therapy. Mortality occurring during the first 72 hours after hospitalization reflects severity of illness rather than inadequacy of therapy[21]. Perhaps host factors, such as sepsis mediators may explain the unaltered high early mortality. The severity of pneumococcal infection may in part be genetically mediated. Several authors have demonstrated that homozygosis of a neutrophil receptor for Fc (FcgR11a-R131) and genetic polymorphism of cytokines are associated with BPP and septic shock, explaining the higher predisposition to BPP and mortality[22, 25].

All the initial antibiotics chosen were effective against the isolated strain. Young patients without underlying conditions (all of them grade I or II of PSI)[9] were successfully treated as outpatients with oral antimicrobials. This observation coincides with the concept that antibiotic levels above MIC of common pathogens can be sustained with oral therapy and that the transient bacteriemia that is common by seen in patients with pneumococcal pneumonia, may be easily cleared with one or two doses of IV or oral antibiotics[26]. The lack of uniformity of the antibiotic therapy administered, prevented us from drawing any conclusion regarding the relationship between the different types of antibiotics used and the final outcome.

Most of the patients had non-productive cough; on the other hand, only half of sputum were of adequate quality for processing, and few of them resulted in pneumococcus isolation. This low bacteriologic yield of sputum in BPP has been referred to in previous studies[27]. The practical usefulness of bacteriology of sputum in the diagnosis of pneumonia remains controversial[28]. In contrast, blood culture was a useful tool in the etiologic diagnosis. Blood culture is one of the ways to obtain confirmatory evidence on the etiology of CAP, particularly if obtained at the onset of the disease before the start of therapy; especially taking into account that most of the patients do not provide adequate sputum for bacteriologic evaluation[28, 29, 30]. Penicillin resistant *Streptococcus pneumoniae* is more commonly isolated among patients with non-bacteremic pneumonia[31]. Drug resistance is low in our area and did not cause therapeutic failure in this study. Nevertheless, the potential presence of co-pathogens may justify the use of a combination of aminopenicillins with macrolides, tetracyclines or fluoroquinolones.

In conclusion, the incidence of BPP in our area is similar to that of previous reports in other areas of the world. Mortality rate was low (11.8%), and occurred early. Survivors and non-survivors had significantly different clinical presentation, radiographic patterns or underlying conditions. Sputum bacteriology had a low yield in BPP. The low level of resistance of *Streptococcus pneumoniae* to penicillin observed in our area indicates that aminopenicillins remain as a cost-effective antimicrobial option for the therapy of most of the patients with documented BPP.

