Prevalence and Spectrum of Invasive Pneumococcal Disease (IPD) in Patients Admitted to the PICU of a Tertiary Care Hospital in Navi Mumbai

Ridhima Vardhineni*, Vivasvan Parekh**, Sheetal Aggarwal**, N. Revathi***, Jeetendra Gavhane***

Abstract

Objective: **Prevalence of invasive pneumococcal disease in PICU patients and study its spectrum and sensitivity.**

Material and methods: **Retrospective study done at PICU of a tertiary centre from January 2012 - April 2013. First culture positive cases for Streptococcus pneumoniae were included.**

Results: **Out of the 347 children, majority of the cases were of < 2 yrs of age. 32 of them had culture proven Streptococcus pneumoniae infection. Of them, 13 had meningitis, 15 had septicaemia, 6 had empyema, 5 had lobar pneumonia, 2 had pneumonia with meningitis and 3 had empyema with septic shock. Sensitivity suggested susceptibility to penicillin and oxacillin group. Prevalence of invasive pneumococcal disease was 9.22% among the PICU patients with a case fatality rate of 12.5%.**

Conclusion: **Streptococcus pneumoniae is the most common infection among the patients admitted in PICU for infective aetiology with a higher frequency in ages < 2 yrs and high case fatality rate.**

Introduction

Invasive pneumococcal disease is defined as an infection confirmed by the isolation of Streptococcus pneumoniae from a normally sterile site like blood or cerebrospinal fluid. The incidence of invasive pneumococcal disease in any population is affected by geographic location, time of year, serotype prevalence, age, comorbidities, and vaccination status. The highest incidence of invasive pneumococcal disease occurs in children < 2 years of age, and in those with certain underlying conditions, such as HIV infection.

The risk of invasive disease appears to be closely related to type of serotype present.[1,2] The magnitude of this effect was addressed in a meta-analysis that evaluated isolates from patients with invasive disease and nasal or nasopharyngeal isolates from asymptomatic children in seven different locations.[1] Certain serotypes (e.g., serotypes 1, 5 and 7 were up to 60 times more likely to be found in patients with invasive disease than other serotypes (e.g., serotypes 3, 6A, and 15) commonly isolated from asymptomatic individuals.

The risk of invasive pneumococcal

*Resident, **Senior Resident, *** Associate Professor, Dept. of Paediatrics, MGM Medical College, Navi Mumbai

disease seems to be associated with the presence of viral respiratory illnesses, such as influenza.[3,4] This association may be related to enhanced expression of receptors for pneumococcal attachment on virally activated respiratory epithelial cells.[3]

A temporal association between invasive pneumococcal disease and exposure to common respiratory viruses during winter months was observed in a prospective study of 4147 invasive pneumococcal disease episodes.[5] The weekly frequency of invasive pneumococcal disease correlated directly with the weekly frequency of isolation of respiratory syncytial virus (RSV) and influenza.

The clinical manifestations of invasive pneumococcal infection depend upon the primary site of infection and the presence or absence of bacteraemia. Pneumococcal meningitis is the most frequent and severe suppurative complication associated with pneumococcal bacteraemia. Even with appropriate antimicrobial treatment, pneumococcal meningitis has a mortality rate of 20 to 30 percent.[6]

Pneumococcal endocarditis and other suppurative complications of pneumococcal infections, such as pneumococcal arthritis, ileitis, and pericarditis, were much more common in the preantibiotic era.

Other manifestations of invasive pneumococcal disease including abdominal infections like peritonitis, appendicitis, terminal ileitis which has been primarily described in case reports or small case series.[7,8] These infections may occur with or without concurrent or recently detected bacteraemia.[7] S. pneumoniae may cause suppurative abdominal complications, such as peritonitis and ileitis, particularly in patients with nephrotic syndrome.

Purulent pericarditis, septic arthritis, osteomyelitis, and epidural and brain abscess due to S. pneumoniae are rarely recognised in modern practices.[9,10,11] Pneumococcal tenosynovitis, chorioamnionitis, and abscesses involving the psoas, liver, pancreas, spleen, and kidney are even less common.[11] Despite their rarity, case reports of sporadic cases underscore an important clinical point; S. pneumoniae can cause suppurative infections in almost any site.

