Guidelines for the Care of Patients in the UHN Red Blood Cell Disorders Program

The aim of these guidelines is to:

- Facilitate staff in managing patients with Sickle Cell Disease, Thalassemia, other Red Blood Cell disorders, and iron chelation therapy, both Clinic Staff and others at UHN and in the wider Community
- Define minimum standards of care
- Enable relevant and co-ordinated research to be undertaken

These guidelines represent the consensus opinions of the physicians in the UHN RBCD Program and are based on review of the current published literature and relevant clinical trials, and comments from experts. However, due to the paucity of well-designed studies in adult patients with Hemoglobinopathies, the quality of evidence is generally Grade B. As a result, areas for suggested future research are given in each section.

Red Blood Cell Disorders Clinic
UHN - Toronto General Hospital
12 West (Clinical Services Building), Room 1274
200 Elizabeth Street, Toronto, ON, M5G 2C4

Clinic Reception: 416 340 4882

Web: http://www.uhn.ca/Clinics & Services/clinics/RBCD/index.asp
Appendix C: UHN Emergency Department Orders for Acute Sickle Cell VOC Episode

Iron Chelation

Thalassemia/Iron Overload & Complications

Cardiovascular Complications

Neurological Problems

Hepatobiliary Disease

Priapism And Renal Disorders

Musculoskeletal And Skin Complications

Women’s Health

Infection Prevention

Anesthesia

Hydroxyurea

Blood Transfusion for Hemoglobinopathies

Red Blood Cell Exchange Transfusion

Thalassemia & Other Transfusion Dependent Anemias

Cardiac Iron Overload & Complications

Hepatology

Splenectomy in Thalassemia

Endocrinopathies

Osteoporosis

Thalassemia Intermedia (TI)

Fertility

Iron Chelation

Appendix A: Routine Investigations for RBCD Clinic Patients

Appendix B: Contact List for Common RBCD Specialist Referrals

Appendix C: UHN Emergency Department Orders for Acute Sickle Cell VOC Episode

Appendix D: RBCDP Opiate Contract

Appendix E: Partial Manual Exchange Orders

Appendix F: List of RBCDP Patient Information Leaflets

Appendix G: Referral Proforma for Patients Transfused in the Community
About the RBCD Program

Contact Details
Red Blood Cell Disorders (RBCD) Clinic
UHN - Toronto General Hospital
12 West (Clinical Services Building), Room 1274
200 Elizabeth Street, Toronto, ON, M5G 2C4

Clinic Reception: ☎ 416 340 4882
Clinic Fax: ☎ 416 340 4559
Clinic Email: ✉ RBCD@uhn.ca

TGH Switchboard: ☎ 416 340 4800

The Team
Clinic Clerks - Lisa Austin; Nadia Auciello, ext. 4882
Nurse Practitioners (NPs) – Kate Uchendu, ext. 4025; Colleen Johnson, ext. 4650
Social Worker - Heather Gordon ext. 3866
Clinic Manager - Brenda Perkins-Meingast ext. 3510
Physicians – Drs. Kevin Kuo, Jacob Pendergrast, Madeleine Verhovsek, Richard Ward & Erik Yeo

TGH Outpatient Pharmacy - ☎ 416 340 4075
Medical Surgical Day Unit (MSDU) - ☎ 416 340 4488
MSDU Manager – Donna Williams, ext. 3920

Philosophy of Care
These are chronic disorders of variable and intermittent severity. The problems adult patients face extend well beyond the medical complications of their condition, and one must take into account possible psychological morbidity, and problems with money, relationships, accommodation. There is often a sense of low self-esteem, frustration about under achievement and that their situation is not understood. Sometimes there is antagonism with hospital staff which may be due to perceived under-responsiveness to specific needs or as a result of cumulative past experiences.

The aims include:
• Emphasis on care and support in the community for less serious complications
• Building of long-term relationships of trust and respect between patients and team members
• Education around the conditions and their complications to enable more effective self-care
• Easy, rapid and reliable access to hospital services for acute complications

Organisation of Care
The clinic operates a holistic team approach to providing care. Patients may be seen by one or more of the following at each visit: physician, nurse practitioner, social worker, and resident/fellow. All patients must be reviewed by a physician in clinic at least once a year. For patients receiving regular blood transfusions or iron chelation therapy, review is quarterly, and for Hydroxyurea therapy every 6 months.
Blood transfusions are administered either on Medical Surgical Day Unit (MSDU) at Toronto General Hospital or by the Apheresis Unit at Princess Margaret Hospital, headed by Dr David Barth. These units will coordinate all care pertaining to the transfusion visits. Patients referred as an emergency for automated red cell exchange must be accepted by Dr Barth prior to transfer. The Program will work with patients who wish to receive their transfusion at a facility closer to home, to facilitate this.

There is currently no capacity for drop-in visits in clinic and any acute problems (e.g. acute sickle cell painful episode) will be directed to the Emergency Department. However, an emergency assessment slot is provided in clinic each day. If patients need to be seen urgently or before their next scheduled appointment, they should phone and speak with a NP, see their family doctor, or go to the Emergency Department.

Inpatients are looked after by the Internal Medicine (GIM) service, with the Hematology Consults service (UHN and Mount Sinai), Acute Pain Service, and other specialists available on request.

**Clinic Non-Attendance**

It is essential that patients are seen on a regular basis to ensure their health maintenance, to provide ongoing education of their disease, and to detect any new organ damage at an early stage. This can be very challenging to achieve if patients do not follow-up on their agreed care plan, in particular scheduled appointments.

It is especially important for patients to keep their “Specialist” appointments and tests (e.g. cardiology, neurology, ECHO, MRI etc.). In the event they are not able to attend the appointment, they need to contact the relevant office directly to rebook appointments. Some physician offices and departments may charge for non-attendance or refuse to rebook the appointment if missed the first time. Appendix B lists the contact phone numbers for common referrals from the clinic.

The RBCD clinic will not automatically rebook missed appointments, and instead discuss any patient issues or concerns that may have led to this and to explain the importance of attending. However, due to the difficulty in providing effective care, patients will be discharged from the clinic if they miss 3 consecutive appointments without an acceptable reason or have not been seen in the clinic for 1 year. A new referral to the clinic would mean being placed on the waiting list.
Sickle Cell Disease (SCD)
SCD Clinic Guide

The following is a template for seeing a patient with SCD in the clinic, along with the clinic processes. It is designed to facilitate trainees rotating through the clinic.

Flow
The team meets 15 minutes prior to clinic starting to discuss cases and troubleshoot. This also gives time for residents to review the histories. Reception will notify the team when patients are ready to be seen. The patient is escorted from reception with their clipboard-mounted follow-up sheet to the designated clinic room. At the end of the consult, all orders should be entered in EPR and/or on paper reqs that are then attached to the clipboard. The follow-up also needs to be documented on the follow-up sheet. All referral forms and other paperwork are available in the clinic rooms. If the patient needs to see the SW or NP, call their extension and leave the patient in the room with the clipboard. At the end of the patient’s visit they will return to reception with the entire paperwork and follow-up sheet. Use the team room to dictate the note. No Shows are reviewed by the Staff/NP at the end of clinic to determine appropriate follow-up.

Diagnosis
Genotype (SCD-SS / SCD-SC / SCD-S/βthal)
Significant past SCD events (ACS, CVA, ICU admissions, operations, etc.)
Active SCD problems (priapism, pain syndrome, etc.)
Other active or significant medical diagnoses

Meds & Vaccines
Current drugs and compliance
Allergies
Immunisations: Flu shot (q1yr), Pneumococcal shot (q5yr), Meningococcal and HiB (one time booster)

Pain
No of admissions to hospital in last year/since last visit
No of pain episodes managed at home since last visit/frequency in last year
Analgesia used and reasons for not using certain drugs
Precipitants of pain – weather, menses, housing issues, inappropriate job, psychological stresses
Chronic pain syndrome/opiate dependency - have they signed an opiate contract?

Systems Review
Cardiac
Chest pain, SOB, exercise tolerance, palpitations
Exercise and weights training
Date last seen by cardiology
ECHO (q3-5 yr) – RVSP/TRJV and EF, ECG, BNP

Respiratory
History of ACS, PE, or asthma
SOB, pneumonias, exercise tolerance, pleuritic chest pain
Previous abnormal PFT?

GU/Renal
Clinical Guidelines 2012

Nocturia, hyposthenuria, urinalysis result
Priapism (males)
Obstetric history, menses, COCP (females)
Family planning/genetic counselling

GI
Hepatitis C status and previous treatment
Hep B/C and HIV serology in past year?
Sequestration history
Gallstones
Cholecystectomy/splenectomy

Neuro
Headaches, visual disturbance, TIA symptoms
Date of last MRI/A (& Doppler results if young) if relevant
Previous laser or surgery to eye
Ophthalmology Referral: q1-2yr

Dermatology
Keloid, leg ulcers

Transfusion
No of top-up/simple transfusions (units and freq)
No of emergency exchange transfusions
Other facilities where transfused (Blood Bank can then contact for Ab history)
Abs, Reactions
Specific requirements
Access (line/port/vein), anticoagulation and complications

Chelation (if relevant)
Chelating agent (mg/kg dose, compliance)
Ophthalmology & audiology review date if on Desferal (q1yr)
Ferritin, MRI liver and heart – result and last date and next scheduled scan

Social
Local Hospital
Job – inappropriate tasks
Education – time missed
Drug plan
Housing issues
Social work request
Psychiatry support request
Member of pt advocacy group

Examination
Weight, BP, HR, O₂ sats
General physical examination

Management Plan – see Appendix A for EPR for order sets
Labs, incl urine dip, Imaging, Referrals, Next visit, cc list
Acute Sickle Cell Painful Vaso-Occlusive (VOC) Episode

Background
This is the most frequent complication of Sickle Cell Disease and a common reason for presentation to hospital. Most attend infrequently with pain, but a few are much more regular. A sympathetic, friendly, and non-judgemental attitude is extremely important. Typically the patient will present with limb, back or chest pain. The majority of patients only come to hospital when the pain is sufficiently severe that analgesics at home are no longer working. An enquiry into this as well as potential precipitating factors should be made e.g., coryzal symptoms, dehydration, over-exertion.

The aim is perform a rapid clinical assessment and provide rapid, adequate, and sustained analgesia.

The mainstay of the management of acute Sickle Cell pain is supportive and includes:
- Fluid replacement
- Oxygen
- Pain relief
- Antibiotics

Assessment
This should focus on site, severity and duration of pain, precipitating factors, and analgesia used prior to attending, as well as the patient’s previous analgesia preference. Enquire about respiratory, neurological and other sites of infection producing symptoms. Ascertain transfusion history and prescribing of Hydroxyurea.

Clinical examination should be focussed on early signs of Acute Chest Syndrome, possible sources of infection, priapism and sequestration syndromes.

For a simple, painful vaso-occlusive episode there is no indication for lab tests or CXR, as it is unlikely to change management. However, any patient presenting with a sickle episode accompanied by fever, even if they otherwise appear well, should have a CXR obtained to rule out an incipient acute chest syndrome, which may initially manifest mild or no respiratory symptoms. In patients with hypoxia unexplained by CXR findings consideration should be given to pulmonary embolism and pulmonary hypertension. Hematologist consultation is indicated in either case.

Transfusion therapy carries specific risks in patients with sickle cell disease and should only be ordered by a consulting Hematologist; in the great majority of cases there is no role for transfusion therapy in management of uncomplicated acute pain. The blood transfusion laboratory at UHN and MSH will not release blood for a SCD patient unless Hematology has been consulted.

Fluid Replacement
Many patients with Sickle Cell Disorders have reduced tubular concentrating ability. Continued fluid loss without adequate replacement causes a reduction in plasma volume with an increased blood viscosity and aggravation of sickling. The oral route is always preferred. However, in those who are unable to tolerate this due to pain, abdominal / respiratory problems, IV fluids may be required. The goal of hydration should be to replace estimated deficits followed by maintenance. For most patients, Intravenous therapy should be stopped once the patient is stable and pain is controlled.
Pain Relief
Refer to “UHN ER Acute Sickle Cell Crisis Protocol” (Appendix C)

The aim is to deliver rapid and adequate analgesia to relieve pain and then to maintain a sufficient level of analgesia. It has shown that rapid relief of pain can result in fewer admissions and reduced duration of crises. Analgesia should therefore be initiated within 30 minutes of presentation, with adequate pain control achieved within 60 minutes. Pain should be reassessed and vital signs checked every 20 minutes until pain is controlled. For patients with complex pain (e.g. inability to control pain without inducing significant side effects of excessive sedation), consultation with the Acute Pain Service is required. Patients with sickle cell pain have usually been exposed to opiate analgesia previously, and often require greater doses of opiates than other, opiate-naive patients. Multimodal analgesia should be used with the use of NSAIDs and gabapentin in combination with an opiate.

The IM route should not be used. Patients often have poor venous access and avoidance of IV canulation and IV administration can preserve veins for urgent situations. PO fluids should be encouraged and oral opiates offered. Subcutaneous administration of analgesia is a suitable alternative. Both Morphine Sulfate and Hydromorphone are available for IV and subq administration, and also in oral form as liquid and tablet. The oral formulation is either immediate acting or slow release. This allows for background analgesia with prn dosing. It also permits patients to be discharged on a weaning dose of opiate without needing to switch class of agent. Oxycodone has the disadvantage of greater tendency to opiate dependency. Fentanyl PCA is the drug of choice for acute chest syndrome due to its preferential safety profile. Morphine Sulfate has been associated with an increased risk of ACS developing. Meperidine is contraindicated due to cerebral toxicity and should not be used. With prolonged opiate use, laxatives and antihistamine should be prescribed.

Hydroxyurea Adjustment
In the absence of an infection, Hydroxyurea should not be withheld during an acute pain episode. At the present time, the recommendation is to temporarily stop Hydroxyurea in the presence of documented infection, due to concern over blunting neutrophil responsiveness. However, there is some emerging data to suggest that Hydroxyurea may be beneficial in limiting the harmful effects of an exaggerated immune and inflammatory response. If withheld, it should later be recommenced, once afebrile and having completed the

course of antimicrobials, at the same dose as previous.

**Antibiotics**
Refer to “UHN Guidelines for Antimicrobial Use” (via UHN intranet).

Sickle cell patients are particularly susceptible to severe overwhelming bloodstream infections. Always look for a focus of infection when the patient is febrile and obtain blood cultures. Common causes of septicemia include are Streptococcus pneumoniae, Haemophilus influenzae, and Salmonella spp, while atypical organisms such as Mycoplasma, Chlamydia and Legionella spp are common in patients with acute chest syndrome. In suspected sepsis, Hydroxyurea and chelation therapy should be stopped due to the risk of cytopenia and promoting growth of siderophore organisms, respectively.

Any patient with a sequestration syndrome, chest syndrome, or sepsis must receive IV antibiotics. Any patient with two temperatures of 38.0°C in one hour and one at 38.3°C, but who appears mild to moderately ill should also receive IV antibiotics. If there are signs of chest infection as well as the above, add in oral macrolide to cover atypical organisms and request Mycoplasma serology and urine for Legionella antigen. Patients receiving iron chelation therapy with Deferoxamine should have stool cultures sent for Yersinia spp.

If the decision is taken to treat for osteomyelitis, antibiotics should be chosen to cover for *Salmonella, Streptococcus and Staphylococcus spp*. Orthopaedics and the Infectious Disease service should be consulted, but surgery must not be contemplated without prior discussion with the on call Hematologist. Intravenous therapy should be between 7 – 14 days, and total treatment for 6 weeks.

**Disposition Planning**
Patients may be discharged from the Emergency Department if their pain can be adequately controlled with oral analgesia within 24 hours of presentation. All other cases should be admitted to hospital. Due to the complex interrelationship between pain crises and psychosocial stressors in patients with sickle cell disease, social work consultation should be sought for all admitted patients. Patients should have outpatient follow-up arranged with the RBCD clinic within 2 weeks of hospital discharge.

**KEY POINTS:**
- The mainstay of acute pain management is hydration, oxygen, and analgesia.
- Analgesia should be rapid, sustained and adequate with regular objective assessments of efficacy
- Do not transfuse for simple pain episode

**RESEARCH OPPORTUNITIES:**
- Alternative analgesics and routes of administration in managing acute vaso-occlusive pain
- Audit of UHN ED PPO set

**References**
A Sickle Crisis? A report of the National Confidential Enquiry into Patient Outcome and Death (2008)
Clinical Guidelines 2012

Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, Sickle Cell Society 2008
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition
The Use of Opiate Analgesia

Appendix D is 2 documents concerning opiate analgesia. The first outlines the management of pain and is an introduction to the second, which is a contract for all patients using opiates to sign. This approach is in keeping with the advice of the CPSO and MOHLTC.

The RBCD clinic utilises the MOHLTC’s Drug Profile Viewer to verify the use of analgesia by patients. Emergency Departments are encouraged to only prescribe sufficient analgesia to treat the immediate pain, with further medication prescribed by the Clinic. To this end, there is an emergency assessment slot in each clinic.

