CLINICAL PRACTICE

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Care of the Asplenic Patient

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 23-year-old man sustained abdominal trauma in a motorcycle accident that required a surgical splenectomy. He received the 23-valent pneumococcal polysaccharide vaccine (PPSV23) after surgery. Six months after his surgery, he calls his primary care provider because he has fever. What is the appropriate management? Are other prophylactic measures available and indicated?

THE CLINICAL PROBLEM

Mortality among patients with postsplenectomy sepsis can be as high as 50%. Most commonly caused by *Streptococcus pneumoniae*, this infection often has a sudden onset and a fulminant course. The clinical presentation is nonspecific, with a very short prodromal period of fever, chills, sore throat, muscle aches, vomiting, or diarrhea. There is commonly no localized focus of infection, but in some cases there is associated pneumonia or meningitis. Deterioration of the patient's condition is abrupt, often occurring within hours. Shock may develop, and patients can have disseminated intravascular coagulation[1] and profound hypoglycemia.[2] The bacteremia can be of sufficiently high grade that gram-positive cocci (indicating *S. pneumoniae*) are visible in stained smears of peripheral blood.[2,3] Postsplenectomy sepsis should be suspected in an asplenic patient presenting with severe illness or a febrile illness of any severity.

The asplenic population is heterogeneous and includes patients with surgical asplenia, functional asplenia, and congenital asplenia. Surgical asplenia may occur in otherwise healthy patients (e.g., after trauma) or in patients with an underlying hematologic or immunologic indication for splenectomy (e.g., hereditary spherocytosis, immune thrombocytopenic purpura, hypersplenism, or sickle cell disease).[4] In patients with sickle cell anemia, functional asplenia develops by approximately 1 year of age, and anatomical asplenia due to autoinfarction develops after 6 to 8 years of age.[5] As measured by the percentage of erythrocytes with "pits," splenic dysfunction in patients with functional asplenia is not as severe as that which occurs after splenectomy. Chronic graft-versus-host disease after stem-cell transplantation, severe celiac disease, and untreated human immunodeficiency virus infection are the disease states most likely to be associated with hyposplenism; up to 50% of patients with these conditions may have impaired splenic function.[6,7] Congenital asplenia is a rare condition that may be isolated but is more likely to be associated with other anomalies, particularly congenital heart disease (the Ivemark syndrome).

Mortality from bloodstream infection after splenectomy was 46% in reports from 1966 through 1996[8] and did not vary materially with the patient's age, the indication for splenectomy, or the interval after splenectomy.[8,9] In contrast, the case fatality rate among children with sickle cell disease who were hospitalized for invasive pneumococcal disease was 18% in the mid-1980s[10] and ranged from 2 to 10% in studies of cases occurring between 1994 and 2007.[11-13]

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KEY CLINICAL POINTS

CARE OF THE ASPLENIC PATIENT

- Asplenic patients are at risk for episodes of rapidly progressive septicemia that are fatal in up to 50% of cases.
- Asplenic patients should be informed that any illness with fever or severe symptoms without fever could indicate the onset of a life-threatening infection.
- Asplenic patients in whom fever develops should receive empirical antimicrobial therapy immediately.
- Vaccinations against pneumococci, *Haemophilus influenzae* type b, meningococci, and influenza virus are recommended for asplenic patients.
- Prophylactic antimicrobial therapy is generally recommended for asplenic children younger than 5 years of age and may be considered for older children and adults during the initial 1 to 2 years after splenectomy, with lifelong prophylaxis for persons who have had an episode of postsplenectomy sepsis.

Approximately 25,000 surgical splenectomies are performed annually in the United States,[14] and the total number of asplenic persons in the United States is currently estimated at 1 million, including 70,000 to 100,000 persons with sickle cell disease.[15] On the basis of reports published during the 1980s, the calculated risk of fatal postsplenectomy sepsis was approximately 0.29 cases per 100 patient-years among children and 0.10 to 0.13 cases per 100 patient-years among adults.[16] In a review of case series reported during the 1980s and 1990s, there was a 3.2% incidence of postsplenectomy sepsis during a median follow-up of 6.9 years; infection was fatal in one third to two thirds of episodes.[8] In addition to conferring an increased risk of septicemia, surgical splenectomy was reported to be a risk factor for hospitalization due to pneumonia or meningitis and death from pneumonia in male U.S. military veterans.[17]

All the data on the risk of sepsis among patients who have undergone surgical splenectomy predated the introduction, in 2000, of universal vaccination with the heptavalent pneumococcal conjugate vaccine (PCV7) in young children in the United States. This vaccine has markedly reduced the incidence of invasive pneumococcal disease among children younger than 5 years of age and has also reduced invasive disease in all age groups as a result of herd-type immunity.[18] The 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in 2010, resulting in additional reductions in invasive pneumococcal disease in young children and also, indirectly, in older children and adults. The specific benefit in patients with surgical asplenia has not been defined.

