4. IMMUNIZATIONS AND ANTIMICROBIAL PROPHYLAXIS

Principles

- To reduce the incidence of bacteremia and associated complications due to *S. pneumoniae, N. meningitides,* and *H. influenzae B* among children with sickle cell disease (SCD).
- To prevent hepatitis B, seasonal influenza, and *S. typhi* infections among children and adults with SCD.

Recommendations

1. General

- Advocate for *universal newborn screening* to ensure early identification of children with SCD.
- Antimicrobial prophylaxis should be given to all children with SCD.
- In addition to routine immunizations, children with SCD should receive additional vaccinations to reduce their risk of *S. pneumoniae, N. meningitidis,* hepatitis B, and seasonal influenza infections.

2. Antimicrobial Prophylaxis

- Penicillin V Potassium (VK) is the first-line choice for antimicrobial prophylaxis for children with SCD. Amoxicillin is an effective alternative in situations where penicillin VK is not available.
- The dose given is dependent on the patient's age. Tablets are preferable to suspension formulations due to their longer shelf life, and they may be crushed for younger children.

Age	Dose of Penicilin VK
≥2 months to 3 years)	125 mg twice daily
≥3 years	250 mg twice daily

- Patients with a penicillin allergy may be placed on the equivalent dose of oral cotrimoxazole or erythromycin.
- All children with SCD should receive antimicrobial prophylaxis from age 2 months to at least 5 years.
- Children with SCD who have had previous invasive pneumococcal disease such as pneumonia, septicemia, or meningitis, those whose immunizations are not up-to-date, and those who have had a surgical splenectomy should continue on penicillin prophylaxis indefinitely. Indefinite prophylaxis should also be considered for children with inconsistent compliance with antimicrobial prophylaxis.
- Patients and families must receive adequate education about the importance of antimicrobial prophylaxis to ensure compliance. They must also be counseled to seek medical attention immediately if children with SCD develop fever, regardless of oral antibiotic status.
- Special consideration should be made for continuing antimicrobial prophylaxis for individuals with SCD who have undergone hematopoietic stem-cell transplantation, solid organ transplantation, and/or have human immunodeficiency virus (HIV) infection. An Infectious Disease specialist may be consulted for these circumstances.

3. Immunizations

Children with SCD should receive all routine childhood immunizations as recommended by the current Canadian Immunization Guide.

S. pneumoniae

- ***Pneumococcal conjugate vaccine:*** Pneu-C-13 (PCV13) vaccine is the product of choice. Infants with SCD should receive three doses of PCV13 at least 8 weeks apart beginning at 2 months of age and followed by a booster at 12 to 15 months of age.

- Infants 7 to 11 months of age who have not been previously immunized against *S. pneumoniae* should receive two PCV13 doses at least 8 weeks apart and a third dose after 12 months of age, at least 8 weeks after the second dose.
- Children between 12 and 23 months of age who have not been previously immunized against *S. pneumoniae* should receive two doses of PCV13 at least 8 weeks apart.
- Children aged 24 months and over who have not been previously immunized against *S. pneumoniae* require only one dose of PCV13.
- Children who have received complete, age-appropriate vaccination with Pneu-C-7 or Pneu-C-10 (i.e., 0 doses of PCV13) should receive a single dose of PCV13 at least 8 weeks after previous PCV.
- Immunization with PCV after age-appropriate childhood vaccination is not necessary.

- ***Pneumococcal polysaccharide vaccine*** (PPV23) should initially be given at 24 months of age. PPV23 should not be administered sooner than 8 weeks after PCV13.
  - PPV23 should be re-administered to children ≥24 months of age once after the initial immunization. The interval between PPV23 immunizations will depend on the child's age at the initial immunization.
  - <11 years of age at the initial immunization: A single re-immunization with PPV23 vaccine 3 years after the initial immunization is recommended.
  - ≥11 years of age at the initial immunization: Re-immunization should take place 5 years after the initial immunization with PPV23 vaccine.
  - No more than two lifetime doses of PPV23 should be administered.
- For individuals ≥24 months of age who have not received PCV13 or PPV23, PCV13 should be given first.

