Special Article

Pneumococcal Infections in High-Risk and Immunocompromised Hosts

Olarn Prommalikit MD*,
Krisana Pengsaa MD**, Usa Thisyakorn MD***

** Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand*
*** Department of Pediatrics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand*
**** Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Streptococcus pneumoniae is an important cause of morbidity and mortality worldwide, it is responsible for invasive pneumococcal disease (IPD) (e.g. meningitis, bacteremic pneumonia and bacteremia) and non-IPD (e.g. pneumonia, acute otitis media, and sinusitis). IPD is preceded by nasopharyngeal colonization with high incidence of disease among young children, the elderly, persons with underlying medical conditions and immunocompromised hosts.

The term "immunocompromised host" is generally applied to a variety of patients with various immune defects. The factors that contribute to the development of IPD include host immunity (specific and innate), genetic and environment. Specific defects in host responses to pneumococcal infections may due to very young age, deficiencies in levels of antibodies and complement factors, and splenic dysfunction. The combinations of these defects contribute to the increased rates of IPD. The immunocompromising and other conditions that predispose to pneumococcal disease were described.

Keywords: *Invasive pneumococcal disease, S.pneumoniae, Immunocompromised hosts*

J Med Assoc Thai 2010; 93 (Suppl. 5): S61-S70
Full text. e-Journal: *http://www.mat.or.th/journal*

Streptococcus pneumoniae colonizes the human nasopharynx and causes invasive pneumococcal disease (IPD) (*e.g.* meningitis, bacteremic pneumonia and bacteremia) and non-IPD (*e.g.* pneumonia, acute otitis media and sinusitis). Colonization was found most often in children, peaking approximately at 3 years of age[1,2]. Colonization is an essential part of disease pathogenesis.

The term "immunocompromised hosts" is generally applied to a variety of patients with various immune defects. IPD and recurrent pneumococcal infections usually occur in immunocompromised patients and patients with underlying conditions[3-5]. As many as a quarter of children with IPD in the developed world have a significant underlying medical conditions[6]. The children with immunocompromising conditions suffer from IPD more frequently and with greater mortality than healthy children. In adults, immunocompromise and high-risk conditions accounted for nearly two-thirds of the total IPD burden in the United States[7]. In the developing world, human immunodeficiency virus (HIV) was the major risk factor to adult pneumococcal diseases.

The specific defects of host responses may due to immature immunity in very young age, deficiencies in levels of antibodies and complement factors, and splenic dysfunction. The combinations of host immune defects contribute to the increased risk of IPD in patients with sickle-cell disease (SCD), nephrotic syndrome, neoplasms, and underlying medical conditions[8-10]. The number of risk factors are greatest and the rates of IPD are highest in patients with HIV infection[8]. The list of immunocompromising and other conditions that predispose to pneumococcal disease are shown in Table 1.

Antimicrobial resistance among pneumococci has escalated dramatically over the past three decades. The incidence of resistance is influenced by patterns of antibiotic use. Judicious usage of antibiotics and development of effective vaccines with expanded coverage are critical for prevention of pneumococcal infections in high-risk patients.

Correspondence to:
Prommalikit O, Department of Pediatrics, Faculty of Medicine, Srinakharinwirot University, 114 Sukhumvit 23, Bangkok 10110, Thailand
Phone: 08-9927-1040
Email: drolarnp2002@yahoo.com

Table 1. Conditions that predispose to pneumococcal infection and mechanisms of susceptibility

Conditions	Mechanism of susceptibility
HIV infection	Defective antibody, reduced mucosal clearance
SCD	Defective antibody, complement deficiency, phagocyte dysfunction
Asplenia (functional and anatomic)	Defective antibody, complement deficiency
Transplantation	Defective antibody, phagocyte dysfunction
Malignant disease	Defective antibody, reduced mucosal clearance, anatomical defects
Immunosuppressive therapy	Defective antibody, phagocyte dysfunction
Congenital immunodeficiency	Defective antibody, phagocyte dysfunction
Chronic heart disease	Reduced mucosal clearance
Chronic pulmonary disease	Reduced mucosal clearance, anatomical defects, phagocyte dysfunction
Chronic renal disease	Defective antibody, complement deficiency
Liver cirrhosis	Anatomical defects, phagocyte dysfunction
Alcoholism	Reduced mucosal clearance, phagocyte dysfunction

HIV Infection

Children and adults with HIV have increased rates of infections with encapsulated bacteria, especially *S. pneumoni*ae[11-15]. The incidence of IPD is estimated to be 20-100 fold higher than that in children and adults who are not infected with HIV[16-19].

In 1985, Bernstein et al investigated 46 HIV-infected children and reported 27 episodes of sepsis in 21 children. The most common pathogenic agent was *S. pneumoniae*[16]. Krasinski et al also found *S.pneumoniae* in 31% of blood cultures in HIV-infected children[20].

In 1994, Farley et al, prospectively followed up a cohort of HIV-infected infants from birth and found an incidence of IPD of 11.3 per 100 children-year during the first three years of life compared to 0.5 per 100 children-year in the control group[21].

