Splenic studies: prevention of pneumococcal disease on organisational, clinical and experimental level

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Chapter 5

Recommendations to prevent severe infection in patients with asplenia or hyposplenia

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submitted
Abstract

Each year, up to a thousand splenectomies are performed in the Netherlands. There is also a large group of patients with hyposplenia or functional asplenia due to other primary diseases. All these patients are at risk of developing severe infections, such as post-splenectomy sepsis (PSS), with high mortality. The syndrome of PSS can be prevented if simple measures are taken, such as immunizations and prophylactic early use of antibiotics. Unfortunately, healthcare workers in the Netherlands are generally not well informed about these measures, resulting in suboptimal management of patients. In this article, updated recommendations are given regarding vaccination and prescription of antibiotics to prevent severe disease in this group of patients.

Introduction

Patients with asplenia or hyposplenia are at risk for overwhelming infection. Surgical removal of the spleen is performed for several reasons, including malignancy, immunological diseases and iatrogenic trauma \(^1\). There is however a variety of diseases associated with diminished splenic function, such as sickle cell disease and inflammatory bowel disease \(2-4\). In absence of a functional spleen there is an immunological defect. The spleen contains 50% of all B cells, as well as the B cell subpopulation that is responsible for synthesis of opsonizing antibodies against encapsulated bacteria \(^5\). After splenectomy, the number of these B cells decreases rapidly \(^6\). These cells are particularly important early in the host response to infection, since they are capable of T cell independent production of IgM \(^7\). In addition to the impaired humoral response, it has been shown in mice that splenic marginal zone macrophages are capable of phagocytosis of whole encapsulated pneumococci directly from the circulation \(^8,9\). Therefore, in absence of a (functional) spleen there is a significantly increased risk for invasive disease caused by encapsulated bacteria and certain intracellular parasites \(10-12\).

The major risk associated with asplenia is the syndrome of Post-splenectomy sepsis (PSS), which carries a high mortality \(^11,12\). Although PSS can largely be prevented if adequate preventive measures are taken, in the Netherlands patients are currently not managed according to best practice \(^1,4,13\). This was already described in this journal in 2004, by Melles \textit{et al.} \(^14\). Suboptimal care for asplenic patients in the Netherlands might be due to the absence of a national guideline for prevention of infections during asplenia or hyposplenia. We have therefore recently submitted recommendations for the management of these patients in the Nederlands Tijdschrift voor Geneeskunde [unpublished]. With publication in this journal we hope to provide even more caregivers in the Netherlands with a tool to improve the management of patients with diminished splenic function or asplenia.
Post-splenectomy sepsis

In absence of the spleen, encapsulated bacteria are not filtered from the circulation and can duplicate rapidly. Furthermore, since opsonizing antibodies are lacking, the infection is mostly irreversible within hours. The clinical syndrome of PSS is characterized by a short and mild onset with flu-like symptoms. However, in hours rather than days a fulminating septic shock can develop with diffuse intravascular coagulation (DIC) and purpura. Focal infections such as meningitis are common in children under five years of age. Mortality associated with PSS has been described to be as high as 70%, where 68% of patients die within 24 hours and 80% within the first 48 hours after the first symptoms.¹¹,¹²

Incidence

The incidence of PSS varies in the literature, but is estimated to be 2-5 per 1000 asplenic patients each year.¹⁰ Risk factors for developing PSS are dependent on the indication for splenectomy, on age and on the interval after splenectomy. The highest risk is associated with splenectomies due to hematological malignancies, patients with hemoglobinopathies and children under the age of 5 years (due to absent circulating antibodies against encapsulated bacteria).¹²,¹⁵-¹⁸ It has been reported that over 50% of overwhelming infections occurs within the first 2 years after splenectomy,¹¹ but the risk remains increased lifelong.

