This article has been accepted for publication in ADC following peer review.
The definitive copyedited, typeset version is available online at 10.1136/archdischild-2019-317862

Higher oxygen saturation with hydroxyurea in paediatric sickle cell disease

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Short title: Higher oxygen saturation on hydroxyurea

Abbreviations:
ACS Acute Chest Syndrome
FEV_1 Forced Expiratory Volume in the first second
FVC Forced Vital Capacity
HU Hydroxyurea
Hb Haemoglobin
HbF Foetal Haemoglobin
HbSS Homozygous sickle cell disease
ODC oxygen-haemoglobin dissociation curve
OSA Obstructive Sleep Apnoea
pCO_2 partial pressure of carbon dioxide
SDB Sleep disordered breathing
SCD Sickle cell disease
SpO_2 arterial oxygen saturation as measured by pulse oximetry
TRJV Tricuspid Regurgitant Jet Velocity

Funding source: None

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest: The authors have no conflicts of interest relevant to this article to disclose

Table of Contents summary: A retrospective study to evaluate the effect of hydroxyurea on nocturnal and daytime oxygen saturations in children with sickle cell disease.

What's Known on this Subject: Hypoxaemia and intermittent oxygen desaturation frequently occur in children with SCD and contribute to the associated morbidity. Hydroxyurea reduces the incidence of painful crises and acute chest syndrome by increasing fetal haemoglobin percentage in the blood.

What this Study Adds: Children with sickle cell disease had higher overnight oxygen saturation on sleep studies and higher day-time spot oxygen saturation checks after starting hydroxyurea. Hydroxyurea is a potential treatment for persistent hypoxaemia in SCD pending further evidence from randomised controlled trials.

Contributor statement:

Dr. Gupta conceptualized and designed the study, led on the analysis and interpretation of the data and contributed to the manuscript.

Dr. van Geyzel contributed to the design of the study, carried out the data collection and drafted the initial manuscript.

Dr Arigliani contributed to the analysis, contributed to the manuscript and drafted the subsequent revisions.

Dr. Singh carried out the data collection, analysis and reviewed the initial manuscript.

Dr.Bossley, Dr. Chakravorty, Dr. Inusa, Dr. Kozlowska, Dr. Ruiz and Professor Rees contributed to the study design and critical revision of the initial manuscript as well as subsequent revisions.

All authors approved the final manuscript as submitted.

ABSTRACT

Introduction: Sickle cell disease (SCD) is one of the most common inherited diseases worldwide. It is associated with lifelong morbidity and reduced life expectancy. Hydroxyurea (HU) has been shown to reduce the frequency and severity of vaso-occlusive episodes in SCD. Hypoxaemia and intermittent nocturnal oxygen desaturations occur frequently in children with SCD and contribute to the associated morbidity, including risk of cerebrovascular disease and vaso-occlusive episodes.
Objective: To evaluate the effect of HU on oxygen saturation (SpO_2) overnight and on daytime SpO_2 spot checks in children with SCD.
Methods: A retrospective review of children with SCD and respiratory problems who attended two UK tertiary sickle-respiratory clinics and were treated with HU. Longitudinal data was collected from 2 years prior and up to 3 years after the commencement of HU.
Results:
Forty three children, 23 males (53%) with a median age of 9 (range 1.8-18) years were included. In the 21 children who had comparable sleep studies before and after starting HU, mean SpO_2 was higher (95.2% from 93.5%, p=0.01) and nadir SpO_2 was higher (87% from 84%, p=0.009) when taking HU. In 32 of the children, spot daytime oxygen saturations were also higher (96.3% from 93.5%, p=0.001).
Conclusion: Children with SCD had higher oxygen saturation overnight and on daytime spot checks after starting HU. This data suggests HU may be helpful for treating persistent hypoxaemia in children with SCD pending more evidence from a randomised clinical trial.

INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent inherited diseases, affecting approximately 300.000 newborns globally each year.[1] Hypoxaemia, a frequent complication of SCD, increases the risk of painful crises,[2] cognitive dysfunction,[3] central nervous system events,[4] and acute chest syndrome (ACS).[5] Children with SCD also have a high prevalence of obstructive sleep apnoea (OSA) which may contribute to nocturnal hypoxaemia.[6–9] Hydroxyurea (HU) increases production of fetal haemoglobin (HbF).[10,11] HbF percentage (HbF%) can rise from a mean of 5-10% to 15-20% during treatment with HU.[12] Increasing HbF% lowers the concentration of HbS within red cells resulting in less polymerisation and increased total haemoglobin. This results in fewer episodes of pain, hospitalisation and ACS.[13] The drug has a good safety profile in children with SCD.[11,14] Among possible side effects, mild gastrointestinal symptoms,[11] hyperpigmentation of the skin and darkening of the nails have been reported,[15] beyond the most common excessive myelosuppression, which is transient and reversible.[12] Chronic hypoxaemia is one the complications of SCD for which hydroxyurea therapy is now recommended in the UK.[16] However, evidence of a better oxygenation on HU has only been reported anecdotally by a case report,[17] a small study using spot pulse oximetry,[18] and a cross-sectional study comparing children with SCD and suspected OSA who were on HU with a larger group who were not.[19] To our knowledge, there have been no longitudinal studies looking at the effect of HU on oxygen saturations in SCD. As part of routine respiratory assessment in our centres, we have often conducted overnight oximetry/capnography in children with SCD who had respiratory complaints. Many who subsequently started HU therapy for various reasons had repeated sleep studies. We therefore had longitudinal data upon which to test the hypothesis that oxygenation would improve in children with SCD on HU.

METHODS

Our study group were children followed at a tertiary respiratory clinics (King's College Hospital) or joint respiratory-sickle cell clinics (Evelina London Children's Hospital). As per standard practice, these children would have been assessed for respiratory co-morbidities (most commonly including wheezing and asthma, sleep disordered breathing -SDB-, chronic hypoxemia, recurrent acute chest syndrome, chronic cough and lung function abnormalities) and treated accordingly. We retrospectively collected longitudinal data on children with SCD who were seen in these clinics and who were commenced on HU between March 2006 and July 2014. We reviewed electronic and paper medical records for spot pulse-oximeter oxygen saturation (SpO_2) readings recorded routinely in clinic. A Nonin GO_2 pulse oximeter (Nonin, Plymouth, MN, USA) was used to measure SpO_2, with the value recorded after at least two minutes of stable SpO_2 readings and a clear pulsatile photoplethysmographic signal. Median values of these readings taken from 6 months prior to commencement of HU were compared to median values of readings taken up to 2 years after. Over the same time periods before and after starting HU, haemoglobin and fetal haemoglobin concentrations and spirometry data were also collected and averaged for comparison. Those who had oximetry/capnography sleep studies (TCM 4/40 monitoring system, Radiometer®, software version 3.0, SpO_2 averaging time 3 sec) done from 2 years before and up to 3 years after starting HU were identified for comparison of sleep study parameters within the same patient. Sleep studies were ordered in those patients who reported symptoms of SDB (e.g. loud snoring, witnessed apnoeas, restless sleep and mouth breathing) or had a previous history of OSA and were performed over a single night, during which parents or guardians kept a sleep diary. Artefacts due to poor perfusion, low signal identification and movement were manually excluded, as well as periods of wakefulness according to the sleep diary's records. Studies with less than 4 hours of artefact-free data were excluded. Analysis software provided standard measures

including overnight mean and nadir SpO_2 and oxygen desaturation index (ODI), defined as the number of validated desaturations of at least 3% per hour of sleep.

All the assessments were performed when the patients were at steady state, outside acute SCD-related acute events (e.g. vaso-occlusive crisis, acute chest syndrome etc).

Statistical analysis

Descriptive statistics are reported as medians with inter-quartile range. Group comparisons were performed using *Wilcoxon* matched-pairs signed-rank test, *chi-squared* test or *Fisher*'s exact test as appropriate. The relationship between night-time or daytime SpO_2 and age at each data point was evaluated through *Spearman's* rank correlation. A p-value <0.05 was considered as statistically significant. Statistical analysis was performed using Graphpad, version 6 for Windows (GraphPad Software, La Jolla California USA).

RESULTS

Forty three children, 23 (53%) male, were included. Three children were excluded due to lack of comparable data. Median age was 9 years (range 1.8-18). One child had HbS/β^0thalassaemia, all the others had HbSS. There were no smokers among the adolescent patients enrolled. Six (14%) children had a history of recurrent ACS (figure 1) and two had severe hypoxaemia. Fifteen of them (35%) had asthma, which had been diagnosed at least one year before starting HU. Moreover, 17 children (40%) had previously undergone adenotonsillectomy for OSA, 3 of them after they started HU.

Both at baseline and after starting HU, there were no statistically significant differences in median values of spot daytime SpO_2 and overnight mean SpO_2 between patients with or without asthma (data not shown).

The majority started HU due to frequent painful crises or very low steady-state haemoglobin. (Figure 1) The median dose of HU at 1-2 years after commencement was 22 mg/kg (IQR 20-26, range 15-30),

Overnight oxygenation

Comparable sleep studies before and after starting HU were available on 21 children. Parameters from sleep studies done a median of 9 months (Interquartile range (IQR) 3.5 – 15 months) before starting HU were compared to parameters from studies done a median of 9 months (IQR 5-16months) after. Mean overnight oxygen saturations rose significantly from 93.5 to 95.2% on HU (*P*=0.01), whilst nadir overnight oxygen saturations were also significantly higher (84 to 87%) on HU (*P*=0.009) (Table 1). There was no significant difference in the ODI. None of these parameters was related to age at each data point. When removing from the analysis three patients who underwent adenotonsillectomy after starting HU, increases of mean and nadir overnight SpO_2 from baseline to endpoint were still significant (*P*< 0.05 for both outcomes; data not shown).

Among 18 children with SDB and comparable ODI results from nocturnal oximetry before and after starting HU, the frequency of ODI ≥3, a cut-off highly predictive of OSA in children with SDB,[20] decreased from 8 (44%) pre-HU to 6 (33%) post-HU (*P*=0.7). Of these, 5 participants who had previously undergone adenotonsillectomy for OSA, had an ODI persistently ≥3, both before and while taking HU.

Table 1. Changes in oxygen saturation parameters and haematological indices with hydroxyurea.

	Patients with comparable data n.	Before HU Median (IQR)	After HU Median (IQR)	*p value
Mean overnight SpO_2 (%)	20	93 (88-97)	95 (93-98)	0.01
Nadir overnight SpO_2 (%)	20	84 (77-89)	87 (83-91)	0.009

3% ODI overnight (events/hour)	18	3.0 (1.5-5.2)	2.8 (1.1-4.6)	0.08
Spot daytime SpO_2 (%)	32	93 (91-97)	96 (94-98)	0.001
Hb (g/L)	42	76.0 (69.5 – 86.5)	83.0 (72.7-87.7)	0.04
HbF (%)	37	6.1 (3.7-12.9)	8.8 (6.0-16.0)	<0.001
Neutrophil count (10^9/L)	42	5.7 (4.3-6.8)	5.4 (3.9 – 6.2)	0.1

Definition of abbreviations: IQR = Interquartile Range; ODI = Oxygen desaturation index; HU = Hydroxyurea

Averaged spot daytime oxygen saturation and other measures

Comparable spot-checks of SpO_2 in the daytime before and after starting HU was available in 32 of the children. The median SpO_2 rose by 2.8% (from 93.5% to 96.3%) after starting HU (Table 1). Before the intervention, SpO_2 had a moderate negative correlation with age (r_s = -0.44, p = 0.01), but this relationship lost significance after HU was introduced (r_s = -0.18. p = 0.2). As expected Hb and HbF rose significantly on HU. There was a moderate positive correlation between changes in daytime SpO_2 and changes in HbF level from baseline to endpoint (r_s = 0.47, p = 0.02), as well as between changes in SpO_2 and Hb concentration (r_s = 0.51, p = 0.007). No statistically significant changes in FEV1 and FVC % of predicted were found on HU but longitudinal lung function data was available on only 10 children (data not shown).

Among SCD patients with asthma and with previous adenotonsillectomy, changes in daytime and nocturnal oxygen with HU therapy were similar to those of the whole sample but only variations of spot daytime SpO_2 resulted significant (table S1), probably also for the limited number of observations in these subgroups.

DISCUSSION

Our principal finding was that overnight mean SpO_2 and nadir SpO_2 were significantly higher after the commencement of HU in children with SCD. Averaged spot daytime oxygen saturations were also higher in the children when they were on HU.

Hypoxaemia in SCD is reported to occur in 33-44% of patients[5,21] and is associated with increased risk of stroke,[22] pain crises,[2] increased tricuspid regurgitant jet velocity (TRJV)[23] and left ventricular abnormalities.[24] A low oxygen saturation in patients with SCD may depend on several causes, including elevated levels of carboxyhaemoglobin and methaemoglobin that are unable to carry oxygen,[25] asleep hypoxaemia due to disordered breathing,[7] and the rightward shift of the oxygen-haemoglobin dissociation curve (ODC) when HbS polymerizes.[26–28] In addition chronic anaemia, besides reducing oxygen carrying capacity, also leads to increased 2,3 DPG production and rightward shift of the ODC, resulting in a lower than expected oxyhaemoglobin saturation at a given PaO_2.[29]

There is limited evidence for the effect of HU on oxygenation in children with SCD. In 2008, Singh et al[17] published a report of 3 cases of children with SCD, recurrent episodes of ACS and chronic hypoxaemia. Spot daytime oxygen saturations were measured before and after the commencements of HU. Oxygenation improved soon after the commencement of HU and this effect was sustained up to the last follow up, 20-24 months later.
Pashankar et al conducted a small prospective study[18] of 13 children with HbSS/Sβ0thalassemia who were prospectively treated with HU for 12 months for an elevated TRJV which has been associated with oxygen desaturation. HU significantly increased spot oxygen saturation and the improvement was sustained at 12 months post treatment.
Compared to these reports, our study included a larger number of patients and integrated data from both nocturnal and daytime SpO_2 from several data points for each patient, in order to

minimize possible bias due to variability in spot daytime SpO_2 values at steady state.[26] Narang et al[19] evaluated cross-sectionally overnight oxygen saturation in 37 children with SCD who were receiving HU compared with 104 who were not receiving HU. Patients enrolled were mainly referred with a history suggestive of OSA. Overnight sleep parameters for oxygenation (as well as awake spot oxygen saturations) were significantly higher in the HU group than in the non-HU group. However, the cross-sectional design of this study precludes the possibility of inferring whether its findings depended on the effect of HU or on different baseline characteristics of the study and control group. Moreover, the fact that most of the patients included suffered from SDB hinders the generalization of its conclusions to the entire SCD population. Our study confirmed the preliminary cross-sectional findings of Narang et al[19], showing that median asleep and waking SpO_2 increased, respectively, by 2% ($p = 0.01$) and 3% ($p = 0.001$), on a longitudinal evaluation covering up to 3 years from the introduction of HU.

The precise mechanism by which HU increases HbF is not fully understood. Various theories have been postulated including a cytotoxic effect of HU on late erythroid precursors leading to recruitment of early erythroid precursors with increased capacity to produce HbF,[30] modification of transcription factors which alters the ratio of HbA to HbF[31] and a nitric-oxide derived mechanism for HbF induction.[32] New theories continue to emerge, but all culminate in an increased production of HbF, which decreases the rate of HbS polymerisation thereby reducing the downstream pathological events, including haemolysis, anaemia, inflammation and tissue infarction. Besides, HbF has a higher affinity for oxygen than HbS or HbA due to its lower affinity for 2,3DPG, shifting the ODC to the left and increasing oxyhaemoglobin saturation for a given oxygen partial pressure in arterial blood. Interestingly, in the present study, though median increase of HbF after commencing HU was lower than

expected (table 1), we could still appreciate a significant increase of asleep and waking SpO_2, moderately correlated with changes in Hb and HbF.

Chronic hypoxaemia is an indication for children with SCD to be offered HU in the UK, although the recommendation is based on poor quality evidence (1C).[16] There is a need for evidence of clinical benefit that this study attempts to provide. Only two of the children in this study started HU due to hypoxaemia but a significant increase in oxygenation was still observed. We could only speculate whether a larger effect might have been seen if more of the children had had low baseline oxygen saturation.

In our study, the majority of patients were started on HU because of frequent episodes of pain. They were on moderate doses of HU with some leeway for making increases. It is possible that larger improvements in oxygenation might have been achieved on higher doses. Reaching the maximum tolerated dose may be an appropriate strategy if hypoxaemia were the indication for HU.

A strength of this study is that, at the best of our knowledge, it is the largest longitudinal evaluation of the effects of HU on oxygen saturation in patients with SCD. Furthermore, integrating both asleep and waking SpO_2 data from multiple data points for each patient when they were asymptomatic, allowed to minimize possible biases due to intra-subject variability in SpO_2 values, especially as regards to spot daytime SpO_2.[33]

A major limitation is the absence of a control group of patients with SCD who did not start HU treatment. This does not allow to exclude that changes in SpO_2 over the study period were due to factors other than HU. For example changes in daytime and overnight oxygen saturation with HU in patients with asthma were similar to those of the general sample (table S1) but, since information on changes in severity of asthma symptoms and therapy over the

study period was not available, we cannot exclude that the improved oxygen saturation in this subgroup was due to an better asthma control from baseline to endpoint. Moreover, since in participants with SDB only data from nocturnal oximetry but not from polysomnography was available, the exact prevalence and trends of OSA over the study period could not be established. However, considering that the frequency of ODI≥3 in children with SDB did not change significantly from baseline to endpoint, it is unlikely that variations in the prevalence of OSA affected the results of nocturnal oximetry pre- and post-HU. Furthermore, when we performed the analysis excluding three patients who had adenotonsillectomy for OSA after starting HU (in these children improvements of SpO_2 could depend on relief of upper airway obstruction rather than HU), differences in nocturnal SpO_2 remained significant. Regarding other potential confounders, over the study period the centres involved did not apply major changes in the standards of care for SCD patients (apart from increasing use of HU), and the SpO_2 would have been expected to decrease, rather than increase, by time.[5,21,34] Therefore, it is unlikely that variables not taken into account had a relevant influence on changes in oxygen saturation in patients on HU.

Another limitation of this study is related to the use of pulse oximetry as measure of steady state oxygen saturation in children with SCD, as pulse oximetry tends to overestimate arterial oxygen saturation compared to co-oximetry (gold standard).[25,35]

We were unable to measure adherence to HU therapy but the rise in HbF provided some induction that it was being taken. This relatively small study's retrospective design meant data gaps were inevitable. There were not enough lung function data available to draw any conclusions here. Comparable sleep study data was available on only half the children who were receiving HU, and even then the reports were not easily available and some data had to be extracted from clinic letters. Selection bias could not be excluded as we only looked at children with SCD who were referred for respiratory symptoms. Indeed it was not possible to

control for confounding factors that may have affected SpO_2 in addition to HU. To do so, a randomised placebo-controlled trial of HU therapy in children, would be required. Ethical approval for such a trial now may not be straightforward. Confining a study to a particular sub-group of children with SCD e.g. those with respiratory complaints in our case, or a particular indication for HU, helps to reduce confounding factors but then begs the question of whether conclusions can be generalised to other children with SCD.

Conclusions

Granting all the limitations of this study, the data does indicate higher oxygenation, both on overnight and daytime measurements, with HU therapy. This was despite the fact that less than 5% of the children with SCD had started HU because of persistent hypoxaemia. In other words, even children without resting hypoxaemia appear to have higher SpO_2 on HU. This study therefore provides important preliminary evidence upon which to justify giving HU to treat persistent hypoxaemia in children with SCD until better evidence from a randomised controlled clinical trial is forthcoming.

REFERENCES

1 Piel FB, Patil AP, Howes RE, *et al.* Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet* 2013;**381**:142–51. doi:10.1016/S0140-6736(12)61229-X

2 Hargrave DR, Wade A, Evans JPM, *et al.* Nocturnal oxygen saturation and painful sickle cell crises in children. *Blood* 2003;**101**:846–8. doi:10.1182/blood-2002-05-1392

3 Hollocks MJ, Kok TB, Kirkham FJ, *et al.* Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia. *J Int Neuropsychol Soc JINS* 2012;**18**:168–73. doi:10.1017/S1355617711001469

4 Kirkham FJ, Hewes DK, Prengler M, *et al.* Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. *Lancet Lond Engl* 2001;**357**:1656–9.

5 Rackoff WR, Kunkel N, Silber JH, *et al.* Pulse oximetry and factors associated with hemoglobin oxygen desaturation in children with sickle cell disease. *Blood* 1993;**81**:3422–7.

6 Salles C, Ramos RTT, Daltro C, *et al.* Prevalence of obstructive sleep apnea in children and adolescents with sickle cell anemia. *J Bras Pneumol Publicacao Of Soc Bras Pneumol E Tisilogia* 2009;**35**:1075–83. doi:10.1590/s1806-37132009001100004

7 Rosen CL, Debaun MR, Strunk RC, *et al.* Obstructive Sleep Apnea and Sickle Cell Anemia. *Pediatrics* 2014;:peds.2013-4223. doi:10.1542/peds.2013-4223

8 Willen SM, Rodeghier M, Rosen CL, *et al.* Sleep disordered breathing does not predict acute severe pain episodes in children with sickle cell anemia. *Am J Hematol* 2018;**93**:478–85. doi:10.1002/ajh.25013

9 Rogers VE, Lewin DS, Winnie GB, *et al.* Polysomnographic characteristics of a referred sample of children with sickle cell disease. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2010;**6**:374–81.

10 Ferster A, Tahriri P, Vermylen C, *et al.* Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood* 2001;**97**:3628–32. doi:10.1182/blood.v97.11.3628

11 Kinney TR, Helms RW, O'Branski EE, *et al.* Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. *Blood* 1999;**94**:1550–4.

12 Strouse JJ, Lanzkron S, Beach MC, *et al.* Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008;**122**:1332–42. doi:10.1542/peds.2008-0441

13 Thornburg CD, Files BA, Luo Z, *et al.* Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood* 2012;**120**:4304–10; quiz 4448. doi:10.1182/blood-2012-03-419879

14 Wang WC, Ware RE, Miller ST, *et al.* Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *The Lancet* 2011;**377**:1663–72. doi:10.1016/S0140-6736(11)60355-3

15 O'branski EE, Ware RE, Prose NS, *et al.* Skin and nail changes in children with sickle cell anemia receiving hydroxyurea therapy. *J Am Acad Dermatol* 2001;**44**:859–61. doi:10.1067/mjd.2001.113471

16 Qureshi A, Kaya B, Pancham S, *et al.* Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease: A British Society for Haematology Guideline. *Br J Haematol* 2018;**181**:460–75. doi:10.1111/bjh.15235

17 Singh SA, Koumbourlis AC, Aygun B. Resolution of chronic hypoxemia in pediatric sickle cell patients after treatment with hydroxyurea. *Pediatr Blood Cancer* 2008;**50**:1258–60. doi:10.1002/pbc.21480

18 Pashankar FD, Manwani D, Lee MT, *et al.* Hydroxyurea Improves Oxygen Saturation in Children With Sickle Cell Disease. *J Pediatr Hematol Oncol* 2015;**37**:242–3. doi:10.1097/MPH.0000000000000251

19 Narang I, Kadmon G, Lai D, *et al.* Higher nocturnal and awake oxygen saturations in children with sickle cell disease receiving hydroxyurea therapy. *Ann Am Thorac Soc* 2015;**12**:1044–9. doi:10.1513/AnnalsATS.201410-473OC

