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Guidelines for the prevention and empiric therapy of bacterial infections for children with asplenia and hyposplenia

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APPHON/ROHPPA supportive care guidelines are developed by Atlantic Provinces health professional specialists using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

Glossary

Asplenia – The absence of a spleen or loss of splenic function.

Hyposplenia – Reduced splenic functioning.

Overwhelming Post-Splenectomy Infection (OPSI) – a rare, rapidly evolving, life-threatening infection that occurs in individuals who are either asplenic or hyposplenic.

Fever – an oral temperature of 38.3°C (or 101°F) or higher.

Abbreviations

OPSI:	Overwhelming Post-Splenectomy Infection
PHAC:	Public Health Agency of Canada
NACI:	National Advisory Committee on Immunization
AAP:	American Academy of Pediatrics
ACIP:	Advisory Committee on Immunization Practices
RCT:	Randomized controlled clinical trial

Overview of Material

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1. Summary

The following recommendations (Table 1) are adapted from the guideline developed by a working party of the Haematology/Oncology Task Force on behalf of the British Committee for Standards in Haematology (BCSH): "Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen"[1]. In addition, the recommendations that follow are based on a critical evaluation of the available pediatric evidence, expert clinical opinion and the deliberations of the *Guideline panel for the prevention and empiric therapy of bacterial infections for children with asplenia and hyposplenia*. The purpose of these recommendations is to provide clinical institutions and other organizations with a framework on which to build their own institutional protocols and to encourage standardization of protocols across regions to enhance consistency of care for patients and families.

The APPHON/ROHPPA *Guideline for the prevention and empiric therapy of bacterial infections for children with asplenia and hyposplenia Development Panel* recommends, based on the existence of significant research gaps, that APPHON/ROHPPA and other institutions develop trials that can supply evidence to inform future decision-making on management prevention and therapy of bacterial infections for children with asplenia and hyposplenia. Research gaps are presented in Appendix D.

Table 1 - Summary of Guideline Recommendations

Recommendation		Evidence*
4.1 Antibiotic prophylaxis		
4.1.1	All children 3 months and older with asplenia or hyposplenia should receive antibiotic prophylaxis with penicillin VK: a) 25 mg/kg/day up to a maximum of 125 or 150 mg per dose twice daily for 3 months to 5 years of age. **OR** b) 25 mg/kg/day up to a maximum of 250 or 300 mg per dose twice daily for children 5 years and older.	Strong Recommendation, Moderate quality evidence
4.1.2	If children 3 months and older are not able to tolerate penicillin or if penicillin is not available, amoxicillin can be used as an alternative at a dose of a) 10 mg/kg/dose twice daily for children 3 months to 5 years. **OR** b) 250 mg per dose twice daily for children 5 years and older.	Strong Recommendation, Very low quality evidence

Recommendation		Evidence*
4.1 Antibiotic prophylaxis continued		
4.1.3	All children 3 months of age and younger with asplenia or hyposplenia should receive antibiotic prophylaxis with an antibiotic that is also active against E.coli and Klebsiella sp. The authors of this guideline recommend cefixime 8 mg/kg/day once or twice daily.	Strong Recommendation, Very low quality evidence
4.1.4	Children who are allergic to penicillin should see an allergist.	Strong Recommendation Very low quality evidence
4.1.5	Children with asplenia or hyposplenia who are not high risk for overwhelming post-splenectomy infection and who have received their pneumococcal vaccination: a) Should receive antibiotic prophylaxis for at least 2 years post-splenectomy. **AND** b) Can stop antibiotic prophylaxis at age 5 years in consultation with a specialist.	Strong Recommendation Moderate quality evidence
4.1.6	Children at high risk for pneumococcal infection should receive life-long antibiotic prophylaxis.	Strong Recommendation, Low quality evidence
4.1.7	Families non-compliant with antibiotic prophylaxis should be instructed to have available a stand-by supply of prophylactic antibiotics and give their child a dose if their child has a fever or suspect a fever and seek medical attention immediately.	Strong Recommendation Very low quality evidence
4.2 Optimal timing of vaccines around splenectomy		
4.2.1	All children should be vaccinated 14 days prior to a splenectomy if not previously immunized. In the case of an emergency splenectomy all children who were not previously vaccinated should be vaccinated 14 days post-splenectomy.	Strong Recommendation, Moderate quality evidence
4.3 Pneumococcal vaccine		
4.3.1	All previously unvaccinated children 2 years and older should receive one dose of the pneumococcal conjugate vaccine (PCV13) followed at least 8 weeks later by the pneumococcal polysaccharide vaccine (PPV23).	Strong Recommendation, Low quality evidence
4.3.2	All children who previously received only pneumococcal polysaccharide vaccine should receive one dose of pneumococcal conjugate vaccine (PCV13) at least 8 weeks after receipt of the polysaccharide vaccine (PPV23).	Conditional Recommendation Very low quality evidence

Recommendation		Evidence*
4.3.3	All children who have received pneumococcal conjugate vaccine (PCV7 or PCV10) should receive a dose of PCV13 as soon as possible (or at least 4 weeks after the last dose of pneumococcal conjugate vaccine).	Conditional Recommendation Very low quality evidence
4.3.4	A single booster dose with the pneumococcal polysaccharide vaccine (PPV23) should be given: a. If 11 years or older at time of primary vaccination revaccinate at 5 years. b. If 10 years and younger at time of primary vaccination revaccinate at 3 years.	Strong Recommendation, Low quality evidence
4.4 Meningococcal vaccine		
4.4.1	All children with asplenia or hyposplenia should receive the meningococcal quadrivalent conjugate vaccine ACYW: a) 2 to less than 12 months: 2-3 doses given 8 weeks apart with another dose between 12 and 23 months and at least 8 weeks from the previous dose. (Menveo™) b) 12 to 23 months: 2 doses at least 8 weeks apart. (Menveo™) c) 2 years and older: 1 dose (Menveo™ or Menactra™ can also be used)	Strong Recommendation, Low quality evidence
4.4.2	All children 1 year and older with asplenia or hyposplenia not previously vaccinated should receive 1 dose of the meningococcal conjugate C vaccine and: a) 2 doses of the meningococcal quadrivalent conjugate vaccine ACYW (Menveo™) if 12-23 months. b) 1 dose of the meningococcal quadrivalent conjugate vaccine ACYW (Menveo™ or Menactra™) if 2 years and older. All vaccines should be given at least 8 weeks apart.	Strong Recommendation, Very low quality evidence
4.4.3	All children with asplenia or hyposplenia over 5 years of age should receive a booster dose with quadrivalent meningococcal conjugate ACYW vaccine. Either Menveo™ or Menactra™ can be used. a) For those vaccinated at 6 years of age and under: provide a booster dose 3-5 years after the last dose, followed by every 5 years. b) For those vaccinated at 7 years of age and older: provide a booster dose 5 years after the last dose, followed by every 5 years.	Strong Recommendation, Very low quality evidence

Recommendation		Evidence*
4.4.4	All children with asplenia and hyposplenia should receive the meningococcal serogroup B (4CMenB) vaccine. a) 2-5 months: 3 doses at least 1 month apart and a booster dose at 12-23 months. b) 6-11 months: 2 doses at least 2 months apart and a booster dose at 12-23 months (at least 2 months after the 2nd dose). c) 12 months-10 years: 2 doses at least 2 months apart. d) 11-17 years: 2 doses at least 1 month apart.	Strong Recommendation, Very low quality evidence
4.5 *Haemophilus influenzae* vaccine		
4.5.1	All children with asplenia or hyposplenia who have not been previously vaccinated should receive the *Haemophilus influenzae* type B vaccine.	Strong Recommendation, Low quality evidence
4.5.2	All children 5 years of age and older with asplenia or hyposplenia should receive a dose of *Haemophilus influenzae* type B vaccine regardless of vaccination history.	Strong Recommendation, Very low quality evidence
4.6 Influenza vaccine		
4.6.1	All children with asplenia or hyposplenia 6 months of age and older should receive the influenza vaccine once a year.	Strong Recommendation, Moderate quality evidence
4.7 Management of fever		
4.7.1	A blood culture should be collected at presentation to the hospital or clinic.	Strong recommendation Very low quality evidence
4.7.2	Parenteral antibiotics should be given within 60 minutes of presentation to the hospital or clinic.	Strong recommendation Very low quality evidence
4.7.3	Children less than 2 months of age should be treated with cefotaxime and ampicillin in order to provide added protection for *E. coli* and *Klebsiella* bacteria that can cause OPSI in this age group. If the child is critically ill or showing signs of meningitis vancomycin should be added.	Strong recommendation Very low quality evidence
4.7.4	Children 2 months and older should be treated with a third generation cephalosporin. If the child is critically ill or showing signs of meningitis, vancomycin should be added.	Strong recommendation Very low quality evidence

Recommendation		Evidence*
4.7.5	If patient has a confirmed anaphylaxis to penicillin, meropenem can be used as an alternative.	Strong recommendation Very low quality evidence
4.7.6	A macrolide should be added in the treatment of fever or infection to: a) Children 6 months and greater with respiratory symptoms suggestive of atypical pneumonia or mycoplasma. **OR** b) Children who intermittently take their prophylactic antibiotics as these children are at increased risk of resistance.	Strong recommendation Very low quality evidence
4.7.7	When culture and sensitivity results indicate the organism is penicillin susceptible switch to penicillin. For children allergic to penicillin, clindamycin can be administered.	Strong recommendation Very low quality evidence
4.8 Health professional record keeping and education to children and families		
4.8.1	Families and patients should be well educated about the potential signs of infection, associated risks and management and prevention of overwhelming post-splenectomy infections.	Strong recommendation Very low quality evidence
4.8.2	Families of children with a fever should be instructed to immediately take an age appropriate amount of their prophylactic antibiotic if they haven't already and seek immediate medical attention.	Strong recommendation Very low quality evidence
4.8.3	Children and families should be educated as to the potential risk of overseas travel, with special emphasis on malaria and unusual infections, for example resulting from tick and animal bites.	Strong recommendation Very low quality evidence
4.8.4	Patients should be given appropriate written or electronic information and carry a card to alert health professionals to the risk of overwhelming infections.	Strong recommendation Very low quality evidence
4.8.5	Patients may wish to invest in an alert bracelet or pendant.	Strong recommendation Very low quality evidence
4.8.6	Patients should be given written information of their vaccination and re-vaccination status.	Strong recommendation Very low quality evidence
4.8.7	Pediatricians and general practitioners should make sure children with asplenia are up-to-date on all their vaccines.	Strong recommendation Very low quality evidence

*using "GRADE" criteria (Appendix E) [2]

2. Introduction

Overwhelming bacterial infection is a significant risk in patients with no splenic function or absent spleen (asplenia) or a dysfunctional spleen (functional asplenia/hyposplenia). The frequency of overwhelming post-splenectomy infection (OPSI) varies in different studies and according to:

- time since splenectomy
- patient age
- co-morbidities.

The literature reports a 3.3 to 4.25% incidence of sepsis in asplenic children, decreasing to around 0.8% in adults[3,4,5,6]. The incidence of death from sepsis is 50-70% in asplenic/hyposplenic children[7,8,9].

Sepsis-associated mortality is highest in children with underlying hematologic conditions such as sickle cell anemia or thalassemia, in the immunosuppressed, and in the child less than 5 years of age[6]. Despite medical attention, 50% die in the first 48 hours after presentation. However, the mortality from OPSI has been shown to be decreased to 10% in those patients who seek medical attention immediately on feeling unwell[6]. Although there is a 5% lifelong risk of severe sepsis in asplenic/hyposplenic patients, the risk is higher in the first 2 years following splenectomy or the development of a dysfunctional spleen[6,7,8,10,11]. An annual mortality rate of 1-3.8% is reported in this population despite education of patients/families[12,13]. It is not clear whether this is due to a lack of comprehensive education for patients and families, lack of adherence to guidelines for management of asplenic/hyposplenic children, or failure of therapy in established infection.

The most common causes of invasive infection in asplenic/hyposplenic children are encapsulated bacteria. *Streptococcus pneumonia* is the most common pathogen seen in over 50% of cases in older infants and children with *Escherichia coli* being more common in infants less than 3 months of age. Less common causes of sepsis include: *Staphylococcus aureus*, *Streptococcus pyogenes*, Pseudomonas, Klebsiella and *Salmonella* (especially in children with sickle cell disease)[8,14]. Asplenic and hyposplenic patients are at increased risk of *Capnocytophaga* infection following dog, cat and rodent bites. Other significant infections are protozoan infections due to *Babesia* species subsequent to a tick bite and *Falciparum malaria* in endemic countries[8,15]. Education of patients/families on their increased risk for these infections is critical, and they should be advised to seek medical attention as soon as they feel unwell and are exposed to an animal tick or mosquito bite (in an area where malaria is endemic).

2.1 Scope and Purpose

The objective of this guideline is to reduce the incidence of overwhelming post-splenectomy infection and death by:

a) Providing information to healthcare professionals regarding vaccinations, antibiotic prophylaxis and empiric treatment of OPSI.
b) Providing information to patients and families regarding vaccination, antibiotic prophylaxis and actions to take if a person with asplenia/hyposplenia has a suspected infection.
c) Consideration of efficacy, cost, tolerability and toxicity of medications and vaccines recommended.

The *scope* of this guideline includes methods of prevention of overwhelming post-splenectomy infection in asplenic and hyposplenic children. This guideline has been developed based on available evidence. It is acknowledged that due to the paucity of evidence and the limited number of high quality studies in asplenic/hyposplenic children there are many gaps in knowledge. Readers are reminded that implementation of these recommendations will require adaptation to the local context, appreciating factors such as individual patient needs and preferences, clinician knowledge, skill and practice scope, available resources and organizational policies and standards. The choice of antibiotics to treat OPSI may vary based on local resistance patterns, local epidemiology and local antibiotic preferences based on cost and resources.

2.2 Target Audience of the Guideline

The intended users of this guideline are all health professionals within Canada caring for children and youth without a spleen or with a hypofunctioning spleen. The guideline is particularly addressed to physicians (hematology, emergency room, surgery and family doctors), pharmacists, nurse practitioners and nurses working in hospitals where asplenic and hyposplenic patients receive care.