Microbiology

Encapsulated bacteria are the most important causative organisms of PSS. *Streptococcus pneumoniae* causes 70% of bacteraemic episodes after splenectomy. There are 90 serotypes of *S. pneumoniae*, of which 20 serotypes are responsible for PSS. A specific predominant polysaccharide serotype has not been described.¹¹ Other pathogens associated with PSS are *Haemophilus influenzae*, *Neisseria meningitidis* (meningococcus), but also the non-encapsulated *Escherichia coli* and *Pseudomonas spp.*

*H. influenzae* is the second most common causative microorganism of PSS, especially in children, but this has probably changed since Hib-immunization was added to the national vaccination program in the Netherlands (Rijksvaccinatie programma, RVP) in 1993. Also, mortality associated with Hib is estimated to be lower than with pneumococci (37%)¹¹. *Neisseria meningitidis* has been described to be the third most common cause for PSS, although there is no evidence that incidence of meningococcemia is higher in asplenic patients than in otherwise healthy individuals. Other severe infections that are associated with asplenia are caused by *Capnocytophaga canimorsus*¹⁹,²⁰, an anaerobe microorganism causing wound infections after dog- or catbites, *Plasmodium falciparum*²¹, causing fulminating malaria, and *Babesia spp.* that are transferred to the asplenic host through tick bites, causing babesiosis.²²
Dutch figures

Asplenia

In the Netherlands, approximately 1000 splenectomies are performed each year. Indications for surgical removal are: after (high energetic) trauma (15%), idiopathic thrombocytopenic purpura (ITP; 14%), hematological disease/malignancy (20%) and accidental splenectomy (35%), especially during surgery of the stomach/esophagus.

The size of the population of functional asplenic patients is unknown, but there are a large number of diseases are associated with hyposplenia (see Table 1), comprising a heterogeneous group of patients that are at risk for overwhelming infection as well.

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Congenitale cyanotic heart diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Celiac disease, with or without dermatitis herpetiformis Inflammatory bowel disease (ulcerative colitis, Crohns’disease)</td>
</tr>
<tr>
<td>Liver diseases</td>
<td>Cirrhosis, with or without portal hypertension Chronic active hepatitis</td>
</tr>
<tr>
<td>Haematological</td>
<td>Sickle cell anemia Other hemoglobinopathies (hemoglobin-SC or β–thalassemia) Primary thrombocythemia</td>
</tr>
<tr>
<td>Auto-immune / systemic diseases</td>
<td>Vasculitis (splenic infarction) Systemic lupus erythematosus (SLE) or discoid lupus erythematosus Rheumatoid arthritis M. Graves Polyarteritis nodosa Amyloidosis Sarcoidosis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Splenic artery occlusion Splenic vein thrombosis Celiac artery thrombosis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>‘Graft-versus-host’ disease Bone marrow transplantation High dose steroids Splenic irradiation (for instance for Hodgkin’s disease) Severe HIV-infection</td>
</tr>
</tbody>
</table>

Table 1. Diseases that are associated with hyposplenia or functional asplenia.

In contrast to patients after splenectomy, these patients are difficult to identify, probably in part due to lack of a diagnostic test for hyposplenic function. Testing for erythrocytes containing Howell Jolly bodies (presence of DNA remains from the nucleus of the erythrocyte precursor) is a commonly used test for splenic function. Presence of Howell Jolly bodies correlates with asplenia, but not with diminished splenic function, absence of Howell Jolly bodies does not indicate normal splenic function [Lammers/de Porto, submitted 2011].
**Guidelines**

Although preventive measures are described in the literature, to date there is no national guideline available in the Netherlands for patients with anatomical or functional asplenia. This guideline is urgently needed, since physicians currently do not deliver best care for these patients: whereas 85% percent of patients is vaccinated against pneumococci, only one third of patients receives the other 2 recommended immunizations (against *H. influenzae* type b and *N. meningitidis* type C)\(^1\). In over 70% of patients no antibiotics are prescribed (prophylactic or on-demand). Also patients are inadequately educated about the risks associated with asplenia\(^{13}\).

