



**Atlantic Provinces Pediatric Hematology/Oncology Network
Réseau d'Oncologie et Hématologie Pédiatrique des Provinces Atlantiques**

**5850/5980 University Avenue, PO Box 9700, Halifax, NS B3K 6R8
1-902-470-7429, 1-888-470-5888**

*Reviewed and approved by specialists at the IWK Health Centre, NS, and the
Janeway Children's Health and Rehabilitation Centre, NL*

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.

Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for care and Protocols for Management of Acute and Chronic Complications

Comprehensive medical care includes extensive health maintenance with appropriate prophylactic measures, parental education, psychosocial support, and medical assessment with monitoring for the development of chronic organ dysfunction. Appropriate sickle cell disease care also provides for the management of acute illness in a setting where knowledge and perspective about sickle cell disease is available and where physicians have ready access to baseline information about the patient, including results of previous physical examinations, laboratory work and radiographs. Because acute illness in patients with sickle cell disease can prove rapidly life threatening, it is essential that patients have unimpeded access to physicians who have the perspective necessary to quickly recognize and treat potentially catastrophic signs and symptoms. Such care not only reduces morbidity and mortality; it reduces overall medical costs by preventing some manifestation of the disease and by limiting the severity or sequelae of others. Many acute complications can be managed safely on an outpatient basis, reducing the need for hospitalization.

This document provides information about the diagnosis of sickle cell disease, an overview of care, and protocols for the management of some of the more common acute and chronic complications. These products are intended to serve as general guidelines, and it is recognized that deviations from them will be appropriate in individual cases. It is also recognized that this manual addresses only the more common pediatric complications and should be used as a substitute for hands-on-care by providers with experience in the management of sickle cell disease.

These guidelines apply to sickle cell patients. Target users of these guidelines are all health professionals within the Atlantic Provinces caring for sickle cell children and youth.

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I. SCREENING & DIAGNOSIS

Screening

“At risk” group:

- Individuals of African, Hispanic, Middle East or East Indian descent
 - Individuals with a positive family history
- OR**
- General population at birth or prior to/with pregnancy

Testing

- Hemoglobin (Hb) electrophoresis or other modality including High Performance Liquid Chromatography (HPLC), Capillary Zone Electrophoresis (Capillaries) and Isoelectric Focusing (IEF): reliable, time consuming but should be done in everyone at risk and on cord blood sample from every newborn baby in risk population.
- Presence of sickle cells on peripheral smear: a rapid screen, but not reliable before 6 months of age and can be difficult to find/absent in some sickling phenotypes (e.g. SC).
- Hb S solubility test: rapid, not reliable before 6-9 months of age (requires greater than 20% Hb S), does not detect Hb C, not reliable with Hb less than 40 g/L. This test will not distinguish between carriers of Hb S and affected individuals.

Therefore, everyone in the “at risk” group should have Hb electrophoresis (or similar testing) done if results of screening testing are either unreliable or positive, both to confirm or rule out the presence of sickle hemoglobin and to determine the presence of other inherited hemoglobinopathies.

Hospital Emergency Rooms should keep a list of their known local sickle cell patients.

***ALL PATIENTS IN THE “AT RISK” GROUP SHOULD BE
CONSIDERED SICKLE CELL AFFECTED UNTIL
PROVEN OTHERWISE***

II. INITIAL EVALUATION (First Visit)

All children with sickle cell anemia or other sickle cell syndrome [except for isolated sickle cell trait] should see a Pediatric Hematologist *at least once*.

See Appendix 1 for **Baseline Studies at Diagnosis and Follow-up Schedule**.

See Appendix 2 for **Sickle Cell Anemia Monitoring Checklist**.

History

- Temperature, pain, cardio respiratory symptoms, fatigue, infection, jaundice
- Growth pattern, developmental milestones, school performance, vision, dental development
- Priapism
- Enuresis

Complete physical exam and emphasis on

- Growth parameters
- Temperature, pulse, BP, RR, SaO₂
- Pallor, jaundice
- Cardiac function
- Spleen, liver span
- Bone tenderness or bone abnormalities
- Pubertal development

Baseline Laboratory and Other Investigations

- CBC, differential and smear review
- Hb electrophoresis (or comparable test if not already done); family studies as appropriate
- Blood group extended red cell and phenotype (Rh, Kell Duffy, Kidd)
- PT, PTT, fibrinogen
- Reticulocyte count
- AST, ALT, Bili T/D
- BUN, Cr, Na⁺, K⁺, Cl
- Urinalysis
- ECG and echocardiogram (greater than 5 years of age)
- Abdominal ultrasound
- Chest x-ray if greater than or equal to 1 year of age
- Transcranial Doppler in patients with HbSS, HS β thal (greater than 2 years old)
- Chronic transfusion protocol: serology testing for Hep A-B-C, CMV, HIV, EBV

Immunization history

- Up to date on all routine immunizations including pneumococcal and meningococcal vaccines

Preventive measures

- Prophylactic penicillin
- Immunization: *H. influenza*, *pneumococcus*, *meningococcus*, *influenza*, *Hepatitis A* and *Hepatitis B*
- Folic acid supplementation
- Good hydration
- Avoidance of extreme temperatures
- Avoidance of very cold drinks

Patient/parent education should include (see Appendix 3) [Information must be tailored to the child's age and stage of development]

- What is sickle cell anemia?
- Signs and symptoms of anemia and effects of anemia on growth
- Possible complications of disease: infectious, thrombotic, splenic sequestration, gallstones and jaundice, pain and others
- Manifestations of these complications
- Understanding that treatments are supportive, not curative
- Preventive measures
- Genetic counseling
- How to feel the child's spleen
- Provide printed information for child and family

- Letter for emergencies
- Whom to contact in case of problem
- Application for medic-alert

Family support

- Information sources
- Introduction to interdisciplinary team members, including social work, nutritionist
- Contact phone numbers
- Known community resources

III. FOLLOW-UP

See Appendix 1 for **Baseline Studies at Diagnosis and Follow-up Schedule**.

See Appendix 2 for **Sickle Cell Anemia Monitoring Checklist**.

After initial diagnosis, perform monthly follow-up x 2 and then depending on age and severity of disease:

- Sickle cell anemia [SS] or Sickle- β^0 thalassemia [$S\beta^0$ thal]
 - less than 3 years old: every 3 to 4 months
 - 3-5 years old: every 6 months
 - greater than 5 years old: every 6 to 12 months
- Sickle-C disease [SC] or Sickle- β^+ thalassemia [$S\beta^+$ thal]
 - less than 5 years old: every 4 to 6 months
 - greater than 5 years old: every 6 to 12 months
- Homozygous Hemoglobin C disease [CC], C- β thalassemia, Hemoglobin E disease [EE]
 - No follow-up is necessary after the initial 1 or 2 visits to establish the diagnosis, document in the child's chart, inform and educate the parents and referring physician. Hemoglobin E- β^0 thalassemia should be ruled out by family studies [if possible] for patients with a predominance of Hemoglobin E.
- S-hereditary persistence of fetal hemoglobin [S-HPFH]
 - Annual visits at all ages

At each visit

- Verify compliance with medications and vaccination
- Verify understanding of the risk of complications and recognition of alarming symptoms
- Reinforce preventive measures
- Encourage adequate physical activity

IV. PREVENTIVE MEASURES

- All children 3 months and older with asplenia or hyposplenia should receive antibiotic prophylaxis with penicillin VK:
 - a) 25 mg/kg/day up to 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.
- 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
- 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.
- Children who are allergic to penicillin should see an allergist
- 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.
- Children at high risk for pneumococcal infection should receive life-long antibiotic prophylaxis.
- 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.

Table 1 - Pneumococcal Vaccines

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

Table 2 - Meningococcal Vaccines

Age		4 Valent Meningococcal Conjugate Vaccine ACYW Menveo or Menactra*				
		1 st 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 st 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 st 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 (greater than or equal to 2 months after last dose whichever is later
	1 st 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 st course complete	2 doses, 2 months apart	
5 years and older (regardless of previous vaccination)			1 dose

Infants should be immunized with H. influenza 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.

V. FEVER (EMERGENCY TO BE EVALUED AS URGENT PRIORITY)

Definition of a fever

- 37.5° C axillary
- 38.3° C oral/tympanic
- 38.5° C rectal

NB: EVERY PATIENT IN THE “AT RISK GROUP” WITHOUT A KNOWN DIAGNOSIS SHOULD BE CONSIDERED AFFECTED BY SICKLE CELL ANEMIA/DISEASE UNTIL PROVEN OTHERWISE.