N. meningitidis

- Children between 2 and 11 months of age should receive 2 or 3 doses of Menveo™ given 8 weeks apart, with another dose between 12 and 23 months of age (at least 8 weeks from the previous dose), and booster doses as below.
- Children between 12 to 23 months of age should be given 2 doses of Menveo™ at least 8 weeks apart and booster doses as below.
- Children and adults 24 months of age and older should receive 2 doses of any of the Men-C-ACYW-135 vaccines at least 8 weeks apart, followed by booster doses as below.
- Booster doses of Men-C-ACYW-135 vaccines are recommended every 3 to 5 years for those vaccinated at 6 years of age and younger, and every 5 years for those vaccinated at 7 years of age and older.
- Bexsero® (4CMenB) has been recently approved for serogroup B vaccination in Canada. The recommended dosing schedule according to the manufacturer is as follows:[24]
  - Infants should receive 3 doses of the vaccine at 2, 4, and 6 months of age. A booster should be administered between 12 and 23 months of age.
  - Infants between 6 and 11 months of age who have not received Bexsero® should receive 2 doses of the vaccine ≥2 months apart. A booster should be administered between 12 and 23 months of age, and 2 months or more from the preceding dose.
  - Children between 12 and 23 months of age should receive 2 doses of the vaccine at least 2 months apart. A booster dose should be administered between 12 and 23 months after the primary series.
  - Children between 2 and 10 years of age should receive 2 doses of the vaccine at least 2 months apart. The need for a booster dose after this primary series has not been established.
  - Patients >10 to 17 years of age should receive 2 doses of the vaccine at least 1 month apart. The need for a booster dose after this primary series has not been established.

H. influenza B (Hib)

- The recommended vaccination schedule for Hib is a primary series of 3 doses given at age 2, 4, and 6 months with a booster dose at age 18 months.
- All patients 5 years of age or older who never received Hib immunization or missed one or more doses should receive one dose. Some experts recommend one additional dose of Hib vaccine for all asplenic patients over 5 years of age, even if previously fully immunized.
- Children with asplenia who present with life-threatening Hib infections should receive a Hib vaccine, as the infection itself does not confer lifelong protection.

Other immunizations

- Children with SCD who are 6 months of age or older should receive the seasonal influenza vaccine each year to decrease the risk of the superimposed bacterial infections that are associated with influenza infections.
- All asplenic patients travelling to less developed areas of the world may be at risk of Salmonella infection, and should receive *Salmonella typhi* immunization.
- Children with SCD should be offered hepatitis A vaccination during infancy, according to the routine immunization schedule.
- In provinces where hepatitis B vaccine is not administered during infancy, children with SCD should receive the hepatitis B vaccination during infancy or as soon as they are identified to have SCD. The vaccine should be administered 0, 1, and 6 months apart, between ages 0 and 12 months.

Background

Children with sickle cell disease (SCD) require the same routine immunizations for vaccine preventable diseases, which are given to well children without SCD. Patients with SCD, however, are at high risk of fatal septicemia caused by polysaccharide-encapsulated organisms such as *Streptococcus pneumoniae* (Pneumococcus), *Neisseria meningitidis* (Meningococcus) and *Hemophilus influenzae* type B (Hib). An important reason for the increased predisposition to infection is the splenic dysfunction that occurs in SCD. Functional asplenia occurs in 94% of patients with sickle cell anemia (HbSS) SCD by the age of 5 years.

In the era before antimicrobial prophylaxis and routine immunization, the highest rates of bacteremia in SCD were seen in children less than 2 years old, with *Streptococcus pneumoniae* being the predominant pathogen.[1] At that time, patients with SCD had a 12.5% risk of developing septicemia or meningitis. In those with homozygous sickle cell anemia (HbSS), the risk increased to 15.2%.[2] Case-fatality ratios for sepsis and meningitis were 35% and 10%, respectively. Disease complications due to *S. pneumoniae* occurred almost exclusively among children with HbSS disease who were under the age of 5 years.

Patients with SCD are also at an increased risk of contracting blood-borne infections such as hepatitis B and C, as they may receive multiple red blood cell transfusions (*see Part I, section 2 on Transfusion*).

Preventive strategies for reducing the risk of infection include patient and family education, antibiotic prophylaxis, empiric antibiotic use for febrile episodes, and immunizations.

Streptococcus pneumoniae

Pneumococcal polysaccharide vaccines (PPV) were licensed in North America over 30 years ago. A 23-valent vaccine (Pneu-P-23) is currently available, and has been shown to increase antibody levels and reduce the incidence of invasive pneumococcal disease (IPD) in older children and adults with SCD. Its efficacy is limited in children less than 2 years of age due to poor immunogenicity.[3] Prevnar-7 is a pneumococcal conjugate vaccine that contains seven capsular polysaccharide antigens from the bacterium Streptococcus pneumoniae. It is effective against pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, and may have cross-reactivity against other serotypes, such as 6A.

More recently, the Prevnar-13 pneumococcal conjugate vaccine (PCV) has been released, and induces immunity against thirteen pneumococcal antigens. It expands upon the antigenicity of Prevnar-7 to include serotypes 1, 3, 5, 7F, 19A, and 23F. Unlike the 23-valent pneumococcal vaccine, pneumococcal conjugate vaccines elicit T cell-dependent immune responses, which result in enhanced immunogenicity among young children, including infants with SCD.[3-5] In 2007, Halasa *et al* reported a 93.4% decrease in invasive pneumococcal disease (IPD) among SCD patients aged less than 5 years following introduction of the PCV.[6] Rates of IPD also decreased among children with SCD who were aged ≥5 years, but the difference was not statistically significant (161 cases per 100,000 person-years during the pre-PCV period to 99 cases per 100,000 person-years during the post-PCV period; *P*=0.36). In a 2008 study on the efficacy of the PCV in children with SCD in a metropolitan U.S city, a 68% reduction in IPD was noted after PCV licensure.[7] Patients with SCD who are aged 2 years and older have higher antibody concentrations when given a combined schedule of both 7-valent PCV and 23-valent vaccines.[8]

The efficacy of prophylactic penicillin in preventing IPD was clearly demonstrated in the penicillin prophylaxis study (PROPS 1), which was terminated 8 months early.[9] Children with SCD who were younger than 3 years of age were enrolled in the study and randomized to receive either oral Penicillin V or placebo, twice daily. After an average of 15 months of follow up, there was an 84% reduction in infection rates, and there were no deaths from pneumococcal septicemia in the penicillin group compared with the placebo group. In 1995, the PROPS 2 trial evaluated the effect of discontinuing penicillin prophylaxis at age 5 years in children with SCD.[10] The authors concluded that children with SCD without prior severe pneumococcal disease and who had not had a splenectomy could safely stop penicillin prophylaxis at age 5 years. It is important to note, however, that, since the 1990s, there has been a marked increase in the worldwide prevalence of penicillin-resistant pneumococci. In Canada, it has been estimated that approximately 8% of *S. pneumoniae* isolates have decreased in their susceptibility to penicillin.[11] Another caveat is that it is unclear whether the risk of bacteremia is the same or increased for surgically splenectomized individuals with SCD compared with those individuals with functional asplenia alone. There are no studies that have evaluated the optimal duration of penicillin prophylaxis in surgically splenectomized patients with SCD.

Hemophilus influenzae type B (Hib)

H. influenzae is a gram-negative coccobacillus, which may be encapsulated or non-encapsulated. Encapsulated (or typeable) strains of *H. influenzae* are grouped into six different serotypes ("a" through "f") according to their polysaccharide capsule. Encapsulated strains are more likely to cause invasive disease while non-encapsulated strains usually cause milder infections. Hib is the most pathogenic of all *H. influenzae* strains, and caused 95% of invasive disease prior to the implementation of routine immunization programs.[12] Risk factors for Hib include splenic dysfunction, antibody deficiency, Inuit descent, exposure to group child care, and cochlear implantation.[12]

Hib is most prevalent in children between 2 months to 2 years of age, and occurs worldwide. In young children, Hib can cause bacterial meningitis, pneumonia, and other serious invasive infections. In countries where Hib conjugate vaccines are widely used, invasive Hib disease in children has been virtually eradicated.[13] The clinical efficacy of Hib vaccines is high, and has been estimated to be between 95% and 100%. In Canada, Hib is given routinely to all children during their primary immunization schedule.[14] Since 1988, when Hib vaccines were introduced in Canada, the overall incidence of reported Hib-related disease has decreased by 94%.[12] In Canada, there are three forms of Hib vaccines currently available. Act-HIB® is a Hib-tetanus toxoid conjugate vaccine. Pediacel® contains diphtheria and tetanus toxoids and acellular pertussis vaccine combined with inactivated poliomyelitis vaccine and Hib conjugate vaccine. Infarix hexa™ is an adsorbed vaccine containing acellular pertussis, diphtheria and tetanus toxoids, recombinant hepatitis B, inactivated poliomyelitis, and conjugated Hib vaccine.