Pneumococci are one of the major causes of meningitis, pneumonia and sepsis in children[12] and such invasive pneumococcal disease (IPD) is a leading cause of death and significant morbidity in young children in developed countries, particularly in those under the age of two.[13]

Our objective of the study was to find the prevalence of invasive pneumococcal disease in PICU patients and study their spectrum and sensitivity pattern.

Material and Methods

This was a retrospective study done at Paediatric ICU of MGM Hospital, Kalamboli, a tertiary care centre in Navi Mumbai, where all the admissions to PICU from January 2012 to April 2013 were reviewed and those cases with the first

culture positive for Streptococcus pneumoniae infection were included and then the spectrum of presentation was studied.

Results

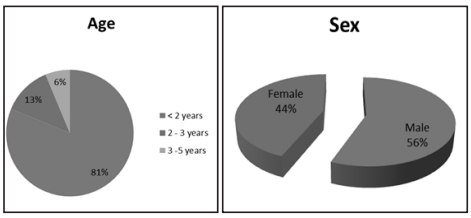

Fig. 1: Distribution According to Age and Sex

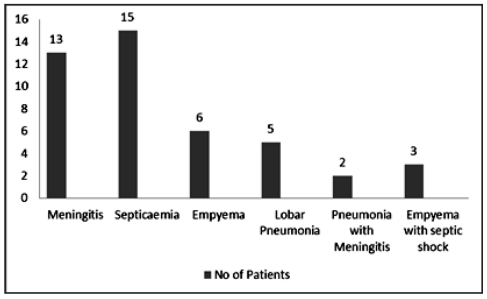

Fig. 2 : Distribution according to Presentation

32 patients had culture proven Streptococcus pneumoniae infection. Out of these, 24 were with routine culture method and 8 were by BACTEC method. Sensitivity pattern was suggestive of susceptibility to penicillin group, oxacillin group (3rd generation cephalosporin) and 10% were resistant to macrolides. 4 patients (12.5%) succumbed to the disease.

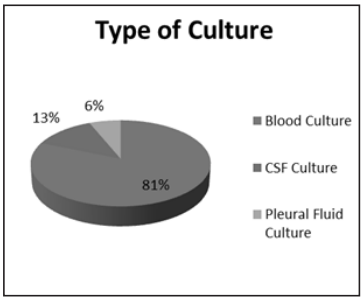

Fig. 3 : Type of culture

In our study we found prevalence of invasive pneumococcal disease to be 9.22% among the PICU patients admitted during this period with a case fatality rate of 12.5%. Septicaemia and meningitis were the most common presentation for S.pneumonia infection followed by empyema & pneumonia.

Discussion

Definitive diagnosis of pneumococcal bacteraemia or invasive pneumococcal infection requires the culture of S. pneumoniae from the blood or another normally sterile site. S. pneumoniae is rarely found as a skin contaminant. Thus, when S. pneumoniae is recovered from blood cultures, it is considered to be a pathogen.

A study by AL Musawi M[14] showed the greatest disease burden in children < 2 years old which included 75% of meningitis cases, 89.2% of septicaemia/ bacteraemia cases and 81.5% of pneumococcal pneumonia cases. In our study 13 patients (40.62%) presented as meningitis, 15 patients (46.87%) presented as septicaemia, 6 patients (18.75%) presented as empyema, 5 patients (15.62%) presented as lobar pneumonia, 2 patients (06.25%) presented as pneumonia with meningitis and 3 patients (09.37%) presented as empyema with septic shock. In a study by Ma JS et al, 38.88% children presented with meningitis, a presentation similar to the one seen in our study.[15]

General laboratory findings in patients with invasive pneumococcal infections and bacteraemia are nonspecific, typically

there is a leucocytosis (>12,000/mL) and anaemia is common.

There is a continuing debate as to whether infection with pneumococcal strains that are resistant to beta-lactam antibiotics affects outcome when infection occurs in extra meningeal sites.

Risk factors for penicillin nonsusceptibility were examined in a prospective international observational study of 844 patients with pneumococcal bacteraemia.[16] Two risk factors were found to be statistically significant using multivariate statistical methods, the presence of an underlying immunosuppressive condition (HIV infection, splenectomy, haematological malignancy, autoimmune disorder, or transplant or chemotherapy within the preceding four weeks) and prior receipt of antibiotics (defined as use of antibiotics for ≥1 day in the past three months).

