0021-7557/08/84-03/276
Jornal de Pediatria

Invasive pneumococcal disease in HIV seropositive children and adolescents

Sonia M. Mattei,[1] Luiza Helena Falleiros-Carvalho,[2] Nilton J. F. Cavalcante[3]

Abstract

Objective: Invasive pneumococcal disease (IPD) primarily affects children less than 5 years old, the elderly and certain at-risk groups; especially people infected by the human immunodeficiency virus (HIV). The objective of this study was to analyze invasive pneumococcal diseases (IPD) in children and adolescents infected by the human immunodeficiency virus (HIV), with relation to morbidity, the case fatality ratio, pneumococcus serotypes, susceptibility to penicillin and ceftriaxone and to the proportion of susceptible and resistant *Streptococcus pneumoniae* (Sp) included in the 7-valent pneumococcal conjugate vaccine that has already been licensed.

Methods: A total of 19 cases of IPD were identified among HIV seropositive patients aged from 1 month to 20 years and hospitalized between 1993 and 2000. Data were recorded on standardized charts containing information on age, clinical diagnosis and progression, serotypes and the susceptibility to penicillin and ceftriaxone of the Sp strains identified in cultures. When the minimum inhibitory concentration was < 0.1 mcg/mL, Sp were defined as susceptible to penicillin (SpSPn), and all other strains were defined as not susceptible (SpNSPn).

Results: Of the 19 HIV seropositive cases with IPD, 16 (84%) had pneumonia and three (16%), had meningitis; 13 (68%) cases were children less than 2 years old and 16 (84%) were less than 5 years old. The case fatality ratio was 10%. Seven (54%) of the 13 cases less than 2 years old were SpNSPn and 10 (77%) were caused by serotypes covered by the 7-valent pneumococcal conjugate vaccine. From the 10 isolated serotypes the most frequent were 14, 6B and 23F, all them susceptible to ceftriaxone. From the three patients with meningitis, two were caused by SpNSPn.

Conclusion: In this study most of the IPD occurred in children less than 2 years old; 77% of the strains and 86% of the serotypes of SpNSPn were covered by the 7-valent pneumococcal conjugate vaccine.

J Pediatr (Rio J). 2008;84(3):276-280: Pneumococcus, Streptococcus pneumoniae, children, adolescents, HIV seropositive, meningitis, pneumonia, invasive pneumococcal disease, antipneumococcal vaccine.

Introduction

Streptococcus pneumoniae (Sp) is one of the main etiologic agents of community acquired pneumonia, meningitis, sinusitis, acute otitis media and bacteremia. Invasive pneumococcal disease (IPD) primarily affects children less than 5 years old, the elderly and certain other risk groups, among whom those infected by the human immunodeficiency virus (HIV+) are prominent.[1-4] The risk of HIV+ patients developing pneumonia is 10 to 100 times greater than for the uninfected.[1] In Brazil, although HIV infection is one of the primary risk factors for IPD, studies of IPD in this group of patients remain scarce. We were unable to identify studies published up to August of 2007 that provided information on Sp serotype identification in HIV+ children with IPD and the corresponding profile of susceptibility to penicillin and ceftriaxone.

1. Mestre. Chefe, Disciplina de Moléstias Infecciosas, Faculdade de Medicina de Taubaté (UNITAU), Taubaté, SP, Brazil.
2. Doutora, Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil. Professora adjunta, disciplina de Moléstias Infecciosas, Faculdade de Medicina de Marília (FAMEMA), Marília, SP, Brazil. Titular de Pediatria, Universidade Metropolitana de Santos (UNIMES), Santos, SP, Brazil.
3. Doutor, Universidade de São Paulo (USP), São Paulo, SP, Brazil. Coordenador, Programa de Pós-Graduação em Infectologia em Saúde Pública, Instituto de Infectologia Emilio Ribas, São Paulo, SP, Brazil. Coordenadoria, Controle de Doenças, Secretaria da Saúde de São Paulo, São Paulo, SP, Brazil.

No conflicts of interest declared concerning the publication of this article.

Suggested citation: Mattei SM, Falleiros-Carvalo LH, Cavalcante NJ. Invasive pneumococcal disease in HIV seropositive children and adolescents. J Pediatr (Rio J). 2008;84(3):276-280.

Manuscript received Aug 27 2008, accepted for publication Nov 21 2007.

doi:10.2223/JPED.1762

The availability of new conjugate vaccines[5] for the prevention of IPD in children less than 5 years old, together with the increased prevalence of IPD caused by resistant strains, have increased interest in identifying the main serotypes causing this entity and their resistance profiles.