Current guidelines suggest >200mg/day oral Morphine Sulphate is the safe limit for non-cancer pain. Patients with complex chronic pain should be referred to the Comprehensive Pain Clinic at TWH (Dr Angela Mailis). Dr Mailis has requested to be emailed with details prior to sending the formal referral. The patient will be asked to phone to schedule the (2 hour) appointment directly. Patients demonstrating behaviour suggestive of physical or psychological dependency should be referred to the Wasser Pain Clinic at MSH (Dr Allan Gordon). The referral process for the Wasser is lengthy and the social worker often needs to assist patients in completing the assessment questionnaire. CAMH’s drug dependency clinic accepts referrals only for the highest risk patients, and is generally not relevant to this patient population.

<table>
<thead>
<tr>
<th>Table B Appendix 8.1 Oral Opioid Analgesic Conversion Table</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equivalence to</strong></td>
</tr>
<tr>
<td><strong>oral morphine</strong></td>
</tr>
<tr>
<td><strong>30 mg:</strong></td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Meperidine</td>
</tr>
<tr>
<td>Methadone and tramadol</td>
</tr>
</tbody>
</table>

National Pain Centre; Equivalence to oral morphine 30 mg

Daily, thrice weekly, or weekly partial-fill prescribing of opiates can be helpful in regulating the use of these medications.

Attention should be paid to ruling out end organ damage or thromboembolic disease as a cause for chronic pain. All patients should be given a trial of Hydroxyurea therapy if suffering repeated pain episodes. Use of multimodal analgesia is recommended, eg NSAIDs, gabapentin, duloxetine. Socio-economic precipitants should be addressed as far as possible.
KEY POINTS:
- Requirement for >200mg daily of oral Morphine Sulfate should be a red flag for further assessment and referral to a specialist pain clinic
- MOHLTC’s DPV is useful tool for verifying opiate prescriptions

RESEARCH OPPORTUNITIES:
- Referral patterns and outcomes from specialist pain clinics for patients requiring daily opiates

References
Pulmonary Complications

Background
Patients with Sickle Cell disorders are at risk of pulmonary diseases prevalent in the general population, as well as Sickle-specific conditions. Asthma should be identified and managed aggressively. Pneumococcal immunisation should be repeated every 5 years and Influenza immunization yearly (CDC Recommendations).

1. Acute Chest Syndrome

Background:
Acute Chest Syndrome (ACS) is an acute illness characterized by fever (>38.5°C), respiratory symptoms and new pulmonary infiltrates on CXR. Precipitants are commonly infection, post-operative atelectasis, and pulmonary fat emboli. ACS is the 2nd most common cause of hospitalization in sickle cell patients. Mortality is ~5%.

Risk Factors
The overall incidence and seasonal variation is less common in adults. SCD-SS phenotype is at highest risk. Previous pulmonary events, including ACS, and a low steady state HbF% are risk factors.

Presentation
- There can often be a rapid clinical course.
- Pain is characterized by a “T-shirt” distribution and its severity will usually cause splinting of the diaphragm, further impairing oxygenation resulting in progressive hypoxia. Coughing is a late symptom.
- Signs of lung consolidation (often bilateral), such as bronchial breathing, crackles or reduced breath sounds, accompanied by tachycardia and tachypnea.
Clinical Guidelines 2012

Investigations
- CBC, reticulocytes, Crossmatch, Hb Electrophoresis
- Liver Function, Electrolytes, Creatinine
- Arterial Blood Gas
- CXR
- Sputum and blood cultures
- Serum/urine for atypical screen (Mycoplasma, Legionella)

Management: General
- Inspired O2 to maintain sats >96%
- Adequate pain management - consider Fentanyl PCA
- IV fluids as in painful episodes (avoid fluid overload)
- Regular Salbutamol bronchodilators if history of obstructive/reversible airways disease or in the presence of bronchospasm or wheeze
- Treat underlying infection (Ceftriaxone + Clarithromycin or Levofloxacin if Penicillin allergic)
- Incentive Spirometry and RT referral to prevent further atelectasis
- Hourly Vital signs monitoring
- Consider Access Team referral

Management: Transfusion
Early transfusion is often appropriate and frequently lifesaving. The purpose of transfusion is to enhance oxygen-carrying capacity, improve tissue oxygen delivery, reduce HbS concentration to reduce sickling, and to prevent progression to acute respiratory failure. Transfusion commonly results in impressive improvement within hours.

Top-Up Transfusion
- mild or moderate chest syndrome, particularly with falling Hb levels
- aim for a Hb level of no more than 100

Exchange Transfusion
- rapid or significant clinical deterioration
- worsening CXR changes
- O2 sats <90%, suggesting pO2 <70mmHg
- baseline Hb >90

Management: Progress
If no improvement within 12 hours, or deterioration in condition, consider:
- Access Team referral
- Intensify RT support
- Further exchange transfusion
- Non-invasive ventilatory support
- Inhaled nitric oxide
- Steroids – can lead to rebound in VOC pain once stopped
Secondary Prevention
Recurrent ACS is associated with reduced survival. Hydroxyurea has been shown to reduce the frequency of ACS by 50%. Observational data suggests transfusions can also prevent ACS. At present, Hydroxyurea is the 1st line therapy for recurrent ACS.

2. Pulmonary Hypertension

Background
Pulmonary hypertension (PHT) is defined as a mean pulmonary arterial pressure (PAP) >25mmHg. True pulmonary arterial hypertension is seen in only 3% of patients. At present screening is by 2D-ECHO assessment of the tricuspid valve regurgitant jet velocity (TRJV), which frequently overestimates the prevalence, due to the effect of high output state from chronic anemia. However, an elevated BNP (>160) or TRJV (>2.5ms) is a strong prognostic biomarker for premature death in patients with sickle cell disease (mean 25 months). This is independent of the presence of true PHT, and therefore their exact role in assessment of PHT remains uncertain.

A screening ECHO should be performed every 3-5 years or earlier should signs of cardiovascular or pulmonary disease develop (e.g. decreased exercise tolerance, hypoxemia, and arrhythmias). Ideally, the TRJV should be calculated to allow for risk stratification. However, it is unlikely that significant pulmonary hypertension is present in a patient with a right ventricular systolic pressure <40mmHg or without any measurable tricuspid regurgitation (or TRJV <2.8m/s). The risk of premature death is 10 fold greater with a TRJV >3.0m/s (9% of patients). Measurements should only be considered indicative of patient steady state if they are obtained in the absence of a vaso-occlusive pain episode or significant exacerbation of chronic anemia, or at least one month since the resolution of an acute chest syndrome.

Recurrent ACS, pulmonary embolism, sleep apnea, and Hepatitis C or HIV infection are risk factors for PHT.
PHT may lead to cor pulmonale, recurrent pulmonary thrombosis, worsening oxygenation and increased painful crises. Symptoms include chest pain and dyspnoea. There may be resting hypoxemia. Investigations for causes unrelated to chronic hemolysis should be performed, including pulmonary function testing, 6 minute walk test, CT angiography or VQ imaging for chronic thromboembolic disease, abdominal ultrasound with portal Doppler and liver function testing, and HIV serology.

Referral
The referral criteria to the joint RBCD-Cardiac clinic for consideration of cardiac catheterization are:
RVSP >40mmHg
Symptoms or signs suggestive of PHT
RVSP <40mmHg with evidence of right ventricular dysfunction or dilatation

Patients assessed as requiring a diagnostic catheterisation are then referred on to Dr Susanna Mak, MSH. A positive right heart catheter study should prompt a referral to Dr Granton for a respiratory consultation (PHT clinic) and consideration of vasodilator therapy.

Patients with RVSP >40mmHg remain at risk and should be followed closely with ECHO, with the proviso that this is not an ideal surrogate for assessing PHT. Cardiac MRI has not yet been validated in this patient population. TRJV abnormality is a risk factor for poor outcome regardless of the presence or absence of pulmonary hypertension.

The bleeding risk of Sildenafil treatment may outweigh any benefit from this drug, and consideration should be given to MRI/A of the brain to rule out AVM. A recent international study assessing the role of Sildenafil (WalkPhasst, NCT00492531) was prematurely stopped by the DSMB due to an excess of pain in the intervention arm. Sildenafil is recognised to cause muscle pains.

$$TRJV = \sqrt{(RVSP – PAP / 4)}$$

**Key Points:**
- ACS – acute hypoxia with pain and respiratory symptoms is ACS until proven otherwise and should be managed with blood transfusion
- PHT – ECHO is unreliable in diagnosing PHT, and right heart catheterisation should be performed in suspected cases prior to treatment

**Research Opportunities:**
- ACS – role of anticoagulation in ACS
- PHT – utility of MRI in non-invasive diagnosis of PHT

**References**
Knight-Madden JM, Hambleton IR. Inhaled bronchodilators for acute chest syndrome in people with SCD. The Cochrane Database
Clinical Guidelines 2012

Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, Sickle Cell Society 2008
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition
Cardiovascular Complications

Sudden cardiac death is not uncommon in sickle cell disease, and may in part be due to autonomic dysfunction. However, most cardiovascular issues are secondary to the chronic anemia and hypertensive heart disease which is prevalent in the African-Caribbean population.

Cardiac examination is rarely normal, with hyperdynamic precordium, cardiomegaly and a systolic murmur present in most. ECG often shows non-specific changes and ventricular hypertrophy.

Anemic patients as a whole tend to run a lower than average blood pressure. However, sickle cell patients seem to have relative hypertension for their degree of anemia. Antihypertensive medication should be commenced with a BP >140/90, or 130/85 if evidence of end-organ damage. In addition, a rise in Systolic BP >20mmHg or Diastolic >10mmHg should also be a trigger. ACEI and Calcium antagonists are effective agents, and diuretics should be used with caution.

Because pulmonary hypertension is a strong prognostic indicator for premature death in patients with sickle cell disease, with possible benefit from early treatment, a screening transthoracic ECHO should be performed every 3-5 years or earlier should signs of cardiovascular or pulmonary disease develop (e.g. decreased exercise tolerance, hypoxemia, and arrhythmias). Ideally, the tricuspid valve regurgitant jet velocity should be calculated to allow for risk stratification. (Refer to Pulmonary Complications chapter for further guidance.) Even, in the absence of Pulmonary Hypertension, a raised TRJV or BNP measurement is a biomarker of poor outcome and consideration given to disease modification with Hydroxyurea.

Patients with sickle cell disease who have developed pump dysfunction or significant arrhythmias should be referred for cardiac MRI if there is suspicion of iron overload (e.g., history of frequent blood transfusions), and stress testing if there is suspicion of coronary artery disease (e.g., regional wall motion abnormalities). Referral to a cardiologist (Dr Ross) should be undertaken in both cases. However, cardiac siderosis is very uncommon in Sickle Cell Disease. Non-compaction is more prevalent in the African-Caribbean population as a whole.

Patients in cardiac failure with severe anemia may benefit from Hydroxyurea (with or without EPO) or judicious transfusions, to increase their Hb.

Statins may be useful in sickle cell disease by multiple mechanisms: Improving endothelial function; antithrombotic via reduced tissue factor and platelet activation; anti-inflammatory; antioxidant; vascular protection.

All patients should be educated with regards to good cardiac lifestyle, smoking cessation and exercise including brisk walking and resistance style circuit training with avoidance of excessive weight lifting.

Investigations
Baseline ECG, ECHO, BNP (and T2* cardiac MRI if iron overload suspected – rare in SCD). Review in joint cardiac clinic q3-5yr if no ongoing concerns or new issues.
Clinical Guidelines 2012

**KEY POINTS:**
- Conventional cardiac risk factors should be addressed in adults, especially hypertension

**RESEARCH OPPORTUNITIES:**
- The natural history of cardiac dysfunction in older adults with SCD

**References**
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition

**Acknowledgements**
Dr Heather Ross, Professor of Medicine, University of Toronto, and Director of the Cardiac Transplant Program at Toronto General Hospital.
Thromboembolic Disease

Sickle Cell Disease is a prothrombotic condition due to several factors:
- Abnormal red cell membrane – mediated coagulation activation
- Abnormal WBC and platelet adhesiveness and activation
- Post splenectomy changes
- Vasculopathy mediated endothelial dysfunction.

The following are considered high risk scenarios for thrombosis, with recommendations for pharmacological thromboprophylaxis:
- For the duration of admission to hospital with an acute sickle cell episode
- 6 weeks post-partum
- Patients with indwelling catheters (INR target of 1.8)

For patients with private drug coverage, Dabigatran is an acceptable alternative, although it has not been studied specifically in sickle cell disease patients.

**Key Points:**
- SCD is a pro-thrombotic condition
- Pharmacological VTE prophylaxis should be used in all high risk scenarios, including admission with simple pain episode

**Research Opportunities:**
- The effect of Hydroxyurea on markers of thrombin generation

**References**

**Acknowledgments**
Dr Erik Yeo, Associate Professor of Medicine and Director of Thrombosis Program, UHN
Neurological Problems

Background
These may present as: acute severe headaches, transient ischemic attacks, seizures, ischemic stroke or hemorrhagic strokes.

1. Stroke
Clinically apparent stroke will occur in approximately 1 in 10 patients with sickle cell disease by age 20, and 1 in 4 by age 45. Risk factors for stroke include elevated blood velocities in the middle cerebral artery, as detected by pediatric transcranial Doppler ultrasound. It is likely that stroke is a consequence of Circle of Willis vasculopathy promoted by inflammatory insults, and by chronic intravascular hemolysis, a condition which results in nitric oxide depletion and pathologic vasoconstriction. Chronic microvascular ischemia results in the proliferation of new and thin-walled blood vessels, the most extreme example of which is Moya Moya syndrome. This is likely why ischemic stroke predominates before age 20, while hemorrhagic stroke predominates afterwards. Patients with SCD-SC and patients with lower markers of hemolysis appear to be at lower risk of stroke. The etiology of infarcts and vasculopathy may well differ, and the treatment of each may therefore not be the same.

The standard of care for treatment and prevention of stroke is blood transfusion. The exact protective mechanism of transfusions is unknown, but it suppresses hemolysis and increases oxygen delivery. Transfusion may be provided through top-up transfusion, partial manual or full automated, depending upon the patient’s baseline Hb and clinical status. The goal of transfusion support is to increase the HbA to 70% (i.e., reduction of HbS to < 30% in patients with SCD-SS) while keeping total Hb <110. In the absence of new neurologic events, the target HbA can be relaxed to 50% after three years of therapy. It is important that blood bank be informed that RBCs will be used for exchange transfusion so that Sickledex®-negative units can be selected and plasma volume reduction performed.

Hydroxyurea and other HbF-inducing agents have not been shown in large controlled clinical trials to reduce the risk of stroke and should therefore only be used in patients at risk of stroke for whom transfusion is absolutely contraindicated, where patients have declined blood (Jehovah’s Witness), or as part of a clinical trial.

Management of acute stroke
Confirmation of suspected stroke should be pursued immediately with a non-contrast CT scan of the brain; if results are negative and high clinical suspicion remains, then contrast-enhanced MRI/MRA brain should be
arranged. The management of acute stroke in patients with sickle cell disease should include all aspects of care provided for non-sickle patients, including aggressive control of blood pressure, administration of antiplatelet therapy, and DVT prophylaxis; tPA, while not absolutely contraindicated in sickle cell patients, should be used with care given the increased risk of intra-cerebral hemorrhage. Neurology should be consulted for additional assistance, and referral should be made to the stroke service. Nimodipine should be considered to reduce vasospasm.

In addition to the above, however, patients with sickle cell disease should undergo immediate exchange transfusion. Arrangements for automated exchange should be sought as soon as stroke is confirmed by paging the therapeutic apheresis physician on-call; for patients with poor venous access, placement of a dialysis line may be required. If automated exchange is not available, manual exchange transfusion should be performed. Hematology consultation should also be sought to provide ongoing management of the sickle cell disease, including treatment of any accompanying comorbidities such as vaso-occlusive pain, acute chest syndrome, and so on. Patients with transient ischemic attacks (neurologic deficits lasting < 24 hrs. and unaccompanied by visible lesions on neuro-imaging) should not be initiated on chronic transfusion support but should be closely monitored, with investigations for secondary causes.

Once stable, patients should be referred to the stroke prevention clinic at TWH to address any other possible causes for stroke, including:
- MRI/A
- Carotid Doppler
- ECHO
- ECG
- Fasting lipid profile
- Investigations for thrombophilia
- Neuropsychometric testing

**Secondary prevention of stroke**

For all patients in whom a documented stroke can be attributed to their sickle cell disease, lifelong transfusion support should be continued. The SWiTCH study was terminated early due to increased rate of events in those patients switched from transfusion to Hydroxyurea. Transition from automated to either top-up transfusions or partial manual exchange transfusions should be pursued as soon as the patient’s clinical status has stabilized. Partial manual exchange transfusions are preferred due to the lesser iron accumulation. Assuming no new neurologic deficits have occurred, a pre-exchange HbA level of 70% can be relaxed to 50% after 3 years of transfusion support. However, the post-transfusion Hb should be kept < 110. Patients on chronic transfusion support should be monitored for the development of iron overload and treated accordingly. In the absence of specific contraindications, patients requiring in-dwelling venous catheters should be maintained on full anticoagulation. Revascularisation procedures may be appropriate in patients with recurrence or deterioration, but are a high risk procedure. Patients on chronic transfusion program for primary or secondary stroke prevention should undergo annual MRI/MRA screening to determine the effectiveness of treatment. If new neurological or radiological findings are detected, consideration should be given to tightening the transfusion target back to HbS 30% and a Hb 100, the latter to ensure adequate cerebral perfusion. If there are further abnormalities, hydroxyurea can be given in addition. Although there is no evidence base to this recommendation, theoretically benefit may be gained through modifying endothelial, white cell and platelet responses with the drug.
Primary prevention of stroke
All patients with confirmed middle cerebral artery blood flow > 200 cm/s by pediatric transcranial Doppler should be started on chronic transfusion support following the same protocol as for secondary prevention. The TWiTCH study is currently addressing the role of Hydroxyurea in this patient group. Patients with “silent” ischemia (radiologic evidence only) should not be placed on transfusion support outside of a clinical trial (SIT study).

