Prevention of infections in hyposplenic and asplenic patients: an update

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A B S T R A C T

Patients with functional or anatomic asplenia are at a significantly increased risk of overwhelming infection, particularly involving the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*. The risk is highest in infants and young children, but adults also have an increased risk of infection. Preventive strategies are very important and fall into three major categories: immunoprophylaxis, antibiotic prophylaxis, and education. Studies have shown that many asplenic patients are unaware of their increased risk for serious infection and the appropriate health precautions that should be undertaken. In this article we emphasise the need for preventive measures in hyposplenic and asplenic patients. We discuss the value of newly developed conjugate vaccines and the need for revaccination. Finally we draw up a recommendation for the preventive management in functional and anatomical asplenic patients.

I N T R O D U C T I O N

Patients with functional or anatomic asplenia are at a significantly increased risk of overwhelming infection (postsplenectomy sepsis [PSS]), particularly involving the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*. In 1919, Morris and Bullock recognised the importance of the spleen in resistance to infection in studying splenectomised rats. The first reported case of postsplenectomy infection was by O’Donnel in 1929. It was not until 1952 that attention focussed on the subject, when King and Shumacker reported five cases of severe infection in infants who had undergone splenectomy for spherocytosis.

Preventive strategies against PSS fall into three major categories: immunoprophylaxis, antibiotic prophylaxis, and education. Different studies report a low adherence to these preventive measures in hyposplenic and asplenic patients. Family practitioners and medical specialists should inform the patients at risk and make every effort to increase the coverage of recommended vaccines and chemoprophylaxis in this group. Furthermore, the recent development of new conjugate vaccines has enhanced the options for preventive management in (functional) asplenic patients. This article calls attention to the importance of vaccination after splenectomy and reviews the recent developments with relation to immunisation, revaccination and other preventive measures.

S P L E N E C T O M Y A N D H Y P O S P L E N I S M

Surgical removal of the spleen is performed for several reasons, including trauma, immunological diseases, hypersplenism and malignancy. In a major university hospital the most common reasons for performing splenectomy were haematological and immunological diseases (31%), while trauma accounted for only 16% (table 1). Figure 1 shows the absolute incidence of splenectomy in the Netherlands from 1997 to 2002. Growing awareness of possible long-term complications has more recently led to an increasingly conservative approach toward resection and greater efforts to preserve splenic tissue. In Hodgkin’s disease, splenectomy is...
no longer a routine procedure. However, the procedure remains important in the management of patients with hereditary haemolytic anaemias, spherocytosis in particular. Functional hyposplenism is associated with a wide variety of diseases, including several immunological and haematological diseases. In infants, asplenia is usually linked to serious organ malformations (Ivemark’s syndrome), but isolated congenital asplenia diagnosed in adults can occur. The true incidence of hyposplenism is unknown, mainly because the recognition requires a high index of suspicion.

The presence of Howell-Jolly bodies in the erythrocytes on a peripheral blood film is an important clue to the diagnosis of asplenia or functional hyposplenism. Howell-Jolly bodies are nuclear remnants normally removed by the spleen and may not occur with mild hyposplenism. Their presence in erythrocytes is thought to represent a risk for PSS. The ‘pocked erythrocyte count’ (pit count) is a more sensitive indicator of splenic clearance and can be visualised by interference phase microscopy. Pocks are membrane vesicles removed only by the spleen, and the presence of more than 12% pocked red cells is indicative of asplenia. A pocked erythrocyte count of less than 2% is expected in normal persons and a percentage of more than 3.5% is strongly correlated with functional hyposplenia.

POSTSPLENECTOMY SEPSIS

Incidence

Singer defined postsplenectomy sepsis (PSS) as septicaemia, meningitis, or pneumonia that is usually fulminant and occurs days to years after removal of the spleen. Estimates of the incidence of postsplenectomy sepsis have frequency been fairly variable for many reasons, including different disease definitions, duration of follow-up, and stratification for age, splenectomy cause and underlying disease.