1. Initial evaluation and treatment (even if a source of infection is identified on P/E): Contact Pediatrician or Pediatric Hematologist on call.
2. Type of sickle cell anemia: SS _____; S/βthal _____; SC _____; Other _____
3. Allergies _____
4. Weight: _____ Intake/output: _____
5. Vital signs: T _____ HR _____ RR _____ BP _____
6. O₂ Saturation: _____ (Notify if Sat less than 93% and give O₂ by mask)
7. P/E by physician:
 - Vital signs
 - Degree of pallor
 - Evidence of systemic or localized infection
 - Cardiopulmonary status
 - Spleen size [compared with baseline]
 - Neurologic exam
8. Blood tests STAT (even if a source of infection is identified at P/E):
 - CBC, differential, Reticulocytes
 - Blood culture
 - Urinalysis and culture
 - Throat swab for viral and mycoplasma PCR
 - Nasopharyngeal swab for C&S, other cultures as clinically indicated
 - Bun, Creat
 - Na, K, Cl
 - Blood gases
 - AST, ALT, Bili T/D
 - Repeat blood cultures at least once daily if febrile and/or if looks ill
 - Type and screen in Hb less than 85 g/L or greater than 10 g/L below normal baseline and/or decreased reticulocytes
9. LP if suspicion of meningitis and if patient is hemodynamically stable.
10. Consider evaluation for osteomyelitis
11. Start D5W +0.9% NaCl IV at 100 ml/m²/hr = _____ mL/hr (1-1½ x maintenance) give the antibiotic IV as mentioned below. Continue IV fluids for 2-3 hours. Avoid over hydration.
12. **THE ANTIBIOTIC MUST BE STARTED IN THE EMERGENCY ROOM OR CLINIC WITHIN 1 HOUR OF PRESENTATION, BEFORE THE CHEST X-RAY AND BEFORE GOING TO THE PEDIATRIC/HEMATOLOGY FLOOR, IF HOSPITALIZED.**

13. INPATIENT TREATMENT AFTER INITIAL EVALUATION AND TREATMENT

NB: BEGIN THIS PROTOCOL ONLY AFTER COMPLETION OF INVESTIGATION AND TREATMENT OF "SICKLE CELL ANEMIA AND FEVER, INITIAL EVALUATION AND TREATMENT".

Medical Assessments

- Admission on pediatric or hematology floor
- Pediatric or hematology consultation

Contact PEDIATRICIAN or HEMATOLOGIST on call as soon as patient is on the floor

- Sickle cell anemia: SS _____; S/βthal _____; SC _____; Other _____
- Normal diet (avoid cold drinks and caffeine)
- Weight _____ (_____ percentile)
- Height _____ (_____ percentile)
- Head circumference _____ cm (_____ percentile)
- Allergies: _____
- If allergic to penicillin and/or cephalosporin and/or vancomycin → infectious diseases consultation. Do not delay giving an antibiotic.
- Vital signs and O₂ saturation on admission and q2h x 24 hours, then q4h x 24 hours, then q6h.
- Notify if saturation less than 93% and give O₂ by mask to keep saturation greater than or equal to 93%.
- CBC with differential and electrolytes once daily.
- D5W + 0.9% NaCl IV at _____ mL/h (1-1½ maintenance needs).

Antibiotics

- Stop prophylactic penicillin
- Refer to algorithm for antibiotic treatment (page 12)
- If pulmonary infiltrate, refer to "Sickle Cell Anemia & Acute Chest Syndrome" Protocol

NOTE: Refer to the apphon website for pre-printed orders for the management of fever

Discharge Criteria

Patient taking medication and fluids by mouth and has been without fever for at least 24 hrs with negative cultures at 48 hrs.

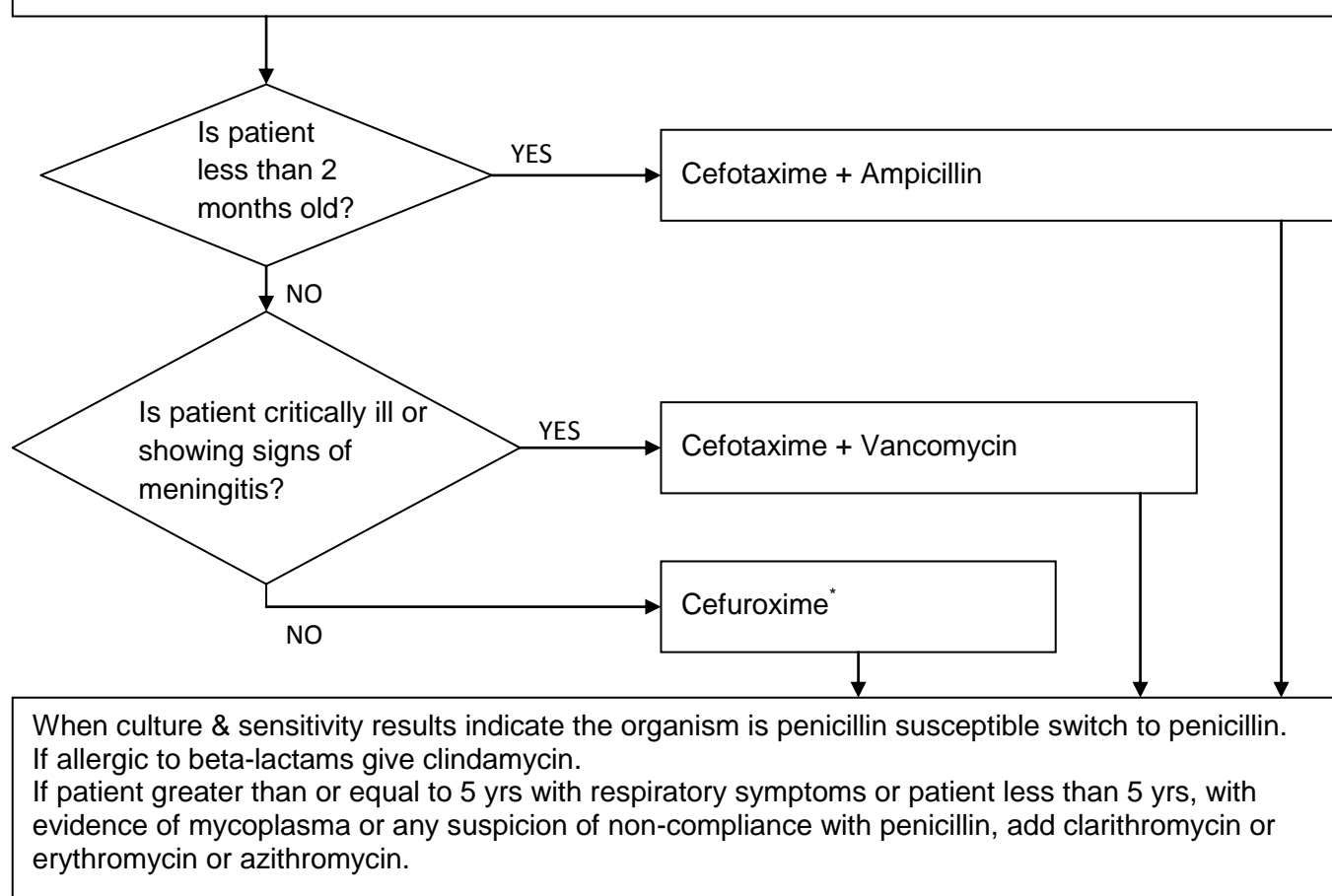
- Oral antibiotic according to physician (documented infection)
- Continue folic acid supplement
- Continue oral antibiotics until culture result available:
 - If culture is negative and child is well consider discontinuing antibiotic(s)
 - If culture is positive continue for at least 10 days from the 1st negative culture.
- When treatment with oral antibiotic ends, restart prophylactic penicillin
- Make sure patient is up-to-date on immunizations
- Follow-up:
 - Less than 5 years old: F/U in 7-10 days with CBC
 - Greater than or equal to 5 years old: F/U according to physician.

14. CRITERIA FOR OUTPATIENT TREATMENT

- Age greater than or equal to 18 months
- Recent dose[s] of prophylactic penicillin has [have] not been missed
- Mouth/ear temperature less than 39.5° C oral
- Clinically non-toxic
- No sign or symptoms suggestive of meningitis
- WBCs less than $30 \times 10^9/L$
- Absolute neutrophils count greater than $0.5 \times 10^9/L$
- Platelet counts greater than $100 \times 10^9/L$
- Hb greater than 60 g/L
- No thoracic or abdominal pain
- No pulmonary infiltrate on chest x-ray
- Saturation greater than 93% at room air
- Normal urinalysis (no UTI)
- Assured phone contact
- Assured reassessment in hospital in 18-24 hours
- Return to hospital time less than 45 minutes
- Assured patient compliance
- Not on a transfusion program for stroke
- Pediatrician or Pediatric Hematologist aware of the patient and agrees to outpatient treatment

Algorithm for the Management of Sickle Cell Patients with Fever or Acute Illness

- Immediate assessment to determine if patient has focus of infection, ex. 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 30 minutes of presentation).
- Stop prophylactic penicillin.
- Close observation for 6-12 hours even if a viral etiology is suspected.



* Where intermediate of high penicillin-resistant pneumococci are prevalent, use a combination Cefotaxime + Vancomycin.

If treated with vancomycin, adjust dosage if abnormal renal function and with levels. Local infections ex. tonsillitis and impetigo can be treated with penicillin; otitis media with amoxicillin. Antibiotic treatment should be modified depending on culture results.

Antibiotic dosing:

Greater than or equal to 2 month old - vancomycin 50 mg/kg/day IV q6h (maximum 1 g/dose; 4 g/day), cefuroxime 75-150 mg/kg/day IV q8h (maximum 6 g/day). Penicillin 250,000 units/kg/day IV q6h (maximum 24 million units/day). Clarithromycin 15 mg/kg/day PO q12h (maximum 500 mg/dose). Erythromycin 40 mg/kg/day IV q6h (maximum 4 g/day). Azithromycin 5 mg/kg/day po once daily (maximum 250 mg/day). Clindamycin 40 mg/kg/day IV q8h (maximum 4.8 g/day).