2. Severe Headache
The differential diagnosis of severe headache is:
- Bacterial or viral meningitis
- intracerebral bleed
- venous sinus thrombosis
- painful vaso-occlusive episode
- hyperviscosity syndrome
- extramedullary masses (less commonly found compared to Thalassemia)

An urgent CT should be followed by lumbar puncture if not contraindicated. Patients with a cerebral haemorrhage should be managed as per stroke guidelines (see above). Bacterial meningitis should be treated as per UHN Guidelines for Antimicrobial Use. Patients with suspected hyperviscosity (severe headache, mental obtundation, hypertension, usually following large volume blood transfusion) should undergo urgent phlebotomy.

3. Retinopathy
Sickle cell retinopathy is more common in SCD-SS but is one of the most common complications of SCD-SC phenotype. The estimated overall incidence is 30%, with 8% having significant retinopathy and 6% visual impairment.

Early stages of sickle cell eye disease are usually without symptoms. It is therefore important for patients to undergo regular screening by an ophthalmologist, with dilatation of the pupil. For patients with known retinopathy, review should be at a minimum every year. For patients with no prior history of retinal complications, 2-yearly review is sufficient. In addition, any new visual symptoms (e.g. visual field loss, monocular blindness, flashes or floaters) in a patient with sickle cell disease necessitate immediate assessment by an ophthalmologist and/or neuroimaging.

Patients with documented proliferative retinopathy require treatment with laser photocoagulation retinopexy to prevent the complication of vitreous hemorrhage and retinal detachment. Vitrectomy surgery is an option for those patients who develop non-clearing vitreous hemorrhage and/or retinal detachment. Alternative and novel therapies include phlebotomy if Hb is raised and intravitreal VEGF monoclonal antibody. The development of complications should not be considered as a stroke equivalent (e.g., chronic transfusion support is not required). However, patients suffering ischemic optic neuropathy (amaurosis fugax) as a complication of their sickle cell disease should be managed as per stroke guidelines (see above). Any patient with trauma to the eye should also be examined as hemorrhage into the anterior chamber can produce glaucoma, resulting in a significant reduction in perfusion of the optic nerve and retina. Patients should also be urgently referred if they report an acute change in vision.
KEY POINTS:
- Exchange transfusion should be performed immediately for a new onset neurological event

RESEARCH OPPORTUNITIES:
- Primary and secondary prevention of stroke in adults with SCD
- Role of hydroxyurea in combination with chronic transfusion for refractory neurological events
- Use of intravitral VEGF inhibitors for retinopathy

References
Condon PI, Serjeant GR. Photocoagulation in proliferative sickle retinopathy: results of a 5
Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, Sickle Cell Society 2008
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition

Acknowledgements
Dr Devenyi, Ophthalmologist-in-Chief and Director of Retinal Services The Donald K. Johnson Eye Center The University Health Network Professor of Ophthalmology and Vision Sciences The University of Toronto
Dr Mandelcorn, Ophthalmologist, Toronto Western Hospital
**Hepatobiliary Disease**

1. **Gall Bladder Disease**
   Chronic hemolysis with accelerated bilirubin turnover leads to a high incidence of pigment gallstones. Certain antimicrobials, such as Ceftriaxone, seem to promote biliary sludge promotion. However, sludge does not always result in stone formation. Caribbean patients seem to be at lower risk of symptomatic biliary disease compared to North American patients. There is no indication for intervention of asymptomatic stones.

   In cases of suspected cholecystitis, a normal ultrasound scan is useful. Management of acute cholecystitis does not differ from that of the general population, with plans for surgery several weeks after an acute episode has resolved.

   Laparoscopic cholecystectomy is classified as an intermediate risk procedure. For standard risk patients, pre-op transfusion should target an Hb of 100, regardless of HbS%. Routine sickle cell surgery preparation measures should be taken (see Anesthesia section).

2. **Viral Hepatitis**
   Patients should be immunized against Hepatitis B, due to their possible need for transfusions. For patients receiving blood transfusions, Hepatitis B & C (and HIV) serology should be checked annually. A positive serological result should prompt PCR testing, liver ultrasound and a hepatology consult. Active hepatitis will elevate the serum ferritin value. Note that transfusional iron overload may also increase transaminase levels, but rarely by more than 2-3x ULN.

   Treatment of Hepatitis C is indicated for persistent serological positivity, PCR positivity, transaminitis or biopsy proven chronic hepatitis. Treatment will be guided by a hepatologist, and may be delayed if liver disease is not advanced. Close monitoring of the CBC is necessary due to the likelihood of additional hemolysis with antiviral therapy and often necessitates additional PRBC transfusions.

3. **Acute Hepatic / Splenic Sequestration**
   Liver vaso-occlusive episode is characterized by right upper quadrant pain, transaminitis (which rapidly normalizes with resolution of pain) fever, jaundice and hepatomegaly. It is managed as any other painful episode. The hepatic sinusoids are low resistance, low pressure system with little resulting damage. However, the high flow hepatic artery bed is prone to ischemic cholangiopathy during a pain episode. Hepatic sequestration presents as rapidly enlarging liver size with a significant drop in Hb accompanied by reticulocytosis. The liver is smooth and tender to palpate. It may be triggered by ingestion of hepatotoxic medications or more commonly the development of sepsis. Exchange transfusion maybe required. Top-up transfusion carries a risk of hyperviscosity as the pain and red cells are de-sequestered. Recurrence is common.

   Splenic sequestration is less common in adults and usually a milder course than in children. Patients with SCD-SC and SCD-S/β thal are at higher risk than SCD-SS due to less splenic atrophy.

4. **Hepatic Iron Overload**
   This is seen in multiply transfused SCD patients and should be managed as with Thalassemia. Refer to Iron Overload section.
KEY POINTS:
- Gallstones are the most frequent cause of abdominal pain in SCD

RESEARCH OPPORTUNITIES:
- Pathophysiology of sequestration syndromes

References
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition

Acknowledgements
Dr M Sherman, Staff Gastroenterologist, University Health Network
1. Priapism
Priapism is a sustained, painful and unwanted erection of the penis. By the age of 20 years, as many as 89% of males with SCD will have experienced one or more episodes. Many patients are not aware that priapism is a complication of sickle disorders and may be reluctant to discuss it. Symptoms should be specifically asked for at clinic visits.

It is caused by vaso-occlusion, causing obstruction of venous drainage of the penis and typically affects the corpora cavernosa. Penile ischemia and acidosis begin to occur about 6 hours into a sustained priapic episode. Recurrent episodes can result in fibrosis and impotence.

<table>
<thead>
<tr>
<th>Low flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penile shaft</td>
</tr>
<tr>
<td>Glans</td>
</tr>
<tr>
<td>Aspirates</td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>pO₂</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Doppler</td>
</tr>
</tbody>
</table>


Triggers to an episode include:
- Fever, dehydration, cold exposure
- a full bladder
- prolonged sexual activity

**Stuttering priapism**
- Recurrent
- Pain of variable intensity
- Erection lasting > minutes but < 3 hours
- Penis may not be fully erect
- Low risk of cavernosal fibrosis and impotence
- Risk of subsequent fulminant attack

**Fulminant priapism**
- Severe pain
- Duration >3 hours
- Penis fully erect
- High risk of cavernosal fibrosis and impotence
- Urgent intervention indicated
Investigations
- CBC, C&T, Hb Electrophoresis
- Liver Function, Electrolytes, Creatinine

Management – General
- Attempt to urinate
- Try warm bath
- IV Hydration
- Opiate Analgesia
- Sedation may be required in severe cases (Diazepam 5mg PO)
- Urology consult

Management - fulminant priapism
If no detumescence within 30 minutes:
- Penile aspiration and Epinephrine irrigation, within 6 hours of onset of symptoms. Monitor BP q15min for 2hrs
- Transfusion – top up or exchange*
- Winter shunt

*ASPEN syndrome
Association of SCD, priapism, exchange transfusion and neurological events

Management - Other options
For prophylaxis against stuttering and fulminant episodes consider:
- Pseudoephedrine 30mg at night
- Bicalutamide (Casodex) 150 mg daily
- Goserelin (Zoladex) 3.6 mg subq q1m
- Diethylstilbestrol 5mg daily for 3-4days

These treatments are expected to cause impotence for the duration of therapy. Blood pressure should be checked and treatment stopped if Systolic >150 systolic, Diastolic >90, or experiencing increased headaches or any symptoms suggestive of TIA.

Long-acting analgesia at nighttime along with benzodiazepines may reduce severity, though caution reduced oxygenation with this combination.

The bleeding risk of Sildenafil treatment may outweigh any benefit from this drug.

A limited transfusion program can also be considered for duration of 6-12 months.

Complications of treatment include bleeding from holes placed in the penis during aspiration, infection, skin necrosis, urethral strictures or fistulas, and impotence. If impotence persists for 1 year, consider a penile prosthesis.
2. Renal Disease
Sickle related nephropathy manifests as nocturia, haematuria, hyposthenuria and proteinuria.

Risk factors for renal failure are:
- SCD-SS, particularly CAR haplotyp
- Hypertension
- Proteinuria
- Hematuria
- Worsening anemia
- Parvovirus infection

The environment of the renal medulla is characterized by hypoxia, acidosis and hypertonicity, all factors promoting sickling of erythrocytes. It is therefore particularly susceptible to damage. Failure to maximally concentrate urine (hyposthenuria) is very common and predisposes to dehydration, worsening crises. Nocturia is a common manifestation of hyposthenuria. Defects in potassium excretion contribute to hyperkalemia. Incomplete distal renal tubular acidosis can also be found in sickle cell nephropathy. Activation of the renin angiotensin system, and increased nitric oxide and prostaglandin levels contribute to renal hyperfiltration (high GFR). Over time, hyperfiltration has been associated with renal injury. It is also important to be aware of a significant overestimation of GFR in patients due to increased creatinine secretion resulting in a lower serum creatinine.

Hematuria results from localized renal medullary sickling and papillary necrosis. It is best managed with bed rest and ensuring a high urine output. However, other, non-sickle cell-related, causes for hematuria should always be excluded at first presentation. This may require a urological or renal consult. Hematuria is one of the few disease manifestations seen in patients with sickle trait, and in very rare cases may indicate the development of renal medullary carcinoma, a highly aggressive malignancy. For this reason, patients with sickle cell trait who develop hematuria should undergo a CT scan of the kidneys.

Up to 40% of patients with nephrotic syndrome may develop end stage renal failure (ESRF). Renal biopsy often shows Focal Segmental Glomerulosclerosis and glomerular enlargement. Urinalysis should be performed every 6-12 months and if more than a trace of protein detected, a sample sent for protein / creatinine ratio. If this is positive (>60mg/mmol), a 24 hour urine collection should be instituted for protein quantification, and a renal consult made to Dr Robert Richardson.

Avoid NSAIDs and other nephrotoxic agents. Administration of an ACEI can be of benefit, and tight control of blood pressure is essential. Diuretics should be used with caution due to the risk of dehydration resulting in a sickle cell VOC episode. There is limited data that ACEI and Hydroxyurea combination gives more renal benefit than either drug alone.

Sickle cell patients in ESRF may require higher doses of EPO than other patients, in part to the right shift of the O2 dissociation curve.

ESRF occurs at an earlier age than in the general population, 35 years compared to 50 yrs. Patients with sickle cell disease and additional co-morbidities for renal disease show a more rapid progression to ESRF. Historical data showed a worse outcome after kidney transplantation, though this is not demonstrated in more
recent series. There is a greater risk of graft failure. Also, vaso-occlusive crises can worsen post-transplant due to changes in blood viscosity.

**Trigger for Nephrology Consult**

- eGFR <60ml/min
- Microalbuminuria (spot PCR >60)
- Macroscopic haematuria – refer to urology
- Sustained hypertension
- Renal failure
- Hypocomplementemia

**Key Points:**

- Priapism lasting >4 hours requires emergency urological intervention to prevent permanent scarring
- All patients should have a urinalysis and ACR performed at least once a year

**Research Opportunities:**

- Long-term follow-up of ACEI and Hydroxyurea to treat proteinuria

**References**

The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition

**Acknowledgement**

Dr S Radomski, Urologist, University Health Network
Dr Robert M.A. Richardson, Division of Nephrology, University Health Network Professor of Medicine, University of Toronto Director of Hemodialysis, Toronto General Hospital
1. **Avascular Necrosis (AVN) / Osteonecrosis**

AVN in sickle cell disease appears to involve the progressive microcirculatory occlusion of juxta-articular bone, with subsequent increase in interosseous pressure and cell death. Joint destruction often includes the anterior superior portion of the proximal femur, where weight-bearing forces are greatest, but also frequently involves the humeral head in the shoulder. Involvement of vertebrae and bones of the hand (dactylitis) are also well-recognized syndromes in sickle cell disease.

MRI is the preferred imaging modality as changes on plain-film radiography are relatively late findings. Patients with SCD-SS accompanied by α-thalassemia and those with frequent painful crises are among those at increased risk of this complication. The overall prevalence of AVN in SSD is 10% but surpasses 50% in patients over age 35. Patients present with pain that may start acutely but then becomes constant and increases with weight-bearing of the affected joint. When affecting the hip, pain may be experienced in the groin, thigh, buttocks, knee or low back. As an infarct completes the pain may abate but leave the patient with limited range of movement or even a joint contracture.

[Pathophysiology of AVN]

Physiotherapy is the mainstay of treatment; a recent randomized controlled trial found no additive benefit of femoral head core decompression. Joint arthroplasty should be reserved for patients who have failed physiotherapy and have become significantly debilitated. A 6-month trial of chronic transfusion support may also be considered as an alternative to surgery. Physiotherapy may involve a number of different interventions, including resistance training, stabilization exercises, hydrotherapy, and range-of-motion exercises. Aggressive treatment of osteoporosis should be considered if present, although there is no evidence from clinical trials that Bisphosphonates are of benefit in sickle cell disease. Due to the lack of effective non-surgical treatment, patients may benefit from a referral to the Comprehensive Pain Clinic at TWH.

Long-term follow-up studies of Hydroxyurea have shown a lower incidence of AVN. Patients with early AVN also had a reduction in pain score, and in some cases resolution of plain x-ray changes.

2. **Osteomyelitis (OM) & Septic Arthritis**

Infarcted bone can provide a protected environment for blood-borne bacteria in patients with reduced
immunity (asplenia).

Diagnosis of OM can be difficult in sickle cell disease as signs and symptoms mimic an acute painful episode or osteonecrosis. Clinical distinction can be difficult especially with the increased use of antibiotics in painful vaso-occlusive crises. Features include fever, pain, swelling and tenderness, in a systemically unwell patient. Presentation can be sub-acute. One should suspect osteomyelitis if pain is unusual and does not resolve as expected for a simple pain episode. No single imaging technique can reliably distinguish acute infection from infarction. Bone and gallium scans, CT scans and MRI may be utilized to evaluate patients for osteomyelitis. Antimicrobial therapy should be guided by UHN Guidelines for Antimicrobial Use, and must cover possible Salmonella organism. Orthopaedics should be consulted, but surgery must not be contemplated without prior discussion with the on call Hematologist.

3. **Leg Ulcers**

10-20% of SCD-SS patients in North America will develop leg ulcers, more frequently in males. The pathophysiology of leg ulcers in SCD is unknown. One possibility is that sickled erythrocytes cause localized hypoxia and infarction of the ankle skin. Trauma, heat and infection then lead to ulceration. Another possibility is that leg ulcers are secondary to increased venous vascular tone secondary to nitric oxide depletion. Continued reduced blood supply often results in recurrence after initial healing.

Secondary causes such as diabetes, varicose veins and connective tissue disorders should be excluded, as should underlying osteomyelitis. An MRI or bone and gallium scans is most helpful for ruling out underlying infection.

Bed rest and elevation, although often impractical, is the most effective intervention. Wet-to-dry dressings applied throughout the day can aid debridement. The ulcers are usually colonized, but do not necessarily require antimicrobials. Oral zinc sulfate (200mg tid) and use of Unna boots may help. All patients should be referred to plastic surgery or the wound care clinic at Women’s College Hospital for further assistance. Hyperbaric oxygen therapy occasional gives benefit.

A short course of transfusions for 3-6 months may help with recurrent or resistant ulcers. The aim should be for HbS% <50 and Hb above 100. Hydroxyurea is not usually appropriate if it has been temporally associated with ulcer development. However, its use can be considered in previously unexposed patients as raising the HbF% is probably beneficial.