The risk of PSS is highest in children, especially those under two years of age and during the first years after splenectomy. There are, however, reported cases of fulminant sepsis 20 to 40 years after splenectomy, indicating that postsplenectomy patients carry a lifelong risk. The incidence of infection after splenectomy is usually quoted from the major collective review of Singer published in 1973, who evaluated 2795 patients with asplenia. The incidence of PSS was 4.25% with a mortality rate of 2.52%. Singer concluded that death from postsplenectomy sepsis is 200 times as prevalent as death due to sepsis in the population at large. However, not all studies confirmed this considerably higher risk for sepsis after splenectomy.

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The risk of PSS can also be stratified by underlying disease. The lowest risk is related to trauma, intermediate risk to spherocytosis, idiopathic thrombocytic purpura, or portal hypertension, and highest risk in thalassaemia or Hodgkin’s disease.

Table 1

<table>
<thead>
<tr>
<th>INDICATION OF SPLENECTOMY</th>
<th>NUMBER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological and immunological diseases</td>
<td>73 (31%)</td>
</tr>
<tr>
<td>Abdominal malignancies</td>
<td>54 (23%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>38 (16%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>57 (24%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Total</td>
<td>235 (100%)</td>
</tr>
</tbody>
</table>

* Figures derived from the department of Medical Data Processing, Erasmus University Medical Centre.

Figure 1

Incidence of splenectomy in the Netherlands (total number)

* Figures derived from Prismant, Utrecht, the Netherlands.
Typical presentation and prognosis

PSS may have a short prodrome of low-grade fever with chills, pharyngitis, muscle aches, vomiting, or diarrhoea. In a few hours this stage can rapidly evolve into severe septic shock with true rigors, hypotension and anuria. There is usually no clinical evidence of a local tissue infection. In children younger than five years of age, focal infections, particularly meningitis, are more common. In severe cases rapid deterioration is often accompanied by disseminated intravascular coagulopathy (DIC) with adrenal haemorrhage (Waterhouse-Friderichsen syndrome). Other complications include purpura fulminans, extremity gangrene, convulsions and coma. The mortality rates of PSS range from 50 to 70%, despite appropriate antimicrobial therapy and intensive medical treatment. Holdsworth et al. reported an overall fatality rate of 55.3% in 149 episodes. The dramatic nature of the illness is further reflected by the time from initial symptoms to death, with 68% of the deaths occurring within 24 hours and 86% within 48 hours. These data emphasise the importance of prevention of PSS.

Microbiology of postsplenectomy sepsis

Streptococcus pneumoniae is the most common organism involved in PSS and the causative agent in 50 to 90% of the cases. A predominant polysaccharide serotype is not found, and there is no difference in serotype distribution involved in PSS from that in other forms of pneumococcal infection. Haemophilus influenzae type b is the second most common organism related to PSS. Most cases occur in children younger than 15 years of age, 86% in one review. Overall incidence of invasive disease decreased significantly with wide usage of conjugated H. influenzae type b vaccine and probably results in a decrease in the overall number of PSS cases associated with H. influenzae, with more of the remaining infection occurring in older, nonvaccinated persons. Low virulent non-b capsular strains (a, c, d, e and f) may cause invasive infection, but are not relevant in PSS. Neisseria meningitidis has been cited as the third most common cause of PSS. However, there is no evidence to suggest that meningococcaemia occurs more frequently or is more severe in asplenic or hyposplenic patients compared with healthy persons. Capnocytophaga canimorsus is a Gram-negative rod and part of the normal flora of dogs and cats. This bacillus can cause fulminant sepsis (purpura fulminans) following dog or cat bites and scratches. Previous splenectomy, alcoholism, and glucocorticosteroid therapy are the most important risk factors for C. canimorsus sepsis. Approximately 35% of the cases of C. canimorsus septicaemia are associated with asplenia. Salmonella species have also been associated with PSS. Salmonella is a prominent pathogen in children with sickle cell anaemia and splenic dysfunction. Less common bacteria isolated from splenectomised patients include Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterococcus species, Bacteroides species, Plesiomonas shigelloides, Eubacterium plautii and Pseudomonas pseudomallei.