20 Chang L, Wu J, Cao L. Combination of symptoms and oxygen desaturation index in predicting childhood obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol* 2013;**77**:365–71. doi:10.1016/j.ijporl.2012.11.028

21 Quinn CT, Ahmad N. Clinical correlates of steady-state oxyhaemoglobin desaturation in children who have sickle cell disease. *Br J Haematol* 2005;**131**:129–34. doi:10.1111/j.1365-2141.2005.05738.x

22 Quinn CT, Lee NJ, Shull EP, *et al.* Prediction of adverse outcomes in children with sickle cell anemia: a study of the Dallas Newborn Cohort. *Blood* 2008;**111**:544–8. doi:10.1182/blood-2007-07-100719

23 Minniti CP, Sable C, Campbell A, *et al.* Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. *Haematologica* 2009;**94**:340–7. doi:10.3324/haematol.13812

24 Johnson MC, Kirkham FJ, Redline S, *et al.* Left ventricular hypertrophy and diastolic dysfunction in children with sickle cell disease are related to asleep and waking oxygen desaturation. *Blood* 2010;**116**:16–21. doi:10.1182/blood-2009-06-227447

25 Needleman JP, Setty BN, Varlotta L, *et al.* Measurement of hemoglobin saturation by oxygen in children and adolescents with sickle cell disease. *Pediatr Pulmonol* 1999;**28**:423–8.

26 Abdu A, Gómez-Márquez J, Aldrich TK. The oxygen affinity of sickle hemoglobin. *Respir Physiol Neurobiol* 2008;**161**:92–4. doi:10.1016/j.resp.2007.12.005

27 Di Liberto G, Kiger L, Marden MC, *et al.* Dense red blood cell and oxygen desaturation in sickle-cell disease. *Am J Hematol* 2016;**91**:1008–13. doi:10.1002/ajh.24467

28 Ortiz FO, Aldrich TK, Nagel RL, *et al.* Accuracy of Pulse Oximetry in Sickle Cell Disease. *Am J Respir Crit Care Med* 1999;**159**:447–51. doi:10.1164/ajrccm.159.2.9806108

29 Caboot JB, Allen JL. Hypoxemia in sickle cell disease: significance and management. *Paediatr Respir Rev* 2014;**15**:17–23. doi:10.1016/j.prrv.2013.12.004

30 Segal JB, Strouse JJ, Beach MC, *et al.* Hydroxyurea for the treatment of sickle cell disease. *Evid ReportTechnology Assess* 2008;:1–95.

31 Dover GJ, Charache S. Hydroxyurea induction of fetal hemoglobin synthesis in sickle-cell disease. *Semin Oncol* 1992;**19**:61–6.

32 Cokic VP, Smith RD, Beleslin-Cokic BB, *et al.* Hydroxyurea induces fetal hemoglobin by the nitric oxide-dependent activation of soluble guanylyl cyclase. *J Clin Invest* 2003;**111**:231–9. doi:10.1172/JCI16672

33 Mullin JE, Cooper B, Seicean S, *et al.* Variability of pulse oximetry measurement over 1 year in children with sickle cell disease depends on initial oxygen saturation measurement. *Pediatr Blood Cancer* 2010;**54**:1017–9. doi:10.1002/pbc.22420

34 Makani J, Tluway F, Makubi A, *et al.* A ten year review of the sickle cell program in Muhimbili National Hospital, Tanzania. *BMC Hematol* 2018;**18**:33. doi:10.1186/s12878-018-0125-0

35 Blaisdell CJ, Goodman S, Clark K, *et al.* Pulse Oximetry Is a Poor Predictor of Hypoxemia in Stable Children With Sickle Cell Disease. *Arch Pediatr Adolesc Med* 2000;**154**:900–3. doi:10.1001/archpedi.154.9.900

FIGURES

Figure 1: Indications for starting hydroxyurea in 43 pediatric patients with sickle cell disease.
*micro-albuminuria, retinopathy, recent severe pneumococcal sepsis