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Invasive and Complicated Pneumococcal Infection in Patients with Cancer

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ABSTRACT

Background: In susceptible patients, *Streptococcus pneumoniae* can cause complicated pneumonia and invasive pneumococcal disease. The aim of this study was to assess the clinical and antimicrobial features of complicated and invasive pneumococcal disease in patients with cancer. **Methods:** We conducted a retrospective study including all *S. pneumoniae* isolates between January 1, 2007 and December 31, 2015 in an oncology center. Capsular serotyping was done in isolates from sterile sites. **Results**: There were 103 episodes: 69 with invasive pneumococcal disease and 34 with complicated pneumonia. Sixty-two patients were male (60%); mean age was 50 years. Eighty-four isolates were susceptible to penicillin (81.6%), 11 (10%) were intermediate, and eight (8.3%) were resistant. Serotyping was performed in 64 isolates; the main serotypes identified were 3 (n = 13) and 19A (n = 11). No patient had a record of vaccination. Mortality at seven days attributed to pneumococcal infection was different in invasive pneumococcal disease (n = 18, 28.6%) vs. pneumonia (n = 3, 8.9%; p = 0.04). Thirty-day mortality related with the infectious process was statistically different between both groups: 21 patients with invasive pneumococcal disease (30.4%) and six with pneumonia (17.6%; p = 0.04). By logistic analysis, the risk factor associated with mortality was not having received appropriate antimicrobial treatment in the first 48 hours. **Conclusions:** *S. pneumoniae* is a pathogen related with high mortality in patients with cancer. Pneumococcal immunization needs to be reinforced in this population. (REV INVES CLIN. 2016;68:221-8)

Key words: Cancer. Invasive pneumococcal disease. Pneumonia. *Streptococcus pneumoniae*.

INTRODUCTION

Streptococcus pneumoniae is an important cause of community acquired pneumonia, bacteremia, and meningitis. In susceptible patients, pneumococcal pneumonia could lead to hospitalization related to respiratory distress and in some cases requiring mechanical ventilation. Invasive pneumococcal disease (IPD) is a serious, life-threatening infection that remains an important global cause of major illness despite the introduction of pneumococcal vaccines[1,2].

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The incidence of IPD and pneumonia is higher in immunocompromised individuals, even in the modern antibiotic era[1,2]. Patients with cancer are especially susceptible to severe pneumococcal infections, which carry significant morbidity and mortality[3-5]. Appropriate empirical antibiotic treatment initiated as soon as the infection is clinically suspected is mandatory to improve outcomes, especially in patients with neutropenia[3,4]. Certain cancer patients are more vulnerable, including those with Hodgkin's lymphoma or multiple myeloma[3].

Information on this group of patients is scarce. Therefore, we assessed the clinical features, antimicrobial susceptibility, serotypes, and outcomes of complicated and IPD in patients with cancer at a tertiary level oncology center in Mexico.

METHODS

Study design and subjects

We retrospectively analyzed all consecutive *S. pneumoniae* infections in patients who were seen at the National Cancer Institute (INCan) in Mexico City, Mexico, between January 1, 2007 and December 31, 2015.

INCan is a 135-bed referral teaching hospital for adult patients with cancer located in Mexico City, with an average of 170,000 medical visits, 35,000 chemotherapy sessions, and 7,500 hospital discharges per year. The study was undertaken with Institutional Review Board approval (INCAN/CI/388/15).

Data on demographic characteristics, underlying malignancies, concurrent diseases, main clinical symptoms, antimicrobial therapy, intensive care unit admission, type of pneumococcal disease, number of days of antimicrobial therapy, type of antimicrobials used (beta-lactams, third-generation cephalosporins, macrolides, fluoroquinolones, clindamycin, and vancomycin), and infection outcomes were retrieved from patients' medical records and computed institutional databases.

Laboratory procedures

Microbiologic evaluations were performed at the INCan Laboratory of Microbiology. *S. pneumoniae* was isolated by standard microbiological procedures. Antimicrobial susceptibility was tested by the oxacillin disk diffusion method for penicillin susceptibility, following the Clinical Laboratory Standards Institute (CLSI) methods and criteria[6]. For non-meningitis isolates, an oxacillin zone of ≥ 20 mm was considered susceptible to penicillin and predicted susceptibility for ampicillin and ceftriaxone. Capsular serotyping was conducted in isolates from sterile sites and was performed at the National Public Health Institute (INSP, Cuernavaca, Morelos, Mexico), by the Quellung reaction with type- and factor-specific antisera (Statens Serum Institut, Copenhagen, Denmark). Minimal inhibitory concentration was determined for penicillin, erythromycin, and chloramphenicol in these isolates.