If patient has confirmed anaphylactic penicillin reaction consult ID. Possible alternatives include meropenem.

NEVER Delay treatment due to an allergy **BUT** be prepared to treat reaction.

15. OUTPATIENT TREATMENT AFTER INITIAL EVALUATION AND TREATMENT

Day 1

- Follow protocol on “Initial Evaluation and Treatment of Sickle Cell Patient and Fever”
- Give information sheet to parents
- Give scheduled appointment to parents in 12-24 hours

Day 2

- Reassess at 12-24 hours post-initial evaluation

Medical Assessment

- Vital signs and O₂ saturation
- Notify house staff if O₂ saturation less than 93%
- P/E by physician
- CBC, differential
- Verify blood culture results x 2; if positive → hospitalize
- Verify urine culture; if positive → hospitalize
- If blood and urine culture negative:
 - Treat with parenteral antibiotics following above algorithm
 - Then oral antibiotics to continue according to physician
 - If site of infection identified, specific antibiotic
 - If no site identified, antibiotic should cover *Streptococcus Pneumoniae*

Oral Antibiotics

- For child less than 2 months old
 - Cefixime 8 mg/kg/day, given once daily to twice daily (maximum 400 mg/day)
- For child greater than 2 months old
 - Cefuroxime 30 mg/kg/day BID (maximum 1 g/day) as suspension
 - OR**
 - 250 mg BID as tablets
 - OR**
 - Cefaclor 40 mg/kg/day TID (maximum 1.5 g/day)
 - OR**
 - Cefprozil 6 month to 12 years: 30 mg/kg/day BID (maximum 1 g/day); greater than 12 years of age: 250-500 mg BID
- **Note:** Patients with anaphylactic allergy to beta-lactam antibiotics may be treated with:
 - Clarithromycin 15 mg/kg/day BID (maximum 1 g/day)
 - OR**
 - Clindamycin 30 mg/kg/day q6-8h (maximum 2g/day)
- Continue oral antibiotics until culture result available:
 - If culture is negative and child is well consider discontinuing antibiotic(s)
 - If culture is positive continue for at least 10 days from the 1st negative culture.
- After completion of antibiotic, restart Penicillin prophylaxis
- Contact Pediatrician or Hematologist on call before sending child back home
- Follow-up visits after completion of antibiotics or as specified by physician

16. INFORMATION FOR PARENT WITH CHILD TREATED AS OUTPATIENT

My child has SS _____; S/βthal _____; SC _____; Other _____ type of sickle cell disease.

My child has received a first dose of _____ on _____ at _____.

Once at home:

- Take the temperature **every 4-6 hours** and note below.

Time	Temperature	Time	Temperature	Time	Temperature

- Give acetaminophen (Tylenol® or generic brand) _____ mg (15 mg/kg/dose) by mouth or rectally (suppository) every 4 hours (maximum 5 doses/24 hrs) or 4 g/day **if temperature is 38.5° C rectal or 38.3° C oral or in the ear** or child is uncomfortable
- Make sure your child drinks lots of liquid

RETURN IMMEDIATELY TO THE HOSPITAL IF YOUR CHILD HAS

- A an oral/tympanic temperature of 40° C or above
- Back pain or chest pain
- Abnormal breathing or pain on breathing
- Significant headaches
- Increasing pain
- Child becomes pale

You have an appointment on _____ at _____ with

Dr. _____, located at _____.

VI. PAIN

A. Home Management

Parent/patient information (it is necessary to know your child's latest weight in kg):

- Increase liquids
- Quiet activities, decreased distractions
- Lukewarm baths
- Moist warm towels or electric heating pad
- Massage
- Medications
 - Acetaminophen (Tylenol® or generic brand) by mouth or rectally q4h as needed (15 mg/kg/dose, maximum 5 doses/day or 4 g/day) for fever or pain.
 - Morphine (0.1 mg/kg/dose) by mouth every 4 hours as needed. Dose may be repeated after an hour if necessary, but if more than 3 doses are required in 6 hours then the physician should be contacted.

Immediately go to the Emergency Department if your child has:

- Chest pain or abnormal breathing
- Abdominal pain
- Pain with fever or redness or swelling
- Significant headache
- Sudden enlargement of the spleen
- If pain is not controlled by the measures named above, your child may be briefly hospitalized. ***Use pain score to assess your child's pain*.**

B. Inpatient Management (NOTE: Refer to Appendix 5 for pre-printed orders for pain management)

Criteria for inpatient admission include any one of the below:

- Child requires more than 2 doses of intravenous opioid within an hour.
- Fever
- Dehydration
- If child looks unwell
 - Admission on pediatric/hematology floor
 - Pediatric/hematology consultation. Contact Pediatrician or Hematologist on call when patient arrives on unit.
 - Diagnosis: Sickle cell anemia SS; S/βthal; SC; or other
 - Determine nature, location, duration and severity of pain
 - Determine analgesics already used
 - Determine associated symptoms – fever, dehydration
 - Determine previous experience with pain and successful treatments
 - Determine any side effects from analgesia, e.g. pruritis, constipation
 - Consider etiologies other than sickle pain crisis [cholecystitis, appendicitis, etc]
 - Use pain score to assess pain
 - Daily weight (percentile)
 - Initial height (percentile) and head circumference (percentile)
 - Daily intake/output
 - Normal diet (avoid cold drinks and caffeine)

- Quiet activities, encourage ambulation at patient's tolerance
- Consider physiotherapy consult

1. Nursing

- Immediate vital signs (temperature, heart rate, respiratory rate, blood pressure and O₂ saturation)
- Vital signs q2h until stable and then q4h and/or as indicated
- Visual observation, respiratory rate, level of sedation
- Repositioning q2h and/or supervised ambulation
- Continuous oxygen saturation monitoring. If O₂ saturation less than 93%, notify physician/pain team and give O₂ by mask to maintain O₂ saturation greater than or equal to 93%
- If patient is cyanotic, apneic or unresponsive, stop opioid infusion, page physician/pain team, apply oxygen and stimulate
- Assess other side effects, i.e. nausea, vomiting, itching/pruritus, urinary retention, constipation

If fever:

- Notify physician
- Refer to "Sickle Cell Anemia and Fever, Initial Evaluation and Treatment" protocol and to "Sickle Cell Anemia and Fever Inpatient Treatment" protocol

2. Investigations

- Initial CBC, reticulocyte count and differential
- Na, K, Cl, ALT, AST, BiliTD, Creat, BUN, venous/cap blood gas
- Then CBC with differential and Na, K, Cl daily x 1 day then q48h
- Initial reticulocyte count, then once daily until count improving and then q48h
- If chest pain or O₂ sat less than 93% or abnormal breathing, **STAT chest x-ray**
- If pulmonary infiltrate, refer to "Sickle Cell Anemia and Acute Chest Syndrome"
- If febrile, refer to "Sickle Cell Anemia and Fever"
- Abdominal ultrasound suggested if RUQ pain, epigastric pain
- ABO and screen if Hb less than 85 g/L or greater than 10 g/L below normal baseline and/or decreased reticulocyte count suggestive of bone marrow suppression

3. Treatment

- Hydration: IV/PO at maintenance needs (avoid over-hydration)
- Analgesia [moderate to severe pain]:
 - If acetaminophen has not been tried at home, give acetaminophen PO/PR q4h prn (15 mg/kg/dose, maximum 5 doses/day or 4 g/day). Physician to reassess acetaminophen requirements once pain controlled.
 - Give morphine IV bolus (0.05 mg/kg/dose). If necessary, repeat every 5-10 minutes until morphine infusion available.
 - Start morphine infusion as per pre-printed orders on the APPHON website.

4. On Discharge

- Continue prophylactic penicillin
- Continue folic acid
- Acetaminophen PO/PR q4h PRN or current dose (15 mg/kg/dose, maximum 5 doses/day or 4 g/day) for fever or pain
- Morphine (0.1 mg/kg/dose) PO q4h PRN or current dose

- Follow-up by phone 24 to 48 hours later
- Follow-up at clinic:
 - Less than or equal to 5 years old: 7-10 days following discharge with CBC
 - Greater than 5 years old: as recommended by physician

VII. ACTUE CHEST SYNDROME (2nd Most Common Complication; Most Common Cause of Death)

1. Symptoms of Presentation:

- | | |
|---------------------------|--------------------|
| • Fever* | • Chills |
| • Cough* | • Wheezing |
| • Chest Pain | • Hemoptysis |
| • Shortness of Breath** | • Productive Cough |
| • Pain in arms and legs** | |

* most common presentation of young children

** most common presentation of adults

2. Physical Signs

- | | |
|------------------------|------------------------------------|
| • Hypoxemia (frequent) | • Dullness to percussion <u>or</u> |
| • Pulmonary rales | • Normal chest exam |

3. Precipitating Causes

- Infections: Pneumococcus, *Mycoplasma pneumoniae*; Legionnaire’s disease; Chlamydia; Viruses – parvovirus, RSV; Influenza, para-influenza
- Hypoventilation/atelectasis – pain, opioid use
- Pulmonary embolism
- Fat embolism (due to bone ischemia) causing pulmonary vascular occlusion
- Pulmonary edema – intravenous fluids
- Bronchospasm (asthma)
- Smoking
- High altitude
- Flight in unpressured airplane
- Vasoconstrictive drugs

Begin this protocol only after completion of “Sickle Cell Anemia & Fever, Initial Evaluation and Treatment Protocol” and “Sickle Cell Anemia Inpatient Treatment Protocol”.

