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# Overwhelming Postsplenectomy Infection with Vaccine-Type *Streptococcus pneumoniae* in a 12-Year-Old Girl despite Vaccination and Antibiotic Prophylaxis

**Summary: This report describes a 12-year-old girl who developed vaccine-type pneumococcal septicemia (type 4, Danish nomenclature) 2 years after splenectomy for recurrent idiopathic thrombocytopenia despite vaccination with the 23-valent vaccine 4 weeks before surgery and antibiotic prophylaxis with penicillin V. The disease presented as high fever with shivering and vomiting followed by disseminated petechiae and a deteriorated general condition. Initial laboratory studies showed severe sepsis with leucocytopenia and thrombocytopenia, a markedly elevated CRP, and disseminated intravascular coagulation. Despite antibiotic treatment, which was initiated with clindamycin, cefotaxime and trimethoprim/sulfamethoxazole and was switched to cefotaxime and penicillin after the result of the blood culture had been obtained, the patient had to be ventilated, and hemofiltration became necessary because of acute renal insufficiency. Furthermore, she required amputation of all her toes because of severe necrosis. No type-specific pneumococcal antibody titers were detected during and after infection. It remains unclear whether the susceptibility to *Streptococcus pneumoniae* was due to primary failure of antibody production or a decline in antibody levels after vaccination. Patients and/or their relatives should be informed that neither vaccination nor continuous antibiotic prophylaxis can guarantee full protection against infection with *S. pneumoniae* in patients after splenectomy.**

## Introduction

Splenectomy patients are known to be at high risk for overwhelming postsplenectomy infection syndrome (OPSI-syndrome [1, 2]). As *Streptococcus pneumoniae* is the most frequent cause of OPSI syndrome, vaccination and continuous antibiotic prophylaxis have been recommended [3–5].

But OPSI syndrome may occur nonetheless [6–10] and several additional risk factors have been identified which increase the risk for OPSI syndrome in asplenic patients.

A very important factor seems to be the age of the patient. The younger the patient is at the time of splenectomy, the higher the risk of OPSI syndrome seems to be. *Pedersen* et al. in 1983 and *Roth* et al. in 1986 reported a much higher incidence of OPSI syndrome if the splenectomy had to be performed before the age of 4 years [2, 11].

The time of vaccination is also of great importance. Children aged 2 years or less show little antibody response to most pneumococcal antigens [12–14], and patients who are vaccinated after splenectomy often fail to develop protecting antibodies against all pneumococcal capsular types [15, 16].

A third risk factor in this syndrome is the underlying disease resulting in splenectomy. In several studies it was shown that patients with an impaired immune system are at higher risk of OPSI syndrome [2, 7].

Our report shows that OPSI syndrome may occur even if none of the additional risk factors described above are present. The patient was 10 years old at the time of vaccination and splenectomy, she had been vaccinated well in advance of surgery and her underlying disease did not implicate deficiency of the immune system.

## Case Report

The patient had splenectomy at the age of 10 years because of recurrent episodes of idiopathic thrombocytopenia (ITP) after therapy with immunoglobulins and steroids had been unsuccessful. Four weeks before splenectomy a single dose of the 23-valent pneumococcal vaccine (Pneumovax 23®, Behringwerke, Marburg, Germany) was administered and the patient was vaccinated against *Haemophilus influenzae* b. After splenectomy, the platelet count rose to normal levels. Antibiotic prophylaxis with penicillin V was initiated and continued for the next 2 years. Two years after splenectomy at the age of 12 years the patient felt unwell for 2 days and took antibiotic prophylaxis irregularly. On the third day she suddenly developed a high temperature of 41 °C with shivering and vomiting. Despite antibiotic therapy with a macrolide her general condition deteriorated and petechiae were noted. She was then transferred to the hospital.