**Key Points:**
- Chronic localised joint pain is highly suggestive for AVN
- Leg ulcers can persist for >12 months and are best managed with bed rest, exclusion of underlying osteomyelitis and specialist wound care

**Research Opportunities:**
- Optimal wound care for leg ulcers
- Use of hydroxyurea to slow progression of AVN

**References**
Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, Sickle Cell Society 2008
Styles LA, Vichinsky EP. Core decompression in avascular necrosis of the hip in sickle-cell
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition

Acknowledgements
Dr C Rotstein, Professor, Department of Medicine in Division of Infectious Diseases, Co-director of Transplant Infectious Diseases University Health Network and Director of Oncologic Infectious Diseases Princess Margaret Hospital.
Women’s Health

1. **Contraception**
There is no clear evidence to guide a particular form of contraception, though Depo-Provera provides a reliable method. Many women report menstruation triggering painful crises. There are reports of progesterone only pills reducing this pain, though with a reduced contraceptive efficacy compared to the combined pill. However, the combined pill has a higher risk of VTE and for this reason should not be first choice. Depo-Provera has been associated with reduced BMD, though not with an increase in fracture risk.

Termination of pregnancy can also be a trigger for a painful episode, due to both physical and emotional stress. The standard measures should be taken to prevent RhD immunization, if appropriate.

2. **Pregnancy**
The patient should have an assessment of end-organ damage prior to conceiving with particular emphasis on cardiac function.

The most common maternal complication of pregnancy is hypertension. The fetus is at risk of small for age (17%), fetal distress in labour (33%), and prematurity (23%). The mother is also at risk of urinary tract infection (13%), venous thrombo-embolism and vaso-occlusive episodes (37%). There is also an increased risk of Pre-eclampsia (HR: 2)

Hydroxyurea should be stopped 3 months prior to conceiving, and contraception used whilst taking the drug. However, the rate of fetal malformation reported is very low, and for patients with a previous severe course to their SCD, referral to Motherisk should be considered for discussion of risks associated with continuing the drug.

Folic acid should continue at 5mg daily without iron supplementation, unless iron deficiency has been confirmed. Calcium and vitamin D supplements should continue.

The family should be offered pre-conception counselling and pre-natal diagnosis.

Prenatal care should be co-ordinated with an obstetrician with an interest in high risk pregnancies (Dr A Malinowski). The hematological care of sickle cell patients attending the obstetric clinic is overseen by Mount Sinai Hospital (Dr N Shehata). Patients will be seen q4w in the 1st trimester, q2w in the 2nd trimester, and weekly in the third trimester.

Acute painful episodes in pregnancy should be managed as at other times, but with monitoring of fetal movements and scans if opiates are used. NSAIDs should be avoided in the 1st trimester and after 32 weeks, due to the risk of premature ductus arteriosus closure. DVT prophylaxis should be used during any admission. After 20 weeks gestation, patients can report to Obstetric Triage at MSH rather than ED for acute care, and Hematology consulted for advice.

Transfusion during pregnancy is controversial but may be required to reduce an increased frequency of painful episodes or for those high risk women or in multiple pregnancies. Regular ultrasound scans of fetal size and placental health at 20, 28, 32 and 36 weeks gestation may also guide transfusions.
Delivery of the fetus should not be delayed beyond 40 weeks. Birth is best by vaginal delivery if possible. IV hydration and supplemental oxygen should be used. Opiate use may affect CTG tracings, and may need to be reversed in the baby at delivery. VTE prophylaxis should be given for 6 weeks post-partum in Sickle Cell Disease.

Standard antenatal care also applies to the pregnant sickle cell patient, including RhD prophylaxis and chromosomal screening.

**KEY POINTS:**
- Pre-conception management should be optimised, with planning of any pregnancies
- SCD can worsen in severity in pregnancy

**RESEARCH OPPORTUNITIES:**
- Safety of Hydroxyurea in pregnancy

**References**
Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. Contraception 2006; 73(2) p195-204
Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK, Sickle Cell Society 2008
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition
Infection Prevention

Refer to UHN Guidelines for Antimicrobial Use for treatment of infections.

Patients who had undergone a surgical splenectomy or splenic atrophy are at risk of overwhelming post-splenectomy infection (OPSI) and should seek urgent medical attention if unwell. Patients should ideally be fully vaccinated 4-6 weeks prior to surgical splenectomy.

**Penicillin V**
Administration of Penicillin V bid prevents 80% of life-threatening episodes of childhood *Streptococcus pneumoniae* sepsis. It is safe to discontinue prophylactic penicillin at age 5 yrs. It may be useful to continue in those patients with recurrent infections.

**Immunisations**

Patients should receive:
- Influenza vaccination q1yr
- Pneumococcal polysaccharide (PPSV) vaccine (Pneumovax 23) with one-time revaccination 5 years later if not previously received, and a further revaccination at 65 years of age
- Hemophilus influenzae (HiB) vaccine, if not immunised in childhood
- 2 doses of Meningococcal conjugate vaccine quadrivalent (MCV4, Menactra) at least 2 months apart if not immunised in childhood. Meningococcal polysaccharide vaccine (MPSV4) is preferred for adults 56 years and older. Patients should be revaccinated every 5 years.

In addition, patients should be vaccinated against Hepatitis B prior to starting blood transfusions and screened annually for Hepatitis B & C and HIV infection.

**Special Circumstances**

Patients receiving iron chelation therapy should interrupt treatment during episodes of infection, and if diarrhoea is present, stool checked for Yersinia.

Patients receiving Hydroxyurea or iron chelation (especially Deferiprone) should interrupt therapy during episodes of infection due to the risk of cytopenias, in particular profound neutropenia.

Malaria and Parvovirus B19 infection are associated with increased haemolytic rate. They should be specifically considered and excluded in patients with a febrile illness.

Antibiotics as prophylaxis for dental procedures are not recommended.

**KEY POINTS:**
- Patients with SCD are at increased risk of infection from encapsulated bacteria
- Signs or symptoms of infection should be promptly treated

**RESEARCH OPPORTUNITIES:**
References

CDC Morbidity and Mortality Weekly Report (MMWR) Recommended Adult Immunization Schedule — United States, 2012; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6104a9.htm?s_cid=mm6104a9_w


The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition


Acknowledgements

Dr C Rotstein, Professor, Department of Medicine in Division of Infectious Diseases, Co-director of Transplant Infectious Diseases University Health Network and Director of Oncologic Infectious Diseases Princess Margaret Hospital.
Anesthesia

All patients with Sickle Cell Disease and Thalassemia should be discussed with the Red Blood Cell Disorders team and Anesthesiologist when they are booked for surgery so that a coordinated plan can be made for their care. No special considerations need be taken for patients with sickle cell trait and pre-operative screening for sickle cell disease is not required in patients for whom there is low clinical suspicion of sickle cell disease.

Patients should be scheduled early on the operating list to ensure they are not likely to be cancelled, and to avoid prolonged fasting time. Care should be taken to avoid factors which may precipitate the development of a VOC episode. These include hypoxia, dehydration, acidosis, cold and pain. Surgery should be delayed in a patient experiencing an acute sickle cell episode. All patients should receive overnight IV hydration the evening prior (>8hrs) to surgery requiring general anesthetic. The majority of crises in the perioperative period occur postoperatively. Particular attention should be paid to respiratory effort and the use of Incentive Spirometry, RT support and aggressive control of post-operative pain to prevent splinting. All sickle cell patients should receive post-operative DVT prophylaxis until they are fully ambulating, regardless of the nature of surgery performed, and for 6 weeks post-partum.

All transfusions will be organised by the hematology team. A valid Crossmatch sample must be organised for all patients. It is essential that the diagnosis and history of past transfusions be entered in the comment field when making the request. Blood bank should be given at least 2 week notice when a patient with sickle cell disease or thalassemia is scheduled for elective surgery so as to allow sufficient time to source phenotypically-matched blood. Similar notification should be provided to the apheresis service for patients referred for perioperative automated red cell exchange. An HbS % is not necessary pre surgery unless exchange transfusion is planned. Transfusions should be performed no more than 1 week prior to surgery. Autologous blood transfusion, either pre-operative deposit or reinfusion of blood shed peri-operatively, is contraindicated in patients with sickle cell disease. Note that the goal of HbS < 30% noted for high-risk surgery refers to patients with homozygous HbS only; for patients with HbS/ß-thalassemia or SCD-SC disease, the goal should be to obtain a HbA > 70%

Low Risk Surgery
Short procedures with minimal risk of perioperative complications in patients who have no other risk factors: Hb should be ≥ 70

Intermediate Risk Surgery
Tonsillectomy, splenectomy, laparoscopic cholecystectomy, hip/knee replacements. History of obstructive sleep apnoea, recurrent chest problems or other chronic health problems: Simple transfusion to an Hb of 100 (regardless of HbS levels).
A recent multicentre, randomised trial (TAPS) examined the role of transfusion versus no transfusion in this risk group. It was prematurely closed by the DSMB due to excess adverse events (mainly SCD-related) in the non-transfused arm.
**High Risk Surgery**
Thoracic, major upper abdominal surgery or neurosurgery and patients with a history of severe sickle related problems, e.g. previous CVA. Consider in eye surgery, surgery involving tourniquets: **Transfuse or exchange transfuse to reduce the HbS <30%. Total Hb should not be >100**

**Key Points:**
- Patients should be admitted the night prior to surgery for hydration
- Pre-operative transfusion need is based on disease severity and surgical risk
- Post-operative care includes VTE prophylaxis, analgesia and incentive spirometry

**Research Opportunities:**

**References**
Howard, J, Malfroy, M, Llewelyn, C, et al; Pre-Operative Transfusion Reduces Serious Adverse Events in Patients with Sickle Cell Disease (SCD): Results From the Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) Randomised Controlled Multicentre Clinical Trial Blood (ASH Annual Meeting Abstracts), Nov 2011; 118: 9
The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition
Hydroxyurea

Rationale for Use
Hydroxyurea is currently the only disease-modifying therapeutic intervention available for patients with sickle cell disease. However, it is not licensed for this indication in Canada.

Hydroxyurea has been shown in a large randomised-controlled study to decrease the frequency of painful vaso-occlusive episodes and of acute chest syndrome in adults with homozygous sickle cell disease. At present, evidence is lacking for its efficacy in the management of priapism, stroke (can maintain neurocognitive performance in adolescents, but no reduction in stroke risk), leg ulcers (may exacerbate as this is a known side effect of the drug), or for the prevention of organ damage (e.g. spleen or kidney). However, data is starting to emerge to show a survival benefit in those on long-term therapy. It is believed that morbidity data will follow as the data matures and the drug is used at an earlier age. Several studies have shown demonstrated its safety in pediatric population (BabyHUG, HUSOFT).

Hydroxyurea is an S phase-specific cytotoxic agent, which has been used for many years to treat myeloproliferative conditions. Its side effects include bone marrow suppression, gastro-intestinal disturbances, and increased skin and nail pigmentation. It is potentially teratogenic. There is also concern about the risk of malignancy which has greatly limited its acceptance by patients with sickle cell disease. However, its association with malignancy is documented primarily in patients with underlying myeloproliferative disease (itself a pre-malignant condition) rather than hemoglobinopathy, and those studies in which such an association was found may have been confounded by previous exposure to alkylating agents and radioactive isotopes. The risk of malignancy in sickle cell disease, if any, must be balanced against what observational studies suggest is in overall mortality benefit. Mutagenic data in SCD is reassuring.

Three effects may be important: (1) Increase in fetal haemoglobin content within the red cell, inhibiting sickle haemoglobin polymerisation. (2) Decreased adhesion molecule expression on the surface of the red and white blood cells and platelets, reducing cell-endothelial adhesion. (3) nitric oxide donation.

In general may take up to 6 months of therapy with hydroxyurea before clinical benefit is observed. Response is poorer in HbSC disease.

Indications
Definite
- Recurrent painful episodes, significantly interfering with lifestyle. (>3 healthcare interactions with vaso-occlusive pain per year.)
- >1 lifetime acute chest syndrome.

Relative
- End organ damage (eg proteinuria, unrelated leg ulcer, priapism)
- Adverse biomarkers, eg TRJV >2.5, elevated BNP
- Severe anemia
- Patient wish to improve quality of life*
- Patient wish as primary prevention against organ damage*

*encouraged more if high baseline HbF level
**Relative Exclusions**
Active infection  
Hb <60 at baseline  
Platelets <100x10⁹ (unless splenomegaly), Neutrophil count <1x10⁹  
Pregnancy or planned pregnancy in next 6-12 months  
On regular transfusion protocol (unless uncontrolled complications despite optimal transfusion regimen)

**Procedure Prior to Starting Therapy**  
Sperm banking should be discussed with all males. Male and female patients should be warned of the theoretical risk to unborn fetus and advised to use contraceptive methods. Ensure that the patient is willing to undergo regular monitoring of blood counts. Patients may require assistance from the social worker to obtain Trillium coverage, as cost exceeds $100 per month.

**Baseline Investigations**
- CBC, reticulocytes  
- Hb Electrophoresis  
- ALT, bil  
- Electrolytes, Creatinine  
- Pregnancy test

**Dosage**
**Initial:**  
Start at 1000mg (~15mg/kg) daily  
Dispense no more than 4 weeks of tablets at a time, with maximum of 5 repeats to ensure patient is reviewed every 6 months.  
**Maintenance:**  
Dose can be increased by 500mg every 4 weeks  
Ideally aim for maximum tolerated dose that controls symptoms while maintaining neutrophils >1.0 x 10⁹, Platelets >80x10⁹  
Consider stopping folic acid if sufficient dietary intake

**Monitoring of Therapy**
**Initial:** CBC: q4w whilst titration of dose  
**Maintenance:** q3m when on stable dosage. Monitor q4w if dosage changed.  
- CBC, reticulocytes  
- Hb Electrophoresis (HbF %)  
- ALT, bil, Cr

**Clinical Assessment q3-6m:**  
Frequency of crises  
Social impact  
Adverse effects
Compliance

**Dose Modification**

1. Criteria: Neutrophils <1x10^9, platelets <80 x10^9, Hb>20 below baseline:
   - Stop medication or reduce by 50%
   - Recheck CBC weekly
   - When counts back to normal, restart Hydroxyurea 500mg below previous dose and continue to check CBC q1-2w until count remains stable.
2. Infection: Hydroxyurea should be temporarily withheld during an acute admission when sepsis suspected due to concern over blunting neutrophil responsiveness. However, there is some emerging data to suggest that Hydroxyurea may be beneficial in limiting the harmful effects of an exaggerated immune and inflammatory response. If withheld, it should later be recommenced, once afebrile and having completed the course of antimicrobials, at the same dose as previous.
3. Hydroxyurea should not be stopped during an uncomplicated acute pain episode.
4. “Drug holiday”: Patients may wish to take “holidays” off Hydroxyurea. They should be warned that symptoms may recur within weeks of stopping therapy. The beneficial effects should return on restarting treatment, but may require 2-3 months.

**Pregnancy:**
Safety data for Hydroxyurea in pregnancy is limited, with several case series showing no adverse events. However, we currently advise stopping Hydroxyurea at the time of conception or a positive pregnancy test. For patients who have had a severe disease course prior to commencing Hydroxyurea, consideration can be given to a referral to “Motherrisk” (fax 416 813 7562) for further counselling around risk-benefit ratio.

**Duration of Therapy**
Assess clinical response, HbF%, and adverse events at 6 months.
If HbF% increment <2.5 and/or clinical response not apparent after 6-9 months, discuss discontinuation of therapy with the patient if compliance has been good.

---

**KEY POINTS:**
- Hydroxyurea is the only effective disease modifying agent in SCD
- Patients should be reviewed monthly during the period of initial dose titration to ensure compliance and tolerability

**RESEARCH OPPORTUNITIES:**
- Long-term follow-up of Hydroxyurea in adults

**References**
human endothelial cells from the micro- and macrocirculation: potential implications in sickle cell disease vasoocclusive events. *Haematologica*, 96, 534-542.


The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition


Blood Transfusion for Hemoglobinopathies

**Products**

All blood in Ontario is sourced from the Canadian Blood Service (CBS) and there are 3 types of RBC product available. The standard issue is normal packed red blood cells (PSL), with a unit meeting the standards of leucoreduction to $5 \times 10^6$, 240-340mL in volume and Hematocrit of 0.8L/L. These specifications are designed to ensure 1 unit raises the Hb by 10g/L in an average sized adult.

Patients who experience more than 1 anaphylactic reaction to RBC transfusion in the absence of IgA deficiency may be offered washed units. These can be prepared by the CBS or the UHN Blood Bank. The washing adds 2-3 hours to the wait time. The system of washing is currently an open system with associated increase in infection risk. Therefore, the units must be used within 24 hours of processing. Additionally, the washing process can reduce the efficacy of the blood by 20-25% leading to increased transfusion requirements and iron burden. For patients experiencing less severe, but troublesome reactions to standard units of blood, premedication should be used. This can be with Claritin PO taken a few hours prior to transfusion, Benadryl (more sedating) and Tylenol. Very occasional corticosteroids are used. An alternative to washed units is Plasma Volume Reduced (PVR). The PVR process is undertaken in the UHN Blood Bank and the additional processing time can lead to significant delays in availability of blood for transfusion. Patients must be refractory to adequate premedication prior to switching the type of product they receive. This is due to 1) the increased processing time and resources required, and 2) the decreased red cell recovery.