Patients with sickle cell disease who are younger than 5 years of age, particularly those homozygous for hemoglobin S, have been considered to be at very high risk for pneumococcal sepsis, with a rate as high as 13.5 episodes per 100 patient-years reported during the mid-1980s.[10] However, from 2000 to 2010, the rate of bloodstream infection among patients with sickle cell disease who were younger than 23 years of age was 0.5 to 1.0 episodes per 100 patient-years.[19] In two studies involving children with sickle cell disease, the routine use of PCV7 was associated with reductions in the rate of invasive pneumococcal disease of 68% among children younger than 10 years of age[12] and 93% among those younger than 5 years of age,[13] with a 65% reduction in hospitalizations for invasive pneumococcal disease among children of any age, as compared with the rates before routine vaccination.[11]

The risk of postsplenectomy sepsis varies according to several factors, including the indication for splenectomy, the patient's age at the time of the surgery, and the interval since splenectomy. With respect to indication, the risk is lowest among otherwise healthy persons who undergo splenectomy because of trauma, intermediate among patients with hereditary spherocytosis or immune thrombocytopenic purpura, and highest among surgically asplenic patients with β-thalassemia, sickle cell anemia, or portal hypertension.[8] With respect to age, the risk of sepsis is highest among infants with surgical or congenital asplenia.[9] Children younger than 5 years at the time of splenectomy have a higher risk than older children or adults,[20] but this finding may in part reflect the increased risk associated with the underlying conditions that warranted

splenectomy (e.g., thalassemia major and sickle cell anemia). With respect to the interval since splenectomy, the risks of sepsis and associated death are highest in the first year after splenectomy, at least among young children, but remain elevated for more than 10 years and probably for life.[9,16,17,21] In a combined analysis of several case series of postsplenectomy sepsis, the mean time between splenectomy and the occurrence of sepsis was 23 months but was longer in patients with trauma as the indication for splenectomy and shorter in patients with hematologic or immunologic indications.[8]

The reasons for an increased risk of bloodstream infection among asplenic patients are the impaired clearance of bacteria from the bloodstream and a humoral immune deficiency. The spleen is the most efficient organ for clearing IgG-coated bacteria and is critical for the clearance of virulent encapsulated bacteria that are not opsonized by antibodies or complement.[7,22] Asplenic animals require an increased level of opsonization (i.e., an increased number of antibody molecules per bacterium and an increased concentration of serum anticapsular antibodies) for hepatic clearance.[23,24] Asplenic persons also have humoral immune dysfunction, with a reduction in serum IgM antibodies to polysaccharides as well as a reduction in memory B cells producing IgM antibodies. Furthermore, the development of IgM antibodies to polysaccharide antigens is impaired, with a delayed and lower magnitude response to vaccination, as compared with the response in persons with an intact spleen.[7]

The pathogen that most commonly causes sepsis in patients who have undergone splenectomy, as well as in children with sickle cell disease, is *S. pneumoniae* (pneumococcus).[9,19] Another encapsulated bacteria, *Haemophilus influenzae* type b (Hib), which primarily affects children younger than 5 years of age, is now rare because of universal use of the Hib conjugate vaccine in the United States. Although *Neisseria meningitidis*, *Escherichia coli*, and *Staphylococcus aureus* each accounts for a small proportion of bloodstream isolates from asplenic persons, whether asplenia is actually a risk factor for infection with these pathogens has not been established. Asplenia is an important risk factor for serious infection with *Capnocytophaga canimorsus* or *C. cynodegmi* (after an animal bite), babesia (after a tick bite), and *Bordetella holmesii*. Whether malaria is more severe in asplenic persons than in persons with an intact spleen has not been established. Bloodstream infections with *E. coli* and klebsiella species have been observed in young infants (<6 months of age) with congenital asplenia, but the clinical severity of these infections is similar to that observed in young infants with intact spleens.[25] Among adults with sickle cell disease, bloodstream infections with gram-negative bacilli and *S. aureus*, often related to the use of a vascular catheter, are more common than bloodstream infection with *S. pneumoniae*.[26]

STRATEGIES AND EVIDENCE

The mainstays of prevention of fatal postsplenectomy sepsis include education, vaccination, prophylactic antimicrobial therapy in selected patients, and early empirical antimicrobial therapy for febrile episodes. It is critically important to educate patients regarding the lifelong risk of postsplenectomy sepsis, the importance of vaccinations, and the need for urgent action in response to a febrile episode.