The guideline will also be relevant to the administrators of health care institutions, public health agencies and insurance companies who must ensure sufficient resources are available to provide vaccines and antibiotic medications.

2.3 Health Questions

The following clinical questions guided the development of this guideline:
1) What is the appropriate vaccination schedule for children with asplenia or hyposplenia?
2) What is the appropriate antibiotic prophylaxis schedule and duration for children with asplenia or hyposplenia?
3) What is the appropriate treatment of fever in children with asplenia or hyposplenia?

3. Methods

The initial stages of this project were informed by the guideline adaptation methodology developed by the ADAPTE Collaboration [16] and CAN-ADAPTE[17]. The ADAPTE process is a systematic approach to considering the use and/or modification of existing guidelines developed in one context for application in a different context, so as to enhance the efficient production and use of high-quality adapted guidelines. The strategies for searching for guidelines, guideline adaptation and the primary literature search are outlined in Appendix F.

APPHON/ROHPPA identified the prevention of overwhelming post-splenectomy infection in children with asplenia or hyposplenia as an important area to provide guidance. The APPHON/ROHPPA Asplenia Working Group was formed in 2008. Members were selected from each relevant discipline across Atlantic Canada with the aim to have an inter-disciplinary team including individuals with content expertise and guideline development experience. In 2011, a panel was formed to up-date the guidelines (see appendix J for membership list).

3.1 Literature Search Strategy

In March of 2011, the Asplenia Panel completed a comprehensive literature review with librarian support to identify guidelines on the prevention of OPSI in asplenic and hyposplenic children. The guideline search was conducted through to March 2011. The search details including search terms are provided in Appendix F.

Literature searches of MEDLINE (Ovid SP; 1966 to June Week 2 2010), Cumulative Index to Nursing & Allied Health Literature (CINAHL; Ovid SP and EBSCO host; 1980 to June 2010) and PubMed were performed. Grey literature was searched using the search engine Google. Individual panel members also reviewed their personal files, professional association documents and their own institutional documents for guidelines that should be included for review. This search was then updated in May 2013.

3.2 Guideline and Evidence Selection Criteria

The guideline inclusion/exclusion criteria are outlined in detail in Appendix F. Guidelines identified through the search were reviewed by the Panel for relevance. Each guideline considered potentially relevant was independently reviewed and scored by 4 reviewers, using the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument[18]. The AGREE instrument provides a framework for the evaluation of guideline quality on the basis of 6 domains: scope and purpose; stakeholder involvement; rigour of involvement; clarity and presentation; applicability; and editorial independence. Domain scores and overall assessments from each reviewer were compiled for each guideline, and results were presented for discussion at an in-person panel meeting. Panel members were provided copies of all guidelines to facilitate discussion of the results and reach consensus on the suitability of each guideline for guideline adaptation via the ADAPTE process. Each guideline was discussed as to why

they were or were not recommended. Particular attention was paid to rigor scores and guideline scope.

The guideline selected for adaptation, the source guideline, was to be updated by literature published since its development and any available pediatric literature was to be added. As such, a literature search was conducted focusing on vaccines and antibiotic prophylaxis in asplenic and hyposplenic children in addition to a search for literature in adults and children published since the source guideline. All types of evidence were included in this search; however, the focus was on randomized controlled trials. Outcomes of interest included: protective vaccine titres in asplenic and hyposplenic children, vaccine adverse reactions, antibiotic resistance and compliance and OPSI related mortality.

The source guideline was further supplemented by pediatric references obtained through database searches, references cited in the papers, papers from the personal files of panel members, and unpublished supplementary data from the research of panel members and content experts.

For the purpose of this guideline sickle cell anemia will be considered an asplenic or hyposplenic state.

3.3 Decision process of the panel

Decisions were established through panel discussions, whereby any differences of opinion were resolved by consensus. If consensus was unable to be reached, a vote was cast. The quality of evidence and strength of recommendations were assessed using the GRADE system developed by Guyatt et al[19], by the lead author and confirmed through discussion with the remaining panel members. The Panel included patient input by way of published literature reviews regarding issues around antibiotic prophylaxis tolerability and compliance. Patient preferences regarding personal views around vaccination were not sought as it was felt the benefit of vaccinating outweighed the discomfort of vaccination. However, the impact of antibiotic prophylaxis and vaccination on patients was considered when making the recommendations, including tolerability and adverse effects. Cultural issues were considered, but none were identified for this guideline.

3.4 Results

Only one guideline on the prevention and treatment of infection in patients with an absent or dysfunctional spleen was identified and assessed using the AGREE instrument[18]. Based on the overall assessment of the guideline it was decided by the panel that this guideline should be used as the source guideline and the ADAPTE process followed rather than developing a de novo guideline. This guideline, “Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen” was prepared on behalf of the British Committee for Standards in Haematology by a Working Party of the Haematology-Oncology Task Force.

Despite the fact that this guideline does address the prevention and treatment of infection in asplenic and hyposplenic subjects, it was felt that the guideline did not meet the standard of rigor required for GRADE. As a result, it was acknowledged that a separate literature search for empirical studies would be necessary to supplement the recommendations that address the health questions of interest in the present guideline.

4. Supporting Evidence and Information for Recommendations

4.1 Children with asplenia or hyposplenia should receive antibiotic prophylaxis with penicillin

4.1.1 All children 3 months and older without a spleen or with hyposplenia should receive antibiotic prophylaxis with penicillin VK:

a) 25 mg/kg/day up to a maximum of 125 or 150 mg per dose twice daily for 3 months to 5 years of age.
OR
b) 25 mg/kg/day up to a maximum of 250 or 300 mg per dose twice daily for children 5 years and older.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, moderate quality of evidence.

Note: the authors of the source guideline (BCSH) assigned quality (level) of evidence "B" (requires the availability of well-conducted clinical studies but no randomized clinical trials on topic of recommendation) and "C" (requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities).

Evidence:

Table 2 - Summary of studies on antibiotic prophylaxis in Asplenia used to inform recommendation 4.1.1

Studies		Results
Penicillin vs placebo		
Gaston et al. 1986[20]	Intervention: 105 children 3 to 36 months of age with sickle cell anemia (considered asplenic) received penicillin 125 mgs BID group vs 110 asplenic subjects received placebo. 70% of children received the pneumococcal vaccine prior to study entry, 95% in the penicillin group and 93% of placebo group.	• Design: Double blind RCT 13/110 (11.81%) in the placebo arm developed pneumococcal bacteremia vs 2/105 (1.9%) in the penicillin arm; 10% absolute risk reduction in pneumococcal bacteremia. (p=0.0025 equals an 84% reduction in the risk of bacteremia in the penicillin group).

Studies		Results
Gaston et al.1986[20] continued		• No deaths in the penicillin group and 3 deaths in the placebo group. • No difference in adverse events.
John et al. 1984 [21]	232 children age 6 months to 3 years with homozygous sickle cell disease (97 received penicillin prophylaxis + 14 valent pneumococcal vaccine) and (46 received penicillin + *Haemophilus* B vaccine Hib) (62 received pneumococcal vaccine alone) and (27 received *Haemophilus* B vaccine alone). All children in the penicillin groups received penicillin up to their 3rd birthday.	• Design: Random allocation to (penicillin + pneumococcal vaccine) or (penicillin + *H. influenzae* vaccine) or (pneumococcal vaccine alone) or (*H. influenzae* vaccine alone). • Pneumococcus was isolated in 7/97 in the penicillin + pneumococcal vaccine and 4/62 in the pneumococcal vaccine alone group. • No isolates occurred while the children were receiving penicillin. (penicillin was stopped in all children on the 3rd birthday). • 4 isolates occurred within 11 months of stopping penicillin. • 2/27 pneumococcal isolates occurred in the Hib vaccine alone group and no isolates 0/46 occurred in the Hib + penicillin group. • 2 deaths occurred in the penicillin + pneumococcal vaccine group. • No adverse events from penicillin were reported.
Falletta et al. 1995[22]	400 children, greater than 5 years old with sickle cell anemia, who had received prophylactic penicillin for two years and pneumococcal polysaccharide vaccine at age 2-3 years, without prior bacteremia or meningitis.	• Randomized, controlled, blinded allocation to 250 mg bid of penicillin or placebo. • All children were given an additional pneumovax vaccine within 1 year of randomization if they had not already received the vaccine within the previous year.

Studies		Results
Falletta et al. 1995[22] continued		• 201 in the penicillin group and 199 in the placebo group. • 4/199 (2.01%) in placebo group developed systemic *S pneumoniae* infection vs 2/201(<1%) in the penicillin group. ARR=1.02%.Relative risk of 0.5 (95% CI 0.1, 2.7). • No deaths.
El-Alfy M et al. 2004[23]	318 patients 5-26 years of age with splenectomy, cross sectional survey.	• Prevalence of OPSI among the population was 5.7% (n=18). • Of these 10 (56%) occurred within the first 6 months post-splenectomy and 6 (33%) up to 2 years post-splenectomy and 2/18 patients (11%) had OPSI during and up to 10 years post- splenectomy. • Patients reporting penicillin prophylaxis had a lower frequency of OPSI than those not taking prophylaxis (2.7 v. 10%).

Discussion:

Changes from Source guideline:

- The source guideline (BCSH) did not review all primary literature on antibiotic prophylaxis.
- **Dose**: The dose of penicillin that was studied in the Gaston et al[20] study was 125 mg bid and included children 3 months to 36 months. The Falletta et al[22] study included children aged 5 years and older who received penicillin 250 mg bid.

Penicillin:

There have been two well designed, randomized, controlled trials comparing penicillin to placebo in children with sickle cell anemia[20, 22]. Both studies showed that penicillin prophylaxis reduced development of OPSI. A third trial by John et al.[21], included 232 children, randomized children to receive penicillin prophylaxis + pneumococcal or Hib vaccine vs no penicillin prophylaxis + pneumococcal or Hib vaccine. This trial showed that penicillin prophylaxis reduced the development of pneumococcal isolates. These trials along with the risk of death from OPSI form the basis for the current strong recommendation in this guideline.

Approximately 80% of OPSI infections are due to *S. pneumoniae*[24]. Penicillin-resistant *S. pneumonia* frequencies vary in different settings, but the impact of resistance on the efficacy of prophylaxis is not known. The use of prophylactic antibiotics with a broader spectrum than penicillin or amoxicillin is likely to result in increased antimicrobial resistance.

Dosing:
The source guideline (BCSH) does not give dosing recommendations. The dosing of penicillin in Gaston et al[20] was 125 mg twice daily, and is the recommended dose by the American Academy of Pediatrics Red Book 2012[25]. 250 mg twice daily for children 5 years and older is also recommended by the American Academy of Pediatrics Red Book 2012. The Panel concurs with this recommendation.

4.1.2 If children 3 months and older are not able to tolerate penicillin or if penicillin is not available, amoxicillin can be used as an alternative at a dose of:

a) 10 mg/kg/dose twice daily for children 3 months to 5 years.
   OR
b) 250 mg per dose twice daily for children 5 years and older.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
No studies have been conducted to look at antibiotic alternatives for children who cannot tolerate penicillin. The Panel felt that amoxicillin has sufficient coverage for the most common organism implicated in OPSI. The dosing is based on the Australian Society of Infectious Disease.[26]

Recommendation 4.1.2 is not addressed in the source guideline.

4.1.3 Children 3 months of age and younger without a spleen or with asplenia/hyposplenia should receive antibiotic prophylaxis with an antibiotic that is also active against E.coli and Klebsiella sp. The authors of this guideline recommend cefixime 8 mg/kg/day once or twice daily.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
There is no evidence in the literature that directly supports this recommendation. This recommendation is based on expert opinion that children under the age of 3 months with asplenia/hyposplenia are a vulnerable population and late onset sepsis with Gram negative pathogens (E.coli and Klebsiella) can occur up to 3 months after birth.

Prophylaxis with cefixime 8 mg/kg/day rather than penicillin is recommended as this third generation cephalosporin has good coverage for E.coli and Klebsiella sp, can be given once daily, is well tolerated and is palatable.

The source guideline does not discuss recommendation 4.1.3.

4.1.4 Children who are allergic to penicillin should see an allergist.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
This recommendation is based on expert opinion. The Panel strongly recommends that children without a functioning spleen who are allergic to penicillin receive prophylaxis. The Australian Society of Infectious Diseases[26] recommends erythromycin as a reasonable choice for the penicillin-allergic child as it has broad spectrum coverage for the pathogens implicated in OPSI.

The panel of this guideline has concerns about the use of macrolides in the Atlantic Provinces as the incidence of resistance is increasing. The panel at this time recommends that a child see an allergist to confirm an allergy. Once the allergy is confirmed the panel recommends an infectious disease consultation to determine the appropriate antibiotic choice.

The source guideline did not discuss recommendation 4.1.4.

4.1.5 Children with asplenia or hyposplenia who are not high risk for overwhelming post-splenectomy infection and who have received their pneumococcal vaccination:

a) Should receive antibiotic prophylaxis for at least 2 years post-splenectomy. **AND**
b) Can stop antibiotic prophylaxis at age 5 years in consultation with a specialist.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, moderate quality of evidence.

Evidence:

Table 3 - Summary of studies used to inform recommendation 4.1.5

Studies	Results
Penicillin vs placebo	
Falletta et al. 1995[22]	• Children 5 years one month who received prophylactic penicillin for at least 2 years immediately before their fifth birthday and the 23 valent pneumococcal vaccine between 2 and 3 years of age were eligible for randomization to receive 250 mg bid of penicillin or

Studies	Results
Falletta et al. 1995[22] continued	placebo. All children on the study were given an additional pneumovax vaccine within 1 year of randomization if they had not already received the vaccine within the previous year. • 400 children were randomly selected. 65% had received prophylactic penicillin for more than 4 years. The penicillin group was followed for 3 years two months and the placebo group for 3 years one month. There were 201 in the penicillin group and 199 in the placebo group. • 6 children had a systemic infection caused by S.pneumoniae. 4 in the placebo group and 2 in the penicillin group. Relative risk of 0.5 (95% CI 0.1, 2.7). • No deaths were reported from OPSI.