**Recommended preventive measures**

In 2008 a review was published containing guidelines that are available for asplenic patients, composed by several relevant organizations\(^{25}\). Recommendations present in these guidelines comprise 3 categories: immunization, use of antibiotics and patient education. Preventive measures regarding immunization and use of antibiotics that are recommended by our taskforce, are summarized in table 2. Furthermore, they can be found on the website of the RIVM (Rijksinstituut voor Volksgezondheid en Milieu), see URL: www.rivm.nl/Onderwerpen/ Ziekten_Aandoeningen/A/Asplenie

**Immunizations**

Pneumococcal vaccination is recommended for all patients with hyposplenia and asplenia. The available pneumococcal polysaccharide vaccine (PPV)-23 (Pneumo 23\(^a\), Sanofi Pasteur MSD) is protective against invasive pneumococcal disease, also after splenectomy, and contains 23 serotypes of *S. pneumoniae* that collectively cause 85-90% of invasive disease episodes\(^{26}\). Polysaccharide vaccines are not immunogenic in children under the age of 2, and they do not induce immunological memory. Therefore, protection of this vaccine is limited and revaccination is necessary when antibody titers decrease\(^{9-12}\).

Recommendations regarding revaccination in the literature are variable. The Advisory Committee on Immunization Practices (ACIP) recommends a single revaccination, whereas the British Committee for Standards in Haematology recommends lifelong revaccination every 5 years\(^{27, 28}\). Generally, revaccination is well tolerated. When the interval to the second immunization is 4 years or longer, the potential adverse effects are comparable to the first vaccination\(^{27, 29-31}\). Although there are no studies available on the quality of responses to repeated revaccination, there is reason for concern on theoretical grounds\(^{32}\). It was shown that a second or third dose of PPV-23 can result in hyporesponsiveness, possibly due to depletion of the B cell pool that is needed for anti-polysaccharide antibodies. This phenomenon is probably time-dependent; the response to the second vaccine is higher when the interval between the first and second immunization increases\(^{32}\).
Lifelong revaccination with PPV-23 is currently not recommended by our taskforce, since the combination of a polysaccharide with a conjugated vaccine (see next paragraph) probably results in additional protection, as compared to polysaccharide vaccination alone. Studies on the combined effect are not available yet, we therefore recommend a single revaccination of PPV-23 after 5 years.

The available conjugated pneumococcal vaccine PCV-7 (Prevenar®) is protective against 7 serotypes of *S. pneumoniae*. The vaccine is conjugated to a protein which induces immunological memory; therefore revaccination in adults is not necessary. In contrast to PPV-23, PCV-7 is also immunogenic in children under the age of 2 years and was added to the RVP (national vaccination program) in 2006. Furthermore, antibodies generated after conjugated immunization potentially have better avidity (antibodies of better quality) 33.

Currently, two new conjugated pneumococcal vaccines are registered in the Netherlands, offering protection against 10 and 13 serotypes respectively. We therefore recommend vaccinating with a conjugated vaccine containing the most serotypes available (*i.e.* PCV-13), until data about effectiveness of the two vaccines becomes available. Conjugated vaccination should be followed by PPV-23 immunization. Several studies have shown that administration of PCV-7 prior to PPV-23 results in higher antibody titers for the 7 serotypes in PCV-7. We recommend an interval of 2 months between PCV-7 (or a higher number of serotypes) and subsequent PPV-23 vaccination 32, 33.

If patients have already been vaccinated with PPV-23 more than 5 years ago, it is still recommended to complete the described schedule above (*i.e.* PCV-13, followed after 2 months by a repeated PPV-23).

Dutch children have been immunized by the RVP with PCV-7, which has been replaced by the 10-valent vaccine in April 2011. For this group, it is still recommended to combine the conjugated vaccine with subsequent 23-valent polysaccharide vaccine above the age of 2 years.