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On admission her general condition had worsened, and she had cyanosis of her lips and nail beds. Her hands and feet were cool and livid, and she showed a fine macular exanthem, mainly on her trunk, and petechiae, particularly on her arms and legs. Her liver could be palpated about 3 cm beneath the costal arch. Auscultation of lungs and heart were normal, as was the neurological examination. Her blood pressure was 81/64 mmHg, and her heart rate 100/min. Initial laboratory studies revealed severe sepsis with leucocytopenia (1,000/µl, no differential white blood count was performed), thrombocytopenia (25,000/µl) and a markedly elevated CRP of 11 mg/dl. Coagulation factors were low (fibrinogen 100 mg/dl, antithrombin 36%), indicating disseminated intravascular coagulation (DIC). Moderate anemia was also noted (hemoglobin 9.1 g/dl). Immunoglobulin levels, determined 3 days after admission were normal (IgG 12 g/l, IgM 1.46 g/l, IgA 4.63 g/l), as was chemiluminescence, which was determined shortly before discharge. In a subsequent blood culture *S. pneumoniae* (type 4, Danish nomenclature) was grown and found to be sensitive to penicillin. Due to these findings antibiotic treatment, which initially had been started with clindamycin, cefotaxime and trimethoprim/sulfamethoxazole, was changed to penicillin and cefotaxime. Cefotaxime was continued on a prophylactic basis because of her further deteriorating general condition, which necessitated intubation and ventilation on the second day after admission. DIC was treated with low dose heparin and fresh frozen plasma. On the third day of therapy the patient developed acute renal failure, requiring hemofiltration. Therapy of sepsis and DIC were free of complications, whereas ventilation had to be maintained for 5 weeks because of severe muscular atrophy. Furthermore, hemofiltration had to be continued for more than 8 weeks, resulting in compensated chronic renal failure.

The patient was discharged from the hospital 6 months after admission. As she had been vaccinated less than 3 years before she was not revaccinated, but antibiotic prophylaxis with penicillin V was continued. No further severe infections have occurred to date. Pneumococcal antibody titers were measured over the subsequent 6 months by an enzyme linked immunosolvent assay (ELISA), as described previously [17]. The complete vaccine (Pneumovax 23) was used as the antigen. Because of the poor binding of carbohydrates to the plastic surfaces, the carbohydrate mixture was derivatized. Within that time period the initial antibody titer (arbitrary units) of 1:325 fell to 1:38. In addition, in an ELISA using single pneumococcal polysaccharide as antigen no antibodies against *S. pneumoniae* could be detected during and after infection.

## Discussion

Splenectomy and functional asplenia are associated with an increased risk of overwhelming postsplenectomy infection (OPSI syndrome, [1, 2]). As *S. pneumoniae*, among other pathogens, plays an important role in this life-threatening infection, vaccination and antibiotic prophylaxis have been proposed.

The Committee on Infectious Diseases of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP) recommend that all children 2 years or older with an increased risk for systemic pneumococcal infections should be immunized with the 23-valent pneumococcal vaccine [3, 4]. If elective splenectomy is to be performed, the patient should be vaccinated at least 2 weeks before the operation. Although revaccina-

Table 1: Infection with vaccine-type strains of *Streptococcus pneumoniae* in splenectomized patients despite vaccination.

| Underlying condition | Age at vaccination (years) | Time after vaccination (months) | Fatal | Strain | Author [ref. no.] |
|---|---|---|---|---|---|
| Trauma | 28 | 12 | no | 1 | *Broome* et al., 1980 [6] |
| Trauma | 3 | 4 | yes | 3 | |
| Hemolytic anemia | 2 | 12 | no | 6A | |
| Hemolytic anemia | 9 | 6 | yes | 18C | |
| Hemolytic anemia | 16 | 2 | no | 23F | |
| Hodgkin's disease | 8 | 4 | no | 14 | |
| Hodgkin's disease | 16 | 12 | no | 14 | |
| Lymphoma | 39 | 6 | no | 6A | |
| Chronic myeloproliferative disorder | 2 | 8 | no | 9F | |
| Splenectomy | 47 | 3 | no | 3F | |
| ITP | 4 | 7 | no | 19F | |
| Hodgkin's disease | ? | 9 | no | 7F | *Belohradsky* et al., 1982 [7] |
| ITP | 64 | 23 | yes | 19F | *Brivet* et al., 1984 [8] |
| Congenital CMV-infection | 3 | 24 | yes | 19F | *Evans* et al., 1984 [9] |
| Sickle-cell anemia | 2 | 10 | no | 6A | *Buchanan* et al., 1986 [10] |
| ITP | 10 | 24 | no | 4 | Present case |
| | Ø = 15.9 | Ø = 10.2 | 4/17 | | |

tion is still being discussed [18], it is recommended for children 10 years or younger 3–5 years after the initial immunization. Older children and adults should be revaccinated only after 5 years or more [3, 4].

As children who are less than 2 years old may show poor antibody response after vaccination, the Cooperative Study of Sickle-Cell Disease recommends immunization of infants and young children with increased risk for systemic pneumococcal infection at age 6, 12 and 24 months [19].

In the future, pneumococcal conjugate vaccines may help to reduce the frequency of pneumococcal infections, especially in early childhood. Initial trials with three doses of a tetravalent and heptavalent conjugate pneumococcal vaccine showed good efficacy in infants aged 2–6 months [20, 21].