Discussion:

A single randomized controlled trial in children with sickle cell anemia provides indirect evidence that chemoprophylaxis can be discontinued at age five years in children who have not had invasive pneumococcal infection, are vaccinated and are receiving medical care (Table 2, Falletta et al 1995).

The source guideline (BCSH) recommends that patients not at high risk for OPSI should be counselled regarding the risks and benefits of lifelong antibiotic prophylaxis. They give this a level of evidence of "C" (requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. This indicates an absence of directly applicable clinical studies of good quality).

Long term antibiotics can be associated with increased antimicrobial resistance[27]. It is the Panel's opinion that children without a functioning spleen and not at high risk for OPSI should receive antibiotic prophylaxis at least up to their 5th birthday. The Red Book published by the American Academy of Pediatrics, 2012[25], also recommends prophylaxis in children with sickle cell anemia until age 5 years. A recent Cochrane Review, 2012[28], also supports the recommendation to stop prophylactic antibiotics at age 5 years for children with sickle cell disease.

For the purposes of this guideline high risk children for OPSI will include all children who have had a previous invasive pneumococcal infection, have not received the pneumococcal vaccine or who have a concurrent immunocompromising condition.

All children who are at **high risk** for OPSI should receive life-long antibiotic prophylaxis. For all other children, the need for continued antibiotic prophylaxis should be reviewed at the end of 2 years of treatment. If the child is less than 5 years of age at the end of the 2 years of treatment, the child should continue antibiotic prophylaxis up to their 5th birthday in consultation with a specialist.

The Panel of this guideline feels that children with asplenia or hyposplenia who have not had a previous pneumococcal sepsis, do not have a concurrent immunocompromising condition and who have received their pneumococcal vaccinations can stop antibiotic prophylaxis at age 5 years in consultation with a specialist.

4.1.6 Children at high risk for pneumococcal infection should receive life-long antibiotic prophylaxis

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, low quality of evidence.

Evidence/Discussion:
Children considered at high risk for invasive pneumococcal infection are those with a history of previous invasive pneumococcal disease[29], a splenectomy for underlying hematological malignancy[13]or an inadequate serological response to pneumococcal vaccination[30]. Although there is no established pneumococcal antibody titre that correlates with protection from invasive pneumococcal disease, an infectious disease and/or immunology specialist may request titres in the decision making for low risk patients who are non-compliant with their antibiotic prophylaxis. The Panel strongly recommends that all children with asplenia or hyposplenia who are at high risk for invasive pneumococcal infection receive life-long antibiotic prophylaxis based on the increased incidence of death due to OPSI.

The source guideline gives this recommendation a level of “C” (requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. This indicates an absence of directly applicable clinical studies of good quality).

4.1.7 Families non-compliant with antibiotic prophylaxis should be instructed to have available a stand-by supply of prophylactic antibiotics and have the child take a dose if the child has a fever or suspect a fever and seek medical attention immediately

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
The source guideline gives this recommendation a level “C” (requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. This indicates an absence of directly applicable clinical studies of good quality).

The Panel consensus is that children who are non-compliant with antibiotic prophylaxis should be strongly educated on the need to carry a supply of antibiotic with them at all times in case of times when they feel unwell. The health professional should instruct

the child and caregiver to take the antibiotic as soon as the child feels unwell and seek medical attention immediately.

4.2. Optimal timing of vaccines around splenectomy

4.2.1 All children should be vaccinated 14 days prior to a splenectomy if not previously immunized. In the case of an emergency splenectomy, all children who were not previously vaccinated should be vaccinated 14 days post-splenectomy.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, moderate quality of evidence.

Evidence:

Table 4 - Summary of studies used to inform recommendation 4.2.1

Studies	Results
Pneumococcal vaccine immunologic response prior to splenectomy	
Shatz et al. 1998[31]	• 59 patients underwent emergency splenectomy. • Number of children unknown (age range 13-67 with a mean 33.6 years). • No significant difference in response between non-splenectomized control group titres and study group titres but day 14 study group did achieve higher titres. 66% of study group (day 1) did not reach the outlined protective titre of >64, 64% of (day 7) and 53% of (day 14) and 19% of the controls.
Shatzet al. 2002[32]	• 38 participants (no children). • No statistical significance between day 14 and day 28 titres. • Day 14, 36% reached the protective titre level and at day 28, 34% reached >64 titre level.

Discussion:
The source guideline panel does support this recommendation but did not give the recommendation a GRADE.

From a biologic rationale, it is ideal for children to receive vaccine before the spleen is removed as the spleen plays an important role in adaptive immunity. There is some evidence from the Shatz et al studies[31, 32] to suggest that vaccines are efficacious when given at least 2 weeks after an elective splenectomy. Therefore, the Panel's recommendation is that children undergoing a splenectomy should receive their vaccines at least 2 weeks prior to the surgery. If this is not possible, then the vaccines should be given 2 weeks after the splenectomy. If there is concern that the child may not be available for the two week post-splenectomy vaccination visit, then vaccines should be given in hospital prior to discharge.

No studies have looked at the optimal timing of vaccines other than pneumococcal vaccine but the Panel felt this information could be extrapolated to include all vaccines.

4.3 Pneumococcal Vaccine

All splenectomised children should receive childhood pneumococcal vaccines according to the Canadian National Advisory Committee on Immunization[35] schedule for high risk children (http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php#a1). High risk children should receive 4 doses of pneumococcal vaccine rather than 3.

4.3.1 All previously unvaccinated children 2 years and older should receive one dose of the pneumococcal conjugate vaccine (PCV13) followed at least 8 weeks later by the pneumococcal polysaccharide vaccine (PPV23)

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, low quality of evidence.

Evidence:

Table 5 - Summary of studies used to inform recommendation 4.3.1

Studies	Results
Pneumococcal conjugate vaccine prior to pneumococcal polysaccharide vaccine	
Orthopouloset al. 2009[33]	• 35 male splenectomized patients with B-thalassemia, age range (12-41), median 30. Control group of 23 non-splenectomized B-thalassemics, median age 30 who had never received PPV23. • 28 of the 35 had previously received PPV23. • Adverse reactions occurred with 42% of primary and 90% of booster doses. • Subjects randomized to get either 1 dose of PCV7 followed by 1 dose of PPV23 or 1 dose of PCV7 followed by 1 dose of PCV7. • All subjects 12 months after primary immunization received a booster of PPV23. Blood was taken before each vaccination and 4-6 weeks later. • Documented IgG antibody levels to the serotypes. • Baseline GMC (geometric mean concentration) was similar in both the study groups A and B. • Both vaccination schedules were adequately immunogenic and significant GMC increases for most serotypes were observed after the first dose of PCV ($p<0.05$). The second dose of either PPV (group A) or PCV (group B) only induced minor further changes. • GMCs after completion of primary immunization were similar in both groups.

Studies	Results
Orthopouloset al. 2009[33] continued	• Baseline levels were non-significantly higher in the study group that had been previously vaccinated compared to the non-vaccinated control group. • PCV followed by PPV induced similar response with 2 PCVs given 1 month apart, and there were no differences in anamnestic immune responses after PPV booster. • Conclusion: It is safe to prime asplenic subjects with PCV7 followed by PPV. Multiple PPV23 vaccinations produce hyporesponsiveness.
Stoehret al. 2005[34]	• 39 splenectomized children with hereditary spherocytosis (2-18 yrs). • All received PCV7 followed 2 months later with PPV23. • All subjects had a significant rise in 5/7 serotypes after the PCV7 vaccine and in the other 2 serotypes after the PPV23 vaccine. • Conclusion: Sequential vaccination of PCV7 followed by PPV23 appears safe in splenectomized children.

Discussion:
The source guideline recommends that all children 2-5 years who are not vaccinated should receive 2 doses of pneumococcal conjugate vaccine followed by 1 dose of pneumococcal polysaccharide vaccine.

The Panel recommends that previously unvaccinated children over the age of 2 years should receive only 1 dose of the pneumococcal conjugate vaccine followed 8 weeks later with the pneumococcal polysaccharide vaccine. The Canadian Immunization Guide also recommends only 1 dose of pneumococcal conjugate vaccine[35].

Efficacy and safety of sequential vaccination of pneumococcal conjugate vaccine followed 2 months later with the polysaccharide vaccine is supported by the Stoehr study[34]. The Orthopoulos study[33] also suggests that it is safe to prime asplenic subjects with pneumococcal conjugate vaccine followed by the pneumococcal polysaccharide vaccine.

The evidence for the following 3 recommendations (4.3.2-4.3.4) is based on The Canadian National Advisory Committee on Immunization (NACI)[36], and the Centers for Disease Control (CDC) and Prevention Advisory Committee on Immunization Practices[37].

4.3.2 All children who previously received only pneumococcal polysaccharide vaccine should receive one dose of pneumococcal conjugate vaccine (PCV13) at least 8 weeks after receipt of the polysaccharide vaccine (PPV23)

Grade of recommendation (GRADE criteria, Appendix E):
Conditional recommendation, very low quality of evidence.

Evidence/Discussion:
The source guideline (BCSH) does not recommend pneumococcal conjugate vaccine in high risk persons over five years of age.

The Panel recommends that all children with asplenia and hyposplenia regardless of age should receive the pneumococcal conjugate vaccine (PCV13), based on the immunogenicity of the pneumococcal conjugate vaccine of the 13 serotypes covered in the PCV13. As the PCV13 is well tolerated[35],the benefit to the patient outweighs the risk.

4.3.3 All children who have received pneumococcal conjugate vaccine (PCV7 or PCV10) should receive a dose of PCV13 as soon as possible (or at least 4 weeks after the last dose of pneumococcal conjugate vaccine)

Grade of recommendation (GRADE criteria, Appendix E):
Conditional recommendation, very low quality of evidence.

Evidence/Discussion:
The source guideline does not address this recommendation. The Panel recommends that all children with asplenia and hyposplenia regardless of age should receive the pneumococcal conjugate vaccine PCV13 even if previously vaccinated with the PCV7 or PCV10 vaccines.

4.3.4 A single booster dose with the pneumococcal polysaccharide vaccine (PPV23) should be given:

a. If 11 years or older at time of primary vaccination, revaccinate at 5 years.
b. If 10 years and younger at time of primary vaccination, revaccinate at 3 years.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, low quality of evidence.

Evidence:

Table 6 - Summary of studies used to inform recommendation 4.3.4

Studies	Results
Pneumococcal conjugate vaccine prior to pneumococcal polysaccharide vaccine	
Smets et al. 2007[38]	• Randomised single centre study of asplenic children over the age of 5 years. Allocation of PPV23 or PCV7 was random. 21 children were included, 19 accessible for analysis. 11 in PCV7 and 8 in PPV23 arm. • All children had received the PPV23 in the previous 3 years. • From the literature, GMC$\geq$0.2 ug/mL for the PCV, $\geq$1 ug/mL for PPV considered protective.

Studies	Results
Smets et al. 2007[38] continued	• Antibody titres were drawn at baseline, 1 and 6 months after vaccination and a greater than 4 fold increase in antibody titres was considered a response. • Most frequent adverse events were local and general reactions (loss of appetite and sleepiness) in 63% and 45% of PCV7 and 62% and 12% of PPV23 recipients. • Half of the PCV7 children responded to 4/5 serotypes and half PPV23 responded to less than 3 serotypes. After 1 month the immune response for serotype 23V was significantly greater after PCV7 vaccination than after PPV23 vaccination (p=0.036). • Conclusion: revaccination with PCV7 is safe and immunogenic in asplenic children previously vaccinated with PPV23. The clinical effect on invasive pneumococcal disease is not known.
Landgren et al. 2004[12]	• 311 splenectomized individuals were included in this prospective study (6-81 years). • Subjects were followed for up to 11 yrs. • Subjects received PPV23 up to 4 doses 3-5yrs apart. • 10 OPSI were reported in 7 pts who had a diagnosis of Hodgkin lymphoma. • Hodgkin lymphoma patients are at increased risk of OPSI and can safely receive PPV23 booster every 3-5 yrs.
Orthopoulos et al. 2009[33]	• 35 male splenectomized patients with B-thalassemia, age range (12-41), median 30. Control group of 23 non-splenectomized B-thalassemics, median age 30 who had never received PPV23. • 28 of 35 had previously received PPV23. • Adverse reactions occurred with 42% of primary and 90% of booster doses. • Subjects randomized to get either 1 dose of PCV7 followed by 1 dose of PPV23 or 1 dose of PCV7 followed by 1 dose of PCV7. • All subjects 12 months after primary immunization received a booster of PPV23. Blood was taken before each vaccination and 4-6 weeks later. • IgG antibody levels to the serotypes were documented. • Baseline GMC was similar in both the study groups A and B. • Both vaccination schedules were adequately immunogenic and significant GMC increases for most serotypes were observed after the first dose of PCV ($p<0.05$). The second dose of either PPV (group A) or PCV (group B) only induced minor further changes. • GMCs after completion of primary immunization were similar in both groups. • Baseline levels were non-significantly higher in the study group that had been previously vaccinated compared to the non-vaccinated control group.

Studies	Results
Orthopoulos et al. 2009[33] continued	• PCV followed by PPV induced similar response with 2 PCVs given 1 month apart, and there were no differences in anamnestic immune responses after PPV booster. • Conclusion: It is safe to prime asplenic subjects with PCV7 followed by PPV. Multiple PPV23 produce hyporesponsiveness.
Giebink GS et al. 1984[39]	• 33 children 5-15 years. • Randomized to either receive 12-valent or 14-valent polysaccharide pneumococcal vaccine. • 23 of the 33 had undergone splenectomy for trauma and 10 for hereditary spherocytosis. • Protective level 300 ngN/mL (as ng of anticapsular antibody nitrogen [ngN/mL]. • 3 serotypes declined below protective levels 1 to 2 years after vaccination.
Weintrub PS et al. 1984[40]	• 75 sickle cell anemia patients, 2-18 years of age at the time of primary vaccination. • 17 patients were available for follow-up and were given a booster immunization. • Interval sera were available for 8 patients between 3 and 5 years after primary immunization and were below protective levels.

Discussion:
The source guideline does not recommend giving a pneumococcal polysaccharide booster.