Debate continues as to whether combination therapy or monotherapy is more appropriate for treatment of known or suspected invasive pneumococcal infection prior to the availability of in vitro susceptibility results. The choice of an empiric antibiotic regimen chosen for the treatment of suspected or known invasive pneumococcal infections depends upon local patterns of in vitro pneumococcal resistance. In all cases, empiric therapy should be reassessed and then adjusted or simplified if possible after susceptibility results are available.

In a study by Yu VL et al,[16] beta-lactam antibiotics were still found to be useful for treatment of pneumococcal infections that do not involve cerebrospinal fluid, regardless of in vitro susceptibility. In our study as well sensitivity pattern was suggestive of susceptibility to penicillin group, oxacillin group (3rd generation cephalosporin).

Poor prognostic factors in patients with extra meningeal invasive pneumococcal disease include coma, respiratory failure, shock, elevated liver function tests (alanine aminotransferase [ALT] >100 IU/L), or leucopenia (WBC < 4000/mL). These prognostic factors have a particularly strong correlation with mortality in children with invasive pneumococcal infections.[15]

Overall mortality rates for patients with pneumococcal bacteraemia have consistently ranged from 15 to 20 percent in the antibiotic era. Risk of death in patients with pneumococcal bacteraemia is highest during the first 72 hours after bacteraemia is identified. In the prospective international observational study by Yu VL et al, it was observed that the overall mortality rate of pneumococcal bacteraemia was 17 percent[16] whereas our study had a case fatality of 12.5%. In another study by Charles Feldman, et al, the case fatality rate was similar to the one seen in our study.[17]

A successful vaccination programme will not only lead to a reduction in the incidence of pneumococcal diseases but will also result in decreased utilisation of antibiotics, thus preserving their efficacy as a primary treatment. It will also slow the

development of antibiotic resistance, especially the resistance to penicillin, β-lactams and macrolides, which has steadily become more prevalent worldwide over the last 30 years.[12,18,19.]

Conclusion

Streptococcus pneumoniae is the most common infection among the patients admitted in PICU for infective aetiology with a higher frequency in ages < 2 yrs, associated with a high case fatality rate.

References

1. Brueggemann AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. *J Infect Dis.* 2004 Oct 1;190(7):1203-11
2. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. *Lancet Infect Dis.* 2005 Feb;5(2):83-93
3. Tuomanen EI, Austrian R, Masure HR. Pathogenesis of pneumococcal infection. *N Engl J Med.* 1995 May 11;332(19):1280-4
4. Ampofo K, Bender J, Sheng X, Korgenski K, Daly J, Pavia AT, Byington CL. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. *Pediatrics.* 2008 Aug;122(2):229-37.
5. Talbot TR, Poehling KA, Hartert TV, Arbogast PG, Halasa NB, Edwards KM, Schaffner W, Craig AS, Griffin MR. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. *Am J Med.* 2005 Mar; 118 (3):285-91.
6. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, Lefkowitz L, Perkins BA. Bacterial meningitis in the United States in 1995. Active Surveillance Team. *N Engl J Med.* 1997 Oct 2;337(14):970-6
7. Petti CA, Ignatius Ou SH, Sexton DJ. Acute terminal ileitis associated with pneumococcal bacteremia: case report and review of pneumococcal gastrointestinal diseases. *Clin Infect Dis.* 2002 May 15;34(10):E50-3.
8. Heltberg O, Korner B, Schouenborg P. Six cases of acute appendicitis with secondary peritonitis caused by Streptococcus pneumoniae. *Eur J Clin Microbiol.* 1984 Apr;3(2):141-3
9. Ross JJ, Saltzman CL, Carling P, Shapiro DS. Pneumococcal septic arthritis: review of 190 cases. *Clin Infect Dis.* 2003 Feb 1;36(3):319-27.
10. Grigoriadis E, Gold WL. Pyogenic brain abscess caused by Streptococcus pneumoniae: case report and review. *Clin Infect Dis.* 1997 Nov; 25 (5):1108-12
11. Taylor SN, Sanders CV. Unusual manifestations of invasive pneumococcal infection. *Am J Med.* 1999 Jul 26;107(1A):12S-27S
12. Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis.* 2004 Mar;4(3):144-54.
13. Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among Streptococcus pneumoniae isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. *Int J Infect Dis.* 2010 Mar;14 (3):e197-209.
14. Al Musawi M. A retrospective epidemiological study of invasive pneumococcal infections in children aged 0-5 years in Bahrain from 1 January 1999 to 31 December 2003. *Vaccine.* 2012 Dec 31;30 Suppl 6:G2-6.
15. Ma JS, Chen PY, Mak SC, Chi CS, Lau YJ. Clinical outcome of invasive pneumococcal infection in children: a 10-year retrospective analysis. *J Microbiol Immunol Infect.* 2002 Mar;35(1):23-8
16. Yu VL, Chiou CC, Feldman C, Ortqvist A, Rello J, Morris AJ, Baddour LM, Luna CM, Snydman DR, Ip M, Ko WC, Chedid MB, Andremont A, Klugman KP; 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 15;37(2):230-7.
17. Feldman C, Anderson R. Recent advances in our

