North West London Haemoglobinopathy Network

Hydroxycarbamide Guideline for the treatment of sickle cell disease patients

1.Background

This guideline focuses on the role of Hydroxycarbamide (HC) in homozygous sickle cell disease (HbSS). HC, also known as Hydroxyurea (HU), is the first oral drug that is well tolerated and proven to ameliorate the clinical severity of sickle cell disease (SCD) by decreasing the frequency of painful crises, reducing the number of episodes of acute chest syndrome, and reducing blood transfusion requirements. While HC has been shown to be of benefit in other types of sickle cell disease e.g. HbSC disease, its use in this setting should be discussed on an individual patient basis. HC also has a role in children with some forms of transfusion dependent anaemias such as Haemoglobin E beta-thalassaemia: it may improve growth and prevent hyposplenism in children with SCD. Evidence indicates HC improves survival in SCD. The mechanism of action is not fully understood, however it is known to increase fetal haemoglobin (HbF), improve red cell hydration, and reduce the degree of leucocytosis and thrombocytosis commonly seen in SCD.

HC should be used with caution but equally offered to patients who may benefit from its therapeutic effects. It is not currently an alternative to transfusion programme for patients with known stroke risk or avascular necrosis.

HC is a chemotherapeutic agent; therefore patients require regular monitoring as it may cause myelosuppression in the short-term. Clinically effective doses often approach or overlap with myelosuppressive dosages. **Patients recently started on HC, those not medically stable on the medication and those receiving the maximum tolerated dose (MTD) require more rigorous monitoring.**

HC has been used for over twenty years in haemoglobinopathy patients and studies monitoring long-term use in this patient group show it is effective and safe. There is still some uncertainty about long-term safety and side-effects as longitudinal observational data are limited though overall survival is better among patients who receive HC. This must be discussed with the patient/parent and monitoring is required throughout treatment.

2. Indications for use in SCD:

HC is reserved for patients with severe or moderate disease.

i. Three hospital admissions for painful episodes in the previous 12 months or repeated painful crises at home requiring regular time off work/school or affecting normal daily routine or

ii. More than one admission with painful episodes in the previous 12 months, and a clear history to suggest they are symptomatic in the community (child missing excessive school), or

iii. Two life-threatening complications of the disease, such as acute chest syndrome, or

iv. One episode of ACS requiring ventilation.

v. There may be other indications, especially in patients with other sickle cell disorders, and these should be discussed with the red cell consultant.

3. Exclusions

i. Pregnancy or breast feeding.
ii. Risk of pregnancy – patient not using contraception.
iii. Liver disease – ALT >2 x upper limit of normal. Unless raised ALT due to iron overload in which case use with caution.
iv. Concerns about ability to attend clinic regularly for monitoring.
v. On transfusion programme.
vi. Renal disease – reduce dose, avoid if severe.
vii. Use with caution in patients with a history of leg ulceration.

NB:	***Caution is advised in prescribing for children under the age of 2 years. The decision should only be made by a consultant paediatric haematologist/consultant paediatrician with expertise in haemoglobin disorders***

4. Discuss fully with patient/parent and obtain written consent

i. Explain present knowledge about side effects and toxicity, such as, short-term cytopenias, nail pigmentation (common but reversible), skin pigmentation (rare but reversible), the theoretical (but unproven) long-term risk of leukaemia/malignancy and the evidence concerning reduced sperm counts and activity.

ii. Advise on avoidance of live vaccines.

iii. Discuss the importance of avoiding pregnancy during treatment and the requirement for adequate contraception. Ensure male patients understand they should not get their partners pregnant while on HC. ***See section 6***.

iv. Discuss the necessity to stop HC three months pre conception in both male and female patients. Females should stop HC for the duration of pregnancy and while breast-feeding. ***See section 6.***

v. Provide patient with a HC information sheet.

vi. Obtain written consent from patient (and parent if under 18 years).

vii. Provide GP, Community Haemoglobinopathy Nurse/Counsellor, patient's local Clinical Haematologist and Nurse Lead (if applicable) with copy of HC guideline and patient information sheet.

5a. Dosage and myelosuppression

i. Decide the objective of treatment: Maximum Tolerated Dose (MTD) or a Fixed Dose regime.
ii. Hydroxycarbamide is available as 500mg capsules and suspension of 100mg/ml.
iii. It may be necessary to alternate daily doses or skip days to get the required weekly dose so that the dose/dg/day is more accurate.
iv. Usual maximum dose is 15-30mg/kg/day or up to 35mg/kg in some cases.
v. **Discuss with hospital pharmacy – in some Trusts there may be special requirements for HC such as completing a chemotherapy referral form.**

5b. MTD: initiation, titration and monitoring schedule

Adults: Start at 15 mg/kg/day to nearest 250 mg, increasing 4-8 wkly by 5mg/kg/day.
Children: Start at 15mg/kg /day, increasing by 5mg/kg/day every 8-12 weeks.