**Risk Reduction**

Due to the high risk of antibody formation from red blood cell transfusions, patients with thalassemia and sickle cell disease should receive RBCs that are prophylactically matched for C,c,E,e and Kell antigens. Patients with sickle cell disease who have already formed an antibody and may therefore be at higher risk of progressive sensitization should have prophylactic matching extended to the Jk$^a$, Jk$^b$, Fy$^a$, S and s antigens. Whenever possible, patients with sickle cell disease should have their red blood cell phenotype determined by genotyping studies so as to identify further opportunities to prevent sensitization due to partial antigens which are common in this population. Prophylactic antigen matching is generally considered unnecessary in other transfusion-dependent anemias, although matching for any identified clinically significant antibodies is still required. Transfusion of sickle cell patients with blood from donors who have sickle cell trait is safe but should be avoided if possible as it may confound post-transfusion measurements of HbS%. Other specialized blood products which patients may require include CMV-negative (for patients who are CMV-negative and pregnant. Detailed guidelines are available on-line in Clinical Policy 3.130.007.

To ensure that the most appropriate product is selected, it is important that the patient’s diagnosis be communicated to the blood bank with every transfusion request. In addition, patients should be provided with an antibody card which can be presented to other facilities, which might otherwise not detect any clinically significant antibodies whose titres have fallen below detectable. Finally, it is important to inform the Blood Bank of the names of other facilities where the patient has been transfused so that a full antibody history can be collated to avoid reactivation of quiescent or transient antibodies that may not be present at each crossmatch. This information can be documented in the comments section of the order entry in EPR. For the same reason, it is essential that the diagnosis of SCD is also provided at the time of ordering.
Prior to initiation of regular transfusions, patients should be immunised against hepatitis B virus. Annual screening for Hepatitis B and C and HIV is recommended.

Patients who have received more than 20 units of blood over their lifetime are at risk of iron overload and consideration given to assessment of liver iron concentration (LIC) by MRI techniques (Ferriscan at UHN).

**Hyperhemolysis Syndrome**

This is a transfusion reaction characterised by destruction of both autologous and allogeneic blood through mechanisms that have not been clearly defined, but including macrophage activation. Typically patients present 7-10 days following transfusion with worsening anemia (compared to pre-transfusion) and reticulocytopenia. An antibody is not always found or implicated; even when present, matching for newly detected antibodies does not protect against worsening post-transfusion haemolytic anemia. Once the diagnosis has been clinically confirmed, repeat transfusions are relatively contraindicated due to the risk of repeated hyperhemolysis. In the acute management, a standard transfusion reaction order set should be triggered along with informing the blood bank. EPO can be used, often at high dose, to temporarily increase the Hb level. EPO in combination with Hydroxyurea can further improve erythropoiesis. Case reports suggest a role of IVIG (2g/kg over 2-5 days) and steroid (eg. prednisone 1 mg/kg/day) in mitigating further hemolysis.

![Diagram of Hyperhemolysis of transfused blood and endogenous reticulocytes](image)

**Rationale and Indications**

The rationale for transfusion in Sickle Cell Disease is to either raise the Hb level to allow greater oxygen carrying capacity, or to reduce the sickling process. The former is achieved through simple, top-up transfusion, and the latter by exchange transfusion. To prevent adverse rheology of the blood (i.e. hyperviscosity) the Hematocrit should be kept less than 0.30. Therefore, top-up transfusion of a patient with a high baseline Hb may not be possible and necessitate exchange.

At UHN and Mount Sinai Hospitals, the blood bank will not issue RBCs to patients with SCD unless a hematologist or transfusion medicine Staff has approved the request. This is to ensure appropriate use of blood in this patient group.

The indications for transfusion in SCD are:

- Acute - neurological event, eg ischemic or hemorrhagic stroke, retinal artery occlusion
  - Acute Chest Syndrome
  - Progressive cholestasis
- Symptomatic, severe anemia, eg parvovirus
- Acute pregnancy complication

Acute indications are almost always managed with exchange transfusion, with the exception of severe anemia or mild acute chest syndrome

Chronic/Non-acute - primary or secondary stroke prevention
- Frequent vaso-occlusive pain episodes unresponsive to Hydroxyurea
- Pre-operatively for medium and high risk surgery

The rationale for transfusion in Thalassemia is the suppression of endogenous erythropoiesis, which is often achieved when the Hb nadir is in the range 95-105. Higher thresholds may be targeted for debulking of symptomatic extramedullary hematopoietic masses. For hemolytic anemias (eg PK deficiency) and red cell aplasia (eg Diamond Blackfan, CDA), the target is to relieve symptomatic anemia, and a lower Hb level often suffices, eg 80-90.

**Key Points:**
- Do not transfuse for simple anemia
- Exchange transfusion is preferred to top-up for most acute sickle complications

**Research Opportunities:**
- Comparison of alternative regimens for exchange transfusion

**References**

**Acknowledgments**
Dr Jacob Pendergrast, Transfusion Medicine, UHN
Red Blood Cell Exchange Transfusion

1. **Automated Red Cell Exchange**

**Indications**

**Acute:** Ischemic stroke, hemorrhagic stroke, acute retinal vein/artery occlusion, acute chest syndrome, acute hepatic episode, severe sepsis, multiorgan failure, priapism resistant to standard therapy

**Chronic/Elective:** Preoperative treatment, recurrent chest syndrome not responsive to standard therapy, chronic pain not responsive to standard therapy, previous stroke, high cerebral artery flow rates, non-healing leg ulcers, recurrent complications of pregnancy

**Location of Treatment**
Patients require in-patient treatment if: hemodynamically unstable, respiratory deterioration requiring oxygen, new acute neurologic impairment, pain requiring frequent narcotic treatment. Patients with severe sepsis, multiorgan failure, acute chest syndrome should be treated in ICU setting. All other patients may be treated in the outpatient apheresis unit.

**Blood Work**

**Initial:** CBC, reticulocyte count, Hb electrophoresis, electrolytes, Cr, AST, ALT, ALP, Bilirubin, Crossmatch.

**Follow up:** CBC, Hb electrophoresis post plasma exchange.

**Venous Access**
PLEX procedures should be attempted via peripheral veins. A 17g arterio-venous fistula needle (draw line) and a 18g angiocatheter (return line) is necessary. In the event that peripheral venous access is not possible, a hemodialysis type CVC will be required. For patients requiring one RBC exchange, the CVC line should be a temporary one, that is removed immediately after the RBC exchange procedure is completed to decrease risk of thrombosis. Patients with CVC should be anticoagulated (INR range: 1.8-2.0) from time that CVC is inserted.

**Medications**
If patient receiving ACE inhibitors, these should be withheld for the duration of plasma exchange procedures. ARBs are acceptable.

**Blood**
Should be matched, plasma depleted, sickle screen negative packed RBC with a hematocrit ~80%. RBC should be ABO, Rh (D,C,E) and Kell compatible if no evidence of antibody, or history of antibody formation. If history of antibody formation, RBC should be ABO, Rh, Kell, specific antibody negative and the RBC should be phenotypically matched as much as possible. This requires blood bank to perform a phenotype on the patient’s RBC.

**Target Parameters**
The exchange should occur to have the following parameters:

- end HbS: <20%, and to keep HbS <30% pre-next RBC exchange
Clinical Guidelines 2012

- End Hct: < 30% for acute indications, < 35% for chronic indications – to reduce risk of hyperviscosity and exacerbation of sickle cell vaso-occlusion.

**Pain**

Discontinuation for successful pain management on Red Cell Exchange should be done during warm months and not in or just prior to the winter months. Ideally, there should be an overlap of several months with initiation of Hydroxyurea. The transfusion interval should be tapered to prevent a rebound.

2. **Partial Manual Exchange (PMXC)**

Patients requiring chronic transfusion support for their SCD should be managed by PMXC. This is less resource intense, uses fewer units of blood and often does not require an indwelling central venous access device. Hb and HbS% levels can be controlled equally well with PMXC, automated exchange and simple transfusion if performed correctly. PMXC is the modality of choice at UHN and the order set is included in Appendix E. The standard prescription is phlebotomy of 2 units and transfusion of 2 units every 4 weeks. Hb and HPLC should be checked pre and post each procedure to monitor efficacy.

**KEY POINTS:**

- Patients must not be transferred to UHN/MSH for exchange transfusion without the approval of the Apheresis physician on call

**RESEARCH OPPORTUNITIES:**

**References**


The Management of Sickle Cell Disease; National Institutes of Health; NIH Publication No. 02-2117; 4th Edition

**Acknowledgements**

Dr David Barth, Therapeutic Apheresis Service, UHN
Thalassemia & Other Transfusion Dependent Anemias
Thalassemia/Iron Overload Clinic Guide

The following is a template for seeing a patient with Thalassemia, DBA or other transfusion dependent anemias in the clinic, along with the clinic processes. It is designed to facilitate residents rotating through the clinic.

**Flow**
The team meets 15 minutes prior to clinic starting to discuss cases and troubleshoot. This also gives time for residents to review the histories. Reception will notify the team when patients are ready to be seen. The patient is escorted from reception with their clipboard-mounted follow-up sheet to the designated clinic room. At the end of the consult, all orders should be entered in EPR and/or on paper reqs that are then attached to the clipboard. The follow-up also needs to be documented on the follow-up sheet. All referral forms and other paperwork are available in the clinic rooms. If the patient needs to see the SW or NP, call their extension and leave the patient in the room with the clipboard. At the end of the patient’s visit they will return to reception with the entire paperwork and follow-up sheet. Use the team room to dictate the note. No Shows are reviewed by the Staff/NP at the end of clinic to determine appropriate follow-up.

**Diagnosis**
- Genotype (β-thal, E/β-thal, Diamond Blackfan, etc.)
- Significant past Thal events (major transfusion reactions, ICU admissions, surgeries, etc.)
- Active Thal complications/ end organ damage (endocrinopathies, iron overload, etc.)
- Other active or significant medical diagnoses

**Meds**
- Current drugs and compliance
- Allergies
- Drug plan

**Transfusion & Chelation**
- Units, product type, and freq
- Hb level, suppressed retics
- Other facilities where transfused (Blood Bank can then contact for Ab history)
- Abs, Reactions
- Access (line/port/vein), anticoagulation and complications
- Chelating agent, mg/kg dosage, compliance
- Hep B/C and HIV serology (q1yr)
- Ophthalmology & audiology review date if on Desferal (q1yr)
- Urine dip result review if on Deferasirox
- Weekly CBC results if on Deferiprone
- Serum ferritin trend

**Systems Review**

**Cardiac**
- chest pain, SOB, exercise tolerance, palpitations
- exercise and weights training
Date of last cardiology appt
ECHO, ECG, BNP
Cardiac MRI T2* result

**Respiratory**
History of PE
SOB, pneumonias, pleuritic chest pain

**GI**
Liver MRI for LIC (Ferriscan)
Hep B/C status, date of last serology, and previous Hep C treatment
US liver, αFP
Gallstones, Cholecystectomy
Splenectomy and Immunisations: Flu shot (q1yr), Pneumococcal shot (q5yr), Meningococcal and HiB (one time booster)

**Endocrine/Bone**
Endocrinologist
Thyroid, diabetes, pituitary, sex hormones, vitamin D, Ca
DEXA scan
Males: testosterone replacement
Females: obstetric history, menses, COCP/HRT
Family planning

**Social**
Local Hospital
Job – inappropriate tasks
Education – time missed
Housing issues
Social work request
Psychiatry support request
Member of pt advocacy group

**Pain**
Chronic pain

**Examination**

**Management Plan – see flowsheet, EPR for order sets**
Labs, Imaging, Referrals, Next visit, cc list
Cardiac Iron Overload & Complications

Background
Iron related heart complications (cardiac failure, cardiac arrhythmia, progressive congestive cardiac failure or sudden death) are the leading cause of death and one of the main causes of morbidity. Patients with a fall in ejection fraction below reference values for the method used have a 35-fold increased risk of cardiac failure and death, with a median interval to progression of 3.5 years allowing time for intensification of chelation treatment. Aggressive iron chelation can restore myocardial function to normality. However, once overt heart failure is manifest, acute survival may be as low as 50%.

The prognostic implications of arrhythmia are related to the degree of myocardial iron-overload. Palpitations must therefore be investigated and treated in the context of the patient as a whole. Treatment is directed towards the relief of iron overload, with a secondary strategy of symptomatic treatment of the documented arrhythmia. Chest pain is uncommon in thalassemia, but may accompany intercurrent illnesses including pericarditis or myocarditis.

Assessment
Tools for monitoring include: ECG, ECHO, Cardiac T2* MRI, BNP measurement, and Holter monitor.

ECG changes commonly include changes in the T-waves and ST segment of the anterior chest leads, and sometimes right ventricular voltages. Occasionally P-waves are also affected, suggesting bi-atrial enlargement. Conduction disturbance in the form of bundle branch block may be seen.

For ECHO examinations a minimum data set should include right and left heart dimensions, biventricular function (LV fractional shortening and EF), estimated intracardiac pressures (PAP, systolic and mean) and Doppler analysis of intra-cardiac flows. Stress/strain analysis ECHO can be useful to detect individuals with subclinical disease in whom the EF fails to rise, or even falls, in response to exertion, and should be requested for all transfusion-dependent patients.

The Cardiac T2* MRI value shortens as the iron concentration increases. A shortening of myocardial T2* to <20 ms is associated with an increased chance of decreased LV function. Recently, it has become possible to convert the T2* value into cardiac iron concentration, CIC. From this new knowledge we believe the heart is exquisitely sensitive to the effects of iron deposition, as the CIC is much lower than that seen in the liver for equivalent dysfunction. The T2* value may identify patients at high risk of developing a fall in LVEF before it occurs permitting a more informed choice regarding patients whose chelation treatment should be intensified. A sudden fall in T2* measurement has also been seen in viral insults.
Management – General
- Maintenance of pre-transfusion Hb 90-100
- Adequate chelation therapy
- Lifestyle modifications including regular brisk walking for 30-60 minutes a day

Management – Chelation Therapy (Refer to Chelation section)
Continuous intravenous doses of Deferoxamine 50-60 mg/kg/day can normalise LVEF in a period of months, significantly before heart iron stores had been normalised. Even in the most overloaded hearts, myocardial iron can improve, with average myocardial T2* values of <6 ms. The average rate of improvement at this level of iron loading of the heart is about 3ms/yr.

In patients with baseline T2* values of between 8-20 ms, subcutaneous treatment at relatively low doses of 35 mg/kg showed an average improvement in T2* of 1.8 ms over one year. At a slightly higher dose of 40-50 mg/kg, five days a week, patients showed an improvement of 3ms over one year.

With salvage therapy, the route of administration is not critical, provided that as close to 24-hour exposure to chelation is achieved (reducing NTBI). For patients with abnormal heart function, combination therapy with Deferiprone and Deferoxamine is an alternative option. One study found that in patients with normal LVEF, Deferiprone given at high doses (92mg/kg) improved heart function. If the drugs are given in combination, they may interact in a process that involves the ‘shuttling’ of iron, which may lead to additional chelation of iron from cells. Combination therapy using variable Deferoxamine regimen plus Deferiprone at 75 mg/kg daily can improve LVEF measured by ECHO. T2* measurements have also been seen to improve with such a regimen. Deferasirox is not recommended for treatment of heart failure. There is limited data to support its use in patients with mild-moderate cardiac siderosis and a normal ejection fraction. Those patients with heavy liver iron are less likely to respond.

Management - Cardiac Drugs
ACEI or ARB: at low dose for cardiac failure or as primary prophylaxis in diabetics (in consultation with endocrinologist)
Digoxin: either as inotrope or for control of AF
Diuretics: use with caution as patients intolerant of reduction in pre-load due to poor diastolic function
β-blockers: for stable cardiac failure and tachyarrhythmia
Anticoagulation: atrial fibrillation and CHADS2 >2, indwelling venous access device, or for confirmed
pulmonary hypertension
Calcium antagonists and Amiodarone: avoid due to negative inotrope effect, and risk of thyroid disturbance, respectively. Patients on Amiodarone should have 3 monthly LFT and TFT monitoring, 6 monthly PFT and annual ophthalmology review.

Pulmonary hypertension (PHT) is currently considered to be the primary cause of heart failure in TI patients. Chronic tissue hypoxia and chronic hemolysis are believed to hold the central pathogenic role. On ECHO, a peak right ventricular systolic pressure of >45mmHg or >40 in the presence of symptoms is suggestive of PHT. (Refer to section on Pulmonary Complications for more details.)

KEY POINTS:
- Cardiac MRI can identify patients at risk of cardiac events allowing pre-emptive intensification of chelation therapy

RESEARCH OPPORTUNITIES:
- Optimal interpretation of Cardiac MRI T2*
- Assessment of fibrosis in patients with arrhythmias
- Inhibition of iron channels in cardiac myocytes

References
Borgna-Pignatti C, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 2004(B); Oct; 89(10):1187-93
Clinical Guidelines 2012


Acknowledgements
Dr Heather Ross, Associate Professor of Medicine, University of Toronto, and Director of the Cardiac Transplant Program at Toronto General Hospital.
Hepatology

1. **Iron Overload**
Excess iron is initially confined to the Kupffer cells but when transfusion requirements produce massive iron overload, spillover to hepatic parenchyma cells quickly occurs, with the risk of late development of fibrosis and cirrhosis. The threshold hepatic iron concentration for the development of fibrosis is about 7 mg/g dry weight liver. R2 MRI (Ferriscan®) appears to be the most accurate non-invasive measure of hepatic iron loading. (For management of iron overload, refer to the chelation chapter.) Hepatomegaly due to iron overload, and more commonly, extramedullary hematopoiesis can cause right upper quadrant capsular pain. Co-inheritance of a mutation for Hereditary Hemochromatosis can exacerbate the iron loading in the liver.

