Pneumococcal Vaccine in Patients With Absent or Dysfunctional Spleen

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Four patients (3 long-term Hodgkin disease survivors and 1 recipient of an allogeneic bone marrow transplant) developed severe infections with Streptococcus pneumoniae after staging splenectomy or due to functional hyposplenism after total body irradiation and bone marrow transplantation. Current guidelines for prevention of infection recommend pneumococcal immunization for patients with Hodgkin disease treated with splenectomy and others with functional hyposplenism. Booster vaccination after 5 years is also advised. Hospital- and community-based vaccination initiatives may help identify at-risk patients.


Case Report

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Increased risk for infections from encapsulated bacteria, especially Streptococcus pneumoniae, is associated with absence of the spleen after trauma, Hodgkin disease treatment with staging splenectomy, or functional hyposplenism secondary to sickle cell anemia, thalassemia major, essential thrombocytopenia, lymphoproliferative diseases, bone marrow transplantation, and total body irradiation.

The spleen plays a central immunologic role by filtering for blood-borne bacteria, intraerythrocytic parasites, and immune complexes (red pulp). It serves also as an important site of humoral and cellular immunity (white pulp). Antibodies against surface polysaccharides are an important element of antipneumococcal immunity. The 23-valent pneumococcal vaccine induces such antibodies and provides effective protection for asplenic individuals. Prophylaxis against pneumococcal infections has been recommended for almost 20 years for patients who have undergone splenectomy, yet it is still underused. Rates of postsplenectomy vaccination in the United States were 0.7% between 1975 and 1980, rising to 35.5% between 1986 and 1990. An average of 16% of all patients had thus received the vaccine between 1975 and 1990, with a clear difference between adults and children (7% in adults and 32% in children). Patients splenectomized for benign diseases had higher vaccination rates.

Long-term Hodgkin disease survivors and recipients of allogeneic and autologous bone marrow transplants may not have received this vaccine and may be unaware of their increased risk for pneumococcal infection. The currently recommended booster injection may not have been given because of previous concerns about its safety.

Recognition of this problem has led to both hospital-based and community-based vaccination initiatives. In such study, information about pneumococcal vaccine was sent to primary care physicians of splenectomized patients and led to vaccination in 65 of 96 formerly unvaccinated patients. The worldwide emergence of drug-resistant S pneumoniae has led to an increased interest in promoting vaccine use.

At our center, 4 occurrences of severe invasive pneumococcal infections were observed recently. Three patients had been treated for Hodgkin disease with staging splenectomy; the fourth patient demonstrated functional hyposplenism after total body irradiation and bone marrow transplantation because of acute myeloid leukemia. These cases underscore the problem of “forgotten” splenectomy/hyposplenism and provide an opportunity to discuss current vaccination guidelines and implementation strategies.

REPORT OF CASES

Case 1

A 40-year-old man consulted his general practitioner because of a fever of 39.0°C and vomiting. Viral illness was suspected and symptomatic therapy administered. One day later the patient was hospitalized for changes in mental status, meningism, and persistent vomiting. Cerebrospinal fluid analysis revealed a white blood cell count of 7.1 × 10⁹/L (97% polymorphonuclear leukocytes), protein level of 1.84 g/L, and glucose level of 0.2 mmol/L with increased intracranial pressure. A Gram stain of the cerebrospinal fluid showed gram-positive diplococci, later identified as S pneumoniae. The patient recovered under treatment with high-dose penicillin G without sequelae. His treatment for Hodgkin disease 20 years earlier included splenectomy, radiotherapy, and chemotherapy. The patient did not re-
member having received a pneumococcal vaccine, and there was no record with his general practitioner or his oncologist.

**Case 2**

The second patient was a 32-year-old woman admitted in the 26th week of her second pregnancy with a brief history of fever and vomiting. The initial work-up revealed fetal death, and the patient rapidly developed a severe sepsis syndrome with disseminated intravascular coagulation. Fatal multiorgan failure ensued in spite of spontaneous delivery of the fetus and placenta, fluid resuscitation, and administration of pressors and antibiotics. An autopsy showed multiorgan failure and signs of disseminated intravascular coagulation with bleeding into the adrenal glands. Blood cultures grew *S. pneumoniae*. Nineteen years earlier she had been treated for Hodgkin disease, including staging splenectomy, radiotherapy, and chemotherapy. According to all available records, she had not been vaccinated against pneumococci.