MTD is reached when the Full Blood Count (FBC) shows one or more features of cytopenia:
Neutrophils < 1.5 x 10^9/L, (have a lower threshold for patients with ethnic neutropenia and remember to look at the trend of the counts) or
Platelets < 80 x 10^9/L, or
Reticulocytes < 1%, or
Change in haemoglobin of 3g/dl from baseline

THEN STOP HC until the FBC has recovered - generally 1-2 weeks - checking the FBC weekly or more often if necessary. Restart at 2.5 mg/kg lower or reduce by 1 capsule (500 mg) alternative or every three days. This is the MTD (if there is no other cause of the cytopenia e.g. infection, aplastic anaemia).

i. Clinical monitoring

a) Collection of routine data (clinical history, physical examination)
b) Last menstrual period (LMP) dates recorded.
c) Assess and discuss risk of pregnancy with patient.
d) Document side effects.
e) Assess and monitor adherence. Implement interventions to improve adherence, if required.
f) It is important to encourage the patient to persevere with treatment until the therapeutic dose is reached. Clinical benefit may not be apparent for several months.
g) Assess efficacy after 12 months – consider stopping if little/no benefit.

ii. Laboratory investigations

Timing	Laboratory tests
At start of therapy	FBC, Hb electrophoresis, reticulocytes (retics), serum ferritin, clotting, U&Es, LFTs, LDH, Hepatitis B and C serology
Every 14 days until MTD reached	FBC, retics, U&Es, LFTs
Every 14 days at MTD until stable (for 8 weeks or until HbF and MCV have plateaued).	FBC, retics, HbF, U&Es, LFTs
Once stable at MTD: Children every 4-6 wks. Adults every 8 weeks.	FBC, retics, U&Es, LFTs, LDH and HbF every six months.
Adults only: Increase to 3-6 monthly if stable for years on HC.	FBC, retics, HbF, U&Es, LFTs, LDH

The monitoring schedule is outlined in appendix A and B.

5c. Fixed Dose Regime

Evidence of HC efficacy was initially shown at MTD. Clinical benefit may be achieved at a dose below MTD and if sustained a decision may be taken to maintain the patient on the lower dose.

6. Fertility and pregnancy

i. No high quality research exists regarding the impact of SCD on fertility or the effect of HC on fertility. Small studies indicate that SCD patients may have abnormal sperm parameters including reduced sperm counts and motility. There is also some evidence that these abnormalities may be exacerbated in SCD patients on HC but no evidence that this adversely affects fertility. Some experts advocate sperm banking prior to commencing treatment in post-pubertal males with SCD but this is not offered to other groups of patients who are prescribed HC. It is recommended that semen analysis is offered to post-pubertal males prior to commencing HC and the option of storage discussed with the patient.

ii) Both male and female patients are required to practice active contraception while on HC. Monitor compliance during follow-up. Check date of LMP at every clinic visit, if necessary, and counsel patients regularly that they or their partner must avoid pregnancy.

iii) Stop HC three months before conception in both male and female patients. Males can restart treatment after conception but it may be prudent to wait until the foetus is three months before restarting. Females must stop HC for the duration of pregnancy and until breast-feeding is stopped. It may be necessary

to commence a transfusion programme as a bridging measure while HC treatment is interrupted.

7. Hydoxycarbamide Side effects

Expected Bone marrow suppression → cytopenias
Rise in haemoglobin and HbF

Warn patients, verbally and in writing, about the potential dangers of cytopenias. Patients/parents should seek medical advice urgently for petechiae, bruising, bleeding or a fever (check neutrophil count). They must inform the medical team that they are on HC.

Common Nail hyperpigmentation, headaches.
Rare Skin hyperpigmentation, nausea, dizziness, skin rash, reduced sperm count and motility.
Splenic regrowth, which has been described in children– monitor for splenomegaly and splenic sequestration.

8. Action to be taken if side effects occur

8a. Bone marrow suppression in adults

If any of these changes happen: neutrophils <1.5 x10^9/L; platelets < 80 x 10^9/L; reticulocytes < 1%; reduction in haemoglobin by 3g/dl from baseline.