Based on the reasons explained above, our goals were: 1) to describe the cases of IPD by Sp in HIV+ children and adolescents, analyzing morbidity, the case fatality ratio, Sp serotypes identified and their profiles of susceptibility to penicillin and ceftriaxone, broken down by age group and IPD topography; 2) to analyze the possible spectrum of coverage against IPD in children less than 5 years old offered by the 7-valent pneumococcal conjugate vaccine (7vPCV).

Methods

This research was carried out at the Instituto de Infectologia Emílio Ribas (IIER), which is a public hospital providing specialist care for patients with infectious diseases and which treats HIV+ individuals. Since 1993, records have been kept of all strains of Sp isolated from cultures of normally sterile clinical material (blood, cerebrospinal fluid, pleural fluid) from hospitalized patients, and IPD cases were identified from these records. Since HIV+ patients are referred to this hospital for treatment, both investigation of risk factors and serological tests for HIV investigation are part of routine care. Once the medical records of patients with positive Sp cultures taken between June 1993 and December 2000 had been identified, the medical records of all HIV+ individuals with IPD and ages of 1 month to 20 years were selected for this study.

The clinical progress of the patients was analyzed by means of a systematic review of their medical records using a standardized assessment protocol, covering the following variables: age, primary and secondary diagnoses, the Sp serotypes isolated from cultures with their respective profiles of resistance to penicillin and ceftriaxone and patient progress.

The techniques employed for the identification and serotyping of bacteria, plus the tests for susceptibility and minimum inhibitory concentration (MIC), followed the system defined for the SIREVA Project and were all carried out at the Instituto Adolfo Lutz in São Paulo, Brazil.[6-8] Strains were defined as susceptible to penicillin (SpSPn) and/or ceftriaxone when their MIC was < 0.1 mcg/mL. Strains with intermediate sensitivity (MIC between 0.1 and 1 mcg/mL) and with full resistance (MIC ≥ 2 mcg/mL) to penicillin were defined as not susceptible (SpNSPn).[8,9]

Data were recorded on standardized charts containing all relevant information and were stored and manipulated using Microsoft Office Excel 2003®.

This study was approved by the Research Ethics Committee at the IIER.

Results

During the study period, 19 children and adolescents with IPD confirmed by culture were identified, 16 (84%) of whom were less than 5 years old; 16 (84%) of the 19 patients had pneumonia and three (16%), had meningitis (Table 1). None of these patients had been vaccinated against Sp.

The serotypes isolated are listed in Table 2, according to the susceptibility of each Sp to penicillin, with the most frequent serotype being 14 (21%), followed by 6B and 23F (16% each).

Almost half of the strains isolated (47%) proved to be SpNSPn. Children less than 2 years old (seven out of 13) exhibited a higher rate of infection by SpNSPn (54%) compared with children over 2 years. All of the strains isolated were susceptible to ceftriaxone.

The case fatality ratio was 10.5%, with a total of two deaths: one child with meningitis and another with pneumonia and co-infection by pulmonary tuberculosis, both less than 2 years of age.

Twelve of the 16 children less than 5 years old had IPD caused by serotypes included in the 7vPCV (75%).

As the results show, we found 19 cases of children and adolescents infected by HIV who also had IPD, which was not a surprise, even over the extended period, since the number of infected children is always much lower than the number of HIV+ adults.

Young age is an important risk factor for IPD. In this study, more than 90% of the IPD were identified in children less than 5 years old, and almost 80% in children less than 2 years of age.

The majority of studies that have been published in Brazil mention Sp serotypes without specifying whether or not the individual concerned was infected with HIV. The majority of these refer to colonization of the airways by Sp, since the difficulties in isolating the bacteria from cultures from people with pneumonia are well known.[4,9-13] The only study published in Brazil on Sp serotypes identified from HIV+ children demonstrated that nasopharyngeal colonization of 112 children was no greater than that described in the literature for healthy children.[3]

In our study, serotype 14 was the most frequent (four cases) and was also the serotype that exhibited greatest resistance to penicillin, which confirms data published in Brazilian literature.[6,8] Three of these cases were SpNSPn in children less than 2 years old; the other was identified in a child aged between 2 and 5 years (Table 1).