VACCINATIONS

Several vaccines are available for some of the pathogens that cause postsplenectomy sepsis, specifically *S. pneumoniae*, Hib, and *N. meningitidis*. The regimen and timing of vaccination differ according to whether vaccination is initiated before splenectomy (in cases of elective splenectomy) or after splenectomy (e.g., for patients in whom splenectomy is performed urgently) (Table 1).

For prevention of pneumococcal infection, administration of PCV13 followed 8 weeks later by PPSV23 is recommended.[27-29] This sequence results in a higher antibody concentration than administration of PPSV23 alone,[27,30] and when PPSV23 is given first, the response to subsequent doses of PPSV23 or to pneumococcal conjugate vaccine may be reduced.[31] Although some data suggest that the response to PPSV23 is impaired if the vaccine is administered during the 2 weeks before or 2 weeks after splenectomy,[32-34] it is not known whether this is the case for conjugate vaccines or other polysaccharide vaccines.

The risk of invasive infection with Hib among adults and older children is very low. Therefore, it is reasonable to limit vaccination of adults or older children with the Hib vaccine to those who were not previously vaccinated.

Quadrivalent meningococcal conjugate vaccine

Table 1. Recommended Vaccinations for Asplenic Patients.*

Vaccine†	Before Elective Splenectomy‡	After Splenectomy
Pneumococcal vaccines	Administer PCV13 if patient has not previously been vaccinated with an age-appropriate regimen. Administer PPSV23 8 wk later and at least 2 wk before splenectomy. Administer a second PPSV23 dose 5 yr later.	Administer PCV13 if patient has not previously been vaccinated with an age-appropriate regimen. Administer PPSV23 8 wk after PCV13. If patient has previously received an age-appropriate PCV13 regimen, administer PPSV23 at least 2 wk after splenectomy. However, if patient follow-up is uncertain, administer PPSV23 before hospital discharge. Administer a second PPSV23 dose 5 yr later.
Hib conjugate vaccine	Administer a single dose of Hib conjugate vaccine if patient has not previously been vaccinated with an age-appropriate regimen.	Recommendation is the same as that before elective splenectomy.
Meningococcal vaccines	Administer a single dose of MenACWY for persons 2 yr of age or older if a dose has not been administered previously. For infants 2 through 23 mo of age, a primary series of MenACWY-CRM (Menveo) or Hib-MenCY-TT (MenHibrix) is recommended.§	Administer a two-dose series of MenACWY with an interval of 8–12 wk between doses for persons 2 yr of age or older if a dose has not been administered previously. For infants 2 through 23 mo of age, a primary series of MenACWY-CRM (Menveo) or Hib-MenCY-TT (MenHibrix) is recommended.§
	A booster dose should be administered every 5 yr. If the most recent dose was administered before 7 yr of age, a booster dose should be administered 3 yr later with subsequent booster doses every 5 yr.	Recommendation for booster dose is the same as that before elective splenectomy.
Influenza vaccines	Administer influenza vaccine annually. Otherwise healthy asplenic patients 2 through 49 yr of age may be vaccinated with live attenuated influenza vaccine, except patients with sickle cell disease, who should receive inactivated influenza vaccine.	Recommendation is the same as that before elective splenectomy.

* In addition to vaccines listed in this table, asplenic patients should receive other vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention on the basis of their vaccination history, age, and risk category. Hib denotes *Haemophilus influenzae* type b, Hib-MenCY-TT the Hib–bivalent meningococcal conjugate vaccine, MenACWY quadrivalent meningococcal conjugate vaccine, MenACWY-CRM MenACWY conjugated to cross-reactive material 197, PCV13 the 13-valent pneumococcal conjugate vaccine, and PPSV23 the 23-valent pneumococcal polysaccharide vaccine.
† Recommendations are consistent with those of the ACIP.
‡ Whenever feasible, indicated vaccinations should be completed at least 2 weeks before splenectomy.
§ If MenACWY conjugated to diphtheria toxoid (MenACWY-D) is used in persons 2 years of age or older, it should be administered at least 4 weeks after the completion of all PCV13 doses.