Both the Giebink and Weintrub[39,40] studies suggest that vaccine induced anti-pneumococcal antibodies in children with asplenia and hyposplenia decline over a 3 to 5 year period. The decline has been suggested to be more rapid in children, Mufson et al.[41] reported that serum antibody levels for most serotypes declined by approximately 25% five years after vaccination and Vella et al.[42] reported that antibody levels declined in adults by about 50% after 3.5 years and in children by 55% after only 21 months. The Panel is recommending revaccination at 3 years for children 10 years and less at initial vaccination and after 5 years for those older than 10 years. The Smets study[38] recommends that the pneumococcal conjugate vaccine be used as an alternative to the pneumococcal polysaccharide vaccine as a booster; but it is not known to date if the clinical significance of a booster dose using pneumococcal conjugate vaccine decreases the risk of invasive pneumococcal infection.

Even though it has been identified in the Langley study[43] that pneumococcal polysaccharide vaccine does not decrease the risk of invasive pneumococcal infection, it is felt that the risk reduction by using pneumococcal conjugate vaccine should be studied further. The Panel, therefore, recommends that the pneumococcal polysaccharide vaccine be used as a booster as it covers more serotypes involved in pneumococcal sepsis. The Orthopoulos study[33] does suggest that multiple doses of

pneumococcal polysaccharide vaccine can cause hyporesponsiveness which is why the Panel is suggesting only one booster dose of pneumococcal polysaccharide vaccine.

4.4 Meningococcal Vaccine

All asplenic and hyposplenic children should receive the meningococcal conjugate vaccine.

4.4.1 All children with asplenia or hyposplenia should receive the meningococcal quadrivalent conjugate vaccine (Menveo™):

All children with asplenia or hyposplenia should receive the meningococcal quadrivalent conjugate vaccine ACYW:

a) 2 to less than 12 months: 2-3 doses given 8 weeks apart with another dose between 12 and 23 months and at least 8 weeks from the previous dose. (Menveo™)
b) 12 to 23 months: 2 doses at least 8 weeks apart (Menveo™)
c) 2 years and older: 1 dose (Menveo™ or Menactra™ can also be used)

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, low quality of evidence.

Evidence:

Table 7 - Summary of studies used to inform recommendation 4.4.1

Studies	Results
Safety and efficacy of meningococcal ACYW conjugate vaccine in infants	
Snape et al. 2008[44]	• Men-C-ACYW-135-CRM with adjuvant (Menomune) compared to monovalent meningococcal C conjugate (Menjugate). • Open-label randomized controlled trial. • N=421 enrolled and randomized to various schedules/products. • hSBA (serum bactericidal antibody) >1:4 used as measure of immunity. • Three dose schedules had better immune responses than two dose schedules. • Using 2,4,6 month schedule, high rates of immunity were achieved one month post vaccination with Men-C-ACYW-135-CRM with adjuvant; which for serogroups A and C fell by 12 months. • GMTs (geometric mean titre) were higher for serogroup C using monovalent meningococcal C conjugate. • Good boosting at 12 months was demonstrated. • Lower GMTs for serogroups A, W135 and Y for those who received primary series with meningococcal C conjugate and then only one dose of Men-C-ACYW-135-CRM at 12 months compared to those who received primary series and 12-month booster with Men-C-ACYW-135-CRM with adjuvant.

Studies	Results
Snape et al. 2008[44] continued	• High percentages (>=90%) of children achieved protective titres for concomitantly administered antigens. • Rates of local and systemic reactions after Men-C-ACYW-135-CRM with adjuvant similar to monovalent meningococcal C conjugate (Menjugate). • Two serious adverse events thought to be possibly related to Men-C-ACYW-135-CRM with adjuvant: idiopathic thrombocytopenia purpura and supraventricular tachycardia.
Perrett et al. 2009[45]	• Men-C-ACYW-135-CRM without adjuvant (Menveo™). Open-label controlled trial. • Canadians randomized at 12 months to Men-C-ACYW-135-CRM or 1/5 dose of quadrivalent polysaccharide vaccine. • N=180 enrolled. • Received Men-C-ACYW-135-CRM at 2, 4 months. • 12 month dose in UK was Men-C-ACYW-135-CRM. • 12 month challenge in Canada with Men-C-ACYW-135-CRM or 1/5 dose of quadrivalent polysaccharide vaccine. • hSBA>1:4 used as measure of immunity. • High rates of immunity were achieved one month post vaccination with Men-C-ACYW-135-CRM which fell for all serogroups by 12 months. • Good boosting at 12 months was demonstrated. • Grade 3 tenderness at injection site in 2-4% after at least one infant dose and 0-1% after 12 month booster of Men-C-ACYW-135-CRM without adjuvant. • No serious adverse events attributed to vaccine.
Halperin et al. 2010[46]	• Men-C-ACYW-135-CRM (Menveo™) compared to monvalent meningococcal C conjugate. (Menjugate) • Open labeled, partially randomized, controlled trial. • Three groups: - Men-C-ACYW-135-CRM at 6 and 12 months; - Men-C-ACYW-135-CRM at 12 months; - Monovalent meningococcal C conjugate at 12 months and Men-C-ACYW-135-CRM at 18 months. • N=175 enrolled to one of three schedules, ages 6-12 months at enrollment. • hSBA>1:4 used as measure of immunity. • Men-C-ACYW-135-CRM at 6 and 12 months had the best immune response for all serogroups except serogroup C which was exceeded by the monovalent meningococcal C conjugate vaccine at 12 months and Men-C-ACYW-135-CRM at 18 month schedule. • For serogroup C, the monovalent conjugate C vaccine and Men-C-ACYW-135-CRM vaccines had similar responses which were

Studies	Results
Halperin et al. 2010[46] Continued	exceeded by the monovalent meningococcal C conjugate vaccine at 12 months and Men-C-ACYW-135-CRM at 18 month schedule. • For serogroup C, the monovalent conjugate C vaccine and Men-C-ACYW-135-CRM vaccines had similar responses at 12 months. • For serogroups A, W135 and Y, the responses to a single Men-C-ACYW-135-CRM 12 months or 18 months were similar and acceptable although less than the response achieved by two doses of Men-C-ACYW-135-CRM at 6 and 12 months. • C-ACYW-135-CRM 12 months or 18 months were similar and acceptable although less than the response achieved by two doses of Men-C-ACYW-135-CRM at 6 and 12 months. • No clear difference in frequency of adverse events between monovalent meningococcal C conjugate vaccine and Men-C-ACYW-135-CRM. • No serious adverse events determined to be vaccine-related.
Vesikari T et al. 2005[47]	• Men-C-ACYW-135-CRM (Menveo™) one dose versus two. • Boost with Men-P-ACYW-135 polysaccharide vaccine at 8 months post vaccination. • Dose finding study. • N=620 enrolled. • Ages 12-16 months. • Received one or two doses of various formulations. • Quadrivalent polysaccharide booster 8 months post vaccination compared to naïve controls. • hSBA>1:4 used as measure of immunity. • Two doses had better immune response than one with percentage achieving hBSA>=1:4 49-70% for the various serogroups after one dose and 91-96% after two doses. • Good boosting with quadrivalent polysaccharide vaccine 8 months after first dose. • Statistically significantly more local and systemic reactions noted with Men-C-ACYW-135-CRM compared to Men-P-ACYW-135. • No serious adverse vaccine reactions judged to be related to vaccine.
Black et al. 2010[48]	• Men-C-ACYW-135-CRM (Menveo™) compared to unconjugated quadrivalent polysaccharide (Men-P-ACYW-135 -Menomune). • Single blinded randomized trial. • N=619 enrolled to one of the two vaccines. • 2-10 year olds. • Single dose. • hSBA>1:4 used as measure of immunity. • Immunity to Men-C-ACYW-135-CRM was statistically superior to Men-P-ACYW-135 at 1 and 12 months after vaccination for almost every serogroup using percent achieving hSBA>= 1:4 and GMTs.

Studies	Results
Black et al. 2010[48] continued	• For Men-C-ACYW-135-CRM, high rates of immunity were achieved one month post vaccination which fell for serogroups A and C by 12 months post vaccination. • Statistically significantly more local and systemic reactions noted with Men-C-ACYW-135-CRM compared to Men-P-ACYW-135. • No serious adverse vaccine reactions judged to be related to vaccine.

Discussion:
The source guideline (BCSH) recommends that all asplenic and hyposplenic children receive the meningococcal conjugate vaccine. They give this a Grade "B" (which requires the availability of well-conducted clinical studies but no randomized clinical trials on topic of recommendation). The source guideline also recommends that all asplenic and hyposplenic children aged 2 years and older should receive 1 dose of a MenC conjugate vaccine followed by a single dose of the quadrivalent MenACWY conjugate vaccine one month later, irrespective of their previous immunization status.

The Panel of this guideline recommend vaccination of all asplenic and hyposplenic children with the meningococcal conjugate quadrivalent ACYW vaccine. The Panel gives this a strong recommendation with low quality of evidence based on the studies by Snape, Parrett, Halperin, Vesikari and Black[44-48] that showed that the quadrivalent conjugate meningococcal vaccine Menveo is immunogenic and well tolerated in infants. Men-C-ACYW-135-CRM (Menveo) is not yet authorized for children less than 2 years of age, therefore, there are no authorized schedules for these children. The Panel recommends the above schedule based on schedules used in published clinical trials and NACI's previous recommendation that a dose of meningococcal conjugate ACYW vaccine be given in the second year of life for children first vaccinated at less than 1 year of age.

4.4.2 All children 1 year and older with asplenia or hyposplenia not previously vaccinated should receive1 dose of the meningococcal conjugate C vaccine and:

a) 2 doses of the meningococcal quadrivalent conjugate vaccine (Menveo™) if 12-23 months.
b) 1 dose of the meningococcal quadrivalent conjugate vaccine (Menveo™) or (Menactra™) if 2 years and older.

All vaccines should be given at least 8 weeks apart.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence:

Table 8 - Summary of studies used to inform recommendation 4.4.2

Studies	Results
Safety and efficacy of meningococcal ACYW conjugate vaccine in infants	
Snape et al. 2008[44]	• Men-C-ACYW-135-CRM with adjuvant (Menomune) compared to monovalent meningococcal C conjugate (Menjugate). • Open-label randomized controlled trial. • N=421 enrolled and randomized to various schedule/products. • hSBA>1:4 used as measure of immunity. • Three dose schedules had better immune responses than two dose schedules. • Using 2,4,6 month schedule, high rates of immunity were achieved one month post vaccination with Men-C-ACYW-135-CRM with adjuvant; which fell for serogroups A and C by 12 months. • **GMTs were higher for serogroup C using monovalent meningococcal C conjugate.** • Good boosting at 12 months was demonstrated. • Lower GMTs for serogroups A, W135 and Y for those who received primary series with meningococcal C conjugate and then only one dose of Men-C-ACYW-135-CRM at 12 months compared to those who received primary series and 12-month booster with Men-C-ACYW-135-CRM with adjuvant. • High percentages (>=90%) of children achieved protective titres for concomitantly administered antigens. • Rates of local and systemic reactions after Men-C-ACYW-135-CRM with adjuvant similar to monovalent meningococcal C conjugate (Menjugate). • Two serious adverse events thought to be possibly related to Men-C-ACYW-135-CRM with adjuvant: idiopathic thrombocytopenia purpura and supraventricular tachycardia.
Halperin et al.[46]	• Men-C-ACYW-135-CRM (Menveo™) compared to monvalent meningococcal C conjugate (Menjugate). • Open labeled, partially randomized, controlled trial. • Three groups: - Men-C-ACYW-135-CRM at 6 and 12 months; - Men-C-ACYW-135-CRM at 12 months; - Monovalent meningococcal C conjugate at 12 months and Men-C-ACYW-135-CRM at 18 months. • N=175 enrolled to one of three schedules, ages 6-12 months at enrollment. • hSBA>1:4 used as measure of immunity. • Men-C-ACYW-135-CRM at 6 and 12 months had the best immune response for all serogroups except serogroup C which was

Studies	Results
Halperin et al.[46] continued	exceeded by the monovalent meningococcal C conjugate vaccine at 12 months and Men-C-ACYW-135-CRM at 18 month schedule. • For serogroup C, the monovalent conjugate C vaccine and Men-C-ACYW-135-CRM vaccines had similar responses which were exceeded by the monovalent meningococcal C conjugate vaccine at 12 months and Men-C-ACYW-135-CRM at 18 month schedule. • For serogroup C, the monovalent conjugate C vaccine and Men-C-ACYW-135-CRM vaccines had similar responses at 12 months. • For serogroups A, W135 and Y, the responses to a single Men-C-ACYW-135-CRM 12 months or 18 months were similar and acceptable although less than the response achieved by two doses of Men-C-ACYW-135-CRM at 6 and 12 months. • C-ACYW-135-CRM 12 months or 18 months were similar and acceptable although less than the response achieved by two doses of Men-C-ACYW-135-CRM at 6 and 12 months. • No clear difference in frequency of adverse events between monovalent meningococcal C conjugate vaccine and Men-C-ACYW-135-CRM. • No serious adverse events determined to be vaccine-related.

Discussion:

The source guideline (BCSH) gives this recommendation to vaccinate all children with asplenia and hyposplenia with the meningococcal conjugate vaccine a level “C” (requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. This indicates an absence of directly applicable clinical studies of good quality).

The Snape and Halperin[44, 46] studies showed that the antibody levels achieved with the meningococcal conjugate C vaccine were higher than the meningococcal conjugate ACYW vaccine in children with asplenia less than 2 years of age. For children 2 years and older Menactra™, can also be given as it is immunogenic in this age group. The Panel feels that, as currently the response to the MenC vaccine is superior to the response to the C component in the quadrivalent ACYW conjugate vaccine (Menveo™), it is prudent to give all children, over the age of 1 year who have not been previously vaccinated a dose of meningococcal conjugate C containing vaccine. Both vaccines are well tolerated.

4.4.3 All children with asplenia or hyposplenia over five years of age should receive a booster dose with quadrivalent meningococcal conjugate ACYW vaccine. Either Menveo™ or Menactra™ can be used:

a) For those vaccinated at 6 years of age and under: provide a booster dose 3-5 years after the last dose, followed by every 5 years;
b) For those vaccinated at 7 years of age and older: provide a booster dose 5 years after the last dose, followed by every 5 years.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
The source guideline does not address this recommendation.