Immunization against *H. influenzae* type b (Hib) was added to the RVP in 1993 (Act-Hib®, Sanofi Pasteur MSD nv). However, titer responses after immunization have been shown to decline since Hib is not circulating in the population anymore (no natural “boosting”), whereas fast protection is dependent on circulating antibodies. We therefore recommend a single revaccination with Hib for all asplenic individuals above the age of 5 years. The elderly have been exposed to Hib during life and gained immunity this way, nevertheless a single revaccination is recommended for this group as well. Hib-vaccination is immunogenic in patients with diminished splenic function 34-37.

Although *Neisseria meningitidis* group B is most prevalent, to date there is no vaccine available for this serogroup. The meningococcal group C conjugated vaccine (NeisVac-C®, Baxter bv.) was added to the RVP in 2002 for all children aged 14 months.

As with Hib vaccination, it is recommended to give all hyposplenic and asplenic patients above the age of 5 years a single revaccination with the meningococcal C vaccine. When traveling to areas
endemic for serogroup A, it is recommended to give additional vaccination with the bivalent (A,C)-
polysaccharide vaccine or with the quadrivalent (A,C,W135,Y)-polysaccharide vaccine. The
conjugated (A,C,W135,Y)- vaccine has been registered in the Netherlands recently (Menveo®,
Novartis).
Finally, it is recommended that all patients with diminished splenic function are immunized with
the annual vaccination against influenza virus, to prevent secondary bacterial infection with
pneumococci or *H. influenzae*.

**Timing of immunizations**

All recommended vaccines should be administered, when possible, at least 2 weeks before the
splenectomy. In case of urgent splenectomy, it is recommended to keep an interval of at least 2
weeks after the surgery before administering the immunizations, since titer response have been
shown to be more adequate by that time. In case of immune-modulating therapy, such as corticosteroids (for instance for ITP), it is
recommended to postpone the immunizations until 6 months after ceasing the medication.

**Antibiotics**

Antibiotic therapy during asplenia is either prophylactic or on-demand/therapeutic therapy.
Prophylactic use of antibiotics in asplenic children has significantly reduced the incidence of sepsis
and mortality with 47% and 88% respectively.
Since the increased susceptibility to overwhelming infection remains lifelong, theoretically
antibiotic prophylaxis should be used permanently. However, in anticipation of patient
incompliance, development of bacterial resistance, and potential adverse side effects, it is advised
to use continuous prophylactic antibiotics for at least the first two years after splenectomy that
carry the highest risk. For children it is advised to use antibiotics until the age of sixteen (see Table
2)
<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Adults</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV-13 (^{a, b})</td>
<td>Once (catch-up)</td>
<td>2 months before PPV-23.</td>
</tr>
<tr>
<td>PPV-23 (^{a})</td>
<td>Repeat after 5 years (once) (^{c})</td>
<td>2 months after PCV-13.</td>
</tr>
<tr>
<td>Hib</td>
<td>Once (catch-up)</td>
<td></td>
</tr>
<tr>
<td>NeisVac-C</td>
<td>Once (catch-up)</td>
<td>Additional vaccination upon travelling to high risk areas: (A,C,W135,Y) (^{d})</td>
</tr>
<tr>
<td>Influenza</td>
<td>Yearly</td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Feneticillin, 2dd 250 mg, or 1dd 500mg</td>
<td>During the first 2 years after splenectomy. In case of allergy: azithromycin, 1dd 250 mg or clarithromycin 1dd 500 mg.</td>
</tr>
<tr>
<td>‘On-demand’</td>
<td>Amoxicillin Clavulanate 3dd 500/125 mg</td>
<td>In case of allergy: clarithromycin, 2dd 500mg or (when macrolides were given as prophylaxis): moxifloxacin, 1dd 400 mg.</td>
</tr>
<tr>
<td>Animal bites</td>
<td>Amoxicillin Clavulanate 3dd 500/125 mg, for 1 week</td>
<td>In case of allergy: clindamycin, 3dd 600 mg and ciprofloxacin, 2dd 500 mg, for 5 days.</td>
</tr>
</tbody>
</table>

**Table 2A.** Recommended preventive measures for adults with (functional) asplenia.

PCV-13 = 13-valent conjugated vaccine/ Prevnar-13\(^{a}\); PPV-23 = 23-valent polysaccharide vaccine, Pneumo 23\(^{a}\), Hib = *H. influenzae* b, NeisVac-C\(^{b}\) = meningococcal group C vaccine. If possible, all vaccines are preferably given before splenectomy.