2. **Hepatitis C**
Active infection is diagnosed by the presence of circulating HCV RNA in blood. 80% of acute HCV infections are asymptomatic. However, chronic infection results in 70-80% and this leads to chronic HCV disease. Cirrhosis takes 20-30 years to develop and occurs in 5-25% of cases, depending on age and co-morbidities. Fibrosis can be reversed with removal of iron. The risk of hepatocellular carcinoma is greatest once cirrhosis has developed, and such patients should be screened with USS six monthly. αFP is a poor screening test for lesions less than 2cm. The risk of cirrhosis is also increased by poor iron chelation.

**Investigations** include: LFTs, INR, US liver, αFP, HCV PCR, HCV genotype, liver biopsy. Fibroscan has not yet been sufficiently validated in Thalassemia to warrant its routine use.

**Treatment:** Patients should be referred to Dr Sherman for management of liver disorders. Treatment is with Peg IFNα and Ribavirin and lasts 6-12 months. New therapies are expected within the next 3 years which may not be associated with hemolysis. Side effects of IFN include: flu like symptoms, mood disturbance, cytopenias and hypothyroidism. Considerations should be given to stopping Deferiprone during treatment as this may exacerbate neutropenia. Ribavirin can induce significant hemolysis, potentially increasing transfusion requirements by 30%. Dose adjustments should be avoided in order to maximize treatment success. Transfusion and chelation therapy may need to be intensified during treatment.

3. **Hepatitis B**
All patients should be immunized against Hepatitis B.

**Serology:**
- Anti-HBs: immunized
- HbsAg, HbeAg, anti-HBc IgM: acute infection
- HbsAg, anti-HBc, anti-Hbe: chronic inactive carrier
- HbsAg, anti-HBc, HbeAg or anti-Hbe with viral load: chronic active carrier
- anti-HBs anti-HBc: previous infection (consider measuring viral load)

Acute infection is usually characterized by jaundice and a prodrome. Progression to cirrhosis is less common than with Hepatitis C infection. There is a risk of hepatocellular carcinoma. This risk seems higher with particular genotypes. Patients should be referred to Dr Sherman for consideration of treatment and ongoing management. Therapy is usually with a nucleoside analogue, sometimes combination therapy. IFN is less
often used.

**Key Points:**
- For patients with significant liver iron deposition, other risk factors for liver disease should be minimised, eg alcohol avoidance

**Research Opportunities:**
- Non-invasive assessment of liver fibrosis

**References**
Deugnier, Y., B. Turlin, et al. (2011). "Improvement in Liver Pathology of Patients with beta-Thalassemia Treated with Deferasirox for at Least 3 Years." *Gastroenterology*.

**Acknowledgements**
Dr M Sherman, Staff Gastroenterologist, University Health Network
Splenectomy in Thalassemia

Splenectomy should be considered when annual blood requirements exceed 1.5 times those of splenectomised patients. For patients who maintain effective chelation therapy despite increased blood requirements, splenectomy may be unnecessary. Leucopenia or thrombocytopenia due to hypersplenism and causing clinical problems is another indication.

Cholecystectomy may be performed at the same time as splenectomy, as can liver biopsy to assess the liver histology. Thrombo-prophylaxis should be used post-operatively. In older studies, the risk of post-splenectomy sepsis in thalassemia major is increased more than 30-fold in comparison with the normal population.

Pneumococcal immunization should be administered at least 2 weeks before splenectomy. Patients who underwent splenectomy without being given pneumococcal vaccine may still benefit from vaccination post-splenectomy. Meningococcal polysaccharide vaccine should also be administered. Yearly administration of influenza virus vaccine is recommended, but the value of Penicillin V prophylaxis after 5 years of age is unproven.

Patients are at increased risk of venous thromboembolism and pulmonary hypertension, long-term. Patients with co-existing duplication of alpha globin genes can experience worsening of hematological and clinical symptoms post-splenectomy due to unmasking of the greater chain imbalance. Therefore, patients with TI should have their alpha globin gene complement checked before proceeding to surgery.

**KEY POINTS:**
- Splenectomy is rarely indicated in thalassemia patients
- Splenectomy in NTDT is associated with increased morbidities

**RESEARCH OPPORTUNITIES:**

References


Endocrinopathies

1. Hypogonadotropic Hypogonadism
This is the most common iron related endocrinopathy, resulting in delayed puberty as a result of pituitary damage. In childhood, the pituitary gland seems exquisitely sensitive to iron, causing irreversible damage. This damage seems to occur mainly in pubertal years and is characterised by reduced volume of the gland. Aggressive Deferoxamine therapy has also contributed to this in the past. Hormone replacement is often used. Testosterone can be administered monthly as an IM injection or in gel formulation, the latter being more physiological replacement. The total testosterone level should be kept within the normal range. A PSA should be performed annually and symptoms of prostatism elicited. In women, estrogen (with progestogen if ovaries intact) replacement is required and adequate replacement should result in a regular menstrual cycle. There is no need to repeat 17-β Estradiol levels once on hormone therapy. HCG is used for inducing spermatogenesis and various options are available for stimulation of ovulation. Patients should be referred to the fertility clinic at Mount Sinai Hospital.

Table 3. PG levels for diagnosis of IFG, IGT and diabetes

<table>
<thead>
<tr>
<th>IFG</th>
<th>2-hr PG in the OGGT (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/L)</td>
<td>4.1–6.9</td>
</tr>
<tr>
<td>IGT (post)</td>
<td>≤7.8</td>
</tr>
<tr>
<td>IGT and OGT</td>
<td>≥7.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥7.0</td>
</tr>
</tbody>
</table>

FG = Fasting plasma glucose
PG = Post glucose glucose
2-hr PG = 2-hour plasma glucose
OGTT = Oral glucose tolerance test
IFG = Impaired fasting glucose
IGT = Impaired glucose tolerance
NA = Not applicable
PG = Plasma glucose

Canadian Diabetes Guidelines 2008

2. Diabetes Mellitus
Impaired glucose tolerance and diabetes mellitus may be the consequence of β-cell destruction secondary to iron overload, chronic liver disease, viral infection and/or genetic factors. A fasting blood sugar or Oral Glucose Tolerance Test (OGTT) should be performed annually. Impaired glucose tolerance may be improved by a strict diabetic diet, weight reduction, and possibly intensive iron chelation therapy. In symptomatic patients, insulin treatment is normally required but metabolic control may be difficult to achieve. ACEI should be used for primary renal and cardiac protection in diabetics. The patient must be followed in a diabetic clinic for regular assessment.

3. Hypothyroidism
This may occur in severely anemic and/or iron overloaded patients, usually appearing in the second decade of life. The condition is uncommon in optimally treated patients. Annual investigation of thyroid function is recommended, with Free T4 and TSH. In patients with mild or overt hypothyroidism, L-thyroxine is given.

4. Hypoparathyroidism
In severe cases, hypocalcaemia, due to hypoparathyroidism may demonstrate tetany, seizures or cardiac failure. In cases with low serum calcium and high phosphate levels, parathyroid hormone should also be evaluated. Parathormone may be normal or low, with low readings for 1,25-dihydroxycholecalciferol
(vitamin D). Some patients require high doses of vitamin D to normalise their serum calcium levels. Calcitriol, 0.25-1.0 microgram twice daily, is usually sufficient to normalise plasma calcium and phosphate levels. In patients with persistently high serum phosphate levels, a phosphate binder (other than aluminium) may be considered. Tetany and cardiac failure due to severe hypocalcaemia require intravenous administration of calcium, under careful cardiac monitoring, followed by oral vitamin D.

**Key Points:**
- Non-compliance with chelation therapy increases the risk of endocrinopathies developing and also the likelihood of non-adherence with endocrine medications

**Research Opportunities:**
- Reversal of endocrinopathies with intensification of iron chelation
- Assessment of endocrine organ iron deposition

**References**
Osteoporosis

Osteoporosis is characterised by low bone mass and tendency to fracture. The causes in thalassemia are multifactorial, and include:

- marrow expansion secondary to ineffective erythropoiesis
- transfusional hemosiderosis
- delayed puberty
- use of chelation agents
- multiple endocrinopathies such as hypogonadism, low IGF1, low vitamin D levels (due to aberrant vitamin D-PTH axis).
- Genetic factors also seem to play an important role in the development of low bone mass.

<table>
<thead>
<tr>
<th>Gene and polymorphism</th>
<th>Possible underlying mechanism of action</th>
<th>Number of thalassemia patients</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALA P' (Sp1 polymorphism)</td>
<td>Down-regulation of structure and synthesis of procollagen type I</td>
<td>188</td>
<td>Wodke et al., 1990</td>
</tr>
<tr>
<td>FVEP* (Fold and fused polymorphism)</td>
<td>Down-regulation of growth factors</td>
<td>108</td>
<td>Ferrara et al., 2002</td>
</tr>
<tr>
<td>TGF-β1 (173-IVSIC and COLA1 Sp1 polymorphism)</td>
<td>Reduced osteoblast function and proliferation</td>
<td>139</td>
<td>Pezzutto et al., 2000</td>
</tr>
</tbody>
</table>

Vaskaridou, B J Haem 2004; 127,127-139

The commonest presentation is bone pain and backache with or without past history of fractures. Patients may also be asymptomatic in 20% cases. Diagnosis is best confirmed by bone mineral density (BMD). WHO criteria for osteoporosis is BMD > 2.5 SD below the normal mean (T score), and for osteopenia BMD > 1.0-2.5 SD below the normal mean. For young adults the Z score maybe more accurate assessment of risk.

Patients should have the following assessments:

- calcium, phosphate, liver function tests
- 25 (OH) vitamin D
- PTH as baseline only
- FSH, LH, testosterone / 17β-estradiol
- AP and lateral X-ray of the spine to rule out (micro)fractures
- DEXA
- MRI of spine to determine extramedullary hematopoiesis, especially in TI patients

The aim is to improve BMD score and prevent/reduce the future risk of fracture.

Vitamin D deficiency must be corrected (oral dose of 2000 IU/day) and calcium supplementation (500-1000 mg/day PO elemental). Diet and exercise should be modified accordingly, and smoking stopped. In TM patients with proven osteoporosis and hypogonadism, it is reasonable to try sex hormone replacement therapy for at least two years.

Bisphosphonate therapy can reduce the risk of vertebral fractures (40–50%) and non-vertebral fractures (20–
40%), including hip fractures. There is a small risk of jaw osteonecrosis and atypical long bone fractures with long-term use. They should not be used in women of child bearing potential. Combination therapy with bisphosphonate and HRT can be used. Patients on L-thyroxine and corticosteroid replacement therapy must be monitored carefully as excess replacement can aggravate osteoporosis.

Regular DEXA scan of the spine and femoral neck to determine the T/Z scores should be performed every 1-3 years. A rise of 1-2% per year is expected in the femoral neck score. After 3 years of Pamidronate therapy the BMD effect usually plateaux. Consideration can be given to cessation of Bisphosphonate therapy after 5 years of exposure. The hip BMD score can be falsely elevated in Sickle Cell Disease due to geometric differences, and any trauma or arthritis can also elevate the BMD result.

**Indications for referral to Osteoporosis Program/Endocrinology**

- Fracture
- Consideration of stopping bisphosphonate
- BMD score < -3.0

**Key Points:**

- Conservative measures should be maximised (Ca, vitD, exercise) prior to consideration of bisphosphonate therapy
- Bisphosphonates should be avoided in women of child bearing potential

**Research Opportunities:**

- Effect on BMD of stopping bisphosphonates after 5yrs in TM

**References**


**Thalassemia Intermedia (TI) / Non Transfusion Dependent Thalassemia (NTDT)**

Thalassemia Intermedia encompasses a wide clinical spectrum. Mildly affected patients experience only mild anemia and maintaining Hb levels 70-100. These patients require only occasional blood transfusions, if any. Patients with more severe TI generally are able to survive without regular transfusion therapy, though growth and development can be retarded. The clinical spectrum of TI indicates the need for an individualized treatment approach.

Most TI patients are homozygotes or compound heterozygotes for β-thalassemia. In general there are 3 mechanisms that reduce severity of disease in TI:
- inheritance of a mild β+ mutation
- presence of a SNP, such as BCL11A, associated with increased HbF
- Co-inheritance of α-thalassemia.

Gallstones are much more common in TI than in Thalassemia Major as a result of ineffective erythropoiesis and peripheral hemolysis. Laparoscopic cholecystectomy has more favourable and feasible outcome than open cholecystectomy. For the same reasons, patients are susceptible to kidney stones.

Extramedullary hematopoiesis is a compensatory mechanism to overcome the chronic anemia of TI, leading to the formation of erythropoietic tissue masses. These masses can be detected by MRI. They may cause neurological problems such as spinal cord compression and paraplegia, and intra-thoracic masses. Management includes transfusion therapy, as well as radiotherapy and Hydroxyurea.

Leg ulcers are more common in TI as are VTE. Pulmonary hypertension is prevalent in TI and the leading cause of heart failure in this population group. Endocrine dysfunction is less common, though osteoporosis is commonly seen and managed with calcium and bisphosphonates. Iron shuttling to the liver is thought to be driven by increased GI absorption from erythropoiesis, in these patients who are not transfused regularly.

Transfusions are indicated for: bone deformities; increasing anemia, significant thrombosis, leg ulcers, and pulmonary hypertension. Red cell allo-immunisation is a relatively common observation in TI as patients have not benefited from immune tolerance in early childhood. This can be a particular problem in women requiring transfusion only in pregnancy. Due to the improvement in iron chelation therapy and the realisation that non-transfused thalassemia is associated with a variety of serious conditions; there has been a trend towards chronic transfusion in many patients with TI over the past few years. Hydroxyurea can be used as an alternative to transfusions, though is ineffective for most patients.
**Hb E / β Thalassemia**

Hemoglobin E has a phenotype similar to mild β thalassemia. However, HbE/βthal has a variable and unpredictable clinical course, including hepatic iron loading, pulmonary hypertension and need for transfusions.

**Hb H Disease**

This is a mild condition characterised by ineffective erythropoiesis and hemolytic anemia. Patients should be screened at baseline as for TI, but unless they have a non-deletional mutation (eg Hb Constant Spring) does not need regular reassessment.

**Key Points:**
- NTDT/TI can accumulate significant liver iron independent of blood transfusions
- Non-transfused patients with related morbidities should be considered for chronic transfusions

**Research Opportunities:**
- Natural history of TI in Canada

**References**


Fertility

1. Conception
Women with Thalassemia Major often require induction of ovulation to bypass the iron-damaged pituitary gland. However, pregnancy is often thereafter uneventful if patients have had their iron chelation optimised pre-pregnancy. Iron chelation therapy should be stopped as soon as there is a positive pregnancy test. Thalassemia Intermedia can have a complicated course in pregnancy, but as fertility is usually preserved, spontaneous pregnancy is the norm.

Pregnancy
The patient should have an assessment of end-organ damage prior to conceiving with particular emphasis on cardiac function. Consideration should be given to a period of intensive chelation therapy prior to conceiving given the likelihood for increased transfusion requirements in pregnancy and the contraindication to chelation.

Folic acid should continue at 5mg daily without iron supplementation, Calcium and vitamin D supplements should continue.

The family should be offered pre-conception counselling and pre-natal diagnosis.

Prenatal care should be co-ordinated with an obstetrician with an interest in high risk pregnancies (Dr A Malinowski). The hematological care of thalassemia patients attending the obstetric clinic is overseen by Mount Sinai Hospital (Dr N Shehata). Patients will be seen q4w in the 1st trimester, q2w in the 2nd trimester, and weekly in the third trimester.

Regular ultrasound scans of fetal size and placental health at 20, 28, 32 and 36 weeks gestation may guide transfusions. Transfusion requirements often increase in the third trimester of pregnancy. Iron chelation therapy is contraindicated in pregnancy, though Deferoxamine is safe during breast feeding, and may be indicated in 2nd and 3rd trimester for those patients with critical cardiac iron overload. Oral chelators should not be used. However, there is usually minimal additional iron accumulation during pregnancy due to the fetus’ demand for iron.

Delivery of the fetus should not be delayed beyond 40 weeks. Birth is best by vaginal delivery if possible. VTE prophylaxis should be given for 6 weeks post-partum in transfusion - independent Thalassemia, especially those who have been splenectomised. DVT prophylaxis should also be used during any admission.

In Thalassemia Intermedia there may be significant marrow expansion from ineffective erythropoiesis, and there can be pelvic-cephalic disproportion and problems with vaginal delivery. Previously transfusion independent patients can be rendered severely anemic in pregnancy, necessitating transfusions with a high rate of allo-immunisation if previously transfusion free.

Standard antenatal care also applies to the pregnant thalassemic patient, including RhD prophylaxis and chromosomal screening.
**Key Points:**
- Pituitary iron deposition is not necessarily a barrier to fertility
- Patients should be referred to a fertility centre early in the family planning process
- Chelation should be optimised in the year pre-conception

**Research Opportunities:**
- Complications of TI and TM in pregnancy
- Fertility rates in the era of oral chelation therapy

**References**
Iron Chelation

Indication
Chelation therapy should be considered in adults who have had at least one year of regular transfusions (>20 units), evidence of iron overload (serum ferritin > 1000μmol/l on at least 2 readings separated by one month) and ongoing need for transfusion support with life expectancy exceeding 5 years. Effective iron chelation is vital to prevent morbidity and early mortality from the toxic effects of transfusion iron overload. In addition, non-transfusion dependent thalassemia (NTDT) is characterised by hepatic iron overload resulting from GI absorption of iron in response to exaggerated erythropoiesis. The ferritin is consistently lower in NTDT patients compared to TM.