8b. Bone marrow suppression in children

If any of these changes happen: neutrophils < 1.5 x10^9/L: platelets < 80 x 10^9/L; reticulocytes < 1%; haemoglobin >2g/dl below baseline or 20% drop from baseline or Hb < 5.5g/dl.

THEN

a. STOP hydroxycarbamide
b. Recheck FBC weekly
c. Restart HC at 2.5mg/kg/day lower than previously once neutrophils > 1.5x 10^9/L and platelets and retics have recovered.
d. Consider G-CSF or blood transfusion on discussion with medical staff.

8c) Rise in haemoglobin

Venesect if Hb rises to greater than 12g/dl or it rises by more than 3 g/dl above baseline with symptoms of hyper viscosity.

8d) Other symptoms

Stop on patient's request.

9. Follow up

i. **MTD Regime:** Medical review and blood tests 6-8 weekly once stable. See section 5b.

ii. **Fixed Dose Regime:** Increase to 3-6 monthly medical and blood test review.
vi. Long-term stable on HC (adults): Increase medical and blood test review to 3-6 monthly.
vii. Annual medical review as per SCD protocol.
viii. **Ensure patient/carer, GP and specialist nurse counsellor has written information about what to do if the patient develops symptoms suggestive of a cytopenic episode.**
ix. Ensure patients/ carers have information sheets.
x. Ensure patients have access to advice and support when required.
xi. Send GP and specialist nurse counsellor the HC guidelines and patient information sheet.
xii. Local hospital lead (e.g. paediatrician/haematologist) and lead nurse, if applicable, to be sent HC guidelines and patient information sheet.

References:

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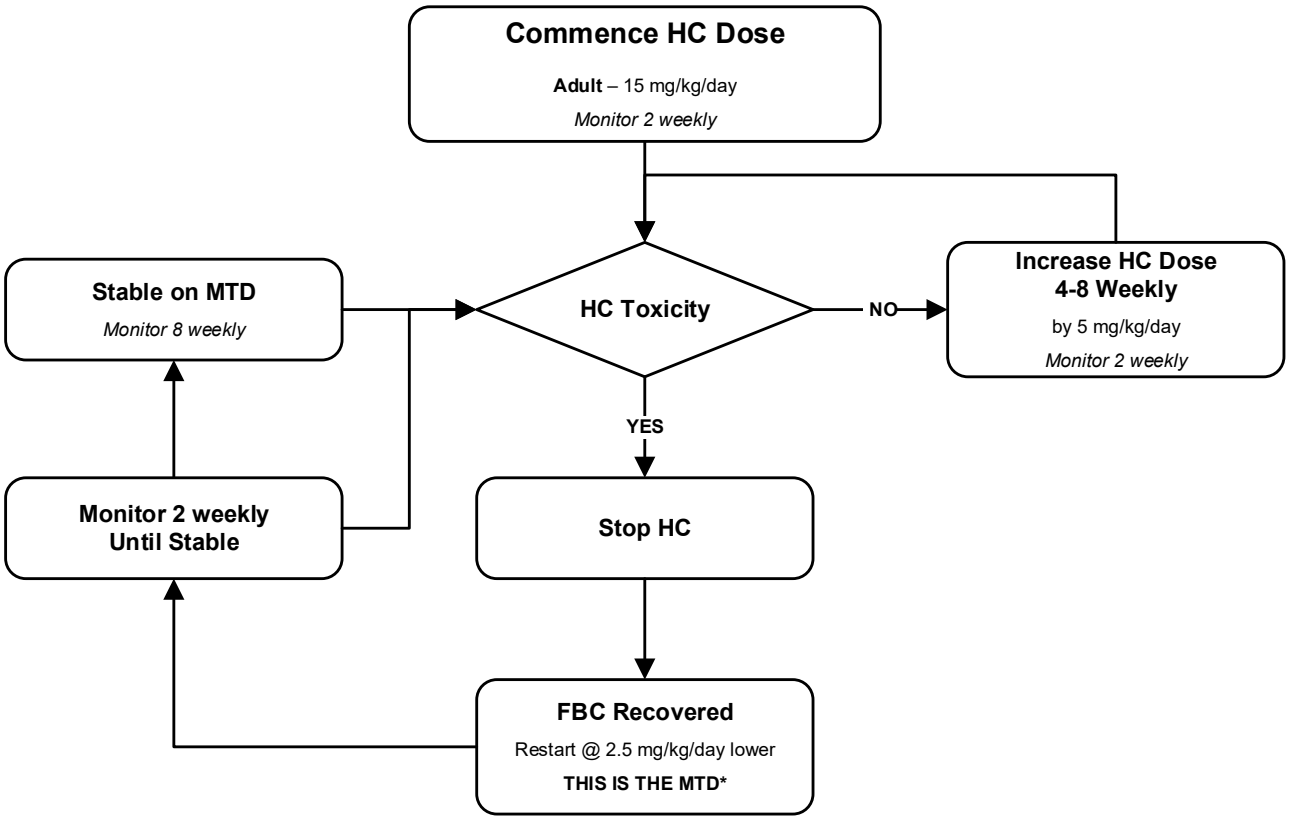
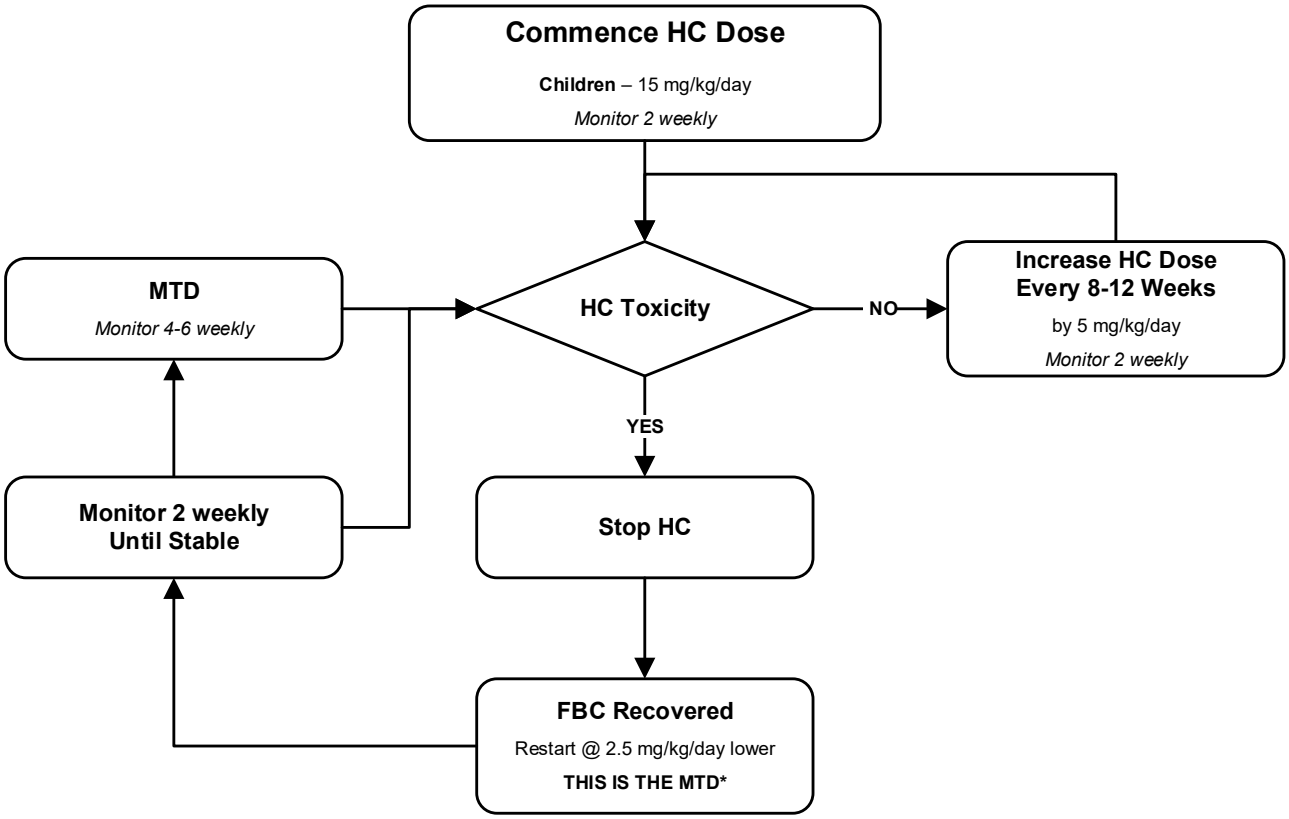
Appendix A: Guidelines for Monitoring Adult Sickle Cell Disease Patients on Hydroxycarbamide (HC) Treatment



* The usual maximum dose is 15-30 mg/kg/day or up to 35 mg/kg/day in some cases.

Appendix B: Guidelines for Monitoring Paediatric Sickle Cell Disease Patients on Hydroxycarbamide (HC) Treatment



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