This recommendation is supported by the Canadian National Advisory on Immunizations and the Canadian Immunization Guide, 2012[35]. There is evidence that vaccine induced meningococcal antibody titres wane over time.

4.4.4 *All children with asplenia and hyposplenia should receive the meningococcal serogroup B (4CMenB) vaccine*

All children with asplenia and hyposplenia should receive the meningococcal serogroup B (4CMenB) vaccine.

a) 2-5 months: 3 doses at least 1 month apart and a booster dose at 12-23 months.
b) 6-11 months: 2 doses at least 2 months apart and a booster dose at 12-23 months (at least 2 months after the 2nd dose).
c) 12 months-10 years: 2 doses at least 2 months apart.
d) 11-17 years: 2 doses at least 1 month apart.

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
The source guideline does not address this recommendation.

While there is good evidence that the 4CMenB vaccine is immunogenic in healthy children and adults, there are no studies in persons with hypo/asplenia. However, since hypo/asplenic children are at increased risk of invasive meningococcal disease the National Advisory Committee on Immunization recommends that it be considered in this context. (http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-104-2014-eng.pdf)[36]

4.5 Haemophilus Influenzae Vaccine

All asplenic or hyposplenic children should receive the conjugate *Haemophilus influenzae* vaccine as per local practice.

4.5.1 All children with asplenia or hyposplenia who have not been previously vaccinated should receive the Haemophilus influenzae type B vaccine

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, low quality of evidence.

Evidence:

Table 9 - Summary of studies used to inform recommendation 4.5.1

Studies	Results
Immunogenicity of *Haemophilus influenzae* in asplenic and hyposplenic patients	
Mikoluc et al. 2011[49]	• Small number of patients (n=20), did include children (5-25 yrs; mean 14 yrs). • All children splenectomized before the age of six years. • Antibody titre levels greater than or equal to 0.15 ug/ml for minimum protection and 1 ug/ml for long term protection. • All 20 patients had a significant increase in geometric mean antibody concentration ($p<0.01$) and 20/20 had values $\geq$0.15 ug/ml and 17/20 had >1 ug/ml. • 4 children had congenital asplenia and 16 were splenectomized. • All of the congenital asplenia children were >1 ug/ml pre-vaccination but did not increase significantly with vaccination. • 3 of the splenectomized children did not reach the 1 ug/ml level but did reach the 0.15 ug/ml level after vaccination which means that 17/20 patients reached the protective antibody levels. No side effects of vaccine were seen.
Cimaz et al. 2001[50]	• 57 patients with thalassemia major, hyposplenic or asplenic, does not state how many children (4-41 mean 21 yrs). • All patients achieved antibody levels >1 ug/ml after vaccination. • The antibody titre average prior to vaccination was 1.98 ug/ml (CI 95% 0.3-15.1) and 15.4 ug/ml (CI 95% 5.3-45.7) after vaccination and 2.8 ug/ml (CI 95% 0.1-58.9) after 1 year. • Fever reported in 2 patients from vaccine.
Webber et al. 1993[51]	• 10 patients (all children) with congenital asplenia. • 9/10 showed good response >1 ug/ml (1 did not respond -0.07 ug/ml). • Pre-immunization antibody titre was 0.3 ug/ml and post 44.7 ug/ml. • The child that did not show a response did respond to a second dose of the vaccine.
Kristensen et al. 1992[52]	• 20 splenectomized patients (4-18yrs). • Patients all had tenderness at injection site. • 10/20 pre-immunization titres were less than 1 ug/ml and all titres were >1 ug/ml after vaccination.
Ambrosino et al. 1992[53]	• 13 splenectomy patients (3-19 yrs) with 15 controls, IgG anti-Hib antibody >1 ug/ml was considered protective. All reached protective titres >1 ug/ml with the splenectomized patients reaching much higher levels than the controls (48 ug/ml vs 10 ug/ml).

Studies	Results
Jakacki et al. 1990[54]	• 23 patients (6-29 yrs) with Hodgkin disease and 12 controls (19-54 yrs). • All reached protective titres and all but 3 patients sustained level of >1 ug/ml 1 year post vaccination. • After immunization, the controls reached higher antibody levels than the study patients (p=0.001). • 1 patient had nausea and 1 had fever.
Meerveld-Eggink et al.2008 [30]	• 129 patients (no children), only 92 received the Hib vaccine. • All but 3 patients reached protective levels of 1 ug/ml. • Mean antibody titres rose statistically significantly (p<0.01) from 1.4 ug/ml (95% CI 1-1.8 ug/ml) to 16.8 ug/ml (95% CI 11.5-24.2 ug/ml).
Konradsen et al. 1997[55]	• 149 patients (14 children below the age of 15), all achieved protective titres ≥0.15 ug/ml and 60% >1 ug/ml.

Discussion:

The source guideline (BCSH) supports this recommendation and assigned it a level "C" (requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. This indicates an absence of directly applicable clinical studies of good quality).

A serum Hib antibody level of 0.15 µg/ml is considered protective in healthy people. Therefore, a level of 1 µg/ml is deemed protective in splenectomized participants. 7/8 studies used the same protective level of 0.15 µg/ml for short term protection and 1 µg/ml to signify long term protection. One study used 1µg/ml as the marker of protection. 4/8 studies report 100% of participants reached titres of greater than 1 µg/ml. 1/8 studies report 97% reaching greater than 1 µg/ml but does not report if the 3% achieved greater than 0.15 µg/ml (as they used 1 µg/ml as the marker of protection). 1/8 studies reported 60% of participants achieved greater than 1 µg/ml and 100% greater than 0.15 µg/ml. 1/8 studies reported 90% achieved greater than 1 µg/ml and 10% did not reach the level of 0.15 µg/ml. 1/8 studies reported 85% achieved greater than 0.15 µg/ml and 70% greater than 1 µg/ml.

In conclusion, approximately 60% of participants in all 8 studies reached the protective long term titre of 1 µg/ml after vaccination. The percent of participants who did not reach protective titres of greater than 1 µg/ml in 4 studies is 20% (range 3-40%). However, only 1 child in all of the studies did not reach the short term protective level of 0.15 µg/ml. No serious adverse vaccine reactions were reported in any of these trials. From the information provided it is recommended to give 1 dose of Hib vaccine to asplenic and splenectomized children as the studies did show significant increases in antibody titres and at least 60% of participants would be considered having long term protection.

We did not identify any longitudinal studies that looked at the incidence of Hib infection in vaccinated vs non-vaccinated splenectomized patients. Adverse effects from the vaccine were mild and transient: fever, local infiltrate, nausea, vertigo, myalgias.

The Panel recommends that all asplenic and hyposplenic children should receive the *Haemophilus influenzae* vaccine as it has been shown to reach protective levels with few adverse effects reported in conjunction with the knowledge that *H. influenzae* is a common isolate in OPSI.

4.5.2 All children 5 years of age and older with asplenia or hyposplenia should receive a dose of Haemophilus influenzae type B vaccine regardless of vaccination history

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, very low quality of evidence.

Evidence/Discussion:
The source guideline recommends children 2 years and older should receive 1 booster of Hib regardless of vaccination history. As the schedule of vaccination in the UK is different than in North America with no 18 month booster then titre would be expected to drop earlier, the panel is recommending a booster at 5 years.

It has been shown that titres after the first month decline but it is not clear when the mean level falls below 0.15 ug/ml[49]. As the Hib vaccine is well tolerated, it is the recommendation of the Panel that all children receive a booster dose of Hib regardless of vaccination history.

4.6 Influenza Vaccine

4.6.1 All children with asplenia or hyposplenia 6 months of age and older should receive the influenza vaccine annually

Grade of recommendation (GRADE criteria, Appendix E):
Strong recommendation, moderate quality of evidence.

Evidence:

Table 10 - The evidence to support recommendation 4.6.1

Studies	Results
Influenza vaccine reduction in incidence of death due to OPSI	
Langley et al. (2010)[43]	• This is a retrospective cohort study from 1990-2002. 427 patients had splenectomy with a hematologic diagnosis and 452 had splenectomy without a hematologic diagnosis. • 28% were children. 467/879 splenectomized patients received the influenza vaccine. • Influenza vaccine was associated with reduced risk of death (adjusted for pneumococcal vaccine, H=0.46 (0.33-0.62). • The hazard ratio for the risk of death for splenectomized patients who did not get the influenza vaccine is 0.46, so the reduced risk of death is 54% for immunized persons compared to unimmunized asplenic persons. • All death data is presented per 1000 person years.

Discussion:

This recommendation is supported by the source guideline and given a level "B" (requires the availability of well-conducted clinical studies, but no randomized clinical trials on the topic of recommendation).

The Langley study[43] was a retrospective cohort study that followed 879 splenectomized patients (28% children); controls were 467 splenectomised persons who did not receive the influenza vaccine. The study found after adjusting for the impact of the pneumococcal vaccine that the influenza vaccine reduced the risk of death by 54% in asplenic persons with an adjusted Hazard ratio=0.46, 0.33-0.62.
The Panel agrees that this provides enough evidence that vaccinating splenectomised adults and children with the influenza vaccine reduces the risk of death.

NOTE: For immunocompromised children, DO NOT use live vaccine products.

All recommendations in section 4.7 and 4.8 are strong recommendations with very low quality of evidence.

4.7 Management of Fever

The source guideline (BCSH) does not discuss recommendation4.7.

4.7.1 A blood culture should be collected at presentation to the hospital or clinic

This recommendation is based on best practice of the need for a blood culture prior to initiation of antibiotics in order to identify a pathogen.

4.7.2 Parenteral antibiotics should be given within 60 minutes of presentation to the hospital or clinic

This recommendation is based on the knowledge that OPSI can spread quickly and treatment with antibiotics has more success when initiated immediately. Sixty minutes is based on allowing time for assessment and blood culture collection.

4.7.3 Children less than 2 months of age should be treated with cefotaxime and ampicillin in order to provide added protection for E.coli and Klebsiella bacteria that can cause OPSI in this age group. If the child is critically ill or showing signs of meningitis, vancomycin should be added

This recommendation is based on the knowledge that children less than 2 months of age require protection against *E.coli* and *Klebsiella* bacteria. No well done studies are available to determine the best antibiotics of choice in this population. The Panel chose cefotaxime due to the risk of hemolytic anemia from ceftriaxone in this age group. Ampicillin should be included to ensure coverage against *Listeria*. Based on the risk of penicillin resistant pneumococcal infection, the Panel recommends the addition of vancomycin for empiric therapy until the laboratory confirmation of the infecting organism is known.

4.7.4 Children 2 months and older should be treated with a third generation cephalosporin. If the child is critically ill or showing signs of meningitis, vancomycin should be added

A study conducted by Sakranet al. in 2012[27] reports a higher number of Gram negative infection as the cause of OPSI than previously thought, possibly due to the increase in the number of asplenic individuals having received the pneumococcal vaccine and penicillin prophylaxis. This author recommends the use of a third generation cephalosporin alone or with a combination with vancomycin or aminoglycosides as initial therapy for OPSI[27].

The Panel of this guideline recommends a third generation cephalosporin as it provides good coverage for *S.pneumoniae*, *N. meningititis* and *H. influenzae,* the 3 main organisms that cause OPSI in this age group.

Based on the risk of penicillin resistant pneumococcal infection, the Panel recommends the addition of vancomycin for empiric therapy until the laboratory confirmation of the infecting organism is known.

4.7.5 If a patient has a confirmed anaphylaxis to penicillin, meropenem can be used as an alternative

The incidence of cross reaction of meropenem and penicillin is small and is a broad spectrum antibiotic appropriate for the empiric management of OPSI.

4.7.6 A macrolide should be added in the treatment of fever or infection to:

a) Children 6 months and greater with respiratory symptoms suggestive of atypical pneumonia or mycoplasma.
OR
b) Children who intermittently take their prophylactic antibiotics as these children are at increased risk of resistance.

This recommendation is based on providing appropriate antibiotic coverage for organisms commonly seen in the different age groups and to overcome resistance in the non-compliant patients. The frequency of Mycoplasma pneumoniae is low in children under five years of age. However C. pneumoniae is a respiratory pathogen that occurs in children under 5 years. Both present as atypical pneumonia and are treated with a macrolide.

The Panel feels that a macrolide provides adequate coverage for asplenic children with respiratory symptoms or who have mycoplasma. The panel recommends azithromycin as the macrolide of choice due to ease of administration and tolerability.

4.7.7 When culture and sensitivity results indicate the organism is penicillin susceptible, switch to penicillin. For children allergic to penicillin, clindamycin can be administered.

This recommendation is based on switching to targeted therapy when an organism and sensitivity are identified to increase efficacy of treatment.

4.8 Health Professional Education to Children and Families

The source guideline supports recommendation 4.8 but does not assign a GRADE.

4.8.1 Families and patients should be well educated about the potential signs of infection, associated risks, management and prevention of overwhelming post-splenectomy infections (see parent/child information sheet Appendix C)

The Panel feels it is very important that families are educated on the risk of infection as it has been shown that seeking immediate medical attention can decrease the risk of death by around 50%.[1]

4.8.2 Families of children with a fever should be instructed to immediately take an age appropriate amount of their prophylactic antibiotic if the child hasn't already and seek immediate medical attention

One of the best methods of reducing risk of death from OPSI is to educate families and children to the importance of taking antibiotics as soon as the child feels unwell and going to the nearest medical facility as soon as possible.

4.8.3 Children and families should be educated as to the potential risk of overseas travel, with special emphasis on malaria and unusual infections, for example resulting from tick and animal bites

Asplenic and hyposplenic children are at higher risk of death from infections caused by insects; for example malaria and Babesia caused from animal bites.[8]

4.8.4 Patients should be given appropriate written or electronic information and carry a card to alert health professionals to the risk of overwhelming infections (see attached example of wallet card)

4.8.5 Patients may wish to invest in an alert bracelet or pendant

4.8.6 Patients should be given written information of their vaccination and re-vaccination status

4.8.7 Pediatricians and general practitioners should make sure children with asplenia or hyposplenia are up-to-date on all their vaccines

5. External Review and Consultation Process

The guideline was reviewed by experts in pediatric hematology/oncology, infectious disease, pediatric surgery, pediatric emergency care, pediatricians, nurses, pharmacists and managers involved in the care of children with asplenia and hyposplenia. They were asked to complete a questionnaire; their responses and the panel's responses are summarized below.