Analysis of bacterial resistance revealed that almost half of the IPD (47%) had been caused by SpNSPn and that, of the 10 serotypes identified, five (50%) were SpNSPn. Several studies undertaken in different parts of Brazil have revealed that the prevalence of SpNSPn is highly variable (15 to

Table1 - Distribution of *Streptococcus pneumoniae* serotypes isolated from HIV-positive children and adolescents and with invasive pneumococcal infections by age group, clinical diagnosis and susceptibility to penicillin

Age group	Meningitis (Sp serotypes)	Pneumonia (Sp serotypes)
1 month to 2 years	6B (S)*	4 (S)*
	23F (NS)	9V (S)*
	14† (NS)	9N (S)*
	-	19A (S)*
	-	19F (S)*†
	-	6B (NS)
	-	14 (NS)
	-	14 (NS)
	-	19A (NS)
	-	23F (NS)
2 to 5 years	0	14 (S)*
	-	6B (S)*
	-	5 (S)*
5 to 10 years	0	19F (S)*
	-	8 (NS)
10 to 20 years	0	23F (NS)
Total strains		
(S)* vs. (NS)	1 (S)* vs. 2 (NS)	9 (S)* vs. 6 (NS)

NS = not susceptible (MIC ≥ 0.1 µg/mL); S = susceptible.
* Strains susceptible to penicillin (MIC < 0.1 µg/mL).
† Patient died.

Table 2 - Most common*Streptococcus pneumoniae* serotypes isolated from HIV positive patients

Serotypes	Cases	Susceptibility to penicillin	
		Susceptible	Not susceptible
14*	4	1	3
6B*	3	2	1
23F*	3	-	3
19A	2	1	1
19F*	2	2	-
4*	1	1	-
9N	1	1	-
5	1	1	-
8	1	-	1
9V*	1	1	-
Total	19	10	9

* Serotypes included in the 7-valent pneumococcal conjugate vaccine.

50%).[8,4,10-12] Of this study, seven (54%) of the 13 children less than 2 years old had suffered IPD due to SpNSPn. It is possible that this high level of penicillin resistance is partially due to the fact that HIV+ patients are often given antimicrobial treatment.

The identification of a high proportion of SpNSPn strains in this sample provides more evidence to support prescribing ceftriaxone in suspected IPD cases among HIV+ patients at our service. Of the 13 children less than 2 years old, and of the 16 children less than 5 years old, 10 (77%) and 12 (75%) respectively had IPD caused by Sp serotypes covered by the 7vPCV.

Discussion

It has been demonstrated that the 7vPCV offers more than 90% efficacy for the prevention of IPD caused by serotypes that are included in it, and also for the prevention of pneumonia diagnosed by X ray, in children less than 2 years old,[14] following a clear decline in the incidence of IPD in the United States, after systematic introduction of the 7vPCV for young infants.[2]

Both the 7vPCV and other conjugate vaccines have proven highly effective for the prevention of IPD in healthy people or those infected with HIV.[5,15] It is therefore essential to know which Sp serotypes are prevalent at each healthcare provider, in order to be able to analyze the spectrum of coverage offered by each of the new conjugate vaccines.

In this study, we identified two cases of IPD caused by serotype 19A, which is currently considered one of the most important in the United States, after the introduction of the conjugate vaccine.[2] Both were isolated from children less than 2 years old and, although the 7vPCV contains the 19F serotype, this does not provide cross protection for 19A. Serotype 19A is included in 13vVPC, which includes the serotypes 1, 3, 5 (one case was identified here), 6A, 7F and 19A, in addition to those already in the 7vPCV. The 13vVPC could potentially offer protection against 89.5% of the strains of Sp isolated from Brazilian children and adolescents infected by HIV.[5]

Another vaccine that is available on the Brazilian market for administration to children over 2 years old is the polysaccharide vaccine (non-conjugate) with 23 Sp serotypes (23vPPV).

We only identified six children older than 2 years whose Sp serotypes were included in the 23vPPV. Furthermore, even children older than 2 years who have HIV infections and were vaccinated with the 23vPPV did not respond well to the polysaccharide antigen, when compared with controls.[16]

Just six children were more than 2 years old at the time of data collection and none of them had been given the 23vPPV, already available at that time, confirming the published data that states that selective vaccination of high-risk groups is less efficient than vaccination of all children.

Attempting to relate clinical diagnoses, serotypes and the profile of pneumococcus susceptibility to penicillin, the three cases of meningitis were caused by Sp serotypes 6B, 23F and 14, two of which were resistant to penicillin (67%) and all of which are covered by the 7vPCV.

In contrast with serotypes 1 and 5, which are rarely resistant to penicillin, serotype 19A is becoming highly resistant. It is interesting to note that, in our study, one of the two cases of IPD caused by serotype 19A was SpNSPn.

In conclusion, our study has shown that a majority of IPD in HIV+ children and adolescents affected those less than 5 years old. The prevalence of SpNSPn was very high (47%).

Six serotypes, responsible for 14 strains isolated from 72% of the 19 patients, are covered by the 7vPCV. Serotypes covered by the 7vPCV were responsible for 75% of all serotypes isolated and for 86% of the SpNSPn serotypes identified in cultures from children less than 5 years old, i.e. they were cases of IPD that could have been avoided if these children had been given the 7vPCV.

