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Use of Hydroxycarbamide in Paediatric Sickle Cell Disease

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NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Hydroxycarbamide has been shown in randomised controlled trials in young children to be safe and to reduce the frequency of painful crisis, dactylitis and acute chest syndrome and to reduce mortality. In long term studies in adults it has been shown to similarly reduce episodes of pain and acute chest syndrome and to reduce mortality. There are also potential benefits in preventing end organ damage; renal, splenic and retinopathy. Hydroxycarbamide also has a role alongside transfusion in primary stroke prevention.

Hydroxycarbamide is likely to have multiple mechanisms of action including the induction of Haemoglobin F production, inhibiting sickle haemoglobin polymerisation within the cell; reduction in adhesion molecule expression; reduction of white cell and platelet counts; and increase in nitric oxide availability.

By its mechanism of action hydroxycarbamide might be expected to have potentially teratogenic side effects and where appropriate patients must be counselled about this risk and the need to use effective contraception during treatment.

There are unresolved concerns about the effects of hydroxycarbamide on male fertility and evidence from prospective studies is lacking. Males with sickle cell disease are recognised to have an increased baseline rate of abnormal sperm parameters; following treatment with hydroxycarbamide oligo- or azoospermia is likely and it is not clear whether this is completely or partially reversible on stopping the drug and effects on fertility are not established.

Two large studies of the long term use of hydroxycarbamide have not shown any increase in the incidence of malignancy, including leukaemia, at 15-17 years of follow-up.

Recommendations

The benefits of hydroxycarbamide should be discussed with all parents of children and adolescents with SS/Sβ0 to enable informed joint decision-making. There should be on-going discussion between provider and patient. Baseline elevation of HbF should not affect the decision to initiate hydroxycarbamide therapy.

- In infants SS/Sβ0 aged 9–42 months, offer hydroxycarbamide regardless of clinical severity to reduce sickle cell complications (pain, dactylitis, acute chest syndrome (ACS), anaemia)
- In children aged >42 months and adolescents with SS/Sβ0, offer treatment with hydroxycarbamide in view of the impact on reduction of mortality
- In children with SS/Sβ0 who have 3 or more sickle cell-associated moderate to severe pain crisis in a 12-month period, treat with hydroxycarbamide
- In children with SS/Sβ0 who have sickle cell pain that interferes with daily activities and quality of life, treat with hydroxycarbamide
- In children with SS/Sβ0 and a history of severe and/or recurrent ACS treat with hydroxycarbamide

- Children who have started regular blood transfusions for abnormal TCD can be switched to hydroxycarbamide therapy (with or without venesection) if they have received at least 1 year of regular transfusions and have no magnetic resonance angiography-defined severe vasculopathy. Transfusion should be continued until they are stable on maximum tolerated dose of hydroxycarbamide

- Children with TCD velocities in the range 170–200 cm/s (conditional risk category) should be treated with hydroxycarbamide therapy to help prevent progression from conditional to abnormal TCD velocity

- Hydroxycarbamide therapy should be considered in children with sickle cell disease (SCD) with genotypes other than SS and Sβ0 thalassaemia who have recurrent acute pain, acute chest syndrome or episodes of hospitalisation

Patient Exclusion Criteria

- Inability to attend clinic regularly for follow up and FBC monitoring
- Abnormal liver function tests (AST or ALT > x 2 upper limit of normal, consult with Pharmacy)
- Pregnancy or not practising effective contraception

Baseline Information

The anticipated benefits and potential risks of hydroxycarbamide should be discussed with patients and their parents/carers on at least 2 occasions, written information provided, and informed consent gained and documented according to local guidance. Current information about known side effects including myelosuppression and the possible risks to fertility and teratogenicity be discussed and documented in the notes. Male patients should be assessed and if post-pubertal offered sperm storage.

Ongoing informed consent should be confirmed for all patients on hydroxycarbamide, at least at each Annual Review.

Side Effects

- Bone marrow suppression (dose dependent)
- Gastrointestinal disturbance – usually mild and short term
- Rash, skin and nail pigmentation
- Leg ulcers (may not be increased incidence compared to baseline)
- Liver dysfunction
- Possible teratogenicity and subfertility risks.

Baseline Investigations

- Height and weight
- FBC, reticulocyte count, HbF%
- Renal and liver biochemistry
- Negative pregnancy test for girls >12 years

Dose and Monitoring

- Start at 20 mg/kg/day – tablets come as 500mg and dose should be rounded to the nearest 500mg whenever possible. A suspension can be prepared for younger patients.
- Monitor FBC, retic count and biochemistry at 2 weeks after starting or dose escalation

IF cytopenias*

- neutrophils < 1.0 $x10^9$/l
- or Platelets < $80x10^9$/l
- or Hb <45g/l
- or retics < $80x10^9$/l (can be lower if Hb > 90g/l)

THEN stop hydroxycarbamide and check weekly until recovered
Restart hydroxycarbamide at same dose if transient drop or reduce by 5mgs/kg