Asplenic and hyposplenic patients appear to be more susceptible to serious infections with protozoans following tick bites (Babesia microti in North America and Babesia bovis in Europe). These micro-organisms infect erythrocytes that are sequestered in the spleen. There is no consistent evidence that malaria follows a significantly more severe course in splenectomised patients.

PREVENTION OF INFECTIONS IN HYPOSPLENIC AND ASPLENIC PATIENTS

Immunoprophylaxis

Pneumococcal-polysaccharide vaccine

Pneumococcal immunisation with polyvalent capsular polysaccharide vaccine is uniformly recommended for asplenic and hyposplenic patients. The currently available pneumococcal polysaccharide vaccine (PPV23) contains capsular polysaccharides from 23 serotypes, responsible for at least 85 to 90% of the serotypes that cause invasive pneumococcal infections among children and adults. Bacterial capsular polysaccharides induce antibodies primarily by T-cell independent mechanisms. Therefore, antibody response to most pneumococcal capsular types is generally poor in children less than two years of age, whose immune systems are immature. The antibody response is also decreased in children under the age of five years. Healthy asplenic adults have been found to have normal or nearly normal antibody responses to polysaccharide antigens by most investigators. But not all investigators. Siber et al. compared the antibody response to pneumococcal capsular polysaccharide vaccine in patients with Hodgkin’s disease, patients with asplenia due to other causes and in healthy adults. The antibody responses to immunisation were similar in these three groups. However, patients with Hodgkin’s disease who started chemotherapy less than ten days after immunisation showed a significantly lower antibody response. Impaired antibody response is related to underlying disease and the medical treatment of this disease. In Hodgkin’s disease, antibody response improves as the time of immunisation after chemotherapy or radiation increases. Giebink et al. reported a normal antibody response in splenectomised children (mean age, 11.6 years) to pneumococcal polysaccharide vaccine. Lee et al. concluded PPV23
to be safe and immunogenic in splenectomised children as well as healthy children above two years of age.43 Several studies conclude polysaccharide pneumococcal vaccination to be efficacious in preventing PSS in hypo-splenic and asplenic patients.32,36,37,44-46 Konradsen et al. reported a considerable decrease of PSS in children since 1982, when antibiotic prophylaxis and pneumococcal vaccination were first recommended in splenectomised patients.32

The vaccine should be given a minimum of two weeks before elective splenectomy to ensure an optimal antibody response. After emergency splenectomy, patients should be immunised soon after surgical recovery or at time of discharge from the hospital.1,2,7,18,33 Immunisation, however, should be delayed at least six months after immunosuppressive chemotherapy or radiotherapy.18 To tide over this period, prophylactic antibiotics should be given. Hyposplenic patients should be immunised as soon as the diagnosis is made. Asplenic or hyposplenic children should be immunised with PPV23 after their second birthday (table 2).35 There is no consensus on the reimmunisation policy in hyposplenic and asplenic patients. Several studies advise revaccination with PPV23, because specific antibody levels decrease in high-risk patients as well as in healthy patients for a few years after first vaccination.16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34 Weintrub et al. studied the duration of antibody response of pneumococcal polysaccharide vaccine and the effect of booster immunisation in patients with sickle cell anaemia.30 They concluded that antibody levels had fallen by three to five years after first immunisation. Mean antibody levels after booster immunisation were significantly increased (which is not what one would expect from a thymus-independent vaccine), and no serious adverse events were noted. Giebink et al. reported in splenectomised patients a linear serum antibody concentration decline by 24 to 32% from the peak antibody level during the first year after vaccination.30 These data suggest a need for revaccination after three to four years. Rutherford et al. advised revaccination between two and six years after splenectomy.47

