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CHARACTERISTICS OF PNEUMOCOCCAL INFECTION IN THE ERA OF IMMUNIZATION

Jamil M Bhatti[1]*, Ayesha Akhtar[2], Syed HM Zaidi[3], Sidra Khan[4], Noshirwan P. Gazder[5], Irshad Batool[6], Uzma Solangi[7], Salman Khan[8].

[1]*MBBS, FCPS, Department of Infectious Disease, Dr Ziauddin University Hospital, Karachi, Pakistan.
[2]MBBS, Department of Respiratory Medicine, Dr Ziauddin University Hospital, Karachi, Pakistan.
[3,4,5,7]MBBS, Department of Medicine, Dr Ziauddin University Hospital, Karachi, Pakistan.
[6]MBBS, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan.
[8]MBBS, Department of Physiology, Ghulam Mohammad Mahar Medical College, Sukkur, Pakistan.

***Corresponding author: -** Jamil M Bhatti
*Email: Muqtadir169@yahoo.com, Contact: +923332790783

Abstract

Background: Invasive pneumococcal disease is a significant contributor to both morbidity and mortality on a global scale. The occurrence of bacteremia in cases of pneumococcal pneumonia is an additional determinant of a poorer prognosis. However, it is essential to note that the most severe form of invasive pneumococcal infection is mainly associated with specific serotypes. The implementation of pneumococcal vaccination as a preventive measure has demonstrated a significant reduction in the occurrence of invasive pneumococcal illness among both vaccinated children and the adult population who have not received the vaccine.

Aims and objectives: The aim of this study was to evaluate and characterize the clinical characteristics of pneumococcal infections in the era of immunization.

Methods: This retrospective cohort was conducted at Dr Ziauddin Hospital from January 2018 to December 2021. 132 patients who tested positive for S-pneumo in a blood culture meeting the inclusion criteria were included in the study.

Results: The mean age of the patients was 62 years. Penicillin resistance was found in more than half of the patients. Besides penicillin, resistance was very high for ciprofloxacin, cotrimoxazole and tetracyclines. Mortality was found to be higher in elderly and dementia patients. The most common source of infection was meningitis, followed by respiratory tract infection. Penicillin use was associated with increased mortality. The need for ICU admission and pleural effusion were independent risk factors for mortality.

Conclusion; Resistance to penicillin and other antibiotics is rising. Common source of infection in this cohort was meningitis. Intensive care unit admission, low platelet count and pleural effusion are associated with increased mortality.

Highlights

- Penicillin resistance is rising for S-pneumo.
- Resistance for linezolid and vancomycin was found in none.
- Need for ICU admission, low platelet count, antibiotic resistance and pleural effusion were independent risk factor for mortality.

Keywords: Streptococcus pneumoniae, Immunization, Penicillin, Pneumonia, Meningitis.

Introduction

The presence of Streptococcus pneumoniae (S-pneumo) infection continues to be a substantial contributor to morbidity and mortality across various age demographics. It is notably the prevailing cause of otitis media, pneumonia, and meningitis [1,2]. A serious public health issue is s-pneumo [3]. The prevalence of sickness is most pronounced in the demographic cohorts of young children and the elderly. The precise prevalence of S-pneumo pneumonia remains uncertain; nevertheless, it has been approximated that this particular strain of pneumonia is responsible for a minimum of 1 million fatalities annually among children aged five, with the majority of cases concentrated in nations with limited resources [4]. Severe S-pneumo infections commonly occur due to the bacteremia and disseminated disease that establish infective focus involving central nervous system, or other anatomical locations that are typically free from microbial contamination. The occurrence of invasive S-pneumo disease has been approximated to range from 15 to 30 cases per 100,000 individuals annually in developed nations. The highest rates are observed among individuals who are 65 years of age or older, with a rate of at least 50 cases per 100,000. Additionally, infants who are 2 years old or younger experience rates exceeding 150 cases per 100,000 [1,5]. The reliance on blood cultures as the primary source of data suggests that these statistics are likely to underestimate the actual occurrence of invasive S-pneumo disease. This is because individuals who were not subjected to blood cultures or whose cultures were drawn after the initiation of antibiotic treatment are not accounted for [6]. Currently, there are two distinct categories of S-pneumo vaccines that are accessible for those at high risk. These vaccinations exhibit distinct immunological properties and encompass varying quantities of serotypes within each category. The 23-valent pneumococcal polysaccharide vaccine elicits a T-independent immune response, resulting in the production of serotype-specific antibodies without the development of immune memory. On the other hand, the 10-valent pneumococcal conjugated vaccine (PCV10) and the 13-valent pneumococcal conjugated vaccine (PCV13) involve the coupling of pneumococcal polysaccharides with a carrier protein, leading to a T-dependent immune response [7]. While the 23-valent pneumococcal polysaccharide vaccine (PPV23) elicits serotype-specific antibodies exclusively, the 13-valent pneumococcal conjugate vaccine (PCV13) stimulates the production of both serotype-specific antibodies and B memory cells, leading to a prolonged duration of immune responses triggered by the vaccination.