In a South African study carried out in 2000, Madhi et al investigated children under 12 years of age who had their blood or cerebrospinal fluid cultured. The authors found 237 IPD cases, of which 64.9% were HIV-infected children. They reported a 41.7-fold increased risk of IPD (95% CI 26.5;65.6) in this population compared to healthy children of the same-age. Multiple drug resistant *S. pneumoniae* was also found more frequently in HIV-infected children compared to HIV-negative children[18]. Another study found that *S. pneumoniae* was the predominate bacterial pathogen identified in HIV-infected children (74%), while it was identified in only 29% among non-HIV-infected children, even prior to the introduction of a Hib conjugate vaccine. Similarly, *S.pneumoniae* was responsible for a higher proportion of bacterial meningitis cases in Malawi among HIV-infected children (52%), than among HIV-uninfected children (32%)[22].

In 2004, Carrol et al investigated 59 HIV-infected children in Malawi. It appeared that there were higher pneumococcal bacterial DNA loads and cytokines (plasma tumor necrosis factor-α, interleukin-1β, interleukin-6, interleukin-10) in the blood and CSF samples of HIV-infected children than of HIV-uninfected children. The DNA and cytokines loads were also significantly higher in nonsurvivors than in survivors, and were significantly higher in children with meningitis than in those with pneumonia. High blood and CSF pneumococcal DNA loads were associated with fatal outcome[23].

HIV infection was estimated to be the attributable cause of at least half of all serious IPD and pneumonia cases in the adult population in Africa[24,25]. Highly active antiretroviral therapy (HAART) has been associated with a 60% decrease in IPD in the United States, but the risk of disease in HIV-infected individuals remained in the order of 30 times greater than that in HIV-uninfected persons[26].

Pneumococcal polysaccharide vaccine has been recommended since 1985 for children older than 2 years who are at high risk of invasive diseases, but it is not recommended for younger children and infants because of poor antibody response in those before 2 years of age[27]. In HIV-infected children in the pre-HAART era, the 23-valent pneumococcal polysaccharide vaccine (PPSV23) was found to have poor immunogenicity[28].

Several immunogenicity studies of PPSV23 have been conducted in HIV-infected adults. All found

significant responses to the vaccination but lower in comparison to HIV-uninfected controls[29-32].

The efficacy of PPSV23 in high-risk and immunocompromised host was inconclusive[31,33]. Pneumococcal conjugate vaccine (PCV) offers an alternative approach to protection. A trial evaluating PCV conjugated to CRM197 protein, a nontoxic mutant diphtheria toxin, (PCV-CRM), in HIV-infected infants who were on HAART demonstrated that PCV-CRM followed by the PPSV23 was well tolerated, and immunogenic. In a south African study, the short-term serotype-specific efficacy for HIV-infected infants was 65%, compared to 85% efficacy for HIV-uninfected children[34]. Those with more severe immune suppression had lower anti-PPS antibody levels than those with less immune suppression, and significantly lower than healthy controls[35,36]. The estimated long-term efficacy among HIV-uninfected children was stable at 77% during follow-up, compared to 83% initially, while the estimated efficacy rates in the HIV-infected cohort dropped from 65% initially to 39% at follow-up[37]. HIV-infected children demonstrated a more rapid decline in antibody concentrations, suggesting a likely need for a booster dose[38]. Current recommendations are that all HIV-infected infants and children should be vaccinated with a three-dose primary series and a booster dose of PCV[39].

The studies of PCV in adults have so far been limited[40-43]. Immunogenicity studies found that PCV was safe and more immunogenic than PPSV23. However, clinical efficacy trials are required.

Sickle-Cell Diseases

SCD encompasses various combinations of abnormal hemoglobin genes that include at least one copy of the gene for hemoglobin S paired with another structural β-chain hemoglobin variant or β-thalassemia gene[44]. Children with SCD have an increased risk of mortality that peaks between the ages of 6 months and 3 years in both low-income and high-income settings[45,46]. Increased early mortality among children with SCD is primarily due to infection. Immune function in SCD is compromised due to deficiency in serum opsonin activity, abnormal neutrophil kinetics, and repeated sickling in the spleen leading to loss of splenic function[47,48].

Children with SCD are particularly susceptible to pneumococcal infection. High rates of IPD in children with SCD were observed in the era before prophylactic antibiotics and vaccines use[49]. Before the introduction of PCV, children with SCD younger than 3 years in the US had a 53-times greater risk of IPD compared with the general population[50].

IPD rates peaked in 1-year-old children at 36 to 63 per 1,000 persons per year in children between 1 and 2 years of age and at 9.5 to 19 per 1,000 persons per year for children under the age of 10[51]. In England during 1983-2005, Telfer et al investigated 252 children with SCD and reported that pneumococcal sepsis rate was 0.3 (95%CI 0.1-0.8) episodes per 100 patient-years[52].

The use of penicillin prophylaxis and PCV has decreased the risk of bacteremia from *S. pneumoniae*[53]. A retrospective chart review of 692 children with SCD visiting emergency department during January 1, 2005 to December 31, 2006, was conducted by Rogovik et al. None of the blood culture of these patients grew *S. pneumoniae*. The absence of *S. pneumoniae* in this cohort was associated with the addition of the 7-valent PCV[54].

Studies of PPSV in children with SCD have not demonstrated consistent immunogenicity or efficacy. The immunogenicity and safety of 7-valent PCV in children and adolescents were found to be safe and immunogenic[55-57]. The use of PPSV23 as a booster vaccine was associated with substantial increases in anti-PPS, while the PCV-PCV-PPSV regimen was shown to induce greater concentrations of anti-PPS than PPSV alone for all seven serotypes in a study of older children and young adults[57]. Based on these immunogenicity results, current recommendations for children with SCD include immunization with 7-valent PCV in infancy, a booster dose at 12 to 15 months, PPSV23 at 24 months of age, and a booster dose of PPSV 3 to 5 years later[39].