Question	Response
Role in care of children with asplenia or hyposplenia?	
Currently following an asplenia guideline?	
If using a guideline, is it consistent with this guideline?	
Rationale for guideline clear?	
Is there a need for this Canadian guideline?	
Literature search complete?	
Evidence described relevant?	
Methods used to summarize effective?	
Results interpreted in accordance with your own interpretation?	
Draft recommendations are clear?	
Agree with draft recommendations as stated?	
Comfortable recommending use of the guideline in own institution?	
Likely to adopt for own practice?	

Comments:

Comment	Response
Is there any evidence that erythromycin is better than clarithromycin? It is so poorly tolerated, I wonder about having clarithroymcin first line in the absence of other evidence	The panel has removed the recommendation for a macrolide to be second line for children allergic to penicillin due to the concern of increased resistance in this region.
Recommendation 4.4.1 and 4.4.2 are the same	Recommendation 4.4.1refers to children with asplenia/hyposplenia who receive meningococcal vaccine from birth. Recommendation 4.4.2 refers to children who start to receive meningococcal vaccine starting at 1 year of age. These children also require a dose of MenC + the meningococcal ACYW as they have not been primed with the infancy doses.
Several comments suggest that 30 minutes to start empiric antibiotics in the emergency room is not realistic.	Increased to 60 minutes as this is the standard for the treatment of febrile neutropenia and felt safe and practical for asplenia patients.
Recommendation 4.7.6 are not children of all ages at risk for mycoplasma and not just those younger than 5 years?	The panel has changed the recommendation to include all children 6 months and older with respiratory symptoms or suspicion of mycoplasma to receive a macrolide. Even though mycoplasma is more common in children over the age of 5 years, children less than 5 years are at risk for C.pneumoniae and since both present as atypical pneumoniae the treatment is the same.
The panel members are not listed	Panel members are now listed
Penicillin may only be available as 150 mg tablets	Updated recommendation 4.1.1 to say 125-150 mg.
Cefixime is a third generation cephalosporin not second generation.	Updated

Comment	Response
Although the recommendation is continue antibiotic prophylaxis for 2 years after splenectomy or to 5 years of age if considered NOT high risk and life-long if high risk I don't see any clear indication of how to differentiate the two.	For the purposes of this guideline high risk will include all children who have had a previous invasive pneumococcal infections, have not received the pneumococcal vaccine or have a concurrent underlying immunodeficiency.
Recommendation 4.4.1 is confusing to how many doses of meningococcal ACYW conjugate vaccine to give for children 2 months to less than 12 months	2 doses given 2 months apart, 1 booster at 12-15 months. A table in the appendix has been created for schedules of all vaccines outlined in the document.
Recommendation 4.3.1 refers to only children 2 and older what about the children under 2 years	Children under 2 years will be captured with routine childhood vaccinations.
Are both the live and dead influenza vaccines acceptable for use in this population	A comment has been added that live vaccine is contraindicated in immunocompromised children.
The vaccine schedule tables in appendix A are confusing	Individual tables have been created for pneumococcal, meningococcal, Hib and influenza vaccine along with an antibiotic prophylaxis table.
The preprinted order is confusing as included information for both asplenia/hyposplenia and sickle cell.	The preprinted order has been redesigned and only includes asplenia/hyposplenia information and not sickle cell information.
The preprinted order is confusing in regards to treatment of a child by age, whether they have meningitis and if they have a penicillin allergy	The preprinted order has been redesigned to make clear which antibiotics to give when.
The danger signs of infection should be listed in the parent/patient information	Have been added
The parent/patient information seems not to be at a grade 6 or less level	Reviewed at a grade 6 level
Define hyposplenia	It is defined as reduced splenic function and it is felt that any further judgement should be on the part of the physician caring for the child
Please add pharmacist to who should know that my child is at increased risk of infection	Done

Comment	Response
On the vaccination record add polysaccharide to pneumococcal booster	Done
Under research gap summary add how to improve compliance with recommendations of this guideline	Done
List qualifications of all acknowledged	Done
Remove trade mark from MenC vaccine as this is not a brand name vaccine	Removed and MenC represented as meningococcal conjugate C vaccine
Spelman 2008 suggests using erythromycin 250 mg per dose once daily for children allergic to penicillin.	Agree and added
Perhaps the word evidence of mycoplasma should be replaced with suspicion	Done
Vancomycin and ibuprofen dosing is different than the IWK formulary	Ibuprofen has been removed from the preprinted orders and the vancomycin dosing is within range so not going to change.
Recommendation 4.3.4 should say 5 years post-splenectomy and 3 years post-splenectomy	A table has been developed to outline the pneumococcal schedule. The 5 years and 3 years refers to the time of the previous vaccinations
On the preprinted order culture any clinically indicated site as follows....why just stool and NPA	The redesigned preprinted order provides options for sites to culture. This population is at risk for meningitis and mycoplasma so an LP and throat swab is included.
Explanation of this statement: The purpose of these recommendations is to provide clinical institutions and other organizations with a framework on which to build their own institutional protocols and to encourage standardization of protocols across regions to enhance consistency of care for patients and families.	This is a guideline and enforcement of the use of these recommendations is not possible. The hope is that all institutions will follow the recommendations in this document in the spirit of providing consistent best practice care to families with asplenia and hyposplenia.

6. Plan for Scheduled Review and Update

The APPHON/ROHPPA Guideline Committee will review this guideline every 3 years and at any time if significant information becomes available.

7. Implementation Considerations

The guideline will be circulated to the APPHON/ROHPPA centres providing pediatric hematology/oncology care for feedback prior to finalization of the guideline. This is an essential step to identify and address concerns and build consensus. This will also allow us to identify center specific barriers to guideline implementation and develop multi-faceted implementation strategies targeting these barriers to change. The aspect most likely to cause difficulty in implementation is the availability and financial burden of some of the recommended vaccines (ex. pneumococcal conjugate vaccine and meningococcal conjugate ACYW menveo). Consequently, administrators of health care institutions, insurance companies and pharmacies will be targeted with educational interventions in implementation of this guideline.

It will also be essential to communicate the recommendations to physicians, nurses and pharmacists at the various APPHON/ROHPPA sites. To accomplish this knowledge transfer, numerous strategies including educational interventions, monitoring and feedback and collaborative care with pharmacists will be employed. We will identify key stakeholders at the various APPHON/ROHPPA hospital sites to conduct small group sessions to disseminate the information to other physicians, nurses and pharmacists with the goal of incorporating these recommendations into protocols.

8. Acknowledgements

The expertise of Tim Ruggles (Dalhousie University Librarian) and Darlene Chapman (IWK Librarian) in conducting the guideline and literature searches is gratefully acknowledged as is the participation of Ben Joudrie (Pharmacy Student) in reviewing literature.

8.1 Panel Members

The Guideline Development Panel included:

- Tamara MacDonald, Clinical Pharmacy Specialist
- Joanne Langley, Pediatric Infectious Disease Specialist
- Vicky Price, Pediatric Hematologist/Oncologist
- Carol Digout, Executive Director, APPHON
- Cathie Watson, MHSc RN, Levels of Care Coordinator, APPHON

The individuals involved in the development of this guideline had no conflicts of interest with respect to the development of the guideline. The guideline was developed independently from any funding body other than listed below.

8.2 Funding Sources

APPHON/ROHPPA (Atlantic Provinces Pediatric Hematology Oncology Network) - **All work produced by the APPHON/ROHPPA Guidelines Committee is editorially independent of its funding agencies.**

8.3 Copyright

9. Disclaimer

The information contained in this document was prepared with care. However, any application of this material is expected to be based on judicious independent medical assessment in the context of individual clinical circumstances or with the input of a qualified clinician. The APPHON/ROHPPA Guidelines Committee does not make any guarantees of any kind whatsoever with respect to the content or use or application of this guideline. The APPHON/ROHPPA Guidelines Committee disclaims any responsibility for the application or use of this guideline.

10. Appendix A – Vaccine Schedules and antibiotic prophylaxis for both healthcare professionals and families

Recommendations for vaccines pre and post-splenectomy with pneumococcal, meningococcal, Haemophilus influenza type B and influenza vaccines. All other routine immunizations should also be kept up to date.

Vaccines **should** be completed 14 days prior to splenectomy. If this is not possible vaccines should be given 14 days after splenectomy. If compliance after discharge is not assured then vaccines should be given before discharge from the hospital even if less than 14 days has elapsed since splenectomy.

Table 1 - Pneumococcal Vaccines

Age		Pneumococcal conjugate vaccine (PCV)		Pneumococcal polysaccharide vaccine (PPV23)		
		Primary Course	Booster	1st dose	Booster	
					11 years or older at time of 1° vaccination	10 years or less at time of 1° vaccination
Less than 7 months		3 doses, minimum 1 month apart	1 dose at 12-15 months of age			
7-11 months	1° series complete		1 dose at 12 -15 months of age			
	No previous doses	2 doses, 1 month apart	1 dose at 12-15 months of age			
12-23 months	1° series complete		1 dose at diagnosis			
	No previous doses	1 dose	1 dose (≥2 months after last dose)			
2-5 years	1° series complete		1 dose at diagnosis	1 dose	1 dose 5 years after the previous dose	1 dose 3 years after the previous dose
	No previous doses	1 dose	1 dose (≥ 2 months after last dose)			
More than 5 years			1 dose			

Table 2 - Meningococcal C and ACYW Vaccines

Age		4 valent Meningococcal Conjugate Vaccine ACYW Menveo or Menactra*				
		1° course	Booster at 12-15 months	Booster		Booster dose every 5 years
				6 yrs and under	7 yrs and older	
2 -12 months		**2-3 doses, 2 months apart**	**1 dose**	**1 dose, 3-5 yrs after last dose**	**1 dose, 5 yrs after last dose**	**1 dose 5 yearly**
Greater than 12 months to 23 months	1° course complete	2 doses, 2 months apart		1 dose, 3-5 yrs after last dose	1 dose, 5 yrs after last dose	1 dose 5 yearly
	No previous doses	1 dose of MenC, followed by 2 doses of ACYW				
2 years and older	1° course complete	1 dose		1 dose, 3-5 yrs after last dose	1 dose, 5 yrs after last dose	1 dose 5 yearly
	No previous doses	1 dose of MenC, followed by 1 dose of ACYW**				

*unless otherwise indicated all doses are to be given as Menveo™ for children under 2 years and Menveo™ or Menactra™ for children 2 years and older.
****MenC and ACYW vaccines should be given a minimum of 8 weeks apart.

Menactra™ (conjugate ACYW) may replace MenC (conjugate C) for the serogroup C coverage, when more information about immune response to the C component of Menactra™ becomes available. Until that time, we recommend both vaccines. Menveo™ (conjugate ACYW) has replaced MenC for the serogroup C coverage in infants vaccinated with Menveo™ from birth. For children greater than 1 year at time of receipt of first dose of Menveo™ should receive a dose of MenC to provide added protection from serogroup C.

Table 3 - Haemophilus influenza type B (Hib) vaccines

Age		Primary course	Booster
Less than 7 months		3 doses, 2 months apart	1 dose at 12 months of age
7 to 12 months	No previous vaccination	3 doses, 2 months apart	1 dose at 12 months of age or ≥2 months after last dose whichever is later
	1° course complete		1 dose at 12 months of age
13 months to less than 5 years	No previous vaccination		1 dose, minimum 2 months after last dose
	1° course complete	2 doses, 2 months apart	
5 years and older (regardless of previous vaccination)			1 dose

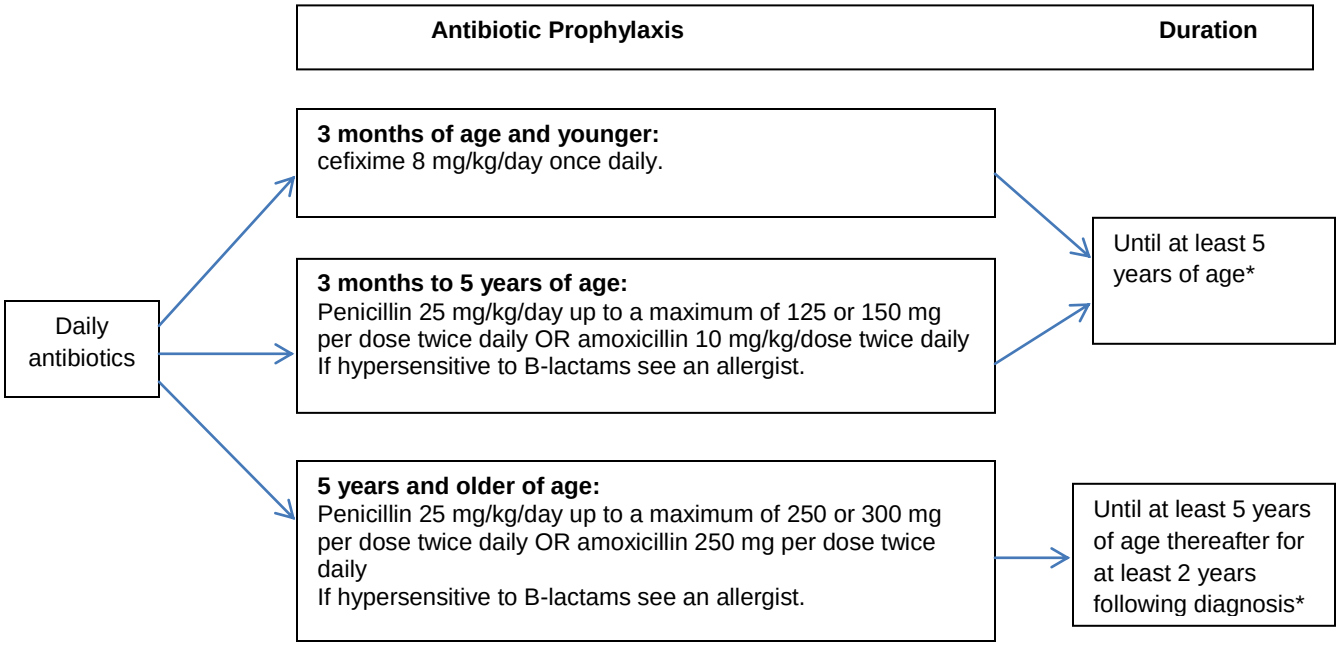
Infants should be immunized with H. influenzae type b according to regional schedule. Those 5 years and older should receive 1 dose of H.influenzae type b regardless of prior vaccination history.