There are few reports on the S-pneumo disease, its clinical spectrum and antibiotic susceptibility pattern of S-pneumo from Pakistan. In this study, we report the prevalence of S-pneumonia infections in the era of immunization, its associated clinical characteristics and antibiotic susceptibility patterns at a tertiary care centre in Karachi, Pakistan.

Methods

Study design and population

All cases of S-pneumonia infection in all age groups at the Dr Ziauddin Hospital, a tertiary care facility, were retrospectively collected. Eligibility was granted to all patients at our hospital who have tested positive for S-pneumo in a blood culture between January 2018 and December 2021.

Exclusion criteria

Cases excluded from the study were patients under 15 years of age, those with incomplete medical records, and patients with polymicrobial bacteremia, including non-pneumococcal or other site infections, within three days of the blood culture with S-pneumo.

Identification and susceptibility testing

S-pneumo was identified using standard microbiologic methods, including colony morphology, Gram stain, optochin susceptibility, and bile solubility [8]. S-pneumo isolates were subcultured twice on blood-supplemented Mueller–Hinton agar. Inoculations were prepared by direct colony suspension to

give a 0.5 McFarland standard dilution and inoculated onto appropriate agar plates to produce a confluent lawn of growth. Etest® and antibiotic discs were applied, and plates were incubated for 20–24 at 35°C in a 5% CO_2 atmosphere [9].

Operational definitions

Pneumococcal Bloodstream Infection; is defined as the isolation of Pneumococci in one or more blood culture samples.

Fever; is defined as an increase in body temperature to over 38.0°C using a tympanic thermometer or over 37.5°C using an axillary thermometer [10].

Data Collection

The trained investigation team members conducted a thorough examination of the medical records, extracting various information such as demographic profiles, hospitalisation dates and duration, ward information, comorbidities, concurrent infections, patients' discharge diagnoses, and clinical outcomes. These outcomes included the date of death, details of antibiotic prescriptions (which consists of dosage and duration of treatment), presence of indwelling catheters, and vital status of the participants.

Clinical and microbiological data were recorded. Data concerning clinical characteristics and the number of positive blood cultures were recorded. Biochemical data obtained on the same day as the blood culture sample were also collected and included in the analyses. The suspected source of infection was recorded from patients' charts. All data were entered in structured proforma.

Statistical Analysis

Initial characteristics of the participants were assessed in terms of laboratory measurements, pre-existing illnesses, and signs and symptoms. Continuous variables were compared using the student t-test (normal) or the Mann–Whitney U-test (non-parametric). We calculated frequencies and percentages for categorical variables and compared them using Fisher's exact test or Pearson's Chi-square test. In addition, results were calculated using both univariate and multivariate analysis. The data were analyzed with IBM SPSS Version 26, and a P-value <0.005 will be judged statistically significant.

Results

A total of 132 patients were included in this study (Figure 1).