Definitions

Pneumonia: Radiographic criteria on chest X-ray or computed tomography scan (CT) plus one or more of the following: fever (≥ 38°C) or hypothermia (< 35°C), new cough with or without sputum production, pleuritic chest pain, dyspnea, and altered breath sounds on auscultation.

Severe or complicated pneumonia: CURB-65 pneumonia severity score of ≥ 2 and the presence of pleural effusion, empyema or cavitation.

Invasive pneumococcal disease: Isolation of *S. pneumoniae* from a normally sterile body fluid such as blood, cerebrospinal fluid, pleural fluid, or ascites.

Appropriate antimicrobial treatment: When an antimicrobial agent had been initiated within the first 48 hours of the first symptoms and if the patient had received it for at least 72 hours, including an antibiotic to which *S. pneumoniae* was susceptible.

Clinical cure: Resolution of clinical symptoms and signs, and/or sterilization of blood or respiratory tract cultures after antimicrobial treatment, and/or radiographic resolution of pneumonia in patients who had presented with pulmonary infiltrates.

Death related with pneumococcal infection: Persistence of a clinical condition of sepsis at the time of death, or when death occurred during the first week after blood cultures were taken.

Overall case fatality rate: Death by any cause within 30 days of IPD onset.

Table 1. Clinical characteristics of 103 patients with cancer and *Streptococcus pneumoniae* infection classified as invasive disease or pneumonia episodes

Characteristic – n (%)	Total (n = 103)	Invasive disease (n = 69)	Pneumonia episodes (n = 34)	p
Age (years)*	52 (35-65)	52 (33-67)	55 (37-61)	0.248
Male	62 (60.2)	39 (56.5)	23 (67.6)	0.278
Body mass index*†	24.5 (22-28)	25.2 (22-28)	23 (21-26)	0.480
Hematologic neoplasia	45 (43.7)	33 (47.8)	12 (35.3)	0.227
Solid tumor	58 (56.3)	36 (52.2)	22 (64.7)	
Status of cancer				0.473
Recent diagnosis	41 (39.8)	24 (34.8)	17 (50.0)	
Progressive disease	36 (34.9)	26 (37.7)	10 (29.4)	
Relapse	12 (11.7)	9 (13.0)	3 (8.8)	
Clinical remission	11 (10.7)	10 (14.5)	1 (3.0)	
Stable disease	3 (2.9)	0	3 (8.8)	
Comorbidities				0.176
Diabetes mellitus	17 (16.5)	14 (20.3)	3 (8.8)	
Current active smokers	27 (26.2)	14 (20.3)	13 (38.2)	
Obesity	18 (17.5)	13 (18.8)	5 (14.7)	
HIV	3 (2.9)	1 (1.5)	2 (5.9)	
Other‡	12 (11.7)	7 (10.1)	5 (14.7)	
Previous hospitalization#	32 (31)	22 (32)	10 (29)	0.798
Lymphocytes (cells/mm^3)*	600 (300-1,050)	555 (265-850)	850 (350-1,450)	0.128
Neutrophils (cells/mm^3)*	5,250 (1,200-10,500)	4,650 (1,050-11,850)	5,850 (2,050-9,550)	0.708
Neutropenia (< 500 cells/mm^3)	21 (20.4)	16 (23.2)	5 (14.7)	0.436
Days of neutropenia*#	2 (1-9)	2 (1.0-10.5)	1 (1-3)	0.327
Recent chemotherapy§	49 (47.6)	37 (53.6)	12 (35.2)	0.08
Days from chemotherapy to infection*	13 (7-24)	13 (7-24)	13.5 (7-23)	0.883

*Interquartile range; †body mass Index = kg/m^2; ‡chronic pulmonary disease, coronary heart disease, liver failure, previous breast cancer, multiple sclerosis, chronic alcoholism; #during the last month; §chemotherapy applied during the previous three months.

Statistical analysis

Quantitative variables were calculated as median and interquartile range (IQR). Categorical data were analyzed using the chi-square or the Fisher exact test, as appropriate. For the analysis, the events were divided into two groups: IPD and severe or complicated pneumonia. A logistic regression model was employed to examine the effects of multiple risk factors on mortality. Variables included in the model were those found to reach a significance level of $p \leq 0.1$ in the univariate analysis. Overall survival (OS) rates were estimated by means of the Kaplan-Meier method and the log-rank test. Values for $p \leq 0.05$ were considered statistically significant. Data was analyzed using STATA v.12 (Stata Corp., College Station, TX, USA) statistical software.

RESULTS

There were 103 episodes of pneumococcal infections during the eight-year study period. Sixty-nine (67%) were classified as IPD and 34 (33%) solely as

pneumonia. Sixty-two patients were male (60.2%); median age was 52 (IQR, 35-65) years. Forty-five patients (43.7%) had a malignant hematological disease. Other clinical and demographic characteristics are depicted in table 1.

The most frequent pneumococcal manifestation was bacteremic pneumonia (n = 43; 41.7%), followed by pneumonia (n = 37; 36%). Ninety-four patients (91.3%) were hospitalized, with a median hospital stay length of eight days (IQR, 4-15 days).

Chest X-ray was performed in 94 patients (91.2%) and 10 patients had CT; 84 (79%) had findings related with lung infection. More than one lobe of the lung parenchyma was affected in 24 patients (23.3%), cavitation was seen in three (2.9%), and pleural effusions of different sizes in 19 (18.5%) patients. Other clinical findings are presented in table 2.

Twenty infections (19.4%) were classified as hospital acquired, with no differences between IPD and non-invasive disease (p = 0.982).

Eighty-four isolates were susceptible to penicillin (81.6%), 11 (10%) were intermediate, and eight (8.3%) were resistant. Serotyping was performed in 64 isolates (60.1%). The main serotypes identified were 3 (n = 13), 19A (n = 11), 19F (n = 5), 4 (n = 4), and 11A (n = 4) (Fig. 1). Forty-nine (76.5%) isolates belonged to a serotype contained in the 23-valent pneumococcal polysaccharide vaccine (PPV-23) (Pneumovax 23®; Merck, USA), and 43 (67.1%) to a serotype contained in the 13-valent pneumococcal conjugate vaccine (PCV-13) (Prevnar 13®; Pfizer, USA). No patient had a record of having received pneumococcal vaccination.

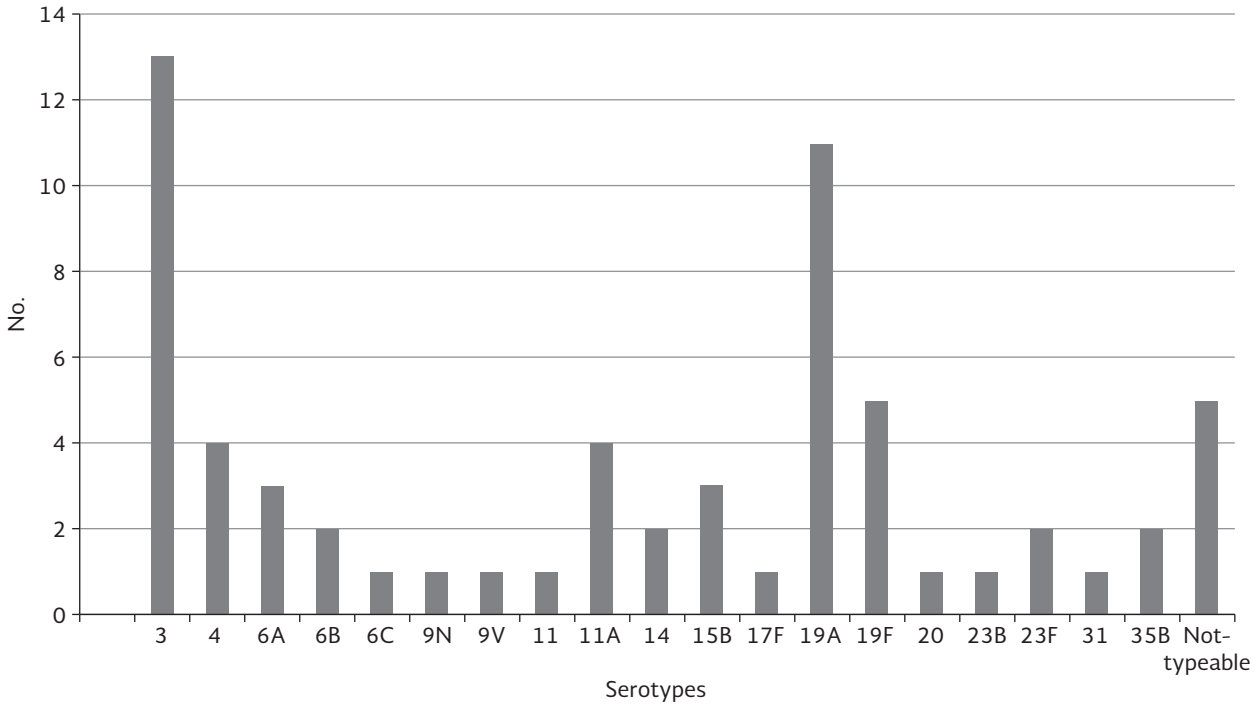
The majority of patients received ceftriaxone (n = 48; 57.1%), followed by vancomycin (n = 29; 34.5%), aminoglycosides (n = 28; 33.3%), β-lactams (n = 25; 29.8%), macrolides (n = 25; 29.8%), and ceftazidime (n = 20; 25%). Two or more effective drugs were simultaneously administered in 55 (65.4%) patients (Table 2). Combined antimicrobial treatment was associated as a protector variable in the univariate analysis for seven-day mortality (p = 0.008), but it was not confirmed in logistic regression analysis (p = 0.726). There were no differences in the analysis of 30-day mortality.

Table 2. Clinical characteristics related with *Streptococcus pneumoniae* infections in patients with cancer (n = 104)

Characteristic	No. of episodes (%)
Main clinical symptoms	
Fever	67 (65.0)
Cough	53 (51.5)
Dyspnea	41 (39.8)
Sputum	41 (39.8)
Malaise	19 (18.5)
Chest pain	15 (14.6)
Abdominal pain	14 (13.6)
Headache	12 (11.7)
Confusion/Disorientation	11 (10.7)
Infection type	
BSI*	7 (6.8)
Pneumonia	37 (35.9)
Pneumonia plus BSI	43 (41.7)
Empyema	3 (2.9)
Lung abscess	1 (1.0)
Meningitis plus BSI	3 (2.9%)
Peritonitis	6 (5.9)
Cholangitis	3 (2.9)
Hospitalization	94 (91.3)
Length of hospitalization (days)†	8 (4-15)
Intensive care unit (ICU) admission	8 (8.2)
Length of ICU (days)†	7 (6.0-9.5)
Deaths in the ICU	5 (5.1)
Patients who received antimicrobial treatment ≥ 48 h	84 (81.6)
Prescription of antimicrobials	
Ceftriaxone	48 (57.1)
Ceftazidime	21 (25.0)
Vancomycin	29 (34.5)
β-lactams	25 (29.7)
Macrolides	25 (29.7)
Clindamycin	14 (16.7)
Fluoroquinolones	13 (15.5)
Combined antimicrobials‡	55 (65.5)
Days with antimicrobials†	10 (7-13)
Outcome (30-day follow-up)	
Complete resolution of infection	61 (59.2)
Death related with pneumococcal infection	27 (26.2)
Death related with another cause	15 (14.6)

*Blood stream infection (BSI) without another documented source of infection; †median interquartile range; ‡combination of antimicrobials: ceftriaxone + clarithromycin (n = 18), ceftazidime + amikacin (n = 9), ceftriaxone + amikacin (n = 7), ceftriaxone + vancomycin (n = 6), ceftazidime + vancomycin (n = 6), piperacillin/tazobactam + clarithromycin (n = 5), and ceftazidime + clindamycin (n = 4).

Figure 1. Serotypes identified in 66 samples from patients with pneumococcal infection.



Fifteen patients (14.6%) died during the first 48 hours, all related with the infectious disease: 11 with IPD and four with pneumonia (p = 0.768). At seven days post-culture, 21 patients (20.4%) had died: 18 with IPD (28.6%) and three with pneumonia (8.9%; p = 0.04). At 30 days, 42 patients had died (40.1%): 32 with IPD (46.4%) and 10 with pneumonia (29.4%; p = 0.09). When deaths were directly attributed to the infectious process, there was a significantly higher mortality in patients with IPD (n = 21; 30.4%) than in those with pneumonia (n = 6; 17.6%; p = 0.04) (Fig. 2).

Logistic regression analysis showed that a risk factor for 30-day mortality was inappropriate antimicrobial treatment (Table 3).

DISCUSSION

This study assessed the disease burden, risk factors, microbiological features, and outcomes of pneumococcal infections in patients with cancer.

The mean age of these patients was younger than that reported in other series (52 vs. 64 years of age)[2,3]. This was probably related with the underlying neoplastic disease since patients with hematologic malignancies, who are usually younger, comprised 44% in our series.

