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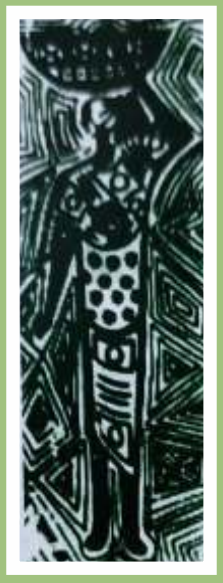

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Synopsis: Hydroxyurea Use in Children with Sickle Cell Disease and the Challenges in Resource-Poor Settings

Adegoke Ademola S.
Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria. E-mail: samueladegoke@oauife.edu.ng

Introduction

Sickle Cell Disease Burden

Sickle Cell Disease (SCD) is a global health problem, although about 90% of the burden occurs in Low-and Middle-Income Countries (LMICs). Globally, about 300,000 babies are born with the disease annually, with about 150,000 of them in Nigeria alone. The Nigeria 2018 Demographic Health Survey estimated the average birth prevalence of homozygous sickle cell disease (HbSS) as 1·21% and 0·24% for the heterozygous state HbSC.[1,2] SCD is a single gene mutation characterized by GAG to GTG transversion resulting in the replacement of soluble glutamic acid by insoluble valine at the sixth position of the β-globin chain (β6 Glu →Val, GAG>GTG).[3] Clinically, it typically manifests as episodic ischaemia and hypoxia, resulting in recurrent pains (the disease hallmark), chronic haemolysis and increased predisposition to infections.

SCD Child mortality in Nigeria (Population analysis from 2018 DHS)

The estimated national average under-five mortality (U5M) for SCD children in Nigeria is about 490 per 1000 live births.[1,2] This U5M in SCD children was estimated to be four (4) times higher than for children with normal haemoglobin (HbAA). Also, in Nigeria, about 4·2% of national U5M was attributable to mortality from SCD.[2] Data from some West African countries show that SCD accounts for between 9 and 16% of U5M.[4] The leading causes of death in children with SCD include infections, anaemia, acute chest syndrome (ACS) and stroke.

Table I below highlights the survival pattern of children with sickle cell disease into adulthood in the United States of America and Nigeria at different times.[5,6] As of the 2020s, the majority of children with SCD now survive into adulthood in the United States because of advancements in SCD care, including newborn screening, penicillin prophylaxis, stroke prevention, and widespread use of Hydroxyureahydroxyurea, among others.

Table I: Survival pattern of children with SCD into adulthood (>18 years) in Nigeria and the United States of America

Timing	United States	Nigeria
In 1970s	<50% of children with SCD survived into adulthood (Scott *et al.* [5])	<10% survived beyond age 5 years (Fleming *et al.* [6])
2020s	>95% now survive into adulthood (Quinn *et al.*[4]). The success can be traced to the following activities: - Newborn screening - Penicillin prophylaxis - Stroke prevention, - Widespread use of Hydroxyureahydroxyurea, etc.	About 50% may survive beyond 10 years (Grosse *et al.*). The reduced survival occurs because comprehensive SCD care is not yet optimal; hence, SCD-related death is still high.
Life expectancy	In high-income countries (HICs): 45 – 55 years	LMICs - No data

Hydroxyurea (HU)

Brand names include *Hydrea*, *SIKLOS*, *and Oxyurea.*

Hydroxyurea, known as hydroxycarbamide with chemical formula $CH_4N_2O_2$, is a monohydroxyl-substituted urea antimetabolite. It is an ideal disease-

modifying therapy approved for SCD. Apart from being prescribed as a monotherapy, it is administered as a single daily oral dose. It is effective and offers long-term benefits for all age groups. The associated side effects, if any, are usually few, mild and short-term.[7]

Since the curative options of stem cell transplantation and genetic therapy in SCD are not currently widely available and affordable, Hydroxyureahydroxyurea is the best available treatment option in many low and middle-income countries. Despite overwhelming evidence supporting Hydroxyurea'shydroxyurea's clinical efficacy and safety, its use is limited.[8] Following ingestion of HU, absorption from the gastrointestinal tract is effective. Usually, following ingestion, the plasma level peaks within 1 – 4 hours.[7] The maximum plasma level may be reached between 20 and 30 minutes after administration for those who are rapid responders. The plasma half-life may take three to four hours.[7] The drug rapidly distributes and concentrates in red and white blood cells and is metabolized in the liver or may undergo minor catabolism in the intestine by some bacteria urease. It is excreted through the kidneys in about 80% of occasions.