OTHERWISE continue current dose and retest at 4-6 weeks

IF after 8-12 weeks

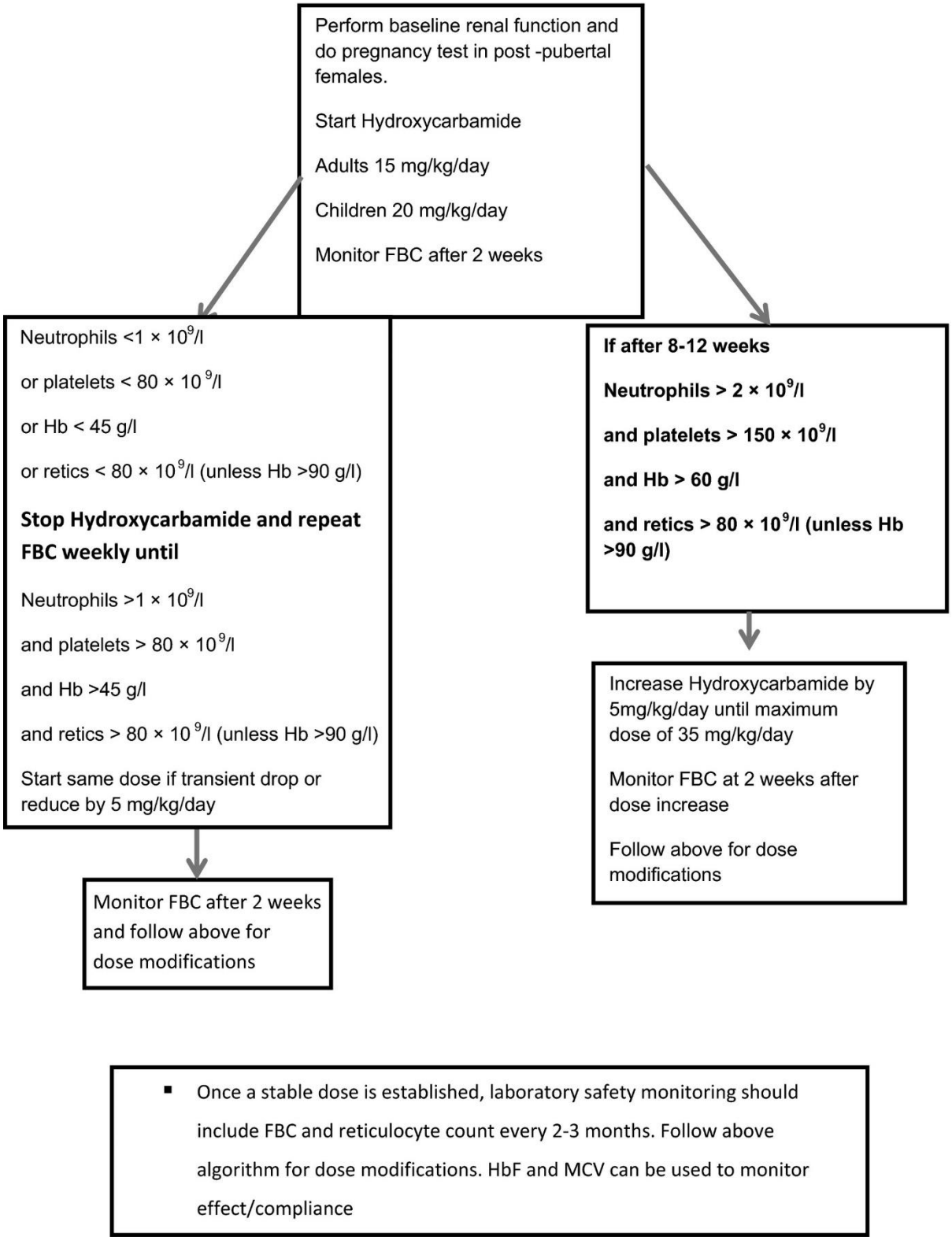
- neutrophils > $2x10^9$/l
- and Platelets >$150x10^9$/l
- and Hb > 60g/l
- and retics >$80x10^9$/l (can be lower if Hb > 90g/l)

THEN increase dose by increments of 5mg/kg/day every 8-12 weeks (max: 35mg/kg/day) and recheck after 2 weeks

OTHERWISE continue current dose and recheck FBC every 6-8 weeks

UNLESS cytopenias* - dose modifications and monitoring as above

- Continue to escalate where counts allow until stable on maximum tolerated dose
- Monitor FBC, HbF% and retic count, biochemistry including LFTs every 8-12 weeks when on a stable dose
- Pregnancy test for girls >12years prior to commencement and then at each clinic visit
- **Patients/parents should be advised to present if febrile/unwell or symptoms of worsening anaemia or bleeding for medical assessment and FBC.**
- Continue hydroxycarbamide during acute admissions unless cytopenias develop.



Algorithm for hydroxycarbamide dosing and monitoring. FBC, full blood count; Hb, haemoglobin; HbF, fetal haemoglobin; MCV, mean cell volume. From Qureshi et al Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease. A BSH guideline. British Journal of Haematology 2018; 181, 460-475

Assessment of Response

- Assess clinical response, HbF and adverse events 3 monthly
- Aim to give the maximum tolerated dose without development of cytopenias (MTD). A 6 month trial on MTD is recommended prior to considering discontinuation due to treatment failure.
- Failure to respond can be classified as failure to improve the frequency or severity of painful episodes or ACS. Failure of response should be based on clinical criteria rather than laboratory data, as benefit can be seen even at a low HbF%
- A significant proportion of failure to respond to hydroxycarbamide is due to non-adherence/compliance or failure to escalate to the maximum tolerated dose.

References

Qureshi et al Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease. A BSH guideline. British Journal of Haematology 2018; 181, 460-475

Thornburg et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. Blood 2012; 120(22): 4304-10

Zimmerman et al. Sustained long term haematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood 2004; 103(6): 2039-45

Steinberg et al. The risks and benefits of long term use of hydroxyurea in sickle cell anaemia: A 17.5 year follow-up. Am J Hematol 2010; 85(6): 403-8

Charache et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anaemia. Multicentre Study of Hydroxyurea in Sickle Cell Anemia. NEJM 1995; 332(20):1317-22

Reproductive issues in sickle cell disease Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):418-24

Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial Lancet. 2016 Feb 13;387(10019):661-70.