**Case 3**

A 22-year-old man had undergone treatment for acute myeloid leukemia (M6 by FAB classification) with a deletion of chromosome 22, which comprised chemotherapy and total body irradiation, followed by allogeneic bone marrow transplantation from an HLA-matched sibling. A graft-vs-host reaction involving the gastrointestinal tract (severe diarrhea) and the skin (vitiligo) complicated this transplantation.

Follow-up 2 years later showed persistent remission, and the immunosuppressive therapy was discontinued. Four months subsequently the patient was hospitalized with fever, chills, and an upper respiratory tract infection of 2 days’ duration. On admission, septic shock was diagnosed with rapidly spreading petechiae and suffusions appearing on the trunk, face, and extremities (Figure 1). Blood tests showed severe disseminated intravascular coagulation. Penicillin-sensitive *S. pneumoniae* was isolated in all blood cultures, and broad-spectrum antimicrobial therapy was switched to penicillin G monotherapy.

The course was complicated by necrotizing hemorrhagic mesenteric infarction involving the right side of the colon and a large portion of the small intestine, most likely induced by disseminated intravascular coagulation. The right side of the colon and most of the ileum were removed in emergency surgery.

Additionally, a gangrenous lesion spread on the right toe. Other hemorrhagic and necrotic skin lesions on the face and on the extremities healed completely. Over the following weeks, the patient recovered progressively, and the hematologic test results returned to normal. It was later discovered that this patient had never been vaccinated against *S. pneumoniae*.

**Case 4**

This patient was a 49-year-old man transferred from a peripheral hospital because of severe *S. pneumoniae* sepsis after an upper respiratory tract infection (Figure 2). Nineteen years earlier, he had been treated for Hodgkin disease with staging splenectomy and polychemotherapy. He had never been vaccinated against pneumococci. The current course was complicated by septic-embolic encephalopathy and recurrent seizures as well as disseminated intravascular coagulation and multiorgan failure.

The patient’s condition improved initially. However, after 4 weeks his clinical status deteriorated with reappearance of fevers, abdominal distention, and meningism. The cultures of cerebrospinal fluid remained sterile, and computed tomography showed no intracerebral bleeding or abscess. Antimicrobial therapy with vancomycin and ciprofloxacin was started. The patient died 4 days later of *Clostridium difficile*-associated toxic megacolon with perforation.

**DISCUSSION**

Patients treated for Hodgkin disease with staging splenectomy, radiotherapy, and chemotherapy are at increased risk for developing serious invasive bacterial infections. Even without staging splenectomy, Hodgkin disease treated with radiotherapy, chemotherapy, or both increases the risk for pneumococcal infections. This predisposition results from lowered concentrations of antibodies to pneumococci and from postradiation functional hypoplasenism. Similarly, splenic dysfunction in long-term survivors of total body irradiation and bone marrow transplantation re-
results in a high susceptibility to infection with encapsulated bacteria, particularly when chronic graft-vs-host disease and immunoglobulin G deficiency are present or when immunosuppressive agents are used.13

*Streptococcus pneumoniae* is involved in roughly half of all invasive bacterial infections. Encapsulated bacteria—*Haemophilus influenzae* and *Neisseria meningitidis*—are the second and third most important.14,15 The estimated frequency of postsplenectomy sepsis varies from 2% to 7%.15-17 One study that collected all culture-confirmed invasive pneumococcal infections in Norway over a 12-month period estimated that invasive infections occur at a rate of 2.7 per 1000 splenectomized individuals per year with 1.3 per 1000 infection-related deaths per year.18 The relative risk compared with nonsplenectomized subjects was increased by a factor of 25 and 75, respectively. Assuming that an average Hodgkin disease survivor lives for 50 years after initial treatment, the patient’s chance of developing invasive pneumococcal infection will be 1 in 7.4 with a 1 in 15.4 chance of dying from overwhelming pneumococcal disease.