- Admit to pediatric or hematology ward
- Obtain a pediatric or hematologic consultation
- Call Pediatrician or Hematologist as soon as the patient arrives on the floor

1. Nursing

- Weight once daily
- Height on admission
- Quiet activities x 24 hours
- Normal diet (avoid very cold drinks and caffeine)
- Strict Intake/Output

- Vital signs q2h until stable, then q4h
- O₂ saturation by continuous pulse oxymeter x 24 h, then q4h
- If O₂ saturation less than 93%, notify doctor and give O₂ by mask to maintain O₂ saturation greater than or equal to 96%
- Incentive spirometer 10 breaths q2h while awake
- Observe for complications of analgesia, e.g. pruritis and constipation

2. Investigation

- CBC, reticulocyte count and differential count
- Na, K, Cl, ALT, ASDT, BiliT/D, Creatinine, venous/cap blood gas
- Then daily CBC with differential, Na, K, Cl once daily
- Reticulocyte count q24h until improving
- Nasopharyngeal swab for viral culture PCR and Mycoplasma PCR from throat swab
- Serology: IgM Parvovirus (if not already known positive)
- Obtain blood cultures
- PPD 5TU if indicated
- Follow-up chest x-ray AP + lateral: frequency determined by clinical findings
- Spirometer **before and after** bronchodilators on day 1 **and** on discharge
- Complete respiratory function tests on day of discharge
- If pain in lower limbs for more than 24 hours, or clinical suspicion of deep vein thrombosis, do Doppler studies
- Type and crossmatch if hemoglobin greater than 10 g/L below normal baseline or less than 85 g/L and decreased reticulocyte count

3. Treatment as per pre-printed orders on APPHON website.

4. Discharge Criteria

Taking oral fluids well, stable hemoglobin, afebrile greater than 24 hours, follow-up in place.

- Cefuroxime (75 mg/kg/day, maximum 4.5 g/day) PO TID
- Add a macrolide if mycoplasma is suspected
- Begin prophylactic penicillin again after completion of antibiotic
- Continue folic acid
- Follow-up at clinic 7-10 days with CBC and chest x-ray if indicated
- Pulmonary function tests in 2 months

VIII. SURGERY

- A Pediatrician or Hematologist must be aware of the case in advance. Children with sickle cell anemia are at risk for post-operative complications, particularly acute chest syndrome.
- The need for pre-op transfusion is determined by the Hematologist/Pediatrician in advance and on an individual basis. In patients with sickle cell anemia (SCA) transfuse red blood cells to bring the hemoglobin level to 100 g/L prior to undergoing a surgical procedure involving general anesthesia. Consult a pediatric hematologist for transfusion guidance for children with Hb SS or Sβ^othal prior to any procedure requiring general anesthesia.
- Notify blood bank in advance so that extended phenotype matched blood will be available.

- Pre-op transfusions should be considered for:
 - a) Seriously ill patients
 - b) Hb less than 15 g/L below baseline
 - c) Major surgery (including laparoscopic abdominal surgery)
 - d) History of pulmonary disease
 - e) Patient with recurrent painful crises
- Except in cases of emergencies, pre-op transfusions are scheduled 2 to 7 days prior to surgery.
- Consultation with Pediatric or Hematologist on admission.
- Consultation with respiratory physiotherapy and with anesthesiology and with surgery.

A. Preoperative preparation is collaboration between the surgical service and the sickle cell team.

1. Surgeon or staff will inform sickle cell Hematology FCC [or Pediatrician] of exact date and time of surgery as soon as case is booked
2. Hematology FCC [or Pediatrician] prepares an admit note for patient's office chart. Original is to be placed on inpatient chart. Copies will be sent in advance to Day Surgery, ENT Clinic, and/or surgeon's office as appropriate.
3. Pre or post-op hospital stays to be on hematology/oncology unit when possible.
4. All outpatient cases should be scheduled as first morning case if possible.
5. Anesthetic management:
 - Room pre-warmed and temperature must be maintained
 - Oxygenated pre-op
 - Induction and intubation with little or no hypoxic insult
 - Avoid tourniquets
 - Monitor O₂ saturation and arterial blood gases closely

B. ENT/Dental cases or Hernia repair

1. These usually are done as day surgery case with outpatient "oral hydration" pre-op, day surgery unit stay and discharged home the same day.
2. Adenoidectomy alone may be handled in this manner:
 - Parent and patient instructed to awaken the patient 4 and 8 hour before the procedure and consume a volume of clear liquids equivalent to 4 hours of maintenance fluids.
 - Patient should receive 35% O₂ by face mask postoperatively until discharged home.
 - Patient may be discharged home when cleared by anesthesia and surgical service.
 - Hematology Team may be reached at 902-470-7723 or 902-470-8888 [Hematologist on call] for additional assistance.
3. Tonsillectomy and adenectomy patients should be instructed in outpatient oral hydration as in (1) above, be admitted postoperatively for 35% oxygen by face mask, incentive spirometry q2-4h by patient/family, IV hydration at maintenance and observation for 18-24 postoperatively as in Section C-4(a-e) below.
4. Any patient with a significant history of recurrent acute chest syndrome may require preoperative transfusion as below.
5. Patients to be admitted postoperatively should be instructed in incentive spirometry by the RT during day surgery preoperative evaluation.

C. Abdominal Cases (Cholecystectomy or Splenectomy or other major surgery – Laparoscopic or Open)

1. Patient should be offered preoperative simple transfusion to hemoglobin between 90-100 g/L unless that is close to their baseline hemoglobin when no transfusion is required.
2. Patient should be admitted to the pediatric hematology unit or pediatric unit by noon on the day before surgery if a transfusion is required, or by 1500 hrs if IV hydration only. Surgery should not be done Monday or on the day following a holiday if possible.
3. IV hydration should be at maintenance starting as soon as possible after arrival.
4. Postoperative – return to pediatric hematology unit [pediatric unit] with aggressive attention to:
 - a) 35% oxygen by face mask for 18-24 hrs regardless of oxygen saturation
 - b) Incentive spirometry q2h while awake, q4h around the clock by patient/family after teaching by respiratory therapist
 - c) IV plus PO hydration at maintenance
 - d) Give morphine IV bolus (0.05 mg/kg/dose). If necessary, repeat every 5-10 minutes until morphine infusion available
 - e) Start morphine infusion as per preprinted orders on APPHON website

D. Generic peri-operative orders

Nursing

1. Weight _____
2. Height _____
3. Allergies: _____
4. Vital signs and O₂ saturation q4h
5. Reserve a bed in intensive care unit for the first 24 hours post-op (for every surgery in sickle cell anemia patient)
6. NPO from _____ (according to anesthesiologist)
7. If fever or pulmonary infiltrate, refer to appropriate protocols and notify doctor immediately.
8. Teach use of incentive spirometer

Investigation

1. CBC and differential prior to surgery on the day of surgery
2. Reticulocyte count
3. BUN, Cr
4. Na, K, Cl, blood gas
5. AST, ALT, BiliT/D
6. Chest x-ray in the 48 hours prior to surgery with report in the chart

Treatment

1. Have 2 units of PRBC extended phenotype matched, sickle-negative on hand for the surgical intervention.
2. Maintenance hydration [IV+PO] to begin at 1600 hours the day prior to surgery for major surgery. D5W + 0.9% NaCl IV if needed to maintain intake at _____ mL/h. If IV infiltrates, reinsert immediately.
3. Transfuse if Hb less than 90. Transfuse _____ mL of unit (15-18 mL/kg, trying to reach a Hb level of 100 g/L).
4. Consider hemoglobin electrophoresis to measure Hb S level prior to surgery.
5. Continue prophylactic penicillin up until NPO.

6. Continue folic acid up until NPO when it can be discontinued until patient is allowed to eat again.

Intra-operative care

1. Minimum of 50% O₂ with anesthetic, minimum of 35% O₂ irrespective of O₂ saturation post-operatively
2. Avoid hypoxemia [continuous pulse oximeter], avoid hypercapnia or hyperventilation
3. Avoid the use of tourniquets
4. Avoid hypothermia

Post-Op Care

1. Consider admission in Intensive Care Unit for at least 24 hours
2. Vital signs q1h x _____ then q4h
3. Aggressive pain management
4. O₂ by nasal cannula at least 2L or by face mask at 35% for 18-24 hr regardless of pulse oximetry. Pulse oximetry for 18-24 hr to ensure that supplemental O₂ sufficient to keep saturation greater than 96%.
5. PO intake + D5W + 0.9% NaCl IV at _____ mL/h (maintenance) x 24 hours, then re-evaluate. Avoid excessive hydration which may precipitate acute chest syndrome.
6. Incentive spirometry – 10 breaths q2h while awake; q4h @ clock. Encourage early ambulation and activity.
7. CBC and differential STAT and once daily
8. Blood gases STAT and once daily
9. Respiratory physiotherapy
10. Where applicable, discharge from Intensive Care Unit after 24 hours according to physician and then observation on pediatric floor for a minimum of 48 hours
11. Prophylactic penicillin to start again at end of IV antibiotics
12. Folic acid to start as soon as patient is allowed to eat
13. Avoid hypothermia

Discharge

Follow-up:

- Less than or equal to 5 years old: in 7-10 days clinic with CBC
- Greater than 5 years old: follow-up in clinic the same day as the surgery follow-up appointment

IX. ACUTE SPLENIC SEQUESTRATION

Definition

An acute illness associated with Hb 20 g/L or more below patient's baseline value with acutely enlarged spleen. Mild to moderate thrombocytopenia is often present. Reticulocytosis equal to or greater than baseline is usually present. If reticulocyte count is decreased, consider coexistent aplastic crisis (see page 23).