Table 4 - Influenza vaccines

Age	Number of primary doses	Booster
6 months to 8 years	2 doses (minimum 1 month apart) in the first year of receiving the influenza vaccine for all children less than 9 years	1 dose annually
9 years and older	1 dose	1 dose annually

Live vaccine is contraindicated in an immunocompromised child.

Table 5 - Antibiotic prophylaxis



*High risk children should receive life-long antibiotic prophylaxis.

11. Appendix B – Information and Tools for Health Professionals

ASPLENIA/HYPOSPLENIA FEVER ORDERS *Adapted with permission from IWK Health Centre*

Patient: _____

Age _____ Wt:_____kg Date of Wt: (dd/mm/yyyy) _____

Allergies: _____

The following orders will be carried out by a licensed healthcare professional **ONLY ON THE AUTHORITY OF AN APPROVED PRESCRIBER. Where choice occurs, check as appropriate.**

Refer to APPHON Guidelines for the prevention and empiric therapy of bacterial infections for children with asplenia and hyposplenia: Infant less than 1 month - refer to IWK Neonate Drug Dosing Guidelines.

Required Evaluations	Daily CBC, Diff Daily Na, K, Cl, BUN, Creatinine Blood cultures prior to administration of antibiotics if possible
	Please check as appropriate
Optional Evaluations	□ Urinalysis □ Urine Culture □ NP (PCR) swab for □ Influenza, □ RSV, □ Adenovirus, □ Other _____ □ Throat swab for mycoplasma □ Chest X-ray □ LP if suspicion of meningitis and if patient is hemodynamically stable □ Other: _____
Vital Signs	Every hour until stable, then q4h and within 30 minutes prior to leaving the hospital

Antibiotics should be started within 1 hour of reaching the hospital. Do NOT wait for CBC results before starting antibiotics.

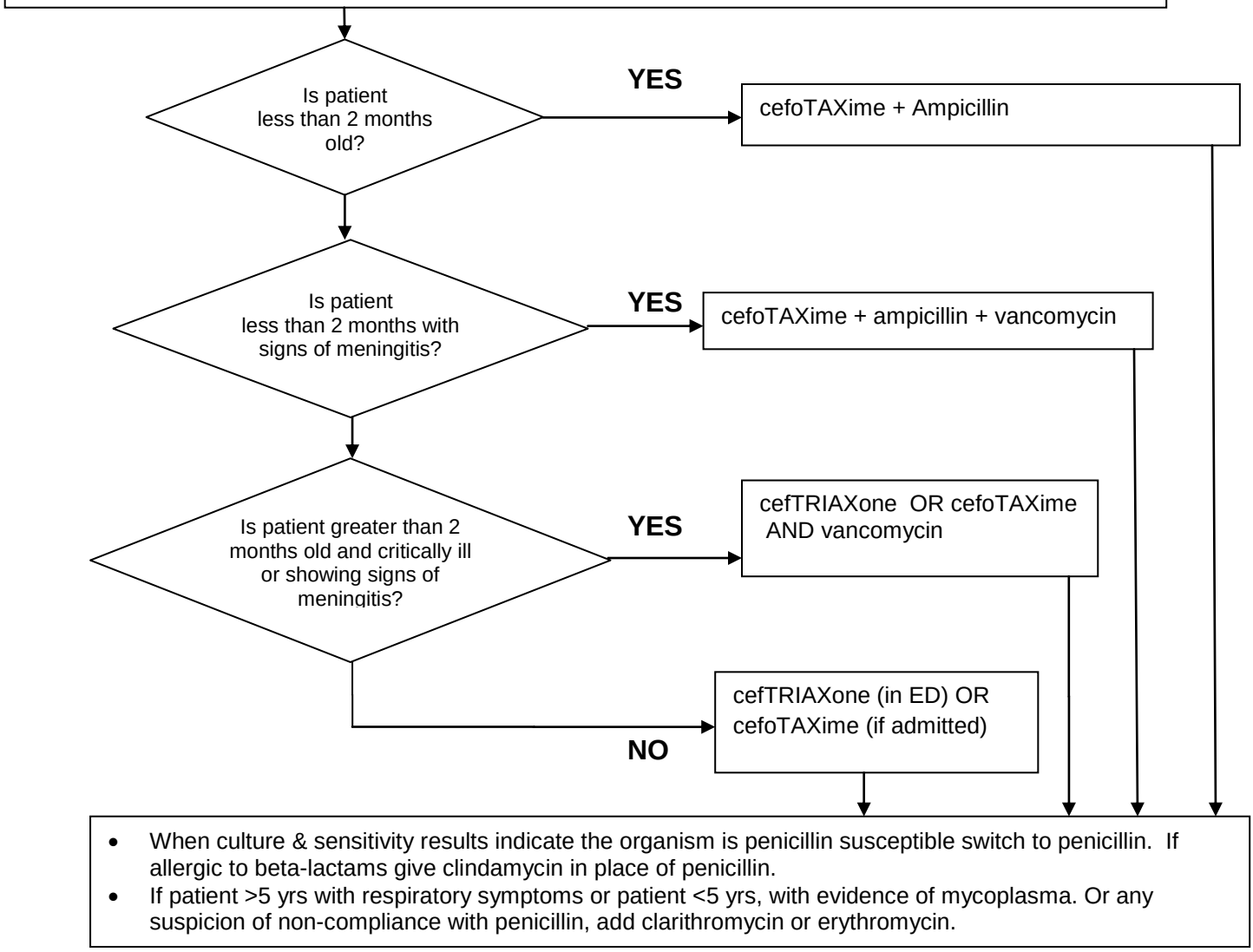
If patient has had a confirmed anaphylactic reaction to beta-lactam antibiotics consult Infectious Diseases. NEVER delay treatment due to an allergy but be prepared to treat a reaction.

	Treatment
Hydration	IV D5W + 0.9% NaCl at 100 mL/m^2/hour = _____ mL/hour (up to 150 ml/hour) or oral equivalent
□ Infant 1 - 2 months	Ampicillin_____mg IV q6h (100-200 mg/kg/24h, maximum 4 g/24h) AND
	cefoTAXime_____mg IV q8h (100-200 mg/kg/24h, maximum 2g/dose and 12 g/24h)
□ Infant 1 - 2 months with suspicion of meningitis	Ampicillin_____ mg IV q6h (200-400 mg/kg/24h, maximum 12 g/24h) AND
	cefoTAXime_____mg IV q8h (200 mg/kg/24h, maximum 2 g/dose and 12 g/24h)
	□If CSF shows positive gram cocci ADD Vancomycin_____ mg IV q6h (50 mg/kg/24h, maximum 1 g/dose and maximum 4 g/24h) Drug levels pre 4th or 5th dose (target 5-15 micrograms/mL)
□ Infant and child greater than 2 months	In emergency □cefTRIAXone_____mg IV q24h (100 mg/kg/24h, maximum 2 g/dose)
	If admitted □cefoTAXime_____mg IV q8h (100-200 mg/kg/24h, maximum 2g/dose and 12 g/24h)
	□ If suspect meningitis ADD Vancomycin_____ mg IV q6h (50 mg/kg/24h, maximum 1 g/dose and maximum 4 g/24h) Drug levels pre 4th or 5th dose (target 5-15 micrograms/mL)
□ If patient is suspected to have mycoplasma ADD Clarithromycin_____ mg PO q12h (15 mg/kg/24h, maximum 500 mg/dose)	

_____	_____	_____	_____
DATE (dd/mm/yyyy)	Time (24hr/hh:mm)	Prescriber Signature	Printed Surname/Registration#
_____	_____	_____	_____
DATE (dd/mm/yyyy)	Time (24hr/hh:mm)	Verified By (Signature)	Printed Surname

Algorithm for the Management of Asplenia Patients with Fever or Acute Illness

- Immediate assessment to determine if patient has focal point of infection, example meningitis etc.
- Appropriate cultures, including a blood culture before antibiotics if possible.
- Usual organisms include: *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*, Salmonella and *Escherichia coli.*
- Early administration of parenteral antibiotics (within 60 minutes of presentation).
- Stop prophylactic penicillin.
- Close observation for 6-12 hours even if a viral etiology is suspected



- When culture & sensitivity results indicate the organism is penicillin susceptible switch to penicillin. If allergic to beta-lactams give clindamycin in place of penicillin.
- If patient >5 yrs with respiratory symptoms or patient <5 yrs, with evidence of mycoplasma. Or any suspicion of non-compliance with penicillin, add clarithromycin or erythromycin.

* Where intermediate of high penicillin-resistant penumococci are prevalent, use a combination cefoTAXime + vancomycin. If treated with vancomycin, adjust dosage if abnormal renal function and with levels.
Local infections, example tonsillitis and impetigo, can be treated with penicillin; otitis media with amoxicillin.
Antibiotic treatment should be modified depending on culture results.

Antibiotic dosing:

- 2 month old - vancomycin 50 mg/kg/24 h IV q6h (maximum 1 g/dose; 4 g/24 h), cefTRIAXone 100 mg/kg/24 h IV q12-24h (maximum 2g/dose), cefoTAXime 100-200 mg/kg/24 h IV q8h (maximum 2g/dose and 12 g/24 h).
- Clarithromycin 15 mg/kg/24 h PO q12h (maximum 500 mg/dose).
- Erythromycin 40 mg/kg/24 h IV q6h (maximum 4 g/24 h).
- Clindamycin 40 mg/kg/24 h IV q8h (maximum 4.8 g/24 h).

If patient has a confirmed anaphylactic penicillin reaction, consult ID. Possible alternatives include meropenem.
NEVER delay treatment due to an allergy BUT be prepared to treat reaction ***Adapted with permission from IWK Health Centre***

12. ***Appendix C – Information for Families***

ASPLENIA/HYPOSPLENIA - Parent/Patient Information:
The spleen is a large organ close to the stomach on the left side of the body. The spleen's most important job is to help protect the body from infection. It does this by filtering bacteria (germs that cause infection) out of the blood. The spleen usually destroys these germs before they can cause serious infection. Asplenia means that the spleen is not there (has been taken out because of an accident or some other medical problem), or hyposplenia where the spleen is still there but does not work properly, for example in a disease called sickle-cell anemia.

Children with asplenia and hyposplenia have a higher chance of getting infections caused by certain kinds of bacteria than children who have a healthy spleen. One of the most important bacteria the spleen removes is called *Streptococcus*. If the spleen is not able to get rid of these bacteria then they can multiply in the blood stream and very quickly cause severe infection.

It is important that children with asplenia or hyposplenia (or their families) know the following information:

- all recommended vaccinations must be received to decrease the risk of serious infection;
- if your child has been instructed by a health care professional to take an antibiotic daily, you should ensure this happens to help prevent infection;
- danger signs to look for that might mean an infection is starting;
  - ❖ Fever and shaking chills or, alternatively, a very low body temperature
  - ❖ Muscle aches
  - ❖ Generalized weakness
  - ❖ Decreased urination
  - ❖ Rapid pulse
  - ❖ Rapid breathing
  - ❖ Nausea and vomiting
  - ❖ Diarrhea
- that they should see a doctor quickly if the child develops a fever;
- that if the child cannot be quickly seen by a doctor, he/she should immediately take a dose of penicillin (or other antibiotic if allergic to penicillin);
- the child should wear a medical alert bracelet or carry a wallet card.

Other important information for children with asplenia or hyposplenia and their families:

- the risk of serious infection lasts for a lifetime;
- serious infections may start from a scratch or wound which breaks the skin, or from animal bites, even by dogs or cats, because of the kind of bacteria they have in their mouths;
- serious infections may also be caused by tick bites;
- bites from mosquitoes that carry malaria can cause serious infections;

- the risk of serious infection is related to the cause of asplenia/hyposplenia. The risk is low (less than 1%) if the spleen was removed because of an accident or because the spleen was destroying blood cells. The risk of infection is higher (about 10%) if the spleen was taken out because of leukemia or lymphoma, or if the spleen works poorly because of sickle cell anemia;
- what may seem like minor signs of infection could mean a very serious infection has started;
- an infection can get much worse, and may even cause death, in a very short time (within hours);
- daily treatment with antibiotics (called prophylaxis) is extremely important to decrease the risk of infections;
- parents/patients should always carry a supply of penicillin with them when traveling;
- parents/patients should keep an updated supply of penicillin in the home or at school if access to a hospital or clinic is not available within an hour;
- see the *Question & Answer* section for other ways to decrease infection.

Common Questions and Answers:

If my child develops a fever, what should I do?

- call your family doctor or pediatrician immediately ;
- if your child's doctor is not available right away, give your child a dose of penicillin and then take him/her to the nearest hospital emergency room;
- in the hospital, if an infection is suspected or seems likely, the doctor will probably take a blood sample to see if bacteria are present and causing infection and immediately start treatment with antibiotics given intravenously (into a vein).

If my child does not look well, even if she or he does not have a fever, what should I do?

- call your family doctor or pediatrician immediately;
- if your family doctor is not immediately available, give your child a dose of antibiotics and then take your child to the nearest hospital emergency department.

What are the chances that my child will develop a serious infection?

- the chance that your child will develop a serious infection is small. It is less than 1% if your child has had her/his spleen removed because of an accident or increased destruction of blood cells. It is less than 10% if your child had her/his spleen removed because of leukemia or lymphoma or if your child has sickle cell anemia. However, the chances are still much higher than those of a child with a normal spleen;
- we cannot tell which child will get a serious infection; therefore, all children with asplenia or hyposplenia need to be seen by a doctor if a fever develops.

What can I do to decrease the risk of my child getting a serious infection?

- make sure that your child takes her/his penicillin daily if they have been instructed to do so by a healthcare professional;
- make sure that your child receives the recommended vaccinations;
- whenever possible, avoid close contact with others who have an infection;
- practice good hand washing habits;
- wash any cuts and scrapes promptly;
- help your child to understand why he or she needs to be extra careful about infections.