Continuous antibiotic prophylaxis has been extensively discussed in the literature [22–24]. Although there is some concern in the literature that this treatment may enhance selection of penicillin-resistant strains of *S. pneumoniae* [22], in a recent study by *Norris* et al. antibiotic prophylaxis did not increase the rate of colonization with resistant strains of *S. pneumoniae* in children with sickle-cell disease [23]. Furthermore, OPSI syndrome has been reported in patients who omitted only one or two doses of the antibiotic [24], as in the case reported here. Therefore antibiotic prophylaxis is recommended, although consensus on the age at which antibiotic prophylaxis for children with asplenia may be discontinued has not yet been reached. Whereas *Buchanan* recommended the continuation of prophylaxis for at least 3 years after splenectomy [25], the Chief Medical Officer in England and Wales suggested penicillin up to the age of 16 years [26]. Neither the Committee on Infectious Diseases of the American Academy of Pediatrics nor the ACIP give recommendations when to discontinue antibiotic prophylaxis [3, 4].

OPSI syndrome after polyvalent vaccination with strains included in the vaccine has been previously reported [6–10, Table 1], but in none of the reports published so far have the authors looked for type-specific antibodies after infection. In our patient, no type-specific antibodies after type 4 pneumococcal infection could be detected. Therefore, we believe that the infection was due to a primary failure of antibody production against the type 4 strain of *S. pneumoniae* rather than a breakdown in the immune response due to a decline in antibody titers. Infection appears to develop early after vaccination (3–24 months [6–10]), which supports our hypothesis of a primary failure of immunization. Antibody titers may thus need to be routinely measured post vaccination in order to assess the risk of pneumococcal infection, and controlled studies should be initiated to evaluate the best time for revaccination in those cases where the patient shows deficiency in antibody production after the first vaccination.

In summary, this case demonstrates that OPSI syndrome may occur even though vaccination was performed, continuous antibiotic prophylaxis had been given and the underlying disease was assumed not to severely impair the immune system. Therefore, the splenectomized patient and/or the parents should be informed that neither vaccination nor antibiotic prophylaxis can guarantee full protection against infection with *S. pneumoniae*.

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## Book Review

G. L. Ada, A. J. Ramsay (eds.)
**Vaccines, Vaccination and the Immune Response**
288 pages, 20 figures, 48 tables
Lippincott-Raven, Philadelphia, PA 1997
Price: $ 102.50

The tremendous increase of knowledge and major advances in methodology during recent years have led to a resurgence of interest in the development of new vaccines. According to a survey carried out by the World Health Organization (WHO), about 300 candidate vaccines are at relatively advanced stages of development. Most of the currently available vaccines have been developed to protect against acute infectious diseases. New vaccines are also needed for chronic persisting infections, such as those caused by HIV or plasmodia in endemic areas. In addition, there are new prospects for immunoprophylaxis or immunotherapy of tumors and autoimmune disease, and for the control of fertility.

The book is organized in six sections. After a short introduction about the historical background, section 1 "Past Achievements and Future Needs" presents a review of traditional-type vaccines including candidate vaccines in advanced clinical trials. This is followed by an overview of immunization programs and a summary of future needs and possibilities. The two types of immune response, innate immunity and specific adaptive immunity, are described in section 2 "The Mammalian Immune System." The authors contributed to a better understanding of regional and mucosal immunity by their own scientific work. Section 3 gives an overview of the "Immune Processes and Their Evasion by Infectious Agents" and also of the immunological preconditions for successful vaccination. Desirable properties and different roles of adjuvants in vaccines are described in section 4 "Immunopotentiation and the Selective Induction of the Immune Response." Section 5 reports on "Newer Approaches to Vaccine Development" including reviews of current knowledge of candidate vaccines based on peptides, anti-idiotypic antibodies, and site-directed replacement of nucleotide sequences. Another chapter of this section deals with approaches using recombinant DNA technology, and includes a short outlook on DNA vaccines and their future. A short chapter shows new possibilities for combination and sequential vaccines. Another category of intervention with vaccination is discussed in section 6 "Vaccination against Self and Self-Like Molecules" considering the current status and future perspectives of immunoprophylaxis and immunotherapy to control tumors, immunotherapy to control autoimmune diseases and immunocontraception to control fertility.

This book provides a concise and up-to-date overview on the principles of vaccines, vaccination, and the immunological basis. The authors succeeded in gathering most of the relevant information on current achievements as well as on new and future developments in vaccinology within the limited space of this compact volume. Many of the tables and figures can be used for teaching purposes. There is a useful and extensive list of references including recent data up to spring 1996. However, this book does not provide detailed practical information about the available vaccines. Overall, the book is an excellent resource for all interested in the immunological basis, current developments, and future perspectives of vaccination.

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