Consults

Hematology

Monitoring

1. Hospitalize
2. Consider ICU admission if signs of cardiovascular compromise

3. Vital signs q2h until stable, then q4h
4. CR monitor
5. Continuous pulse oximetry
6. Record I & O, daily weight
7. Serial exams (initially q2-4h) to reassess cardiovascular status and spleen size

Investigations

1. CBC with differential and reticulocyte count initially, then q4-12h depending on severity of anemia, rate of fall in Hb level, changes in spleen size.
2. Type and cross match sickle-negative RBC stat. Time permitting, consider if available extended phenotype matched RBC.
3. Blood culture, urinalysis and urine culture if febrile. Consider CSF and other cultures.
4. Consider CXR if febrile or if any signs or symptoms of respiratory illness.

Fluids, General Care

1. IV + PO @ 1 x maintenance. More fluids may be needed if insensible losses are increased (e.g. persistent fever) or to support intravascular volume before transfusion.
2. Incentive spirometry – 10 breaths q2h when awake if on parenteral narcotics.

Medication/Treatment

1. RBC transfusion 10 mL/kg for Hb less than 40-50 g/L and/or signs of cardiovascular compromise. ***In severe cases, urgent initiation of transfusion prior to inpatient admission may be life-saving.*** Aim for Hb of 80-90 g/L.
2. If febrile, refer to section on fever for initiation and dosing of antibiotics.
3. If applicable, continue prophylactic penicillin. Penicillin prophylaxis should be discontinued while patient is receiving broad-spectrum antibiotics.
4. O₂ by nasal cannula or face mask if needed to keep pulse O₂ greater than or equal to 96%. The etiology of a new or increasing supplemental O₂ requirement should be investigated. O₂ @ 2 liters by nasal cannula or 35% by face mask can be given empirically for the severely anemic child who is to receive RBC transfusions.
5. Acetaminophen (15 mg/kg/day, maximum 5 doses/24 hrs or 4g/day) PO/PR q4h prn and/or ibuprofen (greater than or equal to 6 months: 10 mg/kg/dose, maximum 40 mg/kg/day or 2.4 g/day) PO q6-8h prn for any fever and/or mild pain. (Hyperthermia may exacerbate cardiovascular compromise with severe anemia).
6. i) Give morphine IV bolus (0.05 mg/kg/dose). If necessary, repeat every 5-10 minutes until morphine infusion available.
ii) Start morphine infusion as per preprinted orders on APPHON website.
7. See other Clinical Care Paths for vaso-occlusive pain, acute chest syndrome, Aplastic crisis, stroke, priapism, if present.

Discharge/Criteria

Acute sequestration usually resolves within 2-5 days.

1. Taking oral fluids; able to take PO medications (e.g. prophylactic penicillin) if applicable.
2. Stable hemoglobin/hematocrit and diminishing spleen size.
3. Afebrile greater than or equal to 24 hr.
4. Outpatient follow-up in place.
5. Recurrent episodes, requiring transfusion, is an indication for splenectomy if the child is greater than 2 years of age. If less than 2 years of age, consider chronic transfusions.
6. For weeks to months following episode of acute splenic sequestration, patients may have persistent splenomegaly and hyper-splenism with lower than usual Hb and platelet values.

X. APLASTIC CRISIS

Definition

An acute illness associated with Hb below patient's baseline value with a substantially decreased reticulocyte count (often less than 1%). Most cases are caused by the acute infection with human parvovirus. If acute enlargement of spleen is present, consider coexistent splenic sequestration. Aplasia is usually limited to 7-10 days, but because this may exceed the patient's mean erythrocytic survival time, profound anemia may ensue. After 7-10 days, antibody mediated viral neutralization occurs and marrow erythroid activity is resumed. At this point, nucleated RBCs are seen on the blood smear.

Consults

Hematology

Monitoring

1. Hospitalize for evidence of cardiovascular compromise, for inability to provide appropriate transfusion support as outpatient and/or for concerns about reliability of follow-up.
2. Vital signs q2h until stable, then q4h if hospitalized
3. Consider continuous pulse oximetry
4. Record I & O and daily weight
5. Where possible, determine patient's baseline Hb

Investigations

1. CBC with differential and reticulocyte count initially, then q12-24h.
2. Type and crossmatch sickle-negative RBC. Consider requesting, if available, extended phenotype matched RBCs.
3. Blood culture, urinalysis and urine culture if febrile. Consider CSF and other cultures.
4. Consider CXR if febrile or if any signs or symptoms of respiratory illness present.
5. Consider diagnostic tests for parvovirus B19 and EBV.

Fluids, General Care

1. IV + oral intake @ 1 x maintenance. More fluids may be needed if insensible losses are increased (e.g. persistent fever). Avoid excessive fluids which may precipitate congestive heart failure.
2. Contact isolation for presumed parvovirus infection (no pregnant care providers).

Medication/Treatment

1. RBC transfusions for symptomatic anemia and/or Hb less than 50 g/L with no evidence of erythroid recovery (i.e. no nucleated RBCs in peripheral blood smear and/or retic count less than 1%); usually 5-6 mL/kg over 4 hours with close observation for fluid overload. Transfusion may need to be repeated; usually transfuse 10-15 mL/kg in total per transfusion.
2. If febrile, most likely due to parvovirus infection, but still do a blood culture and follow fever section for initiation and dosing of antibiotics.
3. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
4. O₂ by nasal cannula or face mask if needed to keep pulse oxymeter greater than or equal to 96%. The etiology of a new or increasing supplemental O₂ requirement should be investigated. O₂ @ 2 liters by nasal cannula or 35% by face mask can be given empirically for the severely anemic child who is to receive RBC transfusions.

5. Acetaminophen (15 mg/kg/day, maximum 5 doses/24hrs or 4 g/day) PO/PR q4h prn and/or ibuprofen (greater than or equal to 6 months: 10 mg/kg/dose, maximum 40 mg/kg/day or 2.4 g/day) PO q6-8h prn for any fever and/or mild pain. (Hyperthermia may exacerbate cardiovascular compromise with severe anemia).
6. See other Clinical Care Paths for vaso-occlusive pain, acute chest syndrome, acute splenic sequestration, stroke, priapism, if present.
7. CBC and reticulocyte count now and again in 10-14 days on siblings or close contacts with sickle cell disease or other chronic hemolytic anemia to exclude simultaneous or sequential parvovirus infection.

Discharge Criteria

1. Taking oral fluids well and able to take PO medications (e.g. prophylactic penicillin) if applicable.
2. Adequate hemoglobin/hematocrit with reliable family and outpatient follow-up in place, including arrangements for follow-up clinic and laboratory monitoring and for additional transfusions if needed.

XI. ACUTE STROKE OR NEUROLOGIC EVENT

Consults

Hematology and Neurology.

Monitoring

1. Hospitalize, consider ICU admission
2. Vital Signs and neuro checks q2h
3. Record I & O and daily weight

Investigations

1. CBC with differential and reticulocyte count initially and as clinically indicated (compare with patient's baseline data).
2. RBC extended phenotype if not previously documented and not transfused in previous 3 months.
3. Screening coagulation profile (PT, PTT, FG).
4. Blood and urine cultures if febrile.
5. Type and crossmatch sickle-negative RBC for partial exchange transfusion (erythrocytapheresis). Consider requesting, if available, extended phenotype matched RBC.
6. Electrolytes initially and daily until stable.
7. MRI and MRA. If not immediately available, CT **without** contrast to exclude intracranial hemorrhage. CT scan may appear normal initially, only after 2-7 days post CVA will show area of infarction.
8. Consider CSF culture if febrile and no contraindication present.

Fluids, General

1. IV + PO at maintenance.

Medication/Treatment

1. Rx seizures if present
2. Rx increased intracranial pressure if present
3. O₂ by nasal cannula or face mask if needed to keep pulse O₂ greater than or equal to 96% or greater than or equal to patient's baseline value (if greater than 93%). The etiology of a new or increasing supplemental O₂ requirement should be investigated.
4. Partial exchange transfusion or erythrocytapheresis to Hb 100 g/L and Hb S (patient's RBC) less than 30% (may require transfusion medicine consult for erythrocytapheresis). Remove femoral or central venous catheter as soon as possible after exchange transfusion to reduce risk of thrombosis.
5. Simple transfusion with RBC to Hb approximately 100 g/L may be considered as an alternative to partial exchange transfusion for stable patients with Hb less than 60-70 g/L (do **not** transfuse acutely to Hb greater than 100 g/L, Hct greater than 30%).
6. Consider hemoglobin electrophoresis after partial exchange transfusion or at discharge.
7. If febrile, refer to fever section for initiation and dosing of antibiotics.
8. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broad-spectrum antibiotics.
9. See other Clinical Care Paths for pain, acute chest syndrome, acute splenic sequestration, aplastic crisis, priapism, if present.