Pneumococcal conjugate vaccine
Recently, a protein-polysaccharide conjugate vaccine (PCV7) was licensed in the United States for use in infants and young children. In 2001, this vaccine was registered in the Netherlands. Conjugation of polysaccharides to proteins changes the nature of the antipolysaccharide response from T-lymphocyte independent to T-dependent. This antigen complex stimulates a T-helper cell response, leading to immunogenicity in early infants (>2 months of age), stimulation of high levels of IgG isotype antibodies and enhanced immunological memory responses.35,52,53 The vaccine contains capsular polysaccharides from seven serotypes, each coupled with a nontoxic variant of diphtheria toxin.52 These seven serotypes are responsible for approximately 64% of the invasive pneumococcal infections in children under the age of two years in the Netherlands.35 PCV7 is safe and effective for use in the general population.54,55 A large-scale efficacy trial in California (Kaiser Permanente Vaccine Study) concluded

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**Table 2**

Recommended schedule for PCV7 and PPV23 vaccination among infants and children with (functional) asplenia^45-59^  

<table>
<thead>
<tr>
<th>AGE AT FIRST DOSE</th>
<th>SCHEDULE FOR PCV7</th>
<th>SCHEDULE FOR ADDITIONAL VACCINATION WITH PPV23 (AGE)</th>
</tr>
</thead>
</table>
| 2-6 months       | 3 doses (4-8 weeks apart)  
|                  | 1 dose at age 12-15 months | 24 months |
| 7-11 months      | 2 doses (6-8 weeks apart)  
|                  | 1 dose at age 12-15 months | 24 months |
| 12-23 months     | 2 doses (8 weeks apart)  
|                  | 1 dose at age 12-15 months | 24 months (≥2 months after last dose of PCV7) |
| 24-59 months     | 2 doses (6-8 weeks apart)  
|                  | 22 months after last dose of PCV7 |

^ Recommendations for adults with (functional) asplenia, see text.  

Jackson et al. studied the safety of revaccination with the pneumococcal polysaccharide vaccine.50 They demonstrated that self-limiting local injection site reactions occur more frequently following revaccination (11%) compared with first vaccination (3%). The risk of these local reactions was significantly correlated with prevaccination geometric mean antibody concentration. However, the risk of adverse events does not represent an absolute contradiction to revaccination with PPV23 for high-risk groups.51 The USA Centres for Disease Control (CDC) and Prevention Advisory Committee on Immunisation Practices (ACIP) recommend revaccination once with PPV23 in hyposplenic and asplenic patients after five years.32 Revaccination after three years may be considered for children with functional or anatomic asplenia, who would be aged ≤10 years at the time of revaccination. Because data are insufficient concerning the safety of pneumococcal polysaccharide vaccine when administered three or more times, revaccination following a second dose is not routinely recommended.34

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an efficacy of 97.4% in preventing invasive pneumococcal disease caused by vaccine serotypes in children with PCV7.\(^{54}\) The CDC and ACIP (USA) recommend that the vaccine should be used in all children aged 2 to 23 months and in children aged 24 to 59 months who are at increased risk for pneumococcal disease, such as children with functional or anatomic asplenia.\(^{54}\) The Health Council of the Netherlands recommends introducing vaccination against pneumococci with PCV7 in the National Vaccination Programme as soon as combined administration of DKTP and Hib vaccines is possible. A combined vaccine for meningococcal C and pneumococcal infections will probably be available in early 2005. If research shows this combined vaccine to be safe, effective and efficient it would make sense to start using it on young infants.\(^{96}\)

In expectation of the introduction of PCV7 in the National Vaccination Programme of the Netherlands, the vaccine should be administered to children less than five years of age who are at increased risk for pneumococcal infection.\(^{83}\) Children with functional or anatomic asplenia who have completed the PCV7 vaccination series before the age of two years should receive one additional dose of PPV23 at two years of age (≥2 months after the last dose of PCV7) to provide additional serotype coverage.\(^{14,35-54}\) So, children with functional or anatomical asplenia between two and five years should be vaccinated with both vaccines (table 2). Of some concern are the results of a Dutch collaborative study showing that the combined vaccine strategy did not prevent infections in children with recurrent otitis media. A shift towards nasopharyngeal carriage of nonvaccine pneumococcal serotypes could be the explanation.\(^{97}\) The need for reimmunisation is unclear.\(^{95}\) Current data do not support a recommendation to replace PPV23 with PCV7 among older children (>5 years) and adults.\(^{55}\) The proportion of invasive pneumococcal isolates covered by PCV7 is only 50 to 60% among older children and adults, in contrast with 80 to 90% coverage by PPV23 among this older group. Additional studies are needed to evaluate potential use of PCV7 in combination with PPV23 among adults at increased risk for pneumococcal infection.