Functional and Anatomical Asplenia

The term 'asplenia' describes a condition of the absence of spleen that is generally due to surgery, local radiotherapy, or congenital condition. The anatomic presence of spleen with a compromised function can be identified as functional asplenia.

The spleen is critical for initiating antibody production and clearing opsonized bacteria from the circulation. The most serious consequence of asplenia is the risk of developing life-threatening infections[58,59]. Life-threatening postsplenectomy infections occur at an estimated incidence of 0.23-0.42% per year, with a lifetime risk of 5%[60]. The highest frequency of life-threatening infectious episodes is observed during the first 2 to 3 years after splenectomy (near 50% within the first 2 years). Age at time of splenectomy seems to play an important role in determining this risk. The

younger age was associated with the shorter the interval to life-threatening infectious complications.

The infections observed in asplenic patients were mainly due to the encapsulated bacteria, with an incidence of 10-50 times higher than that in normal population[58,61]. Overwhelming postsplenectomy infections (OPSI) were caused by *S. peumoniae* in about 80% of the cases[62].

Schutze et al reviewed prospectively the clinical course of IPD in children with asplenia before the release of PCV in United States during 1993-1999. There were 22 asplenic patients with 26 episodes of IPD. This represented 1% of the 2,581 episodes of IPD identified in this study. The most common serotypes isolated were 6B, 23F, 18C, and 19A[63].

Vaccine efficacy of PPSV23 varies by different underlying pathological conditions. There is a recognition that some postsplenectomy individuals did not respond to PPSV, thus remain at high risk for serious disease[64,65]. PCV7 is attractive vaccine for use in splenectomized individuals and was immunogenic with between 2.2% - 14.6% of subjects failing to reach an anti-PPS level of $\geq$ 1 μg/ml[66]. Even though PCV7 might increase protection, 19% of patients had disease caused by serotypes not included in this vaccine[63]. PCV7 has been successfully used to overcome nonresponsiveness to PPSV23 in post splenectomized individuals[67].

Transplantation

S. pneumoniae has been an important pathogen in patients undergoing bone marrow transplantation (BMT) or peripheral blood stem cell transplantation. Two patterns of pneumococcal disease were recognized[68,69]. Early-onset disease was observed in both allogeneic and autologous BMT and peripheral blood stem cell transplant patients within the first 35 days of transplantation. Later-onset disease occurs after 100 days, is more frequent in allogeneic than in autologous BMT. IPD following BMT could be recurring and complicated.

For solid-organ transplantation, recipients were at increased risk of pneumococcal disease. The risk varies with the nature of the transplantation; however, recipients have a lifelong increase risk due to the immunosuppressive therapy required for transplant survival, and recurrent disease was common.

The risk of IPD among renal transplant recipients was approximately 1% per year or 28 infections per 1,000 patient-years (more than 60 times higher than the rate in the general population)[70]. Stovall SH et al reviewed medical records of cardiac transplant patients from March 1990 to November 2000, and found that 9 of 80 patients had 12 episodes of pneumococcal bacteremia, accounted for an incidence rate of 39 cases/1,000 patient years after transplantation. Patients who were African-American, transplanted before 2 years of age and transplanted because of idiopathic dilated cardiomyopathy were at increased risk of IPD ($p < 0.05$)[71].

Furthermore, functional hyposplenism secondary to irradiation, chronic graft-versus-host disease (GVHD), and decreased IgG2 antibody contributed to risk of IPD and the poor outcomes[72].

Several investigators have reported failure to elicit protective response to PPSV when administered within to 2 years after the stem cell transplantation. Similarly for solid-organ transplant patients, immunogenicity of PPSV tends to be poor whether the vaccine is given before or after transplantation[73,74].

In allogeneic transplant recipients, pre-bone marrow harvesting immunization with PCV in donor enhances the response of the recipient to PCV during posttransplant, particularly to the first dose[75]. Similar findings was found in autologous stem cell transplant patients,. Individuals who receive a dose of PCV prior to stem cell harvesting had better responses to the first PCV and overall better responses after three doses[76]. For solid-organ transplant recipients, PCV7 has been studied in adult renal and liver transplantation. PCV7 was no more immunogenic than PPSV23[77].

A recent guidelines for preventing infectious complications among hematopoietic cell transplantation (HCT) recipients endorsed by the Infectious Diseases Society of America recommended 3 doses of PCV7 with the initial dose as early as 3-6 months after HCT, follow by a dose of PPSV23 at 12 months to broaden the immune response for adults or children > 2 years old. For patients with chronic GVHD, a fourth dose of PCV should be considered because of poor response to PPSV23. If possible, the fourth dose of PCV should be given before PPSV23[78].

Malignancy

Individuals with cancer have a relative risk of pneumococcal disease 20 to 50 times that of the general population[7]. The most common type of childhood malignancy with an incidence of approximately 4 cases per 100,000 children below 15 years of age.

It has recently been recognized that children undergoing therapy for acute lymphoblastic leukaemia (ALL) are also at substantial risk for IPD[79]. This

increased risk is due to the chemotherapy-induced impairment of the different arms of the immune system, which may include the loss of specific antibodies and immune memory[80]. As expected, the infection may affect children receiving intensive chemotherapy for ALL, but a significant proportion of IPD also occurs during maintenance chemotherapy in the absence of chemotherapy-induced neutropenia[79]. Lehrnbecher et al indicated that patients with ALL who are unvaccinated against pneumococci have a selective immunodeficiency with an impaired antibody protection against pneumococci for up to 9 months after completion of therapy[81].