Discharge Criteria

1. Clinically and neurologically stable greater than 24 hr after transfusions
2. Afebrile greater than 24 hour
3. Taking fluids and medication orally
4. Hematology and physical therapy follow-up organized
5. On Aspirin
6. Initiate chronic transfusion program (see page 29)

XII. PRIAPISM

Priapism is a prolonged (greater than 30 minutes) painful erection of the penis that commonly occurs in children and adolescents with sickle cell disease, often starting during the early morning hours. It occurs in two forms:

- a) stuttering episodes which last less than 2-4 hours but are often recurrent and may precede a severe episode
- b) severe episodes that last more than 2-4 hours and may eventually result in impotence

Simple maneuvers such as increasing oral fluids, taking analgesics, urination, moderate exercise, and/or taking a bath or shower may help end an episode of priapism and no further specific intervention may be required. Patients who have frequent episodes (greater than or equal to 2 within one month or greater than or equal to 4 within one year) should contact physician for evaluation. For such patients, priapism prophylaxis with pseudoephedrine 30 mg/PO at bedtime (less than 12 years) or 60 mg/PO at bedtime (greater than or equal to 12 years) should be considered. Any episode that lasts longer than 2-4 hours should be considered an emergency that requires prompt medical intervention as described below.

A. Inpatient Management of Prolonged Priapism

Consults

Hematology/Urology

1. History and emphasis on:

- Duration of current episode
- Associated symptoms – especially fever, dysuria, evidence of dehydration, or pain in other locations
- History of prior episodes of priapism, previous treatments and effectiveness.

2. Physical examination with emphasis on:

- Vital signs
- Hydration status
- Degree of pallor and cardiopulmonary status
- Genitourinary (severity of pain, any evidence of detumescence)

3. Laboratory:

- CBC with differential and reticulocyte count (compare with patient's baseline values)
- Blood cultures if febrile, refer to fever section
- Urinalysis and urine culture for history of dysuria or fever
- Type and crossmatch if extreme pallor, respiratory or neurological symptoms, or acute splenic enlargement present. Request, if available, extended phenotype matched, sickle negative RBCs

4. Treatment (discuss with patient, family and Hematologist or primary Pediatrician on-call):

1. **Never** use ice or cold packs. Sitting in a warm bath maybe helpful.
 - a. Give morphine IV bolus (0.05 mg/kg/dose). If necessary repeat every 5-10 minutes until morphine infusion available.
 - b) Start morphine infusion as per preprinted order for pain on APPHON website. Consider use of ketorolac (Toradol) 0.5 mg/kg (15 mg maximum dose) IV q6-8 hr prn for maximum of 3 days in addition to opioid analgesia if no contraindication (i.e. gastritis, ulcer, coagulopathy, or renal impairment). Do not use ibuprofen with ketorolac. Repeated doses of meperidine (Demerol) should be avoided because of the risk of seizures. Monitor pulse O₂ for patients receiving opioid analgesia.
2. Mild to moderately severe pain – acetaminophen with morphine (0.1 mg/kg/dose) PO q4h as needed.
3. Ibuprofen (greater than or equal to 6 months: 10 mg/kg/dose, maximum 40 mg/kg/day or 2.4 g/day) PO q6-8 hr prn if no contraindication (i.e. ketorolac, gastritis, ulcer, coagulopathy, or renal impairment). Limit more frequent dosing to 72 hr maximum duration.
4. Reassess pain control at least twice daily. Analgesics may be weaned as tolerated by decreasing dose, **not** by prolonging interval between doses.
5. If afebrile, refer to fever section for initiation and dosing of antibiotics.
6. If applicable, continue prophylactic penicillin. Prophylactic penicillin should be discontinued while patient is receiving broadspectrum antibiotics.
7. O₂ by nasal cannula or face mask if needed to keep pulse O₂ greater than or equal to 93% or greater than or equal to patient's baseline value (if greater than 93%). The etiology of a new or increasing supplemental O₂ requirement should be investigated.

Avoid excessive or unnecessary O₂ which may suppress the reticulocyte count and exacerbate anemia.

8. Administer one dose of PO pseudoephedrine (less than 12 yr: 30 mg, greater than or equal to 12 yr: 60 mg). Wait 2 hr if no response
9. Immediately contact urologist to perform aspiration and irrigation described below.
10. Review summary of patient's last comprehensive evaluation or seek baseline information by phone.
11. Aspiration and irrigation: the following procedure should be performed by a staff urologist or experienced urology resident **as soon as possible** for episodes that have lasted more than 4 hours from onset of erection. Conscious sedation may be appropriate for selected patients if administered by experienced staff, but usually not required.
 - The lateral side of the penis is prepped with betadine and approximately 0.5 ml of 1% lidocaine is infiltrated subcutaneously into the lateral surface of the penis and then more deeply into the tunica albuginea
 - A 23 gauge needle is inserted into the corpus cavernosum and as much blood as possible is aspirated into a dry 10 ml syringe through a three-way stopcock.
 - Another 10 ml syringe containing 1:1,000,000 solution of epinephrine (i.e. 1 ml of 1:1,000 epinephrine diluted in 1 liter of normal saline) is attached to the three-way stopcock. The corpora cavernosae are irrigated with 10 ml of the 1:1,000,000 epinephrine solution with additional blood aspirated via dry syringes until detumescence has occurred.
 - The needle is withdrawn and five minutes of firm pressure (timed by the clock) is applied by the physician doing the procedure to prevent hematoma
 - Any recurrent episode lasting greater than 2 hours should be treated with repeat aspiration and irrigation.
12. Winter shunt (spongiosum-cavernosum shunt) may be considered if priapism persists for greater than 24 hours, unresponsive to supportive care, drainage and irrigation and transfusions, but is controversial.
13. Observe for severe headache or neurological signs or symptoms. (Ischemic stroke may occur 1-10 days after onset of priapism, especially following transfusion.)
14. See other Clinic Care Paths for acute chest syndrome, acute splenic sequestration, aplastic crisis, stroke, if present.

Discharge Criteria

1. If the patient retains detumescence for greater than or equal to 1 hour, they may be discharged home with Hematologist/Urologist/primary care physician approval and a specific plan for outpatient follow-up. (complete detumescence may take 1-2 weeks)
2. Taking oral fluids well and able to take PO medications (e.g. prophylactic penicillin) if applicable.
3. Adequate pain relief on oral analgesics.
4. Afebrile greater than or equal to 24 hours
5. Resolution of any pulmonary symptoms or documentation of adequate oxygenation in room air
6. Consider starting pseudoephedrine 30 mg PO hs (less than 12 years) or 60 mg PO hs (greater than or equal to 12 years) for priapism prophylaxis.

XIII. CHOLELITHIASIS

Guideline for the management of gallstones in children with sickle cell disease

- Increased hemolysis with increased bilirubin, often results in gallstone formation
- Most evident in children with Hb SS, Hb SC and Hb SB^o thalassemia.
- Abdominal pain in children with sickle cell disease may have many causes:
 - Gallstones
 - Vaso-occlusive crisis
 - Acute hepatic crisis
 - Liver sequestration
 - Splenic sequestration
 - Acute chest syndrome
 - Cholecystitis
 - Pancreatitis
 - Appendicitis
 - Urinary tract infection
 - Pelvic inflammatory disease
- Although there are no prospective studies to address elective cholecystectomy vs. observation, elective laparoscopic cholecystectomy may be safely performed in children with SCD and should be considered at the time of gallstone diagnosis before symptoms or complications develop (see perioperative guidelines).
- Complications of gallstones include:
 - Acute cholecystitis
 - Acute cholangitis
 - Acute pancreatitis
 - Common bile duct obstruction

Treatment

- Patients with fever of 38.5° C or higher or who are in respiratory distress should be assessed immediately. Follow protocols for sickle cell anemia fever and pain.
- History and physical examination
- Investigations:
 - a) CBC and reticulocytes
 - b) Bilirubin, AST, ALT, GGT, ALP
 - c) Abdominal ultrasound
 - d) Antibiotics: for suspected cholangitis: ampicillin, gentamicin and metronidazole
 - e) If patient has beta-lactam allergy: vancomycin, gentamicin and metronidazole
 - f) Assess vitals q4h, daily fluid balance and weight
 - g) Fluids: IV and PO at maintenance. If increased insensible losses [e.g. fever or child dehydrated] give 1½ x maintenance fluids
 - h) Incentive spirometry for children greater than 4 years
 - i) Discuss all cases of suspected cholangitis with general surgery
 - j) All patients with acute cholecystitis should be admitted for monitoring, antibiotics, IV fluids and analgesics
 - k) If elective cholecystectomy is planned, it should be performed after the acute attack has subsided
 - l) Consult GI if obstruction is suspected or if LFTs abnormal compared to baseline

Discharge Criteria

- Billirubin levels returned to baseline
- Afebrile for at least 24 hours
- Taking fluids and medication orally
- Pain relief adequate with PO analgesia
- Concurrent problems resolved

XIV. CHRONIC TRANSFUSION

Overview

Some severe manifestations of sickle cell disease warrant maintenance therapy with chronic blood transfusions. The goal is to suppress erythropoiesis sufficiently and to provide enough normal blood cells to maintain the percentage of the patient's cells (i.e. hemoglobin S) at less than 30%. Experience has shown that this approach significantly reduces the risk of recurrent stroke. Such transfusions also reduce markedly the incidence of many other sickle-related complications such as vaso-occlusive pain and acute chest syndrome. In addition to preventing acute complications, chronic transfusions may prevent the progression of chronic organ damage and even reverse some pre-existing organ dysfunction. This has been shown most clearly in patients with Hb SS and functional asplenia, some of whom who improved splenic reticuloendothelial function after receiving chronic transfusions. Many children with sickle cell disease treated with chronic transfusions also experience an increased sense of well-being, with improved energy levels, exercise tolerance, growth velocity and sexual development. Thus, transfusions to chronically replace sickle cells with normal erythrocytes can be considered as a specific therapy that markedly ameliorates the disease.