understanding of Streptococcus pneumoniae infection. *F1000Prime Rep.* 2014 Sep 4; 6:82.

18. Prymula R, Chlibek R, Ivaskeviciene I, Mangarov A, Mészner Z, Perenovska P, Richter D, Salman N, Simurka P, Tamm E, Tešovi? G, Urbancikova I, Usonis V. Paediatric pneumococcal disease in Central Europe. *Eur J Clin Microbiol Infect Dis.* 2011 Nov;30(11):1311-20.
19. Ochoa TJ, Egoavil M, Castillo ME, Reyes I, Chaparro E, Silva W, Campos F, Sáenz A. Invasive pneumococcal diseases among hospitalized children in Lima, Peru. *Rev Panam Salud Publica.* 2010 Aug;28(2):121-7

The asthmas in 2015 and beyond: a Lancet Commission

It is 25 years since the first British asthma guidelines were published, and that asthma was identified as a disease of airway inflammation. This led to the much more widespread therapeutic use of inhaled corticosteroids instead doses of short-acting β-2 agonists, with great benefit to patients. However progress has stalled in the past 10 years, despite increasing investment in treatment. The UK's National Review of Asthma Deaths report in 2014 showed that preventable deaths continue to occur with depressing regularity. There has not been comparable progress in the development of new treatments for asthma as has been seen in other diseases.

Out central position is that guidelines have inhibited rather than stimulated fundamental thinking, and there has been a failure to appreciate that asthma is an umbrella term for many diseases.

Exactly as feared, we have observed breathlessness and wheeze, and jumped to the conclusion that this means eosinophilic airway inflammation, and that all individuals with wheeze are at high risk of severe asthma attacks.

Already there is a suggestion that neutrophilic asthma driven by infection might respond to antibiotics, but this strategy is ineffective in airway neutrophilia driven by tobacco exposure.

There is a danger that overprescription of asthma inhalers will trivialise the diagnosis of a disease which kills young people, while patients who are at risk of sudden death are not managed with the intensity that is needed. Asthma is a disease that still kills people, and ever more evidence-based guidelines have not addressed our failure to target treatment effectively, or persuade in increasingly sceptical patient population to take long-term treatment.

Inhaled corticosteroids are repeatedly described as safe and effective, but new problems are being discovered. Of course, lip service has been paid to their potential to slow children's linear growth-but does it really matter if you end up 187 cm rather than 188 cm adult height? Meanwhile, the issue of local immunosuppression has been largely overlooked.

We now know that pneumonia, tuberculosis, and atypical mycobacterial infections results from the administration of potent inhaled corticosteroids.

This story, and the success of other monoclonal antibodies that target interleukin 13 and interleukin 4, illustrates well what can be achieved when fundamental truths are questioned and encourages us to believe that further progress is possible.

This Commission is predicated on the assumption that "asthma" is no more a 21st-century diagnosis than "arthritis", we will attempt to liberate this mix of airway diseases from the protective but intellectually destitute umbrella term "asthma" with the aim to progress management to the level that is commonplace in rheumatology.

Andrew Bush, Sabine Kleinert, Ian D Pavord, The Lancet, 2015, Vol 385, 1273-1274