Aim
The aim of therapy with all chelation regimes is to attain and maintain annual liver iron <3 mg/g dry weight, and cardiac T2* >20ms, and ideally to normalise these values. For chronically transfused patients with Thalassemia Major, these goals will correspond with an average serum ferritin of 500μg/l. In general, serum ferritin correlates weakly with hepatic and cardiac iron concentrations and therefore should not be solely relied upon to guide chelation therapy. There is poor correlation in serum ferritin between Thalassemia Intermedia and Major and between individual patients.

Infection
All chelation therapy should be temporarily withheld during episodes of infection until such time as resolution of symptoms or completion of a course of antimicrobials. Patients should be given a clinic chelation card to carry with this information on.

MRI Monitoring
MRI is the primary tool used to monitor and make decisions regarding change in chelator dose or strategy. When requesting the MRI in EPR you must state in the comment line the date you would like it booked for. Ferriscan also requires an out of country application to be approved by the MOHLTC prior to LIC analysis by Resonance Health in Australia. Ferriscan should not be ordered more than 3 months ahead of the booked date due to the window of approval from MOHLTC.

Cardiac T2* MRI should be performed annually, except:
- 6 monthly – T2* <10ms or downward trend in results; drop in EF below 50% or by 10% from
previous, recent change in chelation
  ▪ 18mths - 2 yearly – T2* >20 with continued good compliance with chelator

Liver MRI (R2, Ferriscan) should also be performed annually, except:
  ▪ 6 monthly – recent change in chelator
  ▪ 18mths - 2 yearly – LIC <3 with continued good compliance

**KEY POINTS:**
- Aim of chelation is to normalise total body iron stores and suppress NTBI

**RESEARCH OPPORTUNITIES:**
- Novel chelation regimens
Deferasirox (DFX, Exjade®)

Indication
Deferasirox should be considered first-line therapy for all patients requiring chelation who have a CMR T2* >10ms.

Access to/Funding of Drug
Deferasirox, as monotherapy, is covered by the Ontario Drug Plan via Exceptional Access Program for patients with Sickle Cell Disease, Thalassemia, DBA, CDA and PK deficiency. It is provided free of charge (or with a modest co-payment) by the manufacturer’s patient support program (PSP) to individuals lacking private drug plans and not eligible for ODP coverage. All patients should be enrolled in the PSP as they assist with pharmacy through McKesson, education and patient reminders, and also provide a mixer cup to patients to reduce the time required to dilute the Exjade.

Dose Range
10-45mg/kg (licensed to 40mg/kg)

Relative contraindications
Pre-existing renal disease (Cr Cl <30, on renal replacement therapy)
Pre-existing liver disease (ALT >5xULN unless due to hepatic iron overload)
Cardiac T2* < 10ms
Severe lactose intolerance
Pregnancy

Baseline Investigations
ALT, Creatinine, Urinalysis
Ferritin
Cardiac MRI T2*, R2 Liver MRI (Ferriscan®)

Initial Dose
20mg/kg

Monitoring
q1m
ALT, Creatinine, Urinalysis
q3m
Ferritin
Clinic Visit
as protocol (q1yr)
Cardiac MRI T2*, Liver R2 MRI (Ferriscan®)

Dose Adjustment for Adverse Effects
Adjustments can be made q1m in 5-10 mg/kg increments.
Increase in serum creatinine
If >33%, >ULN or proteinuria >0.3 on two occasions, reduce dose by 5-10mg/kg and repeat after 2-4 weeks. Discontinue if elevation persists and refer to nephrology. Dose can be increased (in 5mg/kg increments) if creatinine stable at <33% ULN for one month.

Diarrhoea/GI upset
Is the most common complaint and may respond to changing the time of day of administration or the diluents or timing with food. It seems to be best tolerated in the evening on a full stomach. If the patient is lactose intolerant suggest lactate supplementation. Dose reduction or cessation with slow, incremental reintroduction can relieve the symptoms. Daily administration is essential to overcome initial GI upset, and a smaller dose on a consistent basis is better tolerated than higher dose with intermittent compliance. Split dosing to bid can also alleviate adverse effects.

Skin rash
This usually resolves without requiring dose reduction. If rash is severe or persisting, discontinue until rash settles, and consider rechallenging following pre-medication with antihistamines and/or steroids. Do not rechallenge if suspicion of TENS (fever, pain, desquamation). A referral can be made to the Drug Allergy Clinic at Sunnybrook Hospital if this is a history of severe rash and re-exposure is required.

Elevated LFTs
>5 ULN, discontinue. Monitor weekly. Consider rechallenging at reduced dosage when LFTs return to normal.

Dose Adjustment According to Iron Stores
This is indicated by a trend of increasing serum ferritin levels (>1500 μg/l), increasing liver or cardiac loading or development of new clinical complications of iron overload. Dose can be increased by 10 mg/kg every month to a maximum dose of 45mg/kg (licensed up to 40mg/kg). The higher dose should be used only under exceptional circumstances. In general, patients with high and increasing iron burden should be treated with alternative regimens.

Once targets have been achieved for hepatic iron (<2 mg/g dw) and cardiac T2* (> 20 ms), the dosage recommended for maintaining iron balance. Interruption of treatment should never be considered but if serum ferritin falls consistently below 500 μg/l or hepatic iron concentration <2 mg/g dw, then tapering of the dose is advised to reduce adverse effects.

**KEY POINTS:**
- DFX is the first-line agent for iron chelation
- Renal and liver toxicity should be monitored monthly, including urinalysis

**RESEARCH OPPORTUNITIES:**
- BID dosing schedule, Long-term cardiac chelation efficacy
Deferoxamine (DFO, Desferal®)

**Indication**
Deferoxamine should continue to be considered for the following patient groups:
- Significant adverse reaction to Deferasirox and Deferiprone
- In combination with an oral chelator for patients with severe iron overload (LIC >15mg/g DW, T2*<10ms). Deferoxamine should be administered by continuous infusion for severe cardiac siderosis to suppress the generation of labile plasma iron (LPI/NTBI)
- End stage renal failure

**Access to/Funding of Drug**
Licensed for use in Canada, funding provided through Ontario Drug Plan. It can only be dispensed by TGH pharmacy, though shipping available for a small pharmacy fee.

**Dose Range**
20-50mg/kg infused 4-7 times a week over 10-14 hrs subq or IV
Ascorbic Acid 100mg PO on days of chelation may increase urinary iron excretion; higher doses or doses taken on non-Deferoxamine days may precipitate cardiac dysfunction.

**Administration**
There are a variety of pumps available for administration of Desferal:
- Baxter Infusor – disposable pump used for weekly continuous IV dosing
- CADD – cassette filled with Desferal. Used for intermittent IV or subq dosing over a course of a week.
- Graseby – vials of 2gm or 500mg Desferal are dispensed for the patient to reconstitute their own drug each night into a syringe. This is an option for intermittent suq dosing only. However, due to the fact patients must make their own drug, this is the least preferred option and should be discouraged.
A referral can be made to CCAC for assistance in pump and CVC care. For Baxter and CADD pumps, the TGH outpatient pharmacy needs to be informed of the day of the week to dispense the drug, and whether it will be collected by the patient, or shipped to a convenient location for a small fee.

**Relative contraindications**
Pre-existing sensorineural hearing loss
Pre-existing macular or retinal pigment epithelial disease
Pregnancy 1st trimester

**Baseline Investigations**
ALT, Creatinine, Ferritin
Ophthalmology and audiology referral
Cardiac MRI T2*, R2 Liver MRI (Ferriscan®)

**Monitoring**
- q3m Ferritin, ALT, Cr
- Clinic Visit
- q1yr
Ophthalmology, audiology referrals

as protocol (q1yr)
Cardiac MRI T2*, R2 Liver MRI (Ferriscan®)

Dose in absence of cardiac siderosis (LVEF > 55%, T2* > 20 ms)

<table>
<thead>
<tr>
<th>Hepatic iron concentration (mg/g dw)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3.2</td>
<td>20-30mg/kg, reassess closely</td>
</tr>
<tr>
<td>3.2 – 7</td>
<td>40 mg/kg, 5 nights/week</td>
</tr>
<tr>
<td>7-15</td>
<td>40 mg/kg 6-7 nights/week</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>50 mg/kg, 7 nights/week</td>
</tr>
</tbody>
</table>

Administration in presence of cardiac siderosis
Prescribe highest tolerated daily dose, based on LIC and therapeutic index (see below)
Administer 7 days/week, each infusion lasting minimum 14 hrs/day
If symptomatic cardiac disease, LV EF<50%, or T2* < 8ms, administer through continuous infusion in combination with oral iron chelator (note that in-dwelling venous catheters will require full anticoagulation for VTE prophylaxis).

Dose Adjustment for Adverse Effects

Therapeutic (Porter) index (thalassemia major only):
mean daily dose (mg/kg) / ferritin (µg/l); targeting the index < 0.025 at all times

Local skin reaction
Ensure correct dilution (10%) and rate of infusion.
Check for dressing allergy
If ulceration of skin, ensure adequate depth of needle insertion
Addition of hydrocortisone 1mg to infusion
Febrile illness or diarrhoea
Interrupt therapy until resolved.

Severe allergy
Consider desensitisation protocol or alternative iron chelator

Audiology
If worsening symptoms of hearing loss or tinnitus, or progressive deterioration noted on pure tone audiometry, hold Deferoxamine and repeat audiogram q1-3months until deficit has stabilized before re-introducing chelation. Base re-introduced dose on re-assessment of hepatic iron concentration, Porter index, or the previously tolerate dose.

Vision
If worsening symptoms of visual loss (esp. night blindness or central scotoma) or new lesions noted on ophthalmologic assessment consistent with chelator toxicity, hold Deferoxamine until symptoms and ophthalmologic findings have complete resolved. Base re-introduced dose on re-assessment of hepatic iron concentration.

KEY POINTS:
- Intermittent subq DFO is not recommended due to its poor control of NTBI
- To reduce toxicities, DFO dose reduction is often necessary when serum ferritin falls

RESEARCH OPPORTUNITIES:
Deferiprone (DFP, Ferriprox®/ L1)

**Indication**
It is most effective for removal of cardiac iron, but can be useful in removal of hepatic iron in patients who have been splenectomised (personal communication Apotex Inc.).

**Access to/Funding of Drug**
Not licensed in Canada or funded through Ontario Drug Plan; available through Health Canada Special Access Program after patient has been enrolled in manufacturer’s compassionate use program (Apotex; LA-04 Protocol). In addition to enrolling patient on the CUP, patients should be asked to sign Disclosure of Medical Information and Consent to Treatment forms. Physician must be prior approved by Apotex for prescribing.

**Dose Range:** 75-100mg/kg/day in 3 divided doses

If trend of increasing serum ferritin levels (>1500 µg/l), increasing liver or cardiac loading or development of new clinical complications of iron overload, 100mg/kg/d is preferred. Consideration should be given to using 100mg/kg dose for all patients where it is being used as monotherapy.

**Relative contraindications**
Pre-existing bone marrow failure syndrome (MDS, DBA)
History of unexplained neutropenia
Pre-existing arthropathy
Pregnancy
End stage renal failure

**Baseline Investigations**
CBC, ALT, Creatinine
Ferritin
Cardiac MRI T2*, R2 Liver MRI (Ferriscan®)

**Initial Dose**
75-100mg/kg/day in 3 divided doses

**Monitoring**
q1w (q5-10d)
CBC
q3m
Clinic Visit
ALT, Creatinine, Ferritin
as protocol (q1yr)
Cardiac MRI T2*, R2 Liver MRI (Ferriscan®)

**Dose Adjustment for Adverse Effects** (refer to LA-04 protocol)
Agranulocytosis (1-2%)
Clinical Guidelines 2012

Stop the drug immediately and consider use of G-CSF.
Do not rechallenge in the future.

**Neutropenia (4%)**
Temporary withdrawal of drug until resolved

In both cases, at least weekly monitoring of CBC until recovery of WCC.

**Arthropathy**
Monitor; analgesia (NSAID), consider dose reduction, x-ray or ultrasound of joint, refer to rheumatology and/or orthopedic surgery if symptoms become debilitating

**KEY POINTS:**
- Weekly CBC is essential in the first 6-12 months, as this is the time period for most episodes of neutropenia/agranulocytosis

**RESEARCH OPPORTUNITIES:**
- Efficacy and tolerability of DFP in Sickle Cell Disease
Salvage Therapy

Salvage therapy should be considered for patients with significant cardiac (T2* < 10ms) or liver (LIC > 15mg/g dw) siderosis, compliant with but unresponsive to single agent chelator.

Deferoxamine + Deferiprone
Deferoxamine 30-50mg/kg/d for 2-7 days/week + Deferiprone 75-100mg/kg daily in 3 divided dose

High Dose Single Agent Chelation
Deferoxamine 50-80 mg/kg/d continuous IV infusion
Deferiprone 100mg/kg/d in 3 divided doses

Deferoxamine + Deferasirox
Deferoxamine 30-50mg/kg/d for 2-7 days/week + Deferasirox 20-40mg/kg daily

Future Options
Deferasirox + Deferiprone oral combination
Shire/Ferrokin Biosciences Drug (Phase 2 studies)
Minihepcidins

References for Chelation Chapter
Limenta, L. M., Jirasomprasert, T., Jittangprasert, et al 2011. Pharmacokinetics Of Deferiprone In Patients With Beta-
Clinical Guidelines 2012

### Appendix A: Routine Investigations for RBCD Clinic Patients

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Transfusion Program</th>
<th>Non-Transfused</th>
<th>Critical Results (Notify MD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, retics</td>
<td>DFP: q1w</td>
<td>HU dose change: q2-4w</td>
<td>Hb &lt; 70 or &gt; 130 (unless chronic)</td>
</tr>
<tr>
<td>Blood Group &amp; Ab</td>
<td>Baseline phenotype</td>
<td>HU stable: q3-4w</td>
<td>neuts &lt;1.5 or &gt;10 (unless chronic)</td>
</tr>
<tr>
<td></td>
<td>Pre-transfusion</td>
<td>DFP: q1w</td>
<td>Plts &lt; 100 or &gt;1000 (unless chronic)</td>
</tr>
<tr>
<td></td>
<td>Repeat phenotype</td>
<td>Other SCD: q12m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with new Ab</td>
<td>Other TI: q6-12m</td>
<td></td>
</tr>
<tr>
<td>Hb Electrophoresis / HPLC</td>
<td>SCD: Pre- and post XC transfusion</td>
<td>HU: q3-4m</td>
<td>Post XC: Hb&lt;120, HCT&gt;0.3</td>
</tr>
<tr>
<td></td>
<td>Others: baseline</td>
<td>Others: baseline</td>
<td>HbA&lt;50%</td>
</tr>
<tr>
<td>PT/INR</td>
<td>Warfarin: Thrombosis Clinic</td>
<td></td>
<td>&gt; 5</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis: q6m</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All others: PRN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na, K, Creatinine</td>
<td>DFX: q1m</td>
<td>Na &lt; 130</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HU dose change: q2-4w</td>
<td>K &gt; 5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HU stable: q3-4m</td>
<td>Cr &gt; 120 (unless CRF) or 33% above</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TI: q12m</td>
<td>last value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCD: q12m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/Bili</td>
<td>DFX: q1m</td>
<td>ALT &gt;3x ULN or 2x last value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HU dose change: q2-4w</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HU stable: q3m</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other TI: q12m</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other SCD: q12m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>DFX: q1m</td>
<td>Any change from previous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCD: q6m</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others: q1yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>q3m</td>
<td>Chelated: q3m</td>
<td>&lt; 500 while on chelation (unless chronic)</td>
</tr>
<tr>
<td></td>
<td>SCD: q6m</td>
<td>TI: q6-12m</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others: q1yr</td>
<td>Others: PRN</td>
<td></td>
</tr>
<tr>
<td>Ca, vitD</td>
<td>Osteopenia POROSIS: q6-12m</td>
<td>Osteopenia POROSIS: q6-12m</td>
<td>Ca&lt;2.0, vit D &lt;75</td>
</tr>
<tr>
<td></td>
<td>Others: q1yr</td>
<td>Others: q1yr</td>
<td></td>
</tr>
<tr>
<td>Endocrine (TSH, FT4, fBS, FSH, LH,</td>
<td>Thyroid disease: q12m</td>
<td>Thryoid Disease: Clinical</td>
<td>TSH: Undetectable or &gt; 10</td>
</tr>
<tr>
<td>testosterone or 17β estadiol)</td>
<td>Diabetes: Endocrine Clinic</td>
<td></td>
<td>fBS: &lt;4 or &gt;20</td>
</tr>
<tr>
<td>PSA</td>
<td>Q1yr if on testosterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>qFP</td>
<td>Cirrhosis: q6m</td>
<td>qULN</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td>Cardiac disease/PHT: q3-6m</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others: q1yr/Dr Ross appt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B &amp;C, HIV</td>
<td>q1yr</td>
<td>Transfusion exposure (max q1yr)</td>
<td>New positive result</td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>DFP: before starting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D ECHO</td>
<td>q1-3yr</td>
<td>SCD: q3-5yr if normal baseline</td>
<td>Positive result</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TI: q3yr if normal baseline</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>Dr Ross appt</td>
<td>LVEF &lt; 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRN</td>
<td>RVSP &gt; 40 mmHg or TRJV&gt;2.5</td>
<td></td>
</tr>
<tr>
<td>Cardiac T2* MRI</td>
<td>Baseline priority for TM</td>
<td>Baseline only if clinical concern</td>
<td>T2* &lt; 10 ms</td>
</tr>
<tr>
<td></td>
<td>&lt;10: q4-6m</td>
<td>T1* in 10% decrease in EF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-25: q1yr</td>
<td>Decrease in T2*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;25: q1.5-2yr</td>
<td>Increase in LIC</td>
<td></td>
</tr>
<tr>
<td>Ferriscan R2 Liver MRI</td>
<td>Baseline for all q1yr</td>
<td>&gt;15 mg/g dry weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>q6m if significant chelator changes</td>
<td>Increase in spleen size*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Liver</td>
<td>Cirrhosis: q6m</td>
<td>Any new lesion increase in spleen size*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible spleen regrowth: PRN*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any new abnormality</td>
</tr>
<tr>
<td>BMD (Osteo Prog)</td>
<td>as report recommends</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFTs</td>
<td>Chronic lung disease: q3-5yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others: PRN</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Audiogram</strong></td>
<td><strong>DFO: q1yr</strong>&lt;br&gt;<strong>Others: PRN</strong></td>
<td><strong>New or progressive deterioration</strong></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------</td>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Ophthalmology</strong></td>
<td><strong>DFO: q1yr</strong>&lt;br&gt;<strong>SCD: q1-2yr</strong>&lt;br&gt;<strong>Others: PRN</strong></td>
<td><strong>Any new lesion</strong></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix B: Contact List for Common RBCD Specialist Referrals