History of hydroxyurea[7-10]

The drug was synthesized in 1869 by German scientists as an antineoplastic agent and was approved for treating solid tumours about a century later by the USA FDA. It is also used in myeloproliferative disorders, especially polycythaemia vera, essential thrombocythaemia, and chronic myelocytic leukaemia. In the mid-1980s, it was shown to induce foetal haemoglobin (HbF) production. In February 1998, its therapeutic value in SCD was recognized, and it was approved for use in adult patients—a major advancement in the management of SCD.

Evidence of HU effectiveness and safety - previous landmark studies on HU [7, 10 - 24]

In the early proof-of-principle studies (1984), HU was found to increase HbF levels in two subjects with SCA. Prospective phase 1 and 2 efficacy trials in adults showed that HU was safe at maximum tolerated doses (1992). The phase 3 National Heart, Lung and Blood Institute (HLBI) – sponsored Multicenter Study (MSH) of Hydroxyurea trial showed clinical efficacy for VOC in severely affected adults (1995) while short-term safety and efficacy studies were done among children in 1995 and 1997. HLBI-sponsored phase 1/2 paediatric trial (HUG-KIDS) in 1999 showed laboratory efficacy and reported that toxicities of Hydroxyureahydroxyurea were mild, similar to adults. Also, no evidence of impaired growth and development was reported in another 2003 study.

The phase 1/2 Hydroxyurea Safety and Organ Toxicity (HUSOFT) trials of 2001 and 2005 showed that infants tolerated Hydroxyureahydroxyurea without short-term adverse events and had substantial laboratory and clinical efficacies.

The other trials and their findings are as follows:

BABY HUG (2004) and the results published in 2010 showed that the risk of bacteraemia or serious infections did not increase.

SWITCH Trial (Stroke With Transfusions Changing to Hydroxyurea) - A multicentre phase 3 trial comparing transfusions to Hydroxyureahydroxyurea for children with SCA and stroke (2006).

TWITCH Trial (TCD With Transfusions Changing to Hydroxyurea) - a multicentre Phase 3 trial comparing standard treatment (transfusions) to alternative therapy (Hydroxyureahydroxyurea) in children with abnormal TCD velocities (2009).

NOHARM (Novel Use of Hydroxyurea in an African Region with Malaria) – HU did not increase the incidence or severity of malaria in Ugandan children (2016).

Hydroxyurea for children with sickle cell anaemia in sub-Saharan Africa – Tshilolo *et al.* in four sub-Saharan African countries (2019). Over 600 children received HU for six months. The outcomes were the effects on malaria, laboratory variables, sickle cell-related events, transfusions, and survival.

Hydroxyurea dose escalation for sickle cell anaemia in Sub-Saharan Africa – John *et al.* in Uganda, 2020. It was a randomized trial to test the efficacy of a fixed dose of 20mg HU vs escalated dose of 30mg of the drug) for 24 months. The escalated group reached a target haemoglobin concentration of 9g/dL and HbF of 20%. They also had lower incidences of malaria, vaso-occlusive crises, acute chest syndrome (ACS) and other complications. However, both groups had similar side effects.

Lagunju *et al.* in 2019 studied the annual stroke incidence in Nigerian children with sickle cell disease and elevated TCD velocities treated with Hydroxyureahydroxyurea. The study determined the effectiveness of HU in reducing the risk of primary stroke in those with high TCD velocities.

SPIN & SPRINT Trials (Hydroxyurea for Primary and Secondary Stroke Prevention in Nigeria Trials) of 2022 and 2023 showed that low and moderate doses of HU are effective for primary and secondary stroke prevention, respectively, at the Aminu Kano Teaching Hospital, Kano, Nigeria.

Figure 1 below summarises the time frame for some landmark studies on the safety and efficacy of Hydroxyureahydroxyurea.