(MenACWY) has replaced quadrivalent meningococcal polysaccharide vaccine for patients without a spleen; a two-dose primary series is indicated for such patients.[35,36] Annual vaccination against influenza virus is recommended because influenza infection confers a predisposition to bacterial pneumonia and sepsis caused by *S. pneumoniae* and *S. aureus*.[37,38]

PROPHYLACTIC ANTIMICROBIAL THERAPY

Prophylactic antimicrobial therapy, typically oral penicillin given twice daily, is recommended for selected patients, in particular asplenic children younger than 5 years of age.[39] Prophylaxis can be considered during the initial 1 or 2 years after splenectomy for older children and adults and on a lifelong basis for an asplenic person of any age who has survived an episode of postsplenectomy sepsis. However, data are lacking to inform decision making in many cases, because studies of the effectiveness of prophylactic penicillin have been limited to children with sickle cell disease. In a placebo-controlled trial of oral penicillin V (125 mg twice daily) in children 3 to 36 months

of age with sickle cell disease, the incidence of pneumococcal septicemia was reduced by 84%.[10] In a trial involving children with sickle cell disease who were 5 years of age or older and had received penicillin for at least 2 years, continued treatment with penicillin did not significantly reduce the incidence of invasive pneumococcal infection.[40] These studies were completed before the universal use of pneumococcal conjugate vaccines in infants[18] and before an increased prevalence of colonization and infection with penicillin-resistant pneumococci. Therefore, the current need for and effectiveness of prophylactic penicillin in patients with surgical or functional asplenia is unclear.

Asplenic persons who sustain a dog bite should receive a prophylactic antimicrobial agent (e.g., penicillin). This may help prevent fulminant sepsis caused by *C. canimorsus*.[41]

MANAGEMENT OF FEBRILE EPISODES

If fever develops in an asplenic patient, immediate administration of an antimicrobial agent is indicated, because fever can be the initial manifestation of a fulminant infection and prompt administration of an antimicrobial agent may prevent the development of clinical sepsis. Ceftriaxone administered intravenously or intramuscularly with or without vancomycin is a reasonable empirical choice. Ceftriaxone is active against most *S. pneumoniae* strains as well as *H. influenzae*, *N. meningitidis*, and many community-acquired gram-negative bacilli, including capnocytophaga. A management algorithm is outlined in Figure 1.

AREAS OF UNCERTAINTY

The risk of postsplenectomy sepsis is uncertain in the context of routine use of PCV13. The indications for booster doses of PCV13, PPSV23, or both and the appropriate timing between doses are unclear for asplenic patients, as is the usefulness of measurement of antipneumococcal antibody concentrations to inform these decisions. It is uncertain whether meningococcal vaccination is needed in asplenic patients, but it is recommended.[35] Data are lacking on the effectiveness of, indications for, and appropriate duration of prophylactic antibiotic therapy in asplenic patients in the current context of pneumococcal antimicrobial resistance and the routine use of PCV13. In patients with conditions that may be associated with functional asplenia, the indications for screening for asplenia and management with regard to vaccination, the indications for empirical antimicrobial treatment of febrile episodes, and the indications for prophylactic antimicrobial therapy are uncertain.

GUIDELINES

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention,[27-29,35,36,42,43] the American Academy of Pediatrics (AAP),[39] and the Infectious Diseases Society of America[44,45] have published guidelines for vaccination in asplenic patients (Table 1). The AAP recommends oral penicillin for the prevention of pneumococcal infection in asplenic children (including those with functional asplenia) younger than 5 years of age and in other persons for at least 1 year after splenectomy and consideration of prophylaxis for children with splenectomy after trauma. The AAP notes that the appropriate duration of penicillin prophylaxis in children is unsettled but suggests that it can be discontinued at 5 years of age in most children with sickle cell disease if they are receiving regular medical care, have received pneumococcal vaccinations, and have not had a previous severe pneumococcal infection or undergone a surgical splenectomy.[39] In contrast, the Haemato-Oncology Task Force of the British Committee for Standards in Haematology recommends lifelong penicillin prophylaxis for all persons with surgical asplenia.[46]

CONCLUSIONS AND RECOMMENDATIONS

Persons who have undergone splenectomy, such as the patient described in the vignette, are at lifelong risk for sepsis. This patient's fever could be indicative of the onset of postsplenectomy sepsis, and he should be advised to obtain medical care immediately. Blood cultures should be obtained, and empirical antimicrobial therapy should be initiated immediately. If he does not appear ill on evaluation, ceftriaxone administered intravenously or intramuscularly with or without vancomycin is a reasonable empirical choice. If he cannot arrive at a medical facility within 2 hours, a dose of an oral antibiotic with activity against *S. pneumoniae* (e.g., 2 g of amoxicillin or 750 mg of levofloxacin), ideally prescribed previously and in the patient's possession, should