References

1. Bartlett JG,Breiman RB, Mandell LA, File Jr TM. Community acquired pneumonia in adults: Guidelines for management. *Clin Infect Dis* 1998; 26: 811-38.
2. Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbactereic pneumococcal pneumonia. A prospective study. *Medicine* 2000; 79: 210-21.
3. Ortqvist A, Kalin M, Julander I, Mufson M. Death in bacteremic pneumococcal pneumonia. *Chest* 1993; 103: 710-6.
4. Moroney JF, Fiore EF, Harrison L, Patterson E, Farley MF, et al. Clinical outcomes of bacteremic pneumococcal pneumonia in the era of antibiotic resistance. C*lin Infect Dis* 2001; 33: 797-805.
5. Mufson MA, Stanek RJ. Bacteremic pneumococcal pneumonia in one American City: a 20 -year longitudinal study, 1978-1997. *Am J Med* 1999; 107 (1A) 34S-49S.
6. Plouffe JF, Breiman RF, Facklam RR. Bacteremia with *Streptococcus pneumoniae.* Implications for therapy and prevention. *JAMA* 1996; 275: 194-8.
7. Casellas JM, Smayevsky J, Jones RN, et al. Prevalence of antimicrobial resistance among respiratory tract isolates in two medical centers in Argentina: 1997 and 1998. Results from the SENTRY Antimicrobial Surveillance Program. 9th International Congress on Infectious Diseases, Buenos Aires, April 2000. Abstract 43.011.
8. Quinteros M, Rojas Molina C, Echeverría A, et al. Análisis de resistencia a penicilina y ceftriaxona en S*treptococcus pnemoniae* aislados de materiales respiratorios. IX Congreso Argentino de Microbiología, Buenos Aires, octubre 2001. Abstract P-97.
9. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low risk patients with community-acquired pneumonia. *N Eng J Med* 1997; 336: 243-50.
10. Mirzanejad Y, Roman S, Talbot J, Nicolle L. Pneumococcal bacteremia in two tertiary care hospitals in Winnipeg, Canada. *Chest* 1996; 109: 173-8.
11. Watanakunakorn C, Bailey TA. Adult bacteremic pneumococcal pneumonia in a community teaching hospital 1992-1996. A detailed analysis of 108 cases. *Arch Int Med* 1997; 157: 1965-71.
12. Musher D. *Streptococcus pneumoniae.* In: Mandell GL, Bennet JE, Dolin R (eds). Principles and Practice of Infectious Diseases. Fifth Edition, vol 2, London: Churchill Livingstone 2000; 2128-47.
13. Soto MD,Van Eeden SF, English D, Hogg JC. Bacteremic pneumococcal pneumonia: Bone marrow release and pulmonary sequestration of neutrophils. *Crit Care Med* 1998; 26: 501-9.
14. Ortqvist A, Kalin M, Julander I, Mufson MA. Death in bacteremic pneumococcal pneumonia. A comparison of two populations: Huntington W Va, and Stockholm, Sweden. *Chest* 1993; 103: 710-6.
15. Gransden WE, Eykyn SJ, Phillips I. Pneumococcal bacteremia: 325 episodes at St Thomas's hospital. *BMJ* 1985; 290: 505-8.
16. Hook EWIII, Hortoon CA, Schaberg DR. Failure of intensive care unit support to influence mortality from pneumococcal bacteremia. *JAMA* 1983; 249:1055-7.
17. Esposito AL, Community acquired bacteremic pneumococcal pneumonia: effect of age on manifestations and outcome. *Arch Int Med:* 1984; 945-8.
18. Lippman ML,Goldberg SK, Walkenstein MD, Herring W, Gordan M. Bacteremic pneumococcal pneumonia: a community hospital experience. *Chest* 1995; 108: 1608-13.
19. Ortqvist A. Pneumococcal disease in Sweden. Experiences and current situation. *Am J Med* 1999; 107 (1A): 44S-49S.
20. Tighman RC, Finland M. Clinical significance of bacteremia in pneumococcal pneumonia. *Arch Int Med* 1937; 59: 602-19.
21. Marrie TJ. Bacteremic pneumococcal pneumonia fatality rate. Is it really different in Sweden. *Chest* 1993; 103; 658-9.
22. Feikin DR,Schuchat A, Kolczac M, et al. Mortality from invasive pneumococcal pneumonia in the era of antibiotic resistance 1995-1997. *Am J Public Health* 2000; 90: 223-9.
23. Yee AMF, Phan HM, Salmon JE, Musher DM. Assotiation between Fc gamma R11a 131 allotype and bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2000; 30: 25-8.
24. Mira JP, Cariou A, Grall F, et al: Association of TNF 2, A TNF-alfa promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. *JAMA* 1999; 282: 561-8.
25. Waterer GW, Quansey MW, Cantor RM, Wunderink RG. Septic shock and respiratory failure in community-acquired pneumonia have different TNF polymorphism associations. *Am J Respir Crit Care Med* 2001; 163: 1599-604.
26. Siegel RE. The significance of serum vs tissue levels of antibiotics in the treatment of penicillin resistant *Streptococcus pneumoniae* and community acquired pneumonia (Are we looking at the wrong places?). *Chest* 1999; 116: 535-8.
27. Barret-Connor. The non value of sputum culture in the diagnostic of pneumococcal pneumonia. *Am Rev Resp Dis* 1971; 103: 845-8.
28. Najendra S, Bourbeau P, Brecher S, Dunne M, LaRocco M, Doern G. Sampling variability in the microbiological evaluation of expectorated sputa and endotracheal aspirates. *J Clin Microbiol* 2001; 39: 2344-7.
29. Duma RJ. Pneumococcal pneumonia. *In:* Bennet JC, Plum F (eds). Cecil Test Book of Medicine, Philadelphia: WB Saunders, 1996; 1569-76.
30. Chalasani NO, Valdecanas AL, Gopal AK, Mc Gowan JE Jr, Jurado RL. Clinical utility of blood culture in adults patiens with community acquired pneumonia without defined underlying risk. *Chest* 1995; 108: 932-6.
31. Ewig S, Ruiz M, Torres A, et al. Pneumonia acquired in the community trough drug resistant S*treptococcus pneumoniae. Am J Respir Crit Care Med* 1999; 159: 1835-42.