Waghorn DJ reported 77 cases of overwhelming infection in asplenia with 50% overall mortality. Underlying hematological malignancy was associated with the highest death rate and *S. pneumoniae* caused approximately 90% of the episodes. Only 31% individuals had received pneumococcal vaccination before OPSI. Seven of 17 pneumococcal infections in immunized cases could be considered vaccine failures[82].

Patients with multiple myeloma are attributed to deficiencies in immunoglobulins and antibody response, as well as decreased complement function and neutrophil migration[83]. Severe infections caused by *S.pneumoniae* has been reported in these patients[84,85]. In a review of 190 patients with pneumococcal arthritis, 6% had underlying multiple myeloma[86].

Immunogenicity studies of PPSV in patients with solid tumors were scarce, but found antibody titer to be as in normal or reduced[87]. In hematologic malignancies, immunogenicity was poor, and asplenia was also a contributing condition in many of these patients[88-91]. There has been no study of PCV in individuals with solid tumors. Further studies are required.

Others

Children with primary immunodeficiencies, for example, X linked agammaglobulinaemia, common variable hypogammaglobulinaemia, IgG subclass deficiency, deficiencies of early components of the classical pathway of complement and C3 deficiency, anhidrotic ectodermal dysplasia with immunodeficiency (caused by impaired NF-kappaB activation), and interleukin-1 receptor associated kinase 4 deficiency are at greatest risk for pneumococcal disease. Patients with other complement deficiencies (alternative and third pathway) and hyperimmunoglobulin E syndrome show a lower risk, whereas patients with other known primary immunodeficiencies, such as phagocytic disorders, do not appear to be particularly vulnerable to *S. pneumoniae*[92,93]. Picard E et al reported the case of a 5-month-old infant with a leukocyte chemotaxis defect who died from *S. pneumoniae* (serotype 23) septicemia several hours after flexible bronchoscopy. They suggested administering prophylactic antimicrobial therapy immediately following bronchoscopy to immunosuppressed children, even when an acute respiratory infection is not suspected, in order to prevent bacteremia and sepsis[94].

Systemic diseases include chronic cardiac, pulmonary (including asthmatics on high dose steroids), renal (including nephrotic syndrome), liver disease, and patients with diabetes mellitus are presumed to be at moderate to high risk of pneumococcal disease. There are insufficient data from which to calculate attack rates of pneumococcal disease in these groups[95-97].

Patients with systemic lupus erythematosus (SLE) may be predisposed to pneumococcal infections[98,99]. Hypocomplementemia and suboptimal concentrations of antipneumococcal antibodies may be the contributing factors. Pneumococcal infections of the soft tissues are uncommon. However, there were least three case reports of pneumococcal necrotizing fasciitis (NF) in SLE patients[99-101]. Furthermore, Frick et al reported two cases of pneumococcal NF occurred after intramuscular injections of nonsteroidal anti-inflammatory drugs and Yamashiro et al also reported a case of NF in non-viral, non-alcoholic liver cirrhosis[102,103].

Neonatal infections due to *S. pneumoniae* has been uncommon, but could be serious. Prommalikit et al reported 3 cases of IPD in neonates[104]. It is clear that low birth weight (LBW) and preterm infants are at an increased risk for IPD. The risk ratio for IPD for LBW infants compared with normal birth weight infants was 2.6 ($p = 0.03$), and for preterm compared with full term infants was 1.6 ($p = 0.06$)[105].

References

1. Lynch JP 3rd, Zhanel GG. *Streptococcus pneumoniae*: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. Curr Opin Pulm Med 2010; 16: 217-25.
2. Mitchell AM, Mitchell TJ. *Streptococcus pneumoniae*: virulence factors and variation. Clin Microbiol Infect 2010; 16: 411-8.
3. Mason EO Jr, Wald ER, Tan TQ, Schutze GE, Brad-