\(^{a}\) = when available, a higher-valent vaccine should be given

\(^{b}\) = not registered for adults in the Netherlands, use guidelines for off-label use

\(^{c}\) = individuals that have been vaccinated with PPV-23 previously: administer PCV-13 five years after prior PPV-23, followed by PPV-23 again after 2 months.

\(^{d}\) = conjugated MenACW135Y is preferred. For high risk areas check the LCR country-list.
<table>
<thead>
<tr>
<th>Vaccinations</th>
<th>2 - 6 months</th>
<th>7 - 11 months</th>
<th>12 - 23 months</th>
<th>2 - 5 years</th>
<th>6 - 16 years</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV</td>
<td>4 times</td>
<td>3 times</td>
<td>Twice</td>
<td>Twice</td>
<td>Once</td>
<td>(catch-up)</td>
</tr>
<tr>
<td>PPV-23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Once</td>
<td>Repeat</td>
<td>every 5 years</td>
</tr>
<tr>
<td>Hib</td>
<td>4 times</td>
<td>3 times</td>
<td>Once</td>
<td>Once</td>
<td>Once</td>
<td>(catch-up)</td>
</tr>
<tr>
<td>NeisVac-C</td>
<td>3 times +</td>
<td>booster in</td>
<td>booster in</td>
<td>Once</td>
<td>Once</td>
<td>(catch-up)</td>
</tr>
<tr>
<td>Influenza</td>
<td>Yearly</td>
<td>Yearly</td>
<td>Yearly</td>
<td>Yearly</td>
<td>From splenectomy until 16 years of age.</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Fenectillen;</td>
<td>Fenectillen;</td>
<td>Fenectillen;</td>
<td>Fenectillen;</td>
<td>In case of allergy: azithromycin 10mg/kg 3x/wk or clarithromycin 7,5 mg/kg 1dd</td>
<td></td>
</tr>
<tr>
<td>On-demand</td>
<td>Amoxicillen;</td>
<td>Amoxicillen;</td>
<td>Amoxicillen;</td>
<td>Amoxicillen;</td>
<td>Azithromycin 10mg/kg 3x/wk or clarithromycin 15 mg/kg in 2 doses. If macrolides are used as prophylaxis, contact pediatric infectiologist or microbiologist.</td>
<td></td>
</tr>
<tr>
<td>Animal bites</td>
<td>Amoxicillen;</td>
<td>Amoxicillen;</td>
<td>Amoxicillen;</td>
<td>Amoxicillen;</td>
<td>In case of allergy: Azithromycin 10mg/kg 3x/wk or clarithromycin 15 mg/kg in 2 doses.</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2B. Recommended preventive measures for children with (functional) asplenia. RVP = Rijksvaccinatieprogramma, National vaccination program of the Netherlands
PCV = conjugated pneumococcal vaccine; PPV-23 = 23-valent polysaccharide vaccine, Pneumo 23®; Hib = H. influenzae group b; NeisVac-C® = meningococcal vaccine group C.
* = choose conjugated vaccine including the highest number of serotypes. 

* = from 2006-2010 children have been vaccinated through the RVP with PCV-7. In 2011 this will be replaced by PCV-10.
However, also PCV-13 has been registered. If a child was vaccinated with PCV-7 or PCV-10 and is diagnosed with (functional) asplenia, it is recommended that additional PCV-13 is given. If the diagnosis is made before an age of 2 months, directly start with PCV-13. Is asplenia is diagnosed during the RVP vaccination-schedule, complete the series and Afterwards administer 2 additional doses of PCV-13, followed by PPV-23 vaccine after an interval of 2 months. 