Aim

Maintain Hb S less than 30% and a pre-transfusion Hb of 80-100 g/L. This is achieved by providing simple transfusions every 3-4 weeks.

Indications for chronic transfusions

1. Stroke
2. Transient ischemic attacks
3. Abnormal Transcranial Doppler (greater than 200 cm/sec x 2)
4. Severe recurrent pain episodes
5. Severe, recurrent acute chest syndrome
6. Recurrent splenic sequestration in young children
7. Severe chronic anemia with cardiac failure
8. Pulmonary hypertension

Points to be discussed with patient and parents before chronic transfusion therapy

1. Patients requiring chronic transfusion therapy should be assessed by a Pediatric Hematologist
2. Inform patient and parents of need for chronic transfusion therapy
3. Inform patient and parents of complications of transfusions: infections, delayed transfusion reactions, iron overload, chelation therapy
4. Obtain consent for transfusions before initiating therapy

Diagnostic evaluation before transfusion program

1. Blood type with extended phenotype
2. Ferritin
3. Hepatitis B and C
4. Hepatitis A and B immunization status
5. HIV status
6. CMV serology
7. Liver enzymes
8. EKG/ECHO

Investigations before each transfusion

- Height, weight, vital signs and oxygen saturation
- CBC with differential and reticulocyte count
- Hemoglobin S
- Type and screen/crossmatch for 10-15 mL/kg of sickle negative, extended phenotype matched RBC

Investigations while on transfusion program

- Height, weight, history and complete physical exam at least every 3 months
- Ferritin every 3 months with CRP
- Liver enzymes, urinalysis every 6 months
- Hepatitis B and C yearly
- Thyroid function, fasting blood glucose and other endocrine studies as indicated
- Consider EKG/ECHO yearly and before desferoxamine therapy
- Consider HIV testing
- Liver biopsy for hepatic iron content after 1 year of regular transfusions
- Consider audiologic and ophthalmologic examination before desferoxamine therapy

Indications for chelation therapy (Iron Chelation Guidelines)

Desferoxamine therapy should be strongly considered when:

1. Liver iron greater than 4 mg/g dry weight or
2. If liver biopsy not available, if ferritin greater than 1500-2000 ug/L or
3. Cumulative blood transfusion greater than 120 mL/kg body weight
4. Chronic transfusions greater than or equal to 1 year

Suggested monitoring while receiving desferoxamine (See Iron Chelation Guidelines)

Oral chelation treatment

Deferasirox (Exjade[®]) is an orally active chelator that is selective for iron (as Fe³⁺). It is a tridentate ligand that binds iron with high affinity in a 2:1 ratio. Although deferasirox has very low affinity for zinc and copper, there are variable decreases in the serum concentration of these trace metals after the administration of deferasirox. The clinical significance of these decreases is uncertain.

Indications for Exjade[®] usage: Currently Exjade[®] is indicated in the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years and older.

Pediatric dosage: It is recommended that therapy with Exjade® (deferasirox) be started when a patient has evidence of chronic iron overload, such as the transfusion of approximately 100 mL/kg of packed red blood cells (approximately 20 units for a 40 kg patient) and a serum ferritin consistently greater than 1000 mcg/L.

Starting Dose: The recommended initial daily dose of Exjade® is 20 mg/kg body weight.

Maintenance Dose: After commencing initial therapy, it is recommended that serum ferritin be monitored very month and the dose of Exjade® adjusted if necessary every 3 to 6 months based on serum ferritin trends. Dose adjustments should be made in steps of 5 to 10 mg/kg and should be tailored to the individual patient's response and therapeutic goals. If the serum ferritin falls consistently below 500 ug/L, consideration should be given to temporarily interrupting therapy with Exjade®. Doses of Exjade® should not exceed 30 mg/kg per day since there is limited experience with doses above this level.

Administration: Exjade® should be taken once daily on an empty stomach at least 30 minutes before food. Tablets should be chewed or swallowed whole (125 mg, 250 mg, and 500 mg). It **should not** be taken with aluminum-containing antacid products. Doses (mg/kg) should be calculated to the nearest whole tablet. Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained.

Investigations for Exjade®:

- Can cause acute renal failure with some documented fatal outcomes
- Serum Creatinine (SrCr) should be assessed twice before initiating therapy
- Weekly SrCr monitoring in the first month and then monthly
- Urine protein
- Maintain adequate hydration
- CBC with differential once weekly x 1 month and then monthly
- Liver function test (ALT/AST) once monthly
- Serum ferritin monthly
- Baseline and annual auditory and ophthalmic function (including slit lamp examinations and dilated fundoscopy)

General considerations:

- The frequency and volume of transfusion is based on the Hb and Hb S concentration prior to the previous transfusion
- A simple transfusion is given over 3 hours
- Hyperviscosity must be avoided in patients with Sickle Cell Disease, therefore, do not transfuse to a Hb (>) greater than 100 g/L
- If the patient has experienced fever or hives or any allergic manifestations during or after blood transfusion, administer pretransfusion medication as per guidelines. Consider using washed red blood cells if the patient has a severe allergic reaction
- Consider a delayed hemolytic transfusion if the patient presents several days after the transfusion with a decreasing Hb, hemoglobinuria and increasing jaundice. Not infrequently, patients may present with a painful episode. This is usually due to alloantibodies against non ABO antigens. Up to 30% of alloantibodies are transient and, therefore, current antibodies as well as previously detected antibodies should be considered in such patients
- Document and inform blood bank of any adverse reactions

XV. HYDROXYUREA

Higher levels of fetal hemoglobin (Hb F) and lower leukocyte counts are thought to be beneficial in patients with sickle cell disease and can be achieved with daily oral administration of hydroxyurea (HU). A placebo-controlled, double-blind, prospective trial in severely affected adults with Hb SS showed that HU significantly reduced the incidence of vaso-occlusive pain, acute chest syndrome and blood transfusions. A multi-center phase I/II trial in children greater than 5 years of age showed safety and hematologic effects similar to those observed in adults. Clinical benefit in children has been suggested by a number of open label studies including the baby-hug trial indicating safe and efficacious use of hydroxyurea in children as young as 9 months. The drug is FDA approved for selected adult patients, with the important caution that the drug is not curative and requires close hematologic monitoring for myelotoxicity and the strict use of contraception by both men and women who are sexually active.

The clinical course of each patient with sickle cell disease should be regularly reviewed by a pediatric hematologist/sickle cell program and the possibility of hydroxyurea treatment and its pros and cons considered. Many patients with severe complications may also be candidates for either a program of chronic transfusions or, if any HLA-matched sibling is available for bone marrow transplantation. HU is not generally considered appropriate for patients with **acute** stroke, and it is not useful in the treatment of **acute** sickle pain. No clinical improvement is expected until the drug has been taken daily for 3-6 months. HU is a potentially toxic chemotherapeutic agent whose long-term toxicity (including concerns about carcinogenicity and teratogenicity) is unresolved. A recent study has shown HbF induction has been sustained for up to 8 years in children without adverse effects on growth or increased numbers of DNA mutations. The potential for using long-term hydroxyurea therapy to reduce the morbidity and mortality of all children with sickle cell disease requires further study. However, given that the mechanism of action of HU in sickle disease is to decrease hemolysis and decrease vasculopathy, HU therapy should be considered in all patients with sickle cell disease even if they are asymptomatic.

Thus, the drug should be initiated and monitored only by Hematologists with expertise in chemotherapy and sickle cell disease and after written documentation of patient education and consent.