ley JS, Barson WJ, et al. Recurrent systemic pneumococcal disease in children. Pediatr Infect Dis J 2007; 26: 480-4.
4. Kuhls TL, Viering TP, Leach CT, Steele MI, Haglund LA, Fine DP. Relapsing pneumococcal bacteremia in immunocompromised patients. Clin Infect Dis 1992; 14: 1050-4.
5. Rodriguez-Creixems M, Munoz P, Miranda E, Pelaez T, Alonso R, Bouza E. Recurrent pneumococcal bacteremia. A warning of immunodeficiency. Arch Intern Med 1996; 156: 1429-34.
6. Scheifele D, Halperin S, Pelletier L, Talbot J. Invasive pneumococcal infections in Canadian children, 1991-1998: implications for new vaccination strategies. Canadian Paediatric Society/Laboratory Centre for Disease Control Immunization Monitoring Program, Active (IMPACT). Clin Infect Dis 2000; 31: 58-64.
7. Kyaw MH, Rose CE Jr, Fry AM, Singleton JA, Moore Z, Zell ER, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis 2005; 192: 377-86.
8. Janoff EN, Rubins JB. Invasive pneumococcal disease in the immunocompromised host. Microb Drug Resist 1997; 3: 215-32.
9. Finn A, Booy R, Moxon R, Sharland M, Heath P. Should the new pneumococcal vaccine be used in high-risk children? Arch Dis Child 2002; 87: 18-21.
10. Fletcher MA, Laufer DS, McIntosh ED, Cimino C, Malinoski FJ. Controlling invasive pneumococcal disease: is vaccination of at-risk groups sufficient? Int J Clin Pract 2006; 60: 450-6.
11. Hill PC, Onyeama CO, Ikumapayi UN, Secka O, Ameyaw S, Simmonds N, et al. Bacteraemia in patients admitted to an urban hospital in West Africa. BMC Infect Dis 2007; 7: 2.
12. Schneider RF, Rosen MJ. Pneumococcal infections in HIV-infected adults. Semin Respir Infect 1999; 14: 237-42.
13. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. Ann Intern Med 1992; 117: 314-24.
14. Mundy LM, Auwaerter PG, Oldach D, Warner ML, Burton A, Vance E, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med 1995; 152: 1309-15.
15. Murray JF. Pulmonary complications of HIV-1 infection among adults living in Sub-Saharan Africa. Int J Tuberc Lung Dis 2005; 9: 826-35.
16. Bernstein LJ, Krieger BZ, Novick B, Sicklick MJ, Rubinstein A. Bacterial infection in the acquired immunodeficiency syndrome of children. Pediatr Infect Dis 1985; 4: 472-5.
17. Andiman WA, Mezger J, Shapiro E. Invasive bacterial infections in children born to women infected with human immunodeficiency virus type 1. J Pediatr 1994; 124: 846-52.
18. Madhi SA, Petersen K, Madhi A, Wasas A, Klugman KP. Impact of human immunodeficiency virus type 1 on the disease spectrum of *Streptococcus pneumoniae* in South African children. Pediatr Infect Dis J 2000; 19: 1141-7.
19. Gordon S. Pneumococcal infections in HIV infected adults—clinical features, reasons behind the association and future hopes for prevention. Trop Doct 2004; 34: 200-3.
20. Krasinski K, Borkowsky W, Bonk S, Lawrence R, Chandwani S. Bacterial infections in human immunodeficiency virus-infected children. Pediatr Infect Dis J 1988; 7: 323-8.
21. Farley JJ, King JC Jr, Nair P, Hines SE, Tressler RL, Vink PE. Invasive pneumococcal disease among infected and uninfected children of mothers with human immunodeficiency virus infection. J Pediatr 1994; 124: 853-8.
22. Molyneux EM, Tembo M, Kayira K, Bwanaisa L, Mweneychanya J, Njobvu A, et al. The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi. Arch Dis Child 2003; 88: 1112-8.
23. Carrol ED, Guiver M, Nkhoma S, Mankhambo LA, Marsh J, Balmer P, et al. High pneumococcal DNA loads are associated with mortality in Malawian children with invasive pneumococcal disease. Pediatr Infect Dis J 2007; 26: 416-22.
24. French N. Community acquired pneumonia in Africa: the contribution of HIV. Int J Tuberc Lung Dis 2003; 7: S133-4.
25. Klugman KP, Madhi SA, Feldman C. HIV and pneumococcal disease. Curr Opin Infect Dis 2007; 20: 11-5.
26. Heffernan RT, Barrett NL, Gallagher KM, Hadler JL, Harrison LH, Reingold AL, et al. Declining incidence of invasive *Streptococcus pneumoniae* infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. J Infect Dis 2005; 191: 2038-45.
27. Overturf GD. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and