* = at age of 2, 3 and 4 months. 

* = administered through the RVP. 

* = at day 0, repeat after 1 month and after 6 months. 

* = with interval of 2 months. 

* = with interval of 1 month. 

* = preferably 2 months before PPV-23. 

* = if available, administer a vaccine with a higher number of serotypes. 

* = conjugated MenACW135Y is preferred, but is not registered for individuals under the age of 11 years, use guidelines for off-label use. For high risk areas check the LCR country-list. 

* = influenza vaccination is not registered under the age of 6 months, use guidelines for off-label use; the first influenza vaccination for children < 6 months should be repeated once after 1 month. Hereafter, one yearly influenza vaccinations is sufficient. 

* = on demand - use of antibiotics in young children can be difficult, since they are not able to communicate their complaints to their parents.
The protective effect of the combined conjugated and polysaccharide immunizations might induce protection during these first two years that will make the use of continuous prophylaxis redundant. However, as long as these data are lacking it is still recommended to use daily prophylaxis during those first two years. After this episode, and after reaching the age of 16, prophylactic antibiotics can be switched to “on-demand” antibiotics, to start in case of (suspected) infection. When symptoms of infection with fever develop, patients should start with therapeutic antibiotics as soon as possible (preferably within one hour), and seek medical attention rapidly to evaluate if antibiotic therapy needs to be continued intravenously. It is strongly advised that patients are physically examined by a physician, and the situation is not evaluated by phone for instance.

Because of the fulminant nature of PSS it is recommended that patients have on-demand antibiotics at their homes, to take directly in case of suspected infection even before seeking medical attention. A major disadvantage of this strategy is the inadvertent treatment of viral infections with antibiotics. However, considering the rapid progression of PSS, the taskforce regards this measure as acceptable because not treating PSS can result in irreversible and fatal consequences within a few hours. The recommended antibiotic therapy is aimed on pathogens that cause PSS (Table 2).

Patient education
Informing patients about the risks associated with asplenia is an important and effective strategy in preventing PSS. Patients should be educated when on-demand antibiotic therapy is indicated. Patients should know the risks that are associated with travelling, such as babesiosis, the importance of malaria prophylaxis as well as simple measures to decrease exposure to the malaria mosquito, additional immunizations and adjusting antibiotic therapy to local resistance patterns. Furthermore, patients should be informed about the risks associated with dog and cat bites. It is advised that asplenic patients carry a “Medic Alert” with relevant information with them.

Potential hyposplenia
Current recommendations are indicated in case of (functional) asplenia. Unfortunately, in case of hyposplenia, the level of dysfunction of the organ is not always clear. The taskforce recommends that in case of sickle cell disease, splenic infarction or splenic irradiation, current recommendations should be applied, considering the high risk of functional asplenia associated with these conditions. For other diseases associated with hyposplenia, such as inflammatory bowel disease and celiac disease, the level of splenic dysfunction cannot be estimated adequately; it is therefore not recommended that all patient groups with potential hyposplenia receive immunizations and antibiotics, but that individual cases are evaluated.
Conclusion

Patients after splenectomy or with diminished splenic function are highly susceptible to overwhelming and often lethal diseases, such as PSS. We hope and expect that with current updated recommendations, based on literature, implementation of preventive measures for these patients will improve.

We are aware that we here offer recommendations that are based on expert opinion rather than evidence based medicine. However, as experts in the field, we also realize the need of a national protocol for these patients. Therefore, to increase quality of care for asplenic patients, we have summarized the recommendations based on the highest evidence available.

Further research is needed to evaluate if publication and implementation of these recommendations will yield higher vaccination rates, improved antibiotic prophylaxis and therapy and better educated patients.
References