Who should know that my child is at increased risk of infection?

- your family doctor, or pediatrician;
- your pharmacist;
- your dentist;
- your child's teacher;
- anyone who might look after your child, for example grandparents, day-care workers, babysitters, etc;
- a medical alert bracelet or wallet card is important to make sure the needed information is available if your child becomes ill or is in an accident.

Medical Alert
Asplenic/Hyposplenic Patient

Patient Name:

_____

Physician Name:

_____

Physician Phone:

_____

Patient is at risk of potentially fatal, overwhelming infections. Medical attention required for:

- Signs of infection- fever >38.3°C, sore throat, chills, and unexplained cough.
- Animal and tick bites.

Vaccination Record

Patient has received the following vaccinations:

□ **Meningococcal C conjugate**
Date given: _____

□ **Meningococcal ACYW-135 conjugate**
Date given: _____

□ **Pneumococcal conjugate**
Date given: _____

□ **Pneumococcal polysaccharide**
Date given: _____

□ **Pneumoccal polysaccharide booster**
Date due: □ 3 years or □ 5 years after initial vaccine
Date given: _____

□ **Hib conjugate vaccine**
Date given: _____

13. ***Appendix D – Research Gap Summary***

1) Schedule of booster vaccine doses:

- What is the best schedule of booster doses for *H.influenzae*, pneumococcal and meningococcal vaccines?

2) Antibiotic treatment of fever and/or OPSI:

- What is the best antibiotic choice for the different ages of children who present with fever who are asplenic or hyposplenic?

3) Alternatives for allergic persons:

- What is the best antibiotic option for penicillin allergic persons for prophylaxis and treatment?

4) Protective titres:

- What is the level of antibodies required to provide protection against infection in asplenic or hyposplenic persons?

5) Longitudinal studies:

- There is a need for more longitudinal studies looking at risk of death in non-vaccinated vs. vaccinated persons with asplenia or hyposplenia.

6) Compliance with recommendations:

- Determine break points of where recommendations are not followed.

14. *Appendix E – Classification of Levels and Quality of Evidence and Strength of Recommendations*

Source Guideline Classification
Current Guideline Classification (US Agency for Health Care Policy and Research)
Grades for recommendations

A. Requires at least one randomized controlled trial, as part of the body of literature of overall good quality and consistency addressing the specific recommendations.

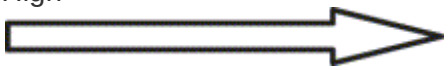
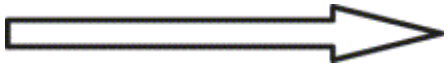
B. Requires the availability of well-conducted clinical studies but no randomized clinical trials on topic of recommendation.

C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality.

Grades for recommendations for current guideline
Quality of Evidence

Quality level	Current definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

A summary of GRADE's approach to rating quality of evidence

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomized trials	High 	Risk of Bias −1 Serious −2 Very serious Inconsistency −1 Serious −2 Very serious Indirectness −1 Serious −2 Very serious Imprecision −1 Serious −2 Very serious Publication bias −1 Likely −2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible residual confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	High (four plus: ⊕⊕⊕⊕)
				Moderate (three plus: ⊕⊕⊕○)
Observational studies	Low 			Low (two plus: ⊕⊕○○)
				Very low (one plus: ⊕○○○)

Strength of Recommendations

TABLE 1 Interpretation of strong and weak/conditional recommendations

Implications	Strong recommendation "we recommend…"	Conditional recommendation "we suggest…"
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

15. *Appendix F – Guideline and Literature Search Strategy*

Search Strategy

In March 2011, the APPHON/ROHPPA Guidelines Panel conducted a comprehensive literature review and environmental scan to identify Guidelines and Standards specific to the management and prevention of infection in children with asplenia and hyposplenia. To ensure the currency of this list, a Librarian Research Consultant used the following search strategy to identify guidelines and standards. This search was updated in May 2013:

1. Review of scientific literature sources using empirical databases - PubMed, Medline, CINAHL were systematically searched by a Research Consultant using the following search terms:
   PubMed, Medline and CINAHL Search terms: splenectomy, asplenia, hyposplenia combined with terms of infection, guideline or practice guideline, recommendations, consensus statements, systematic reviews and meta-analyses.
2. Review of grey literature sources such as annual reports or publications of organizations as identified on the world-wide web - The internet search engine utilized was Google Scholar. Search terms included: splenectomy, asplenia, hyposplenia paired with terms of infection, guidelines and standards, recommendations, consensus statements, systematic reviews and meta-analyses
3. Review of local, provincial, national and international databases -
   a) All hematology professional associations and organizations for asplenia guidelines.
   b) International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development.

Inclusion/Exclusion Criteria

Inclusion:

1. Guidelines focused on clinical practice of practitioners relevant to **asplenia management** for patients and their families**.**
   a. Clinical practice guidelines: those specific to situations in which clinicians are making decisions about direct patient care.
   b. Best practice guidelines: those that identify the best choice from a range of appropriate health care options, as defined by a consensus of experts following review of relevant literature using systematic review methods.
2. Published between the years 2000-2013.

Exclusion:*

1. Guidelines for which it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process (included as topic areas in appendices only).
2. Guidelines focused strictly on assessment.

*Excluded guidelines may have still been considered by the panel during the guideline development process, but were not considered for the basis of guideline adaptation.

**Note:* Preference was given to guidelines and guides to practice that based the development of substantive statements/recommendations on a review of evidence from the literature and/or were based on a source that used evidence to support the guideline development process.

Guidelines Reviewed:

Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. Davies JM, Lewis MP, Wimperis J, Rafi I, Ladhani S, Bolton-Maggs PH. British Journal of Haematology. 2011; 155(3): 308-317.
Included as source guideline.

Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). CDC and ACIP:MMWR Morb Mortal Wkly Rep 2010;59(34):1102-6.
Excluded as specific to the pneumococcal vaccine.

Meningococcal vaccines in Canada: An update. Salvadori M, Bortolussi R. Paediatr Child Health. 2011;16(8):485-6.
Excluded as specific to the meningococcal vaccine.

Update on the recommendations for the routine use of pneumococcal conjugate vaccine for infants. National Advisory Committee on Immunization (NACI). Can Commun Dis Rep. 2006. 1;32(ACS-4):1-6.
***Excluded as specific to the pneumococcal vaccine*.**

Post-splenectomy infection – strategies for prevention in general practice. Jones P et al. Aust Fam Physician 2010;39(6):383-6.
Excluded as a review not a guideline.

Antibiotics for treating community acquired pneumonia in people with sickle cell disease. Marti-Carvajal AJ, Costerno O. Cochrane Database Syst Rev 2012. 17;10.
Excluded as a systematic review and not a guideline.

Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. Hirst C, Owusu-Ofori S. Cochrane Database Syst Rev. 2012 Sep 12;9.
***Excluded as a systematic review and not a guideline*.**

Literature Search

Sources of Evidence:

- The British Committee on Standards in Haematology source guideline which included a review of the literature up until 2010;
- Randomized trials cited in relevant systematic reviews found by the search described above;
- Search of MEDLINE, EMBASE, CCTR (Cochrane Central Register of Controlled Trials) for randomized trials and systematic reviews published after 2000 done 2010 and updated in May 2013.

Inclusion/Exclusion Criteria:

- The population of interest was: children with asplenia and hyposplenia (and their families).
- A broad set of interventions and outcomes were considered eligible for the *evidence review.*

Interventions:

Assessment of antibiotic prophylaxis and vaccine needs of patient including one or more of:

- Physical (absence of OPSI, needs for physical comfort and freedom from pain)
- Informational (to inform patient/family and health professional decision making)
- Psychological (needs related to risk of OPSI)
- Practical (OPSI and mortality risks)

Specific attributes of assessment programs may also reflect sensitivity to the social and cultural context of the patient and special needs arising from social environment or general health issues.

Outcomes:

Septicemia
Overwhelming post-splenectomy infection mortality
Overall mortality
Medication toxicity
Treatment compliance
Quality of life
Cost of antibiotics and vaccines

Search Strategies

The searches were done in March 2011 for the years 2000-2011 and updated in 2013PubMed search strategy

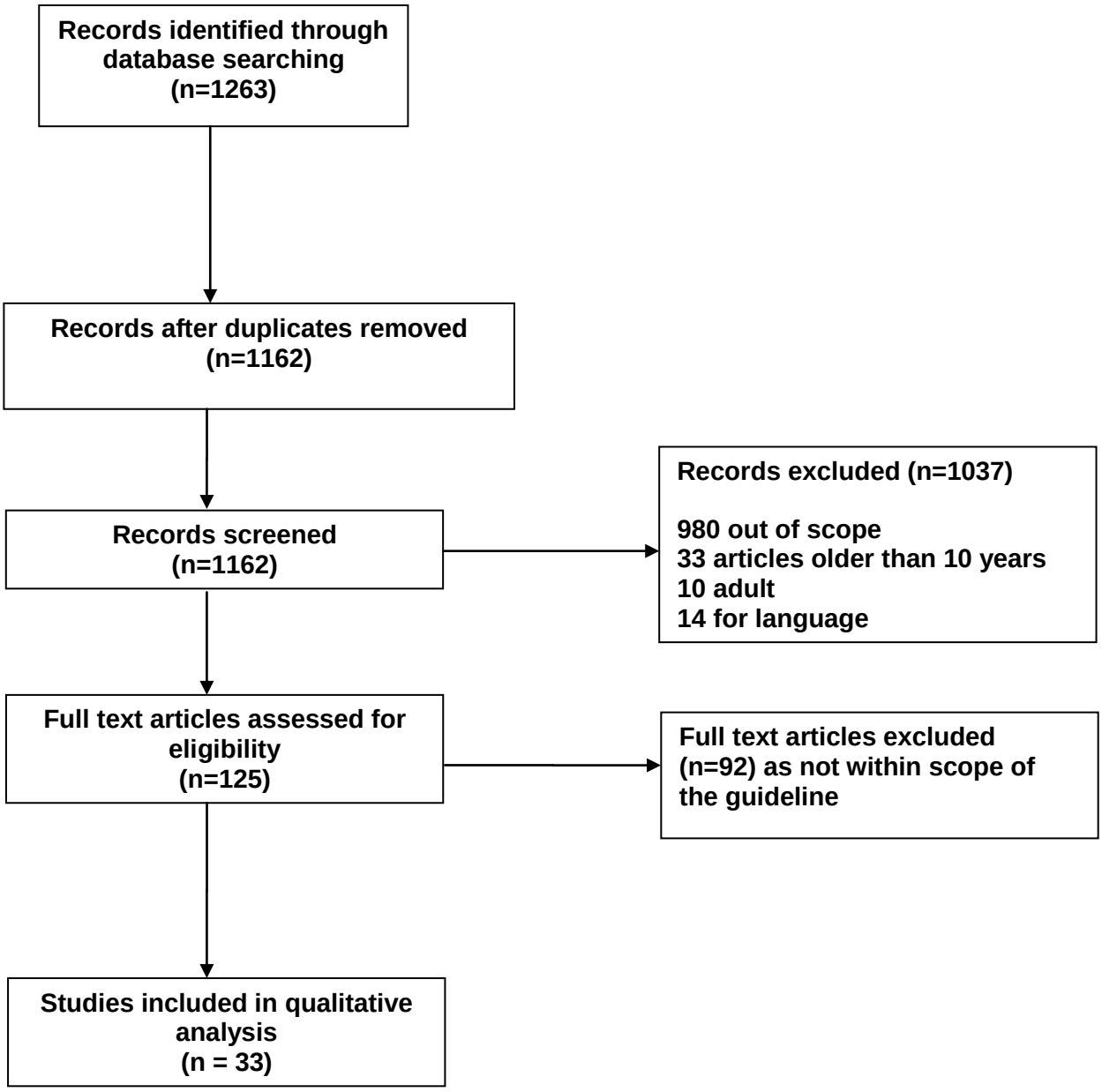
1. **"Splenectomy"[Mesh]**
2. **"Spleen"[Mesh]) OR "Splenic Diseases"[Mesh]**
3. **SPLEEN [TIAB] OR SPLENIC [TIAB] OR SPLENECTOMY [TIAB] OR ASPLENI* [TIAB] OR HYPOSPLEN* [TIAB]**
4. **#1 OR #2 OR #3**
5. **"Bacterial Infections"[Mesh]**
6. **"Streptococcus pneumoniae"[Mesh]) OR "Neisseria meningitidis"[Mesh]) OR "Haemophilus influenzae"[Mesh]**
7. **"BACTERIAL INFECTION" [TIAB] OR "BACTERIAL INFECTIONS" [TIAB]**
8. **streptococcus [TIAB] AND PNEUMONI* [TIAB]**
9. **NEISSERIA [TIAB] AND MENINGITID* [TIAB]**
10. **HAEMOPHILUS [TIAB] AND INFLUENZ* [TIAB]**
11. **HEMOPHILUS [TIAB] AND INFLUENZ* [TIAB]**
12. **#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11**
13. **CHILD OR ADOLESCEN* [TIAB] OR TEEN* [TIAB] OR YOUTH [TIAB]**
14. **#12 AND #13**
15. **Limit to last 5 years**

Embase, Cinahl, Cochrane and web of science were also searched using the above search strategies adapted to each database.

1263 articles were identified.

16. Appendix G – Websites Searched for Guidelines and Standards

Web sites checked: Google, NGC, CMA Infobase and Trip Database.



17. Appendix H – Organizational Barriers and Cost Implications

Potential organizational barriers/cost implications to applying the recommendations found in this guideline include:

- Inability to obtain vaccines.
- Costs of some vaccines.

Patient/family preferences:

- Religious or other objection to vaccines.
- Issues with adherence.

18. Appendix I – Key Review Criteria for Monitoring and/or Audit Purposes

Key review criteria for monitoring/audit include:

- Number of children with OPSI.
- Extent of adherence to guideline recommendations.

19. Appendix J – Membership lists

The APPHON/ROHPPA Asplenia Working Group:
Tamara MacDonald, PharmD
Joanne Langley, MD
Vicky Price, MD
Carol Digout

APPHON/ROHPPA Asplenia Panel:
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