polysaccharide vaccines and antibiotic prophylaxis. Pediatrics 2000; 106(2 Pt 1): 367-76.
28. Arpadi SM, Back S, O'Brien J, Janoff EN. Antibodies to pneumococcal capsular polysaccharides in children with human immunodeficiency virus infection given polyvalent pneumococcal vaccine. J Pediatr 1994; 125: 77-9.
29. Carson PJ, Schut RL, Simpson ML, O'Brien J, Janoff EN. Antibody class and subclass responses to pneumococcal polysaccharides following immunization of human immunodeficiency virus-infected patients. J Infect Dis 1995; 172: 340-5.
30. French N, Gilks CF, Mujugira A, Fasching C, O'Brien J, Janoff EN. Pneumococcal vaccination in HIV-1-infected adults in Uganda: humoral response and two vaccine failures. AIDS 1998; 12: 1683-9.
31. Kroon FP, van Dissel JT, de Jong JC, van Furth R. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD4+ lymphocytes. AIDS 1994; 8: 469-76.
32. Vandenbruaene M, Colebunders R, Mascart-Lemone F, Haerden Y, Van Hove D, Peeters M, et al. Equal IgG antibody response to pneumococcal vaccination in all stages of human immunodeficiency virus disease. J Infect Dis 1995; 172: 551-3.
33. Tangsinmankong N, Kamchaisatian W, Day NK, Sleasman JW, Emmanuel PJ. Immunogenicity of 23-valent pneumococcal polysaccharide vaccine in children with human immunodeficiency virus undergoing highly active antiretroviral therapy. Ann Allergy Asthma Immunol 2004; 92: 558-64.
34. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003; 349: 1341-8.
35. Madhi SA, Kuwanda L, Cutland C, Holm A, Kayhty H, Klugman KP. Quantitative and qualitative antibody response to pneumococcal conjugate vaccine among African human immunodeficiency virus-infected and uninfected children. Pediatr Infect Dis J 2005; 24: 410-6.
36. Schutze GE, Tucker NC, Mason EO Jr. Failure of the conjugate pneumococcal vaccine to prevent recurrent bacteremia in a child with human immunodeficiency virus disease. Pediatr Infect Dis J 2001; 20: 1009-10.
37. Madhi SA, Adrian P, Kuwanda L, Jassat W, Jones S, Little T, et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. Vaccine 2007; 25: 2451-7.
38. Spoulou VI, Tsoumas DL, Papaevangelou VG, Mostrou GI, Theodoridou MC. Immunogenicity and immunological memory induced by a 7-valent pneumococcal CRM197 conjugate vaccine in symptomatic HIV-1 infected children. Vaccine 2005; 23: 5289-93.
39. American Academy of Pediatrics. Pneumococcal infections. In: Pickering LK, editor. 2009 Red Book: Report of the committee on infectious diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: 524-35.
40. Ahmed F, Steinhoff MC, Rodriguez-Barradas MC, Hamilton RG, Musher DM, Nelson KE. Effect of human immunodeficiency virus type 1 infection on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomized trial. J Infect Dis 1996; 173: 83-90.
41. Feikin DR, Elie CM, Goetz MB, Lennox JL, Carlone GM, Romero-Steiner S, et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. Vaccine 2001; 20: 545-53.
42. Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. Enhanced antibody response to pneumococcal polysaccharide vaccine after prior immunization with conjugate pneumococcal vaccine in HIV-infected adults. Vaccine 2000; 19: 886-94.
43. Miiro G, Kayhty H, Watera C, Tolmie H, Whitworth JA, Gilks CF, et al. Conjugate pneumococcal vaccine in HIV-infected Ugandans and the effect of past receipt of polysaccharide vaccine. J Infect Dis 2005; 192: 1801-5.
44. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008; 86: 480-7.
45. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001; 79: 704-12.
46. Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: burden and research priorities. Ann Trop Med Parasitol 2007; 101: 3-14.
47. Davies SC, Brozovic M. The presentation, management and prophylaxis of sickle cell disease. Blood Rev 1989; 3: 29-44.

48. Wong WY, Overturf GD, Powars DR. Infection caused by *Streptococcus pneumoniae* in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination. Clin Infect Dis 1992; 14: 1124-36.
49. Overturf GD, Powars D, Baraff LJ. Bacterial meningitis and septicemia in sickle cell disease. Am J Dis Child 1977; 131: 784-7.
50. Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000; 49: 1-35.
51. Adamkiewicz TV, Sarnaik S, Buchanan GR, Iyer RV, Miller ST, Pegelow CH, et al. Invasive pneumococcal infections in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination. J Pediatr 2003; 143: 438-44.
52. Telfer P, Coen P, Chakravorty S, Wilkey O, Evans J, Newell H, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica 2007; 92: 905-12.
53. Halasa NB, Shankar SM, Talbot TR, Arbogast PG, Mitchel EF, Wang WC, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis 2007; 44: 1428-33.
54. Rogovik AL, Friedman JN, Persaud J, Goldman RD. Bacterial blood cultures in children with sickle cell disease. Am J Emerg Med 2010; 28: 511-4.
55. Nowak-Wegrzyn A, Winkelstein JA, Swift AJ, Lederman HM. Serum opsonic activity in infants with sickle-cell disease immunized with pneumococcal polysaccharide protein conjugate vaccine. The Pneumococcal Conjugate Vaccine Study Group. Clin Diagn Lab Immunol 2000; 7: 788-93.
56. O'Brien KL, Swift AJ, Winkelstein JA, Santosham M, Stover B, Luddy R, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM(197) among infants with sickle cell disease. Pneumococcal Conjugate Vaccine Study Group. Pediatrics 2000; 106: 965-72.
57. Vernacchio L, Neufeld EJ, MacDonald K, Kurth S, Murakami S, Hohne C, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. J Pediatr 1998; 133: 275-8.
58. Sumaraju V, Smith LG, Smith SM. Infectious complications in asplenic hosts. Infect Dis Clin North Am 2001; 15: 551-65, x.
59. Frezzato M, Castaman G, Rodeghiero F. Fulminant sepsis in adults splenectomized for Hodgkin's disease. Haematologica 1993; 78: 73-7.
60. Davidson RN, Wall RA. Prevention and management of infections in patients without a spleen. Clin Microbiol Infect 2001; 7: 657-60.
61. Reinert RR, Bussing A, Kierdorf H, Kuhnemund O, Kaufhold A. Recurrent systemic pneumococcal infection in an immunocompromised patient. Eur J Clin Microbiol Infect Dis 1994; 13: 304-7.
62. Jirillo E, Mastronardi ML, Altamura M, Munno I, Miniello S, Urgesi G, et al. The immunocompromised host: immune alterations in splenectomized patients and clinical implications. Curr Pharm Des 2003; 9: 1918-23.
63. Schutze GE, Mason EO Jr, Barson WJ, Kim KS, Wald ER, Givner LB, et al. Invasive pneumococcal infections in children with asplenia. Pediatr Infect Dis J 2002; 21: 278-82.
64. Konradsen HB, Nielsen JL, Pedersen FK, Henrichsen J. Antibody persistence in splenectomized adults after pneumococcal vaccination. Scand J Infect Dis 1990; 22: 725-7.
65. Abildgaard N, Nielsen JL. Pneumococcal septicaemia and meningitis in vaccinated splenectomized adult patients. Scand J Infect Dis 1994; 26: 615-7.
66. Stoehr GA, Rose MA, Eber SW, Heidemann K, Schubert R, Zielen S. Immunogenicity of sequential pneumococcal vaccination in subjects splenectomised for hereditary spherocytosis. Br J Haematol 2006; 132: 788-90.
67. Musher DM, Ceasar H, Kojic EM, Musher BL, Gathe JC Jr, Romero-Steiner S, et al. Administration of protein-conjugate pneumococcal vaccine to patients who have invasive disease after splenectomy despite their having received 23-valent pneumococcal polysaccharide vaccine. J Infect Dis 2005; 191: 1063-7.
68. Kulkarni S, Powles R, Treleaven J, Riley U, Singhal S, Horton C, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. Blood 2000; 95: 3683-6.
69. Ranchere JY, Gordiani B, Bachmann P. Postoperative infections in immunocompromised patients after oncological surgery. Support Care Cancer 1995; 3: 409-13.
70. Linnemann CC Jr, First MR. Risk of pneumococcal