**Haemophilus influenzae type b immunisation**

Although the efficacy and utility of vaccination against H. influenzae type b (Hib) in preventing PSS is less clear than pneumococcal vaccination, the Hib vaccine is being recommended for hyposplenic and asplenic individuals in the recent literature.\(^{1,2,8,19,31}\) In 1993, the Hib vaccine was introduced in the National Vaccination Programme in the Netherlands. Thus, most children up to 10 years of age have already been vaccinated. Many adults have acquired immunity against Hib through natural exposure, but this may not provide adequate protection in hyposplenic or asplenic patients.\(^{1,2,8}\) The H. influenzae conjugate vaccine should be administered to all adults and children at risk who have not been vaccinated so far.\(^{1,2,18,33}\) The vaccine has been shown to be immunogenic in patients with impaired splenic function.\(^{18,61}\) The need for reimmunisation is unclear.\(^{1,2,7,18,60}\)

**Meningococcal immunisation**

There are two meningococcal vaccines based on capsular polysaccharides: the bivalent meningococcal vaccine (serogroups A and C) and the quadrivalent meningococcal vaccine (serogroups A, C, W135 and Y). Ruben *et al.* concluded that bivalent meningococcal vaccine is immunogenic in asplenic persons, with the exception of those with lymphoma who had received prior chemotherapy and radiotherapy.\(^{62}\) Because of the short duration of protection (two to three years) and the absence of protection against the most common serogroup B, these vaccines are not recommended routinely for asplenic patients.\(^{1,2,7,18}\) However, it should be given to asplenic patients travelling to areas with increased risk of group A infection, such as sub-Saharan regions.\(^{1,2,18}\)

The recently available meningococcal conjugate vaccine is composed of a serogroup C meningococcal polysaccharide conjugated to tetanus toxoid. In 2002 this vaccine was introduced in the National Vaccination Programme of the Netherlands. In contrast to the bivalent and quadrivalent meningococcal vaccines, this conjugated vaccine provides long-lasting immunity and is also effective in children under the age of two years. With the increasing number of infections by *Neisseria meningitidis* group C in Europe and the advantages of conjugated vaccines, patients with asplenia should receive this vaccine.\(^{33}\) Travel to areas where other serogroups of meningococci are prevalent is an indication for revaccination with the bivalent or quadrivalent vaccine.\(^{1,2,8,33}\) A meningococcal vaccine that covers serogroup B strains is still not available.

**Influenza immunisation**

Yearly administration of influenza vaccination is recommended, because it reduces the risk of secondary pneumococcal and *Haemophilus influenzae* infections.\(^{8,19,31}\)

**Vaccine failure**

Sporadic cases of pneumococcal and other vaccine failures have been reported in immunised post splenectomy patients.\(^{63-68}\) So vaccination by itself should never allow a false sense of security. Furthermore, there are several other causative agents related to PSS which can not be vaccinated for.
Prophylactic or empiric use of antibiotics

Most authorities recommend antibiotic prophylaxis for asplenic or hyposplenic children, especially for the first two years after splenectomy. Some investigators advocate continuing chemoprophylaxis until the age of 16 to 18 in children and for at least five years in adults. Traditionally, a daily dose of oral penicillin or amoxicillin is the regime of choice. Local resistance patterns or penicillin allergy may dictate the need to use other antibiotics. Gaston et al. reported an 84% reduction in pneumococcal bacteraemia with the use of oral penicillin prophylaxis in children with sickle cell anaemia. Whether (long-term) antibiotic prophylaxis in children is still necessary after the introduction of the pneumococcal conjugate vaccine has to be investigated.