Children with SCD under 9 years of age have a four-fold increased risk of Hib septicemia compared with children without SCD.[15] The Cooperative Study of Sickle Cell Disease (CSSCD) in the United States reported a 20% mortality from Hib bacteremia.[16] Fortunately, the Hib conjugate vaccine has been demonstrated to be highly immunogenic in infants and children with SCD.[17] In Canada, the recommendations for Hib immunization among children with SCD are the same as those for individuals with hyposplenism or asplenia (*see Immunizations section below*).[12]

Neisseria meningitidis

Virtually all forms of invasive meningococcal disease are caused by *N. meningitidis* serotypes A, B, C, Y, and W-135.[18] Invasive meningococcal infections usually present with an acute febrile illness and rapid development

of symptoms related to meningitis and/or septicemia. Meningococcemia is most often characterized by a non-blanching petechial or purpuric rash and hemodynamic collapse, which carries a high fatality rate. Among children with SCD, fatal *N. meningitidis* infections are most classically associated with disseminated intravascular coagulation (DIC).[18] Adrenal hemorrhage and adrenal venous thrombosis have also been described with severe meningococcal infections.[19]

Men-C-C and Men-C-ACYW-135 vaccines are highly effective, but due to waning immunity, a booster immunization is required during the second year of life if these meningococcal vaccines are administered during infancy.[20,21] In Canada, three monovalent conjugate meningococcal vaccines (Men-C-C) are currently in use: Meningitec®, Menjugate® and NeisVac-C®. Menactra® and Menveo™ are quadrivalent conjugate meningococcal vaccines against *N. meningitidis* serogroups A, C, Y, and W-135. Menomune is the only quadrivalent polysaccharide meningococcal vaccine (Men-P-ACYW-135) that is available for use in Canada.

According to data from the Public Health Agency of Canada, *N. meningitidis* serogroup B caused >50% of invasive meningococcal disease cases between 2002 and 2011, and is now the most prevalent serogroup in Canada.[22] In December 2013, Bexsero® (4CMenB) vaccine was approved by Health Canada for immunization against *N. meningitidis* serotype B.

Individuals who have the highest risk of invasive meningococcal disease include patients with hyposplenism or asplenia (e.g., individuals with SCD); congenital deficiencies in primary antibodies, properdin, factor D, or complement; individuals with more than one episode of invasive meningococcal disease; patients who are prescribed eculizumab; and individuals who work with *N. meningitidis*.[23] Anyone who falls into these categories should be offered immunizations against serotypes A, B, C, Y, and W-135 when available (see Table 2 below).

Table 2: Suggested Immunizations for Individuals with Sickle Cell Disease (in addition to routine immunization schedule)

S. pneumoniae		
All patients aged 2 to 11 months	PCV13	3 doses ≥8 weeks apart + additional dose between 12 to 15 months
7-11 months of age, unvaccinated	PCV13	2 doses ≥8 weeks apart + additional dose after 12 months of age, ≥8 weeks after the second dose
12-23 months of age, unvaccinated	PCV13	2 doses ≥8 weeks apart
≥24 months of age, unvaccinated	PCV13	1 dose
Unvaccinated children who have received complete vaccination with Pneu-C-7 or Pneu-C-10	PCV13	1 dose
All patients ≥24 months of age	PPV23	1 dose ≥8 weeks after PCV13
Booster		
<11 years of age at the initial immunization	PPV23	1 dose 3 years after the initial immunization with PPV23
≥11 years of age at the initial immunization	PPV23	1 dose 5 years after the initial immunization with PPV23
N. meningitidis		
All patients aged 2-11 months	Menveo™ Bexsero®	2 or 3 doses ≥8 weeks apart + additional dose between 12-23 months ≥8 weeks from previous dose
12-23 months of age, unvaccinated	Menveo™	2 doses ≥8 weeks apart
	Bexsero®	2 doses ≥8 weeks apart+ additional dose 12-23 months from previous dose
≥24 months of age, unvaccinated	Men-C-ACYW-135*	2 doses ≥8 weeks apart
2-10 years of age	Bexsero®	2 doses ≥8 weeks apart
>10-17 years of age	Bexsero®	2 doses ≥4 weeks apart

Booster		
<7 years of age at the initial immunization	Men-C-ACYW-135*	Every 3 to 5 years
≥7 years of age at the initial immunization	Men-C-ACYW-135*	Every 5 years
H. influenzae B		
All patients	Primary series	See Canadian Immunization Guide
All patients ≥5 years of age	Consider single booster dose of conjugated Hib vaccine.	
Hepatitis B		
All patients	Hepatitis B vaccine	0, 1 and 6 months apart between age 0-12 months
Hepatitis A		
All patients	Hepatitis vaccine	See Canadian Immunization Guide
Influenza		
Children aged 6 months to <9 years receiving seasonal influenza vaccine for the first time	Seasonal vaccine	2 doses ≥4 weeks apart
All patients ≥9 years of age	Seasonal vaccine	1 dose annually

* Menveo™ or Menactra®

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