Acknowledgements

We are grateful to professor Dr. Lúcia Ferro Bricks for her support, ideas, proofreading and suggestions. We are grateful to Dr. Maria Cristina Brandileone, for her support, for her suggestions and for carrying out laboratory tests and procedures.

References

1. Feldman C, Glatthaar M, Morar R, Mahomed AG, Kaka S, Cassel M, et al. Bacteremic pneumococcal pneumonia in HIV seropositive and HIV seronegative adults. Chest. 1999;116; 107-14.
2. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold AL, et al.; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med. 2006;354:1455-63.
3. Cardoso V, Cervi MC, Cintra OA, Salathiel AS, Gomes AC. Nasopharyngeal colonization with Streptococcus pneumoniae in children infected with human immunodeficiency virus. J Pediatr (Rio J). 2006;82:51-7.
4. Berezin EN, Carvalho LH, Lopes CR, Sanajotta AT, Brandileone MC, Menegatti S, et al. Meningite pneumocócica na infância: características clínicas, sorotipos mais prevalentes e prognóstico. J Pediatr (Rio J). 2002;78:19-23.
5. Scott DA, Konjathy SF, Hu BT, Baker S, Supan LA, Monahan CA et al. Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. Vaccine. 2007;25:6164-6166.
6. Brandileone MC, Vieira VS, Casagrande ST, Zanella RC, Guerra ML, Bokermann S, et al. Prevalence of serotypes and antimicrobial resistance of Streptococcus pneumoniae strains isolated from Brazilian children with invasive infections. Pneumococcal Study Group in Brazil for the SIREVA Project. Regional System for Vaccines in Latin America. Microb Drug Resist. 1997;3:141-6.

7. Brandileone MC, de Andrade AL, DiFabio JL, Guerra ML, Austrian R. Appropriateness of a pneumococcal conjugate vaccine in Brazil: potential impact of age and clinical diagnosis, with emphasis on meningitis. J Infect Dis. 2003;187:1206-12.

8. Brandileone MC, Casagrande ST, Guerra ML, Zanella RC, Andrade AL, Di Fabio JL. Increase in numbers of beta-lactam-resistant invasive Streptococcus pneumoniae in Brazil and the impact of conjugate vaccine coverage. J Med Microbiol. 2006;55:567-74.

9. Laval CB, de Andrade AL, Pimenta FC, de Andrade JG, de Oliveira RM, Silva SA, et al. Serotypes of carriage and invasive isolates of Streptococcus pneumoniae in Brazilian children in the era of pneumococcal vaccines. Clin Microbiol Infect. 2006;12: 50-5.

10. Rey LC, Wolf B, Moreira LB, Verhoef J, Farhat C. S. pneumoniae isolados da nasofaringe de crianças sadias e com pneumonia: taxa de colonização e susceptibilidade aos antimicrobianos. J Pediatr (Rio J). 2002;78:105-12.

11. Nascimento-Carvalho CM, Freitas-Souza LS, Moreno-Carvalho OA, Alves NN, Caldas RM, Barberino MG, et al. Cepas invasivas de pneumococo isoladas de crianças e adolescentes de Salvador. J Pediatr (Rio J). 2003;79:209-14.

12. Mantese OC, Paula A, Moraes AB, Moreira TA, Guerra ML, Brandileone MC. Prevalência de sorotipos e resistência antimicrobiana de cepas invasivas do Streptococcus pneumoniae. J Pediatr (Rio J). 2003;79;537-42.

13. Lucarevschi BR, Baldacci ER, Bricks LF, Bertoli CJ, Teixeira LM, Mendes CM, et al. Colonização de orofaringe por Streptococcus pneumoniae em crianças de creches municipais de Taubaté - SP: correlação entre os principais sorotipos e a vacina pneumocócica conjugada heptavalente. J Pediatr (Rio J). 2003;79:215-20.

14. Lucero MG, Dulalia VE, Parreno RN, Lim-Quianzon DM, Nohynek H, Makela H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive disease and pneumonia with consolidation on x-ray children under two years of age. Cochrane Database Syst Rev. 2004;4:CD004977.

15. Flannery B, Heffernan RT, Harrison LH, Ray SM, Reingold AL, Hadler J, et al. Changes in invasive Pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med. 2006;144:1-9.

16. Carson PJ, Schut RL, Simpson ML, O'Brien J, Janoff EN. Antibody class and subclass responses to pneumococcal polyssacharides following immunizationof human immunodeficiency virus-infected patients. J Infect Dis. 1995;172:340-5.

Correspondence:
Luiza Helena Falleiros Carvalho
Alameda dos Anapurus, 510/51
CEP 04087-000 – São Paulo, SP – Brazil
Tel.: +55 (11) 9659.4652, +55 (11) 5056.0664
Fax: +55 (11) 3287.1097
E-mail: luizahfc@terra.com.br