A previous study reported that multiple myeloma presents a higher risk of pneumococcal infection related with defects in complement activation, neutrophil function, and functional hypogammaglobulinemia[2]. We found lymphoma as the most prevalent hematologic disease (17.5%), followed by leukemia (10.3%), and multiple myeloma (8.3%). We explain this finding because lymphoma is the most frequent hematologic disease seen at our hospital, followed by acute leukemia, and multiple myeloma as the third most frequent hematologic disorder.

About 20% of these cases were classified as hospital-acquired; other studies have reported that the prevalence of hospital-acquired pneumococcal pneumonia is 10-20%[7,8]. This finding is important since hospitalization is a risk factor for multidrug-resistant bacterial pneumonia; thus, it is important to consider penicillin-resistant pneumococcal strains.

Solid tumors comprised 56% of the whole group, with lung cancer being the most prevalent malignancy

Figure 2. Kaplan-Meier curve. Mortality in the first 30 days after *Streptococcus pneumoniae* isolation, divided into invasive disease (n = 69) and pneumonia episodes (n = 34).

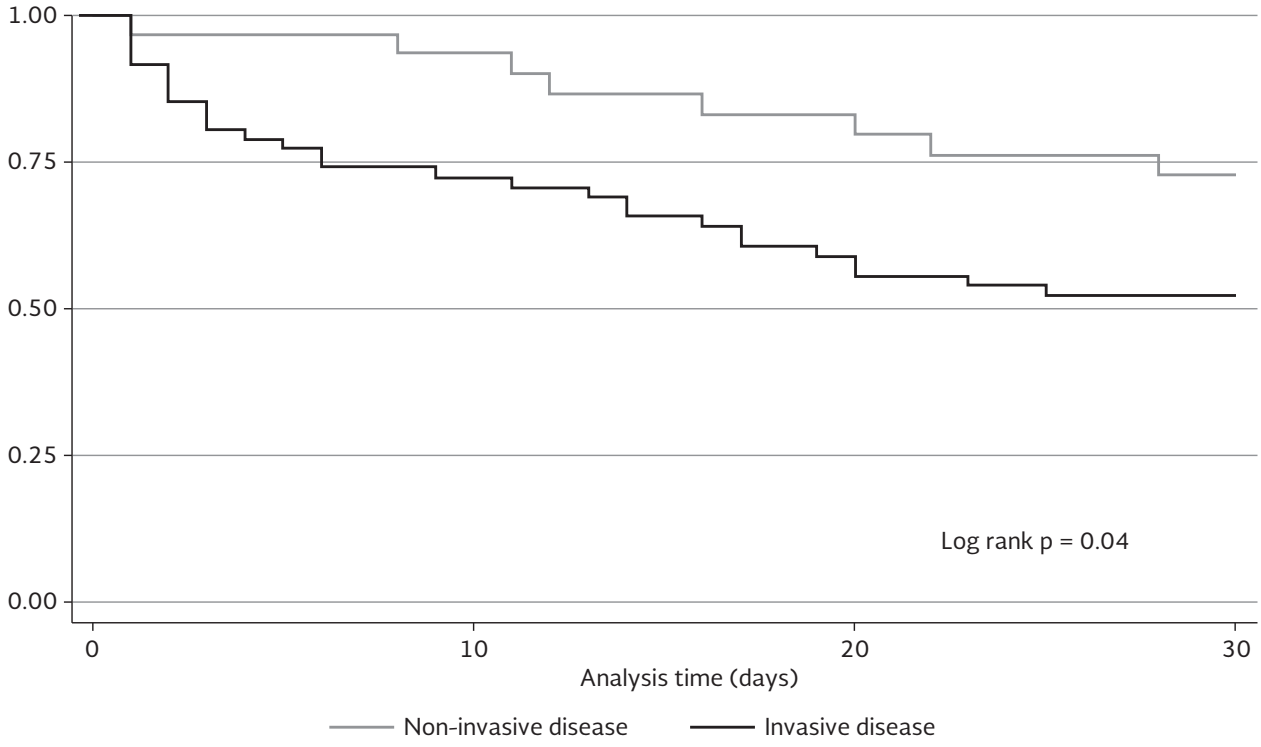


Table 3. Risk factors for 30-day mortality in patients with pneumococcal infection

	30-day mortality					
Characteristic - n (%)	**Alive (n = 56)**	**Death (n = 41)**	**Univariate**		**Multivariate**	
			OR (95% CI)	**p**	**OR (95% CI)**	**p**
Antimicrobial treatment			03.2 (4.8-1501.779)	< 0.0001	34.8 (4.24-286.12)	0.001
Appropriate	55	1				
Inappropriate	25	16				
Invasive disease			2.16 (0.82-5.9)	0.08	2.38 (0.828-6.86)	0.107
No	23	33				
Yes	10	31				
Cancer status			2.12 (0.86-5.25)	0.06	1.61 (0.62-4.15)	0.322
Remission/recent diagnosis	35	21				
Progression/relapse	18	23				

(n = 10; 9.7%) followed by gastrointestinal cancer (n = 9; 9.3%). Other studies in cancer patients have reported lung cancer as the most frequent solid tumor present in patients with IPD[2].