infections in renal transplant patients. JAMA 1979; 241: 2619-21.
71. Stovall SH, Ainley KA, Mason EO Jr, Tucker NC, Frazier EA, Parker JG, et al. Invasive pneumococcal infections in pediatric cardiac transplant patients. Pediatr Infect Dis J 2001; 20: 946-50.
72. Engelhard D, Cordonnier C, Shaw PJ, Parkalli T, Guenther C, Martino R, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. Br J Haematol 2002; 117: 444-50.
73. Blumberg EA, Brozena SC, Stutman P, Wood D, Phan HM, Musher DM. Immunogenicity of pneumococcal vaccine in heart transplant recipients. Clin Infect Dis 2001; 32: 307-10.
74. Kazancioglu R, Sever MS, Yuksel-Onel D, Eraksoy H, Yildiz A, Celik AV, et al. Immunization of renal transplant recipients with pneumococcal polysaccharide vaccine. Clin Transplant 2000; 14: 61-5.
75. Molrine DC, Antin JH, Guinan EC, Soiffer RJ, MacDonald K, Malley R, et al. Donor immunization with pneumococcal conjugate vaccine and early protective antibody responses following allogeneic hematopoietic cell transplantation. Blood 2003; 101: 831-6.
76. Antin JH, Guinan EC, Avigan D, Soiffer RJ, Joyce RM, Martin VJ, et al. Protective antibody responses to pneumococcal conjugate vaccine after autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2005; 11: 213-22.
77. Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. J Infect Dis 2003; 187: 1639-45.
78. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009; 15: 1143-238.
79. Meisel R, Toschke AM, Heiligensetzer C, Dilloo D, Laws HJ, von Kries R. Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukaemia. Br J Haematol 2007; 137: 457-60.
80. Lehrnbecher T, Koehl U, Wittekindt B, Bochennek K, Tramsen L, Klingebiel T, et al. Changes in host defence induced by malignancies and antineoplastic treatment: implication for immunotherapeutic strategies. Lancet Oncol 2008; 9: 269-78.
81. Lehrnbecher T, Schubert R, Behl M, Koenig M, Rose MA, Koehl U, et al. Impaired pneumococcal immunity in children after treatment for acute lymphoblastic leukaemia. Br J Haematol 2009; 147: 700-5.
82. Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. J Clin Pathol 2001; 54: 214-8.
83. Cuesta M, Bernad M, Espinosa A, Herranz P, Martin ME, Gijon BJ. Pneumococcal septic arthritis as the first manifestation of multiple myeloma. Clin Exp Rheumatol 1992; 10: 483-4.
84. Souweine B, Mom T, Bret L, Klisnick A, Baguet JC, Gilain L. Cellulitis due to *Streptococcus pneumoniae* with diminished susceptibility to penicillin in an immunocompromised patient. Scand J Infect Dis 1997; 29: 518-9.
85. Sumrall A, Muzny C, Bell J, Dreiling B. Pneumococcal septic arthritis as the initial presentation of multiple myeloma. Int J Lab Hematol 2008; 30: 82-3.
86. Ross JJ, Saltzman CL, Carling P, Shapiro DS. Pneumococcal septic arthritis: review of 190 cases. Clin Infect Dis 2003; 36: 319-27.
87. Nordoy T, Aaberge IS, Husebekk A, Samdal HH, Steinert S, Melby H, et al. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and *Streptococcus pneumoniae*. Med Oncol 2002; 19: 71-8.
88. Frederiksen B, Specht L, Henrichsen J, Pedersen FK, Pedersen-Bjergaard J. Antibody response to pneumococcal vaccine in patients with early stage Hodgkin's disease. Eur J Haematol 1989; 43: 45-9.
89. Grimfors G, Bjorkholm M, Hammarstrom L, Askergren J, Smith CI, Holm G. Type-specific antipneumococcal antibody subclass response to vaccination after splenectomy with special reference to lymphoma patients. Eur J Haematol 1989; 43: 404-10.
90. Schmid GP, Smith RP, Baltch AL, Hall CA, Schiffman G. Antibody response to pneumococcal vaccine in patients with multiple myeloma. J Infect Dis 1981; 143: 590-7.
91. Shildt RA, Boyd JF, McCracken JD, Schiffman G, Giolma JP. Antibody response to pneumococcal vaccine in patients with solid tumors and lymphomas. Med Pediatr Oncol 1983; 11: 305-9.
92. Barnett ED, Pelton SI, Cabral HJ, Eavey RD, Allen C, Cunningham MJ, et al. Immune response to pneumococcal conjugate and polysaccharide vaccines in otitis-prone and otitis-free children. Clin Infect Dis 1999; 29: 191-2.