The baseline demographics of patients are shown in (Table 1). Mean age of the patients in this cohort was 62.31, with a standard deviation of 18.15. Most of the patients in this cohort were above 64 years of age, with males being the common gender. The most common comorbidities among the patient population were hypertension, followed by diabetes mellitus and ischemic heart disease, and the most common symptoms among the patient population were fever, followed by cough and shortness of breath, respectively. Our patient's most common infection source was meningitis, followed by pneumonia. The complications we have seen in our patient were acute kidney injury and acute liver injury.

Demographic characteristics according to survival are shown in (Table 2). Older age was associated with higher mortality. Besides, higher mortality was observed in patients with dementia and chronic liver disease. Patients presenting with shortness of breath, headache and fits had higher mortality.

Laboratory parameters according to outcome expiry are shown in (Table 3). Patients who expired had significantly lower platelets count. Similarly, those who could not survive had higher median serum alanine transaminase, aspartate aminotransferase, urea, creatinine, procalcitonin and C-reactive protein.

In the multivariate analysis (Table 4), the need for intensive care unit admission, low platelet count and pleural effusion were independently associated with mortality.

Discussion

Infections caused by S-pneumo are recognized as a significant contributor to global morbidity and mortality [11]. S-pneumo illness can be classified into two main categories: non-invasive pneumococcal disease, also known as mucosal infection, and invasive S-pneumo, which occurs when the bacteria infiltrate places that are typically sterile, such as the bloodstream. S-pneumo infections exhibit a bimodal distribution, with a significant occurrence in paediatric and geriatric populations. Several factors influence invasive pneumococcal disease (IPD), such as smoking habits, immune system function, age, and geographic location [12]. Despite the implementation of adequate antibiotic treatment, fatality rates associated with invasive S-pneumo disease remain considerably elevated, affecting approximately 10-25% of patients [13].

The prevalence of antibiotic-resistant forms of S-pneumo is widely recognized in several countries globally. Despite the increasing rates of antibiotic resistance observed globally in recent decades [14], there has been no significant rise in mortality rates associated with invasive pneumococcal disease (IPD) [15]. Reports of treatment failures due to drug-resistant strains have been documented, although a definitive causal relationship has yet to be demonstrated. More than half of the patients in this cohort exhibited penicillin resistance much higher than Doern et al. from the USA, who reported that 34.2% of the isolates were resistant to penicillin [14]. Similarly, resistance to other antibiotics was much lower than reported in this cohort. Although no resistance was observed for vancomycin and linezolid in that study, a finding consistent with this cohort. The cohort study indicates that the resistance of S-pneumo to Vancomycin and linezolid has remained minimal, in contrast to other gram-positive bacteria where resistance to vancomycin is increasing [16].

Different findings are drawn from two distinct systematic reviews and meta-analyses of the available information regarding how S-pneumo penicillin resistance affects outcomes. Over 7500 patients with S-pneumo pneumonia were included in 15 papers that Metlay reviewed [17]. Twelve of the fifteen papers the authors reviewed and evaluated failed to prove a relationship between antibiotic resistance and mortality. In contrast, Tleyjeh et al. carefully analyzed eleven prospective cohort studies, including >3400 patients [18]. They found that penicillin-resistant S-pneumo infections had a mortality rate of 19.4 compared to 15.7% for susceptible S-pneumo infections.

Bacteremia has been linked to a prolonged period of establishing clinical stabilization while hospitalized for pneumonia, as well as an extended duration of hospital stay [19,20]. Moreover, research findings have demonstrated a correlation between the prompt identification of the S-pneumo bacteria in blood samples, as indicated by the time it takes for the blood culture to yield positive results and a more unfavorable prognosis for individuals with bacteremic S-pneumonia pneumonia. This association is characterized by increased hospitalization rates, septic shock, admission to the intensive care unit (ICU), and incidence of meningitis. The previously described early isolation of S-pneumo may be associated with an increased bacterial load in the bloodstream, therefore serving as a potential indicator for the severity of pneumonia [21].