Indications (inclusion criteria) (NOTE: Refer to Appendix 4 for pre-printed orders for hydroxyurea treatment)

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XVII. APPENDIX 1

Schedule for Baseline Studies at Diagnosis and Follow-up

FOLLOW-UP					
	At Dx	Q visits	Q6-12 months	Q12 Months	Other
Family studies CBC, reticulocytes, hemoglobin electrophoresis	X				
Hb Electrophoresis with quantitative Hb F	X				
G6PD	X				
Kleihauer-Betke	X				
Red cell phenotype	X				
Physical exam: <ul style="list-style-type: none"> • Spleen size • Liver span • Cardiac murmur • Height [°lile] • Weight [°lile] • Growth velocity 		X			
CBC, O ₂ sat=n	X	X			
Reticulocyte count	X		X		
Red cell folate	X		X		
Ferritin, serum iron	X		X		
AST, ALT	X		X		
Bili T/D	X		X		
BUN, Cr	X		X		
Uric Acid	X		X		
Na, K, Cl			X		
Urinalysis	X		X		

FOLLOW-UP					
	At Dx	Q visits	Q6-12 months	Q12 Months	Other
Hep A, B, C serology	X			X if transfused	
CMV serology	X			X if transfused	
HIV serology	X			X if transfused	
EBV serology	X			X if transfused	
IgM Parovirus serology					If aplastic crisis
Chest X-ray	X				Every 2 years, when greater than 5 yrs old
Bone age					Every 5 years until mature
Respiratory function tests					If child had chest syndrome
EKG	X				When greater than 5 years old, annually
Echocardiogram	X			When greater than 5 yrs old, if ECG abnormal	
Abdominal U/S	X				When suspicious of gall stones
Ophthalmologic exam					When greater than 5 yrs old every 2 years
Dental			X		
School Assessment				When greater than 5 yrs old	
Developmental		X			
Neuropsychological Assessment					At 5 yrs old
Medical Alert Bracelet	X				
Age/stage appropriate counseling		X			
Immunizations		X			

XVIII. APPENDIX 2

Sickle Cell Anemia Monitoring Checklist

Date							
Physical Exam							
height/percentile							
weight/percentile							
spleen size							
liver span							
cardiac murmur							
growth velocity							
Psychosocial							
development							
school							
neuropsych							
dental							
ophthalmologic							
Investigations							
CBC, retic							
red cell folate							
ferritin							
AST/ALT							
bili T/D							
BUN, creat							
urinalysis							
chest x-ray							

Date							
PFT							
ECG							
echocardiogram							
abdominal U/S							
-bone age							
-viral serology							
Interventions							
penicillin							
routine immunizations							
influenza vaccine							
Hep b vaccine							
pneumococcal vaccine							
meningococcal vaccine							
medical alert bracelet							
Counseling							
genetic							
family supports							
fever							
acute splenic sequest							
dactylitis							
acute chest syndrome							
salmonella prevention							
painful crises							
aplastic rises							

Date							
CNS manifestations							
enuresis							
priapism							
physical activities							
hydration							
avoid temp extremes							
leg ulcers							
avoid drugs, smoking							
retinopathy							
avascular necrosis							
gallstones							
delayed puberty/growth							
sexuality							

XIX. APPENDIX 3

Dear Parent:

Your child has been diagnosed with _____, a type of *Sickle Cell Anemia* syndrome. It is a genetic condition [passed on or inherited from parent to child]. Your child's doctor will probably ask for a blood test on both parents to help understand more about how your child was born with sickle cell anemia. You will also be offered an appointment to meet with the genetics team who are experts in inherited diseases. They will give you information so you will understand better how it is inherited. This is very important, especially if you want to have more children. They will discuss the risk of having another child with a sickle cell syndrome with you.

This disease increases the risk that your child might develop different medical conditions, which range from not very serious to very severe and life-threatening. We will help you to learn to recognize these situations and to be able to help your child and know when you have to contact your doctor.

The available treatments for this disorder will help control the disease, but will not cure it. Sickle cell disease is a life-long chronic disorder. You and your child will learn to live as normally as possible, while giving the appropriate care for your child's disorder. The possible complications will be reviewed and it is very important to understand this information. Please discuss these possible complications with your doctor on a regular basis and do not be afraid to ask questions – your child's health depends on it. As your child gets older, he/she will be able to recognize the signs and learn to do what has to be done.

Possible complications that you will learn more about:

a) Serious and possibly life threatening complications:

1. Increased risk of severe infection
2. Increased risk that small blood vessels in the body will become blocked (called a thrombus); this can occur anywhere in the body and may cause pain, including headaches, bone pain, tummy pain, prolonged and painful erections
3. Increased risk of shock because of blood pooling in the spleen
4. Bone marrow may stop working properly and not produce blood cells needed by the rest of the body
5. Stroke

b) Other less serious problems that may occur:

1. Increased spleen size
2. Low platelet count
3. Slow growth and delayed puberty
4. Gall bladder stones
5. Leg ulcerations (more in older children or adolescents)
6. Iron accumulation in body organs
7. Bed wetting at night

Managing sickle cell disease (Information for patients and parents):

What is Sickle Cell Disease?

Sickle Cell Disease (SCD) is a group of inherited red blood cell disorders. Normal red blood cells are round like doughnuts and they move through small blood tubes in the body to deliver oxygen. Sickle red blood cells become hard, sticky and shaped like sickles used to cut wheat. When these hard pointed red cells go through the small blood tube, they clog the flow and break apart. This can cause pain, damage and a low blood count or anemia.

What makes the red cell sickle?

There is a substance in the red cell called hemoglobin that carries oxygen inside the cell. One little change in this substance causes the hemoglobin to form long rods in the red cell when it gives away oxygen. These rigid rods change the red cell into a sickle shape.

How do you get sickle cell disease?

Sickle cell disease is an autosomal recessive disorder. This means that your child inherited the abnormal hemoglobin gene from both of his/her parents who may be carriers with sickle cell trait or they may have sickle cell disease. It is not contagious. Your child was born with the sickle cell hemoglobin and it is present for life.

What are the symptoms?

Painful events (crises) in the hands or feet, abdomen or chest are the most common acute symptoms of sickle cell disease. This pain may last from hours to days. Many patients with sickle cell disease also experience anemia (a decrease in the number of red blood cells) which is a chronic symptom that needs to be treated.

How is sickle cell disease treated?

Sickle cell disease is a chronic condition. This means that it is important to treat your child's symptoms during acute (crisis) periods as well as during non-acute periods. Your child's medications will be individualized to meet his/her specific symptoms. An important way you can help prevent your child from getting life-threatening infections is by making sure that he/she receives all routine immunizations on schedule. Ask your child's physician for more information on what vaccines your child should receive. Your child should also receive an antibiotic daily in order to reduce the change of getting a life-threatening infection.

What is the outlook for the typical child with sickle cell disease?

Although there is no specific cure for this disease, good medical and home care may make it possible for these children to lead reasonably normal lives. The discovery of antibiotic drugs has made it possible to control many of the complications (infections) so that children live longer. Newer drugs and agents are currently under investigation

Important instructions for children upon discharge from the hospital:

1. Please make sure that your child takes the medicine as prescribed.
2. If your child has been prescribed an antibiotic medicine, be sure he/she finished it all. If your child takes penicillin regularly, then after the prescribed antibiotic is finished, start giving the penicillin as usual.
3. Your child's family doctor, Pediatrician or physician here at the IWK will want to see how your child is doing. If appointments have made for follow-up, please do not cancel or skip them, even if your child seems well.
4. **Take your child to see a doctor right away, or immediately bring your child to the emergency departing if:**
 - Your child has a fever of 38.3°C or higher on a Celsius thermometer, or 100.5°F or higher on a Fahrenheit thermometer
 - He/she has difficulty breathing or is breathing fast
 - He/she is unusually weak or flopping (lethargic)
 - He/she is dehydrated; that is, if he/she will not drink, has thrown up more than once or twice, has no tears when he/she cries, or is passing very little urine
 - He/she is very cranky and cannot be comforted
 - He/she is not answering or reacting to you, or he/she looks confused
 - He/she is very pale
 - You can feel a lump in his/her tummy or he/she has a lot of tummy pain
 - His/her cough is getting worse, or if he/she has a new cough
 - He/she seems weak or has muscles that do not seem to be working well
 - He/she has swelling of the ankles, knees, elbows, wrists, knuckles or other joints
 - He/she has pain that is getting worse, despite taking pain medicine that you have given as prescribed
 - If he has a painful erection of the penis (called priapism) lasting more than 30 minutes

For more information on sickle cell disease, ask your child's physician or other health care professional.

Guideline Development:

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

- Inability to obtain vaccines

Patient/family preferences:

- Not considered applicable
- Appropriate information and support will be provided

Key review criteria for monitoring/audit include:

- Vaccine administration records
- Prophylactic antibiotic compliance
- Number of children requiring admission for fever and infection

The Guideline development group included:

- Tamara MacDonald, PharmD, IWK/APPHON/Dalhousie University
- Vicky Price, Pediatric Hematologist/Oncologist, IWK/Dalhousie University
- Dorothy Barnard, Pediatric Hematologist/Oncologist, IWK/Dalhousie University
- Allan Finley, Pediatric Anesthesiologist, IWK/Dalhousie University
- Noni MacDonald, Pediatric Infectious Diseases, IWK/Dalhousie University

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.

The guideline was piloted at the IWK Health Centre in Halifax, Nova Scotia. The guideline was externally reviewed by Pediatrics, hematologist, oncologist, nurses and psychology.

The guideline will be updated in 5 years by the APPHON Guidelines Committee and resubmitted to the APPHON Board and Cancer Care Nova Scotia Clinical Practice Guidelines Committee for ratification. If significant changes to the prevention and treatment of sickle cell disease changes, based on new evidence or best practice develop prior to 5 years, the guideline will be updated to reflect those changes. As per the standard practice for APPHON guidelines, individuals will be assigned to regularly review application literature to monitor for significant changes. If literature documenting evidence-based or best practice based indication for changes to this guideline, the guideline will be updated with the applicable information as soon as feasible.

XX. APPENDIX 4

Pre-printed forms are on the APPHON/ROHPPA website (<http://www.apphon-rohppa.com>)

- Sickle Cell Anemia Fever Orders – 2015
- Sickle Cell Anemia Acute Chest Syndrome Orders - 2015
- Sickle Cell Anemia Hydroxyurea Orders – 2006 (to be amended)
- Sickle Cell Anemia Pain Orders - 2015