<table>
<thead>
<tr>
<th>PHYSICIAN/CLINIC</th>
<th>CONTACT DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. David Barth</td>
<td>PME, 14th Floor, Telephone: 416-946-4688</td>
</tr>
<tr>
<td>Dr. Leanne Cusenbom</td>
<td>TWH, 5th Floor, West Wing, Telephone: 416-603-3045</td>
</tr>
<tr>
<td>Dr. Rodney Davis</td>
<td>TWH, 1 East Orthopedic Clinic, Telephone: 416-603-3732</td>
</tr>
<tr>
<td>Dr. C. Valente</td>
<td>TWH, 1st Floor, East Wing, Telephone: 416-603-9839</td>
</tr>
<tr>
<td>Dr. Michael Filling</td>
<td>TWH, Telephone: 416-603-2955</td>
</tr>
<tr>
<td>Dr. Philip Guan</td>
<td>TWH, 5th Floor, East Wing, Telephone: 416-603-3766</td>
</tr>
<tr>
<td>Dr. Mark Mandich</td>
<td>TWH, 5th Floor, East Wing, Telephone: 416-603-3785</td>
</tr>
<tr>
<td>Dr. Maria Md</td>
<td>TWH, 3rd Floor, East Wing Eye Clinic, Telephone: 416-603-5311</td>
</tr>
<tr>
<td>Dr. Robert Roper</td>
<td>TWH, 4th Floor, Telephone: 416-340-4053</td>
</tr>
<tr>
<td>Dr. Rong Meng</td>
<td>TGH, 10th Floor, Telephone: 416-340-3050</td>
</tr>
<tr>
<td>Dr. Bruce Peterson</td>
<td>TGH, 12th Floor, Telephone: 416-340-4533</td>
</tr>
<tr>
<td>Dr. Iman George</td>
<td>TGH, 12th Floor, North Wing, Telephone: 416-340-4300</td>
</tr>
<tr>
<td>Dr. Han Liu</td>
<td>TGH, 10th Floor NCHB, Telephone: 416-340-5160</td>
</tr>
<tr>
<td>Dr. Robert Ivanov</td>
<td>TGH, 1st Floor, East Wing, Telephone: 416-340-5600</td>
</tr>
<tr>
<td>Dr. Heather Ross</td>
<td>RBCD CLINIC, Telephone: 416-340-8888</td>
</tr>
<tr>
<td>Dr. Bruce Kohnke</td>
<td>The Sheppard Heart Centre, 105 Sheppard Avenue East, Suite #940, North York, ON M2N 0G1, Telephone: 416-224-0752</td>
</tr>
<tr>
<td>Dr. Angela Mann</td>
<td>TWH, South Pavilion, 4th Floor, Telephone: 416-603-2580</td>
</tr>
<tr>
<td>Dr. Karen Mandich</td>
<td>TGH, Main Pavilion, 4th Floor, Telephone: 416-603-7713</td>
</tr>
<tr>
<td>Dr. Robert Richardson</td>
<td>TGH, 12th Floor, North Wing, Telephone: 416-340-3888</td>
</tr>
<tr>
<td>Dr. Rowan Ekon</td>
<td>TGH, 11th Floor, North Wing, Telephone: 416-340-4000</td>
</tr>
<tr>
<td>Dr. Aparna Malini</td>
<td>Mount Sinai, 3rd Floor, Telephone: 416-340-4000</td>
</tr>
<tr>
<td>Dr. Devin Sherman</td>
<td>Nell, 10th Floor, North Building, Telephone: 416-340-4158</td>
</tr>
<tr>
<td>Dr. David Utech</td>
<td>TGH, 10th Floor, Norman Urquhart Wing, Telephone: 416-340-4584</td>
</tr>
<tr>
<td>Wound clinic, Women’s College Hospital</td>
<td>26 Grenville Street, 10th Floor, East Wing, Telephone: 416-333-6407</td>
</tr>
</tbody>
</table>
Appendix C: UHN Emergency Department Orders for Acute Sickle Cell VOC Episode

1. MONITORING:
   a) TRIAGE
      - Vital Signs: temperature, blood pressure, heart rate, respirations, oxygen saturation
      - Initial pain assessment scale x 1
      - Nurse to inform MD of initiation of pathway
      - First analgesia to be administered within 30 minutes of presentation to ED

   b) SUPPORTIVE CARE
      - Administer oxygen via nasal prongs or mask to maintain oxygen saturation greater than 96%
      - Vital signs q 30 min until pain controlled (BP may not be possible due to pain)
      - Repeat pain assessment scale q 1 h, or until pain resolved

2. LABORATORY TESTS:
   - APPT, INR (NOT necessary for simple painful crisis)
   - CBC, Potassium, Sodium, Chloride, Creatinine, Calcium, Magnesium, Phosphate, Blood Glucose, AST, ALT, Bilirubin, AED/Group & Screen (as needed)

3. DIAGNOSTIC TESTS:
   - ECG for ongoing chest pain
   - CXR: Temperature greater than 38.3°C, SpO₂ less than 95% or respiratory symptoms
   - Blood Culture and sensitivity (CSS) x 2, and urine CSS if temperature greater than 38.3°C

4. IV THERAPY:
   - IV Normal Saline (NS) at 150 mL/h – (ONLY if unable to take PO fluids)

5. MEDICATIONS:
   - NON-OPIOID ANALGESIA (Give both)
     - Acetaminophen 1 g PO q 6 h
     - Ibuprofen 800 mg PO q 6 h (Maximum dose 3.2 g q 24 h)

   - OPIOID (Choose 1 only)
     - Morphine 20 mg PO q 1 h (until pain controlled then q 2 h pm)
     - Morphine 10 mg SC q 30 min (until pain controlled then q 1 h pm)
     - Hydromorphone 2 mg PO q 1 h (until pain controlled, then q 1 h pm)

   ** May adjust starting dose of above according to home maintenance dose **

   - ANTIETEMETIC (Choose 1 only)
     - Dexamethasone (Decadron) 50 mg IV PO q 4 h pm
     - Metoclopramide (Maxolon) 10 mg IV PO q 6 h pm
     - Prochlorperazine (Stemetil) 10 mg IV PO q 6 h pm

6. CONSULTS:
   - Social work for all new patients
   - Consider Acute Pain Service if complex analgesic requirements or inadequate pain relief after 90 minutes
   - Hematology prior to ordering blood transfusion (Note: when requesting red blood cells from blood bank, requisition MUST indicate that patient has sickle cell disease)
   - Urine for protein greater than 4 hours
   - General Internal Medicine if either
   - Organ dysfunction (eg., neurologic symptoms, chest x-ray infiltrates, hepatomegaly)
     - Unable to control pain (eg., pain scale less than 6) with oral medications

   Physician's Signature: Date: / / Time: / /
Appendix D: RBCDP Opiate Contract

**The Use of Opiate Analgesics**

This document and the attached contract are about the use of opiate analgesics. This information on this page describes how to manage your pain. The attached contract is meant for all patients in the Red Blood Cell Disorders (RBCD) program who use opiates.

**Helping You with Your Pain Killer/ Opiate Analgesia**

Living with chronic and complex medical conditions might require treatment for pain episodes. We want to help you lead as normal a life as possible. In order to assist you in the Emergency Department, you may find that having a supply of pain killers/analgesics at home may be helpful in managing your pain. However, if you’re in pain, you should consult with a doctor/nurse practitioner to make sure that no additional complications are happening.

**Attention should be paid to any other causes for chronic pain.**

Opiates are the strongest form of analgesics. They are often used where other painkillers are ineffective. Painkillers and analgesics are all different types of drug, containing a combination of morphine (such as Pethidine and Opioids). Other opiates include Methadone, Hydromorphone (Dilaudid), and Fentanyl.

Usually you should not need pain killers/analgesics on a daily basis – only during the acute pain episode. If you need opiates all the time this may mean that:

- You have a complication from your medical condition that needs investigating (for example, heart or lung damage) – please arrange a clinic visit.
- You are not on a high enough dose and the pain is being undertreated.
- Your body has become tolerant to the pain killers/analgesics and no longer works as well as before (tachyphylaxis).

If you are having an acute episode of pain, the following methods of pain management may be useful:

1. Take your pain medicine when the pain first starts.
2. Drink plenty of fluids.
3. Try to relax.
4. Avoid triggers.
5. Try distraction techniques such as listening to music or watching a DVD or challenging yourself on the phone.
6. Try placing a hot pad on the painful areas.

If you have chronic pain, you may be referred to the Comprehensive Pain Clinic at the Toronto General Hospital (UHN). The pain clinic will assist you to phone the clinic in order to schedule the appointment directly.

The Ministry of Health, the College of Physicians and Surgeons of Ontario, and pharmacists associations are all concerned about the general use of opiates by patients. The reason for this is that there have been cases of death due to inappropriate use of pain killers/analgesics, especially fentanyl.

It is part of our job to make sure that you are not suffering during painful episodes. However, the only way to make contact that you are safe with your physician by understanding how best to use it. If you only need the occasional help with pain medication, we will help you to find alternative pain medications that will be more effective for you.

On the other page you will see the contract of care that our clinic team would like you to agree to. It outlines some basic aspects of care for patients who require opiates as well as the RBCD program’s commitment to you. A contract like this is seen by the College of Physicians and Surgeons of Ontario (CPSO) as part of our duty of responsibility for patients with ongoing pain. This should help maximize the use of patients who are using prescription pain medications more effectively in recent months. If this happens, there may be a delay in receiving your medications.

Should you have questions, please feel free to discuss this with any member of the Red Blood Cell Disorders (RBCD) clinic team.

---

**Opioid (Narcotic) Medication Treatment Agreement**

I understand that I am receiving opioid medication from Dr. J. Pendergast, R. Ward and E. Yao in the RBCD Clinic at Toronto General Hospital. I agree to the following conditions under which this medication is prescribed:

1. I will not see opioid medications from any other physician. Only Drs. Pendergast, Ward and Yao will prescribe opioids for me.
2. If I am discharged from ER or hospital, I will inform the Clinic of any opioids given at discharge.
3. I will not be given opioid medications in larger amounts or more frequently than is recommended and advised by the Clinic.
4. I will not give or sell my medication to anyone else, including family members, nor will I accept any opioid medication from anyone else.
5. I will not use over-the-counter opioid medications such as ibuprofen.
6. I understand that this agreement will be signed by any pharmacists/ doctors who are involved in my care.
7. I understand that if I sign this agreement, I agree to the above conditions.

I understand that if I break these conditions, the Clinic doctors may choose to cease writing opioid prescriptions for me or discharge me.

---

Patient

Clinic Staff

Date

---

Reference:

- UHN Red Blood Cell Disorders (RBCD) Program
- References for authors

Page 83 of 86
Appendix E: Partial Manual Exchange Orders

6. TRANSFUSION:
   - For patients having partial manual exchange, do not start procedure until Hb result available.
   - For patients receiving transfusion only, may start to transfuse at baseline level (as ordered below) prior to Hb result being available.
   - For subsequent units, if Hb between _________ and _________ g/L, then proceed.
   - Notify HMD.

   a) Partial manual exchange procedure in sequence:
      - Place patient in supine position, do not start procedure until Hb result available.
      - Hydrate normal saline NS 500 mL over 30 minutes
      - Place patient in supine position, do not start procedure until Hb result available
      - Notify HMD.

   b) Transfuse via infusion pump:
      - Transfuse units of packed cells at _________ (rate)
      - Transfuse units of washed blood at _________ (rate)
      - Transfuse units of plasma volume reduced packed cells at _________ (rate)

7. MEDICATIONS:
   - Pre-transfusion:
     - Antihistamines (Tavegyl 40 mg PO 1 hour before transfusion for patients with a history of antihistamine allergy)
     - Loratadine (Claritin 10 mg PO within one hour prior to transfusion)
     - Dexamethasone (Decadron 10 mg IV over 15-30 minutes)
     - 1 hour prior to transfusion

   b) Treatment of Transfusion Reactions:
      - Refer to UHN Acute Transfusion Reaction Policy.
      - Acetaminophen (Tylenol) 500 mg PO every 6-8 hours for temperature over 38°C
      - Cefcapene (Zinacef) 250 mg PO every 8 hours for temperature over 38°C
      - 1 hour prior to transfusion

   c) Other Medications:
      - Furosemide (Lasix) 40 mg PO (max 1 dose for fluid overload)
      - Nebulizer (Symbicort) 2-4 puffs every 6 hours for respiratory distress
      - Influenza Vaccine 0.5 mL IM q 4 weeks.

8. POST TRANSFUSION:
   - CBC and Hb Electrochemistry
   - Discharge home after transfusion completes, MDIU admission criteria met, and next appointment booked.

9. Other Orders:
   - Physician's signature: Date: / / Time:
Appendix F: List of RBCDP Patient Information Leaflets

So I Have Sickle Cell Disease

Pain Crisis & Sickle Cell Disease (D5735)

Priapism and Sickle Cell Disease (D5775)

Iron Chelation Therapy (D5736)

Hydroxyurea (D5738)

Calcium, Vitamin D and Bone Health (D5092)
## Appendix G: Referral Proforma for Patients Transfused in the Community

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Date of Birth</th>
<th>Referring Physician</th>
<th>Institution</th>
<th>Address</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>John Smith</td>
<td>01/01/2000</td>
<td>Dr. Johnson</td>
<td>UHN - TGH</td>
<td>123 Main St</td>
<td>416-555-1234</td>
</tr>
</tbody>
</table>

### RED BLOOD CELL DISORDERS PROGRAM

**TRANSMISSION REFERRAL FORM**

**TO:**

**DATE OF REFERRAL:**

**Comments:**

- **Diagnosis:**
  - Diamond–Blackfan Anemia
  - Thalassemia Major
  - Sickle Cell Disease
  - Other:

- **Indication for Transfusion:**
  - Management of Thalassemia
  - Sickle Cell Disease
  - Other:

- **Transfusion Goal:**
  - Target hemoglobin %
  - Target HCT %
  - Other:

- **Post-exchange hemoglobin:**
  - Post-exchange Hb
  - Other:

- **Units of packed red blood cells:**
  - Number of units
  - Other:

- **Iron Chelation Therapy:**
  - Deferoxamine (Defera) Deferasirox (Exjade) Deferasirox (Ferinject)

- **Iron Chelation Monitoring:**
  - Please ensure the following samples are obtained and faxed to the RBCD Clinic at UHN - TGH on a monthly basis:
    - AST
    - ALT
    - ALP
    - Bilirubin
    - Sodium
    - Calcium
    - Creatinine
    - Urea
    - BUN
    - Ferritin (every 6 months)
    - Pre-exchange (Lactate Dehydrogenase)
    - CRP (weekly for patients on deferoxamine)

- **Other information:**
  - Patients should present their UHN issued antibody card at the time of their first appointment with every update. This card should be forwarded to your institution’s blood bank.
  - Please inform UHN RBCD clinic and blood bank of any new antibodies in incompatible cross matching and/or any transfusion reactions.

- **Please see the accompanying notes for supporting documentation.**

---

**For more information, please contact the UHN Red Blood Cell Disorders Program: 416-555-1234**

---

**Please contact the patient directly with appointment details and fax a copy to the Red Blood Cell Disorders Program for our records.**

---

**Please contact the patient directly with appointment details and fax a copy to the Red Blood Cell Disorders Program for our records.**