93. Picard C, Puel A, Bustamante J, Ku CL, Casanova JL. Primary immunodeficiencies associated with pneumococcal disease. Curr Opin Allergy Clin Immunol 2003; 3: 451-9.
94. Picard E, Schlesinger Y, Goldberg S, Schwartz S, Kerem E. Fatal pneumococcal sepsis following flexible bronchoscopy in an immunocompromised infant. Pediatr Pulmonol 1998; 25: 390-2.
95. Ramos Rincon JM, Cuenca EM, Fernandez Guerrero ML. Retrospective and comparative study of pneumococcal bacteremia in patients with chronic hepatopathy. An Med Interna 1996; 13: 313-6.
96. Navarro D, Escribano A, Cebrian L, Gimeno C, Garcia-Maset L, Garcia-de-Lomas J. Type-specific antibodies to pneumococcal capsular polysaccharide acquired either naturally or after vaccination with Prevenar in children with underlying chronic or recurrent lung diseases. Clin Vaccine Immunol 2006; 13: 665-70.
97. Vieira S, Baldacci ER, Carneiro-Sampaio M, Doria FU, Koch VH. Evaluation of antibody response to the heptavalent pneumococcal conjugate vaccine in pediatric chronic kidney disease. Pediatr Nephrol 2009; 24: 83-9.
98. Vargas PJ, King G, Navarra SV. Central nervous system infections in Filipino patients with systemic lupus erythematosus. Int J Rheum Dis 2009; 12: 234-8.
99. Hill MD, Karsh J. Invasive soft tissue infections with *Streptococcus pneumoniae* in patients with systemic lupus erythematosus: case report and review of the literature. Arthritis Rheum 1997; 40: 1716-9.
100. DiNubile MJ, Albornoz MA, Stumacher RJ, Van Uitert BL, Paluzzi SA, Bush LM, et al. Pneumococcal soft-tissue infections: possible association with connective tissue diseases. J Infect Dis 1991; 163: 897-900.
101. Isik A, Koca SS. Necrotizing fasciitis resulting from *Streptococcus pneumoniae* in recently diagnosed systemic lupus erythematosus case: a case report. Clin Rheumatol 2007; 26: 999-1001.
102. Frick S, Cerny A. Necrotizing fasciitis due to *Streptococcus pneumoniae* after intramuscular injection of nonsteroidal anti-inflammatory drugs: report of 2 cases and review. Clin Infect Dis 2001; 33: 740-4.
103. Yamashiro E, Asato Y, Taira K, Awazawa R, Yamamoto Y, Hagiwara K, et al. Necrotizing fasciitis caused by Streptococcus pneumoniae. J Dermatol 2009; 36: 298-305.
104. Prommalikit O, Mekmullica J, Pancharoen C, Thisyakorn U. Invasive pneumococcal infection in neonates: 3 case reports. Presented at the 55th Thai Congress of Pediatrics; December 4-6, 2002; Chiang Mai, Thailand.
105. Shinefield H, Black S, Ray P, Fireman B, Schwalbe J, Lewis E. Efficacy, immunogenicity and safety of heptavalent pneumococcal conjugate vaccine in low birth weight and preterm infants. Pediatr Infect Dis J 2002; 21: 182-6.

โรคติดเชื้อนิวโมค็อกคัสในผู้ป่วยที่มีภาวะภูมิคุ้มกันบกพร่อง

โอฬาร พรหมาลิขิต, กฤษณา เพ็งสา, อุษา ทิสยากร

โรคติดเชื้อนิวโมค็อกคัสเกิดจากแบคทีเรียซึ่งเป็นเชื้อก่อโรคที่สำคัญในเด็ก ผู้สูงอายุ และบุคคลที่มีโรคประจำตัวหรือมีภูมิคุ้มกันบกพร่อง เป็นสาเหตุของการเสียชีวิตและก่อให้เกิดความพิการที่สำคัญ เชื้อดังกล่าวก่อให้เกิดโรคชนิดรุนแรงหรือชนิดแพร่กระจายได้แก่ โรคติดเชื้อในกระแสเลือด และโรคเยื่อหุ้มสมองอักเสบ นอกจากนี้ยังก่อให้เกิดโรคติดเชื้อของระบบอื่นๆ เช่น โรคปอดอักเสบ หูชั้นกลางอักเสบ ไซนัสอักเสบ เป็นต้น ผู้ที่มีโรคประจำตัวหรือมีภาวะภูมิคุ้มกันบกพร่องเช่น การติดเชื้อเอชไอวี การปลูกถ่ายอวัยวะและไขกระดูก โรคมะเร็งและผู้ที่ได้รับยากดภูมิคุ้มกัน ผู้ป่วยตัดม้ามหรือม้ามทำงานบกพร่อง ผู้ที่มีโรคประจำตัวเรื้อรังเช่น โรคหัวใจ โรคไต โรคปอด จะมีความเสี่ยงต่อการติดเชื้อนิวโมค็อกคัสชนิดแพร่กระจายมากกว่าบุคคลอื่น