The value of prophylactic antibiotics in older children or in adults has never been evaluated adequately in a clinical trial. Long-term prophylaxis may be a risk factor for the selection of resistant strains, and efficacy may be reduced by noncompliance. Therefore, long-term antibiotic prophylaxis in adults is not generally recommended. Access to ‘stand-by’ antibiotics is advised for asplenic patients in the current literature. ‘Stand-by’ antibiotics should be taken at the first sign of infection (increase in body temperature, malaise or shivering) if the patient is unable to obtain prompt medical attention. However, in such situations medical help should still be sought without delay. A disadvantage of this strategy is the ‘overtreatment’ of many viral illnesses, but to our opinion the benefits outweigh here.

Patient education

Patient education is an important and effective strategy in preventing PSS. Studies have shown that up to 84% of post-splenectomy patients are unaware of their increased risk for serious infection and the appropriate health precautions that should be undertaken. Patients should be informed about their increased susceptibility to certain infections, the potential seriousness of PSS and its possible very rapidly progressive and life-threatening course. They should be instructed to notify their physician of any acute febrile illness, especially if associated with rigors or systemic symptoms. The different preventive strategies, as immunisation and the importance of re-vaccination, antibiotic prophylaxis and the need to carry ‘stand-by’ antibiotics, have to be discussed with the patients. Several investigators encourage patients to wear a medical alert bracelet or necklace and to carry a card documenting immunisation, any prophylactic antibiotics in use, and a plan for emergencies.

Patients should inform any new healthcare professionals, including dentists, of their asplenic or hyposplenic status.

Patients should be educated about the increased risk for travel-related infections, such as babesiosis. The importance of malarial prophylaxis and (simple) measures to reduce exposure to malaria parasites should be emphasised. Asplenic patients travelling to sub-Saharan Africa, India and Nepal should receive the bivalent meningococcal (serogroups A and C) vaccine. Patients should keep a therapeutic course of antibiotics with them during periods of travel, taking into account the regional resistance patterns of common pathogens. Patients should be warned to seek prompt treatment of even a minor dog bite or other animal bite in view of the increased susceptibility to infection by C. canimorsus.

CONCLUSION AND RECOMMENDATIONS

Fulminant infection, such as postsplenectomy sepsis, is a major long-term risk in functional and anatomical asplenic patients. In consideration of the (recent) literature and the development of new vaccines we recommend a series of preventive measures for hyposplenic and asplenic patients. These are represented in table 3.

Table 3
Recommendation for preventive measures in functional and anatomical asplenic patients

<table>
<thead>
<tr>
<th>IMMUNISATION</th>
<th>AGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal polysaccharide vaccine (PPV23)*</td>
<td>&gt;2 years (table 2)</td>
</tr>
<tr>
<td>Pneumococcal conjugate vaccine (PCV7)</td>
<td>&gt;2 months (table 2)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type b vaccine</td>
<td>&gt;2 months (table 2)</td>
</tr>
<tr>
<td>Meningococcal serogroup C conjugate vaccine</td>
<td>&gt;2 months</td>
</tr>
<tr>
<td>Influenzae vaccine**</td>
<td>&gt;6 months</td>
</tr>
<tr>
<td>ANTIBIOTIC PROPHYLAXIS***</td>
<td></td>
</tr>
<tr>
<td>Daily antibiotic prophylaxis for the first two years after splenectomy in children</td>
<td>&lt;8 years (table 2)</td>
</tr>
<tr>
<td>‘Stand-by’ antibiotics</td>
<td>All</td>
</tr>
<tr>
<td>PATIENT EDUCATION</td>
<td>All</td>
</tr>
</tbody>
</table>

* Revaccination: after five years (after three years for children <10 years of age at time of revaccination); ** revaccination: yearly; *** amoxicillin or claritromycin.

REFERENCES