Most invasive pneumococcal infections occur in the first 2 years after splenectomy, and about one third occur between 5 and 20 years or more after splenectomy,15 as reported herein. Pneumococcal infections are common 3 months or longer after bone marrow transplantation.19 The patient may present with overwhelming postsplenectomy sepsis.14-16 Children may present with meningitis and septicemia combined; half of these infections occur in children between 10 and 19 years of age.14

The currently available pneumococcal polysaccharide vaccine is efficacious in preventing invasive pneumococcal infections.20 In an elegant indirect cohort study, the overall efficacy of the 23-valent vaccine was estimated to be 60% for all current indications and 77% in asplenic patients.2 In Switzerland, the 23-valent pneumococcal vaccine covers 91% of all serotypes isolated from invasive events.21 However, children younger than 2 years have an inherently reduced ability to mount an antibody response to polysaccharide antigens. Several studies have shown an impaired immune response to the polyvalent pneumococcal vaccine after splenectomy or after treatment for Hodgkin disease.22 Patients vaccinated before treatment for Hodgkin disease showed normal antibody responses provided vaccinations took place at least 10 to 14 days before initiation of therapy. Thus, it is advisable to administer the pneumococcal vaccine at least 2 weeks before elective splenectomy.

During the first year after therapy, patients were unresponsive to a booster immunization but showed a normal response if revaccinated at least 2 years after diagnosis of Hodgkin disease.23,24 In bone marrow transplant patients with chronic graft-vs-host disease and ongoing immunosuppressive therapy, numerous studies show poor antibody response to polysaccharide vaccines, particularly when given within 7 months after bone marrow transplantation.19 Current US and British guidelines recommend pneumococcal immunization for patients with splenectomy and functional hyposplenism.12,25-26 Booster vaccination is now recommended after 5 years; the need for additional boosters remains to be defined. Older guidelines discouraged revaccination and warned of potentially serious adverse effects.27 Jackson and colleagues28 have recently shown that revaccination of adults within 5 years with pneumococcal polysaccharide vaccine is associated with a slight increase of self-limited local reactions that were not judged to represent contraindications for revaccination. Bone marrow transplant patients and especially those with chronic graft-vs-host disease should receive appropriate long-term pro-
phylactic antibiotic therapy with penicillin V or trimethoprim-sulfamethoxazole. These patients should keep a supply of amoxicillin at home and use it immediately in the event that fever or other symptoms of infection develop.

Data on vaccine coverage in Switzerland are lacking, but available information suggests that the vaccine is widely underused. A study done in a Swiss university hospital identified 85 invasive pneumococcal infections in 1990 and 1991. Only 1 patient had been vaccinated, but 82% had at least 1 indication for pneumococcal vaccination. Based on the number of pneumococcal vaccine doses distributed, Switzerland holds an intermediate position among European countries with higher numbers of doses sold in Northern Europe compared with the Mediterranean countries. Clearly, Europe lags behind the United States, which may be attributable to different national vaccine recommendations. Switzerland has no official guidelines, and, indeed, the vaccine manufacturers’ recommendations published in the 1997 edition of the Swiss formulary discourage vaccine boosters for all previously vaccinated adults and for those with unknown vaccination status.

The cases described herein emphasize the need to actively ascertain the pneumococcal vaccine status in patients with remote splenectomy and functional hyposplenism. In 3 instances, splenectomy had been performed around the time the 14-valent vaccine became available in 1977. Uncertainty about the original vaccine status combined with concerns in the 1980s and early 1990s about safety of the pneumococcal vaccine booster may have contributed to the lack of appropriate vaccination.

Recently, 7-valent pneumococcal conjugate vaccines have been produced by linking polysaccharide to protein carrier molecules, thus stimulating T and B cells in a concerted fashion. Conjugation results in increased immunogenicity and the ability to prime for booster. The study by Anderson et al shows that this heptavalent pneumococcal conjugate vaccine is immunogenic in young infants and primes young infants for anamnestic antibody responses after a booster dose of native polysaccharide vaccine (Pneumovax 23).

Because of the sporadic nature of pneumococcal disease, not every physician will see it in the course of her or his career and may therefore underestimate the risk involved. As a consequence, an active program needs to be instituted to identify patients at risk and to ascertain proper vaccination status. Options to improve vaccine coverage for those at risk include the implementation of organizational strategies such as standing orders or practice guidelines, community-based programs, and hospital-based vaccine initiatives. Our current strategy combines a hospital-based retrospective vaccine initiative with new practice guidelines.

REFERENCES