It has taken a while to develop an efficient anti-pneumococcal vaccination, primarily due to the low immunogenicity of the bacterial surface polysaccharides that serve as the principal target of opsonizing antibodies. Numerous observational studies and randomized controlled trials have assessed the polysaccharide vaccine's effectiveness as a preventative measure in light of the significant burden of morbidity and mortality linked to S-pneumo illness. There are several areas of doubt regarding the actual efficacy of vaccines, as evidenced by the astonishing number of 17 meta-analyses that have analyzed these studies between 1994 and 2009 [22], the most recent of which was published in 2009. IPD, pneumonia from any cause, pneumococcal bacteria, and mortality are the most frequently assessed and clinically significant outcome markers. Given the limited yield of diagnostic procedures for precisely identifying S-pneumo as the etiological agent, all-cause pneumonia rates are commonly utilized as a surrogate marker for S-pneumo pneumonia. The effectiveness of polysaccharide vaccines in preventing outcomes such as pneumonia or mortality remains uncertain. The Cochrane meta-analysis conducted in 2008 [23] found that the randomized controlled trials (RCTs) examined showed an odds ratio (OR) of 0.71 (95% CI 0.52–0.97) for efficacy

against all-cause pneumonia. However, the results were deemed inconclusive due to significant heterogeneity among the studies included in the analysis.

This cohort reported that the risk of death was associated with older age; this finding concerns the published literature. Catherine A. et al. [24] said that the risk of mortality was found to be significantly associated with several factors, including being 75 years of age or older, having illness syndromes of meningitis and bacteremia without a specific focus, and experiencing invasive disease caused by distinct serotypes. Two more studies have demonstrated a correlation between serotype three and increased mortality rates [25,26]. Furthermore, research has indicated that serotype 3 exhibits relatively low immunogenicity in individuals aged 65 years or older with chronic illnesses, as observed in the polysaccharide vaccine [27,28]. Hence, incorporating serotype 3 in an extended valent conjugate vaccination could yield supplementary advantages for the elderly population by mitigating the transmission of this particular serotype.

In a recent study conducted by T. Chan et al. [29], significant factors contributing to in-hospital mortality among patients with pneumococcal infections were identified. According to the findings, the largest predictor of mortality was admission to the intensive care unit (ICU), as those who were admitted to the ICU were 23 times more likely to experience death during their hospital stay compared to those who were not admitted. Additional criteria that were taken into consideration included individuals aged 85 years or older, a higher Charlson's score, and a diagnosis of IPD. It is imperative for medical teams to take particular notice of the heightened mortality risk among these patients and implement timely interventions to mitigate the likelihood of fatality. This cohort reported higher risk of death in smoker with $p = 0.052$, a finding consistent with available literature. According to a study conducted by Bello et al. [30], individuals who are currently engaged in smoking habits and are diagnosed with pneumococcal pneumonia tend to experience a higher likelihood of developing severe sepsis and necessitating hospitalization at a younger age, even in the absence of a significant number of comorbidities. The smoking is associated with an elevated likelihood of mortality within a 30-day period, regardless of the presence of tobacco-related comorbidities, the individual's age, or any other comorbid disorders.

The present study also possesses certain limitations. Initially, it should be noted that the hospital records did not provide comprehensive information regarding the vaccination status of case patients concerning polysaccharide vaccines. Consequently, due to the limited nature of these data, they were deemed unsuitable for inclusion in the present analysis. Furthermore, the utilization of a retrospective methodology, a relatively smaller sample size, and the restriction to a single-centre experience impose limitations on the generalizability of our findings. Finally, the analysis did not incorporate obstructive airway illnesses, potentially introducing bias into the findings.

Conclusion

This study concluded that the need for intensive care unit admission, low platelet, antibiotic resistance and pleural effusion were independently associated with mortality. The prevalence of bloodstream infections caused by S-pneumo continues to be significant despite the availability of immunisation. The prevalence of antibiotic resistance is on the rise; however, our study did not identify any instances of resistance to vancomycin or linezolid. Prospective studies with larger sample sizes are needed to link causal associations.

Declarations

Conflict of interest

None

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None

Contributor-ship

Jamil M Bhatti, Irshad Batool Conceptualization, data analysis, interpretation and writing.

Ayesha Akhtar, Syed HM Zaidi, Sidra Khan Data curation and methodology.
Noshirwan P. Gazder, Salman Khan Investigating and supervision.

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