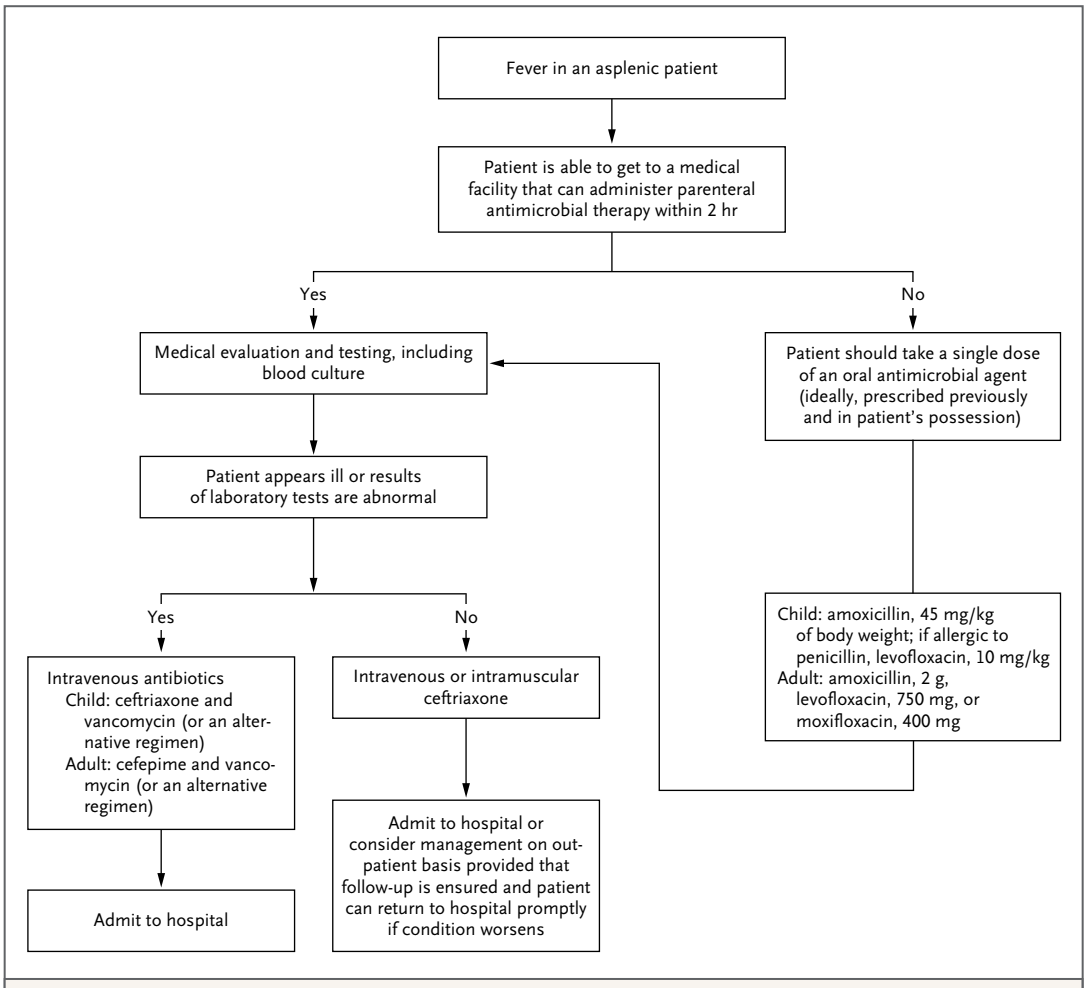

Figure 1. Management of an Episode of Fever in an Asplenic Patient.

Abnormal results of laboratory tests would include a markedly high or low leukocyte count, a leftward shift (immaturity) in the leukocyte differential count, or a low platelet count.

be taken immediately. Patients who have undergone splenectomy should be told to seek medical attention immediately after the onset of every febrile episode.

The patient in the vignette should receive vaccinations in addition to PPSV23. He should be given PCV13 but, according to current ACIP recommendations, only after 1 year has elapsed since the administration of PPSV23. A second dose of PPSV23 should be administered 5 years after the initial dose. His immunization records should be reviewed, if available. Given the patient's age, it is likely that he received the Hib conjugate vaccine in infancy, in which case this vaccine would not be indicated. It is likely that he previously received one or two doses of meningococcal conjugate vaccine, in which case he should receive a booster dose if 5 years have elapsed since his previous dose. If no doses have been administered previously, he should be given two doses 8 to 12 weeks apart, followed by a booster dose every 5 years. He should receive an influenza vaccine (inactivated vaccine or live attenuated intranasal vaccine) each year.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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