Bloodstream infection was the most frequent clinical presentation (52%); these were critically ill patients considering that 20% of them died in the first 48 hours and 47% died in the first month. One study conducted in patients with cancer and bloodstream infection by *S. pneumoniae* reported an early case mortality (< 48 hours) of 4.8% and an overall case fatality rate of 14.3% (< 30 days)[3], considerably lower than our findings. A higher mortality rate of pneumococcal

bloodstream infection (16.9%) has been reported in patients aged > 65 years and with underlying diseases or risk factors for immune suppression[9]. The elevated mortality reported herein could be explained by the fact that we included patients with invasive and complicated infections, such as meningitis, peritonitis, empyema, and lung abscess.

One question addressed in other studies is related to the use of single vs. combined anti-pneumococcal treatment, with other authors suggesting a benefit of employing two active antimicrobials[10]. In this study there was no benefit in survival by using combined antimicrobial treatment.

The prevalence of different pneumococcal serotypes varies by age group and geographic region, and differs with respect to virulence, invasiveness, and the ability to acquire resistance to different antibiotics[11]. Studies performed in patients with malignancy have found a higher prevalence of serotype 6A[2], different from what we found in this study where the main serotypes identified were 3 and 19A (20.3 and 17.1%, respectively). Serotype 3 is one of the most susceptible to beta-lactam antibiotics, while 19A is related with resistance to beta-lactams and is associated with the selection and dissemination of a clonal complex (ST 320)[11,12]. Since 2010, serotype 19A has shown a trend to increase in Mexico, related with PCV-7 used in the pediatric population[11]. Further studies are required to establish which are the major circulating serotypes in cancer patients.

Pneumococcal vaccines provide effective protection against severe and invasive disease in patients with a high risk of pneumococcal infections, such as cancer patients[13]. Nevertheless, it is important to consider that patients who have recently received antineoplastic treatment could present reduced vaccine immunogenicity[14]. In Mexico there are two different pneumococcal vaccines available. The pneumococcal polysaccharide vaccine (PPV-23) is currently recommended in patients with cancer; it is safe, inexpensive, and effective against invasive disease and improves the outcome and recurrences of patients with pneumococcal pneumonia[3]. The conjugated PCV-13 has a stronger and longer-lasting response because it contains a range of serotypes conjugated to a protein that allows for a T-cell-dependent response, thereby facilitating the formation of memory B-cells[3]. Both vaccines are recommended for administration to adults newly diagnosed with hematological or solid malignancies[14]. In data from the Regional System for Vaccines (SIREVA) Mexico network, 70% of the strains isolated were included in PPV-23 and PCV-13[15], similar to what we found in this series (72%). Pneumococcal vaccination policies at our hospital clearly have been insufficient and have impacted in complicated disease with high mortality in this group of patients. We need to increase our patients' coverage and make the rest of the medical team aware of the importance and need of expanding this coverage.

During the study period, 8.3% of *S. pneumoniae* isolates were penicillin-resistant and 10% were reported as penicillin-intermediate, similar to data from SIREVA Mexico network, which reported, in 2013, 12.5% penicillin-resistant and 8.3% intermediate strains. In Europe, penicillin resistance is reported in 9.3%, but in the Asia-Pacific Rim it is considerably higher (25%)[15,16].

This work has some limitations. It is a retrospective study carried out at a single center, although it is a tertiary level referral center, which receives patients from different geographic areas of the country. An important limitation is that we captured patients with positive cultures, so it is possible that some cases may have been missed if cultures were not done or if they were done after the administration of antibiotics.

Invasive pneumococcal disease is a severe life-threatening infection, with high morbidity and mortality in patients with cancer. Early initiation of antibiotics with activity against pneumococcus in patients with fever, respiratory symptoms and/or severe sepsis is essential to improve survival. It is imperative to reinforce pneumococcal vaccination programs.

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