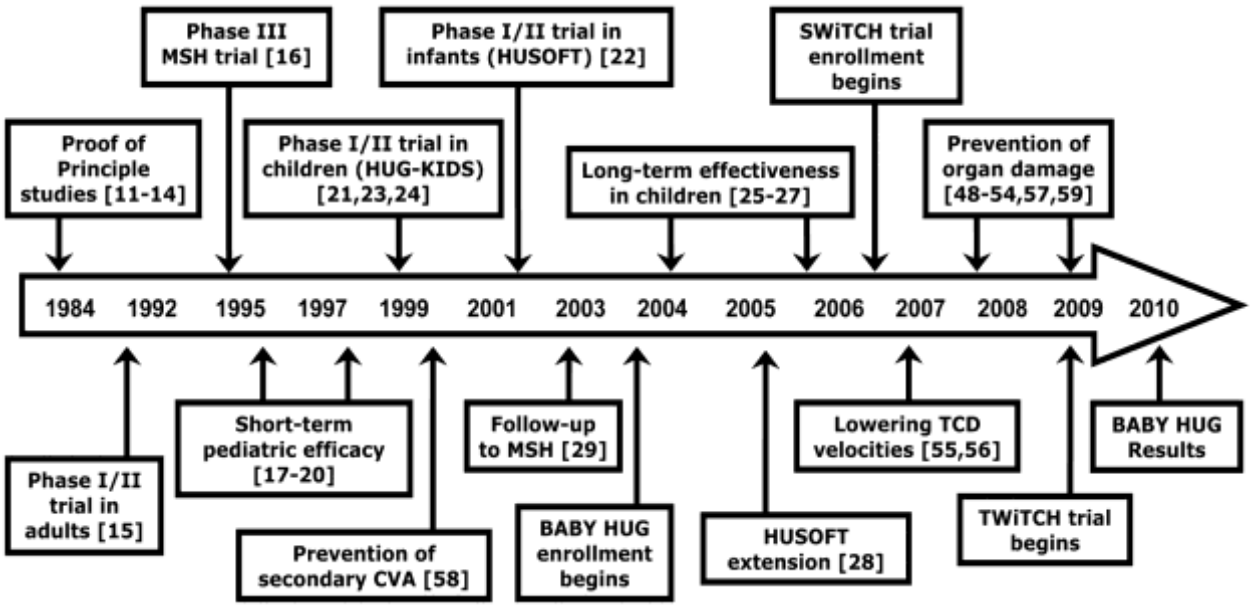

Figure 1: Timeline for various landmark studies on the safety and efficacy of Hydroxyureahydroxyurea in individuals with sickle cell disease [7]

Mechanisms of action of Hydroxyureahydroxyurea

Hydroxyurea inhibits Ribonucleotide Reductase (RR), the enzyme that converts ribonucleosides into deoxyribonucleosides which are the building blocks for DNA synthesis and repair. Potent inhibition of RR leads to decreased intracellular pools of deoxyribonucleotide triphosphates and impedes the progression of cellular division through the S phase.[7, 8]

Mechanisms of inducing HbF [9]

Although the exact mechanism of foetal haemoglobin (HbF) induction is not known, the following processes are thought to be involved:

- HU activates guanylate cyclase (GC).
- GC stimulates the synthesis of cyclic Guanosine Monophosphate (cGMP).
- cGMP upregulates nitric oxide (NO) synthase.
- Nitric oxide directly stimulates foetal haemoglobin (HbF).
- HU is cytotoxic to the more rapidly dividing late erythroid precursors, producing more F cells from primitive progenitors.

Figure 2 and Table II illustrate the mechanisms of action of Hydroxyureahydroxyurea.

Clinical benefits of HU on SCD in LMICs

Several studies have demonstrated the clinical benefits of HU among children and adults with SCD.[9-21] One such study involved 635 children with the disease in four sub-Saharan African countries (DRC, Kenya, Uganda, Angola).[19] Hydroxyurea was commenced at 15 – 20mg/kg and was administered for six months. It was later escalated to the maximum tolerated dose (MTD) for three years. The endpoints assessed included feasibility (adherence to HU), safety (toxic effects), and clinical benefits (malaria, laboratory parameters, sickle cell-related events, transfusions, and survival). The study documented significant improvement in the following events:

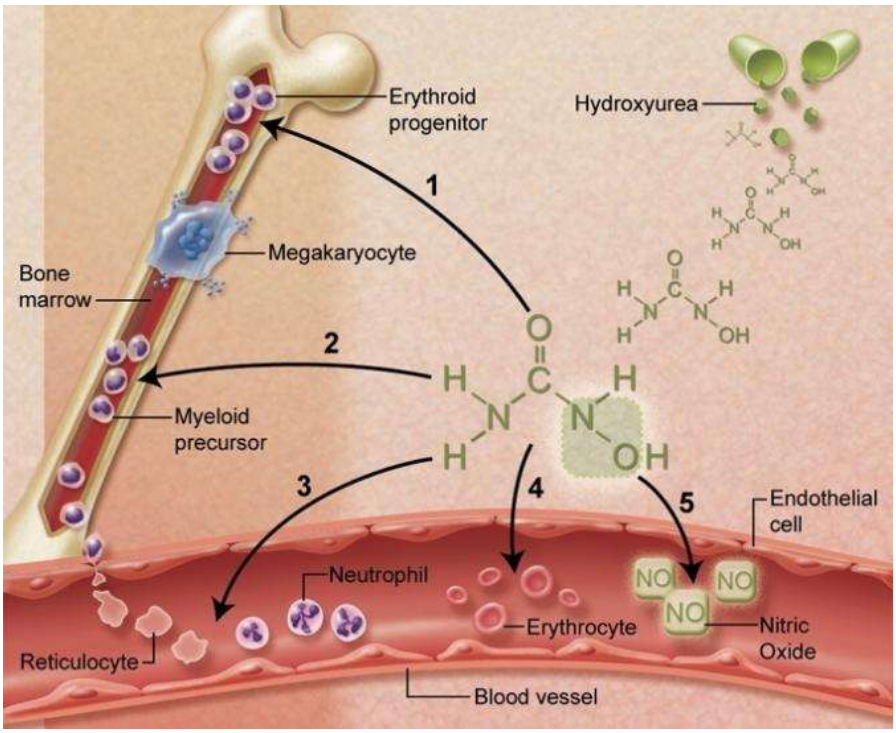

Figure 2: Multiple mechanisms of action of Hydroxyureahydroxyurea.[7]

Table II: Mechanisms of action of Hydroxyureahydroxyurea

Effects of HU	Mechanism of action
Induces HbF production	Acts on erythroid progenitors and stimulates Guanylate Cyclase
Lower neutrophils and reticulocyte counts	Inhibits ribonucleotide reductase with marrow cytotoxicity
Improves blood rheology	Decreases adhesion of neutrophils and reticulocytes
Prevents haemolysis	Improves RBC hydration, enhances macrocytosis, reduces intracellular sickling
Improves vascular response	Enhances synthesis/ release of nitric oxide

Vaso-occlusive events (VOC): (HU reduced VOC from 98.3 events per 100 patient-years pre-HU period to 44.6 events per 100 patient-years after three years of HU use; incidence rate ratio, 0.45; 95% confidence interval [CI], 0.37 to 0.56).
Transfusions: (43.3 vs. 14.2 events per 100 patient-years; incidence rate ratio, 0.33; 95% CI, 0.23 to 0.47).
Malaria: (46.9 vs. 22.9 events per 100 patient-years; incidence rate ratio, 0.49; 95% CI, 0.37 to 0.66).
Non-malaria infection: (142.5 vs. 90.0 events per 100 patient-years; incidence rate ratio, 0.62; 95% CI, 0.53 to 0.72).
Septicaemia: (14.4 vs. 2.5 events per 100 patient-years; incidence rate ratio, 0.18; 95% CI, 0.09 to 0.32).
Acute chest syndrome: (9.0 vs. 5.0 events per 100 patient-years).
Stroke: (1.8 vs. 0.7 events per 100 patient-years).
Acute sequestration crisis: (1.8 vs. 1.1 events per 100 patient-years).
Death (3.6 vs. 1.1 deaths per 100 patient-years; incidence rate ratio, 0.30; 95% CI, 0.10 to 0.88).
Hospitalization: There was no specific mention of the effects of HU on the length of hospitalization. However, a previous BABY-HUG study reported that HU reduced admissions by half and reduced hospital stays by 30%. [14]

Economic benefits of HU on SCD in LMICs

Cost-effectiveness of HU on outpatient care and units of blood: A 2023 study in Kampala, Uganda [25] compared the annual cost implications of OPD

treatment of HU and the HU-naive group and assessed their consumption of blood products. It was shown that HU treatment saved up to 191 USD and 11.2 units of blood per patient per year, despite the cost of drugs and monitoring. The benefits were significantly higher in those on maximum tolerated dose (MTD) than fixed HU dosing. BABY-HUG study reported that the cost of hospitalization was 21% lower among individuals on HU compared to those without HU.[14]

Laboratory effects of HU therapy

From the Sub-Saharan Africa study on the HU trial,[19] one-year of hydroxyurea therapy led to a significant increase in the haemoglobin level, the mean corpuscular volume, and the foetal haemoglobin levels. White cell count, absolute neutrophil count, and absolute reticulocyte count significantly decreased.

Haemoglobin: Increased by 1.0g/dL after 12 months of HU therapy.

Mean Corpuscular Volume: Increased by 13FL.

Foetal haemoglobin: Increased by 12.5%.

White Blood Cells: Decreased by 6,300/µL.

Absolute Neutrophil Count: Decreased by 2,500 /µL.

Platelet Count: Decreased by 6,700/µL.

Absolute Reticulocyte Count: Decreased by 157,000 /µL.

Alanine Transferase (ALT): Decreased by 1.0 U/L.

Creatinine level: Decreased by 0.02 mg/dL.

Initiation, escalation and monitoring of patients on HU

Approach to hydroxyurea use (See the proposed protocol below)

The first step is to identify patients that need HU.

Specific indications for HU therapy:

- Severe SCD (HbSS, Sβ-Thal, SO-Arab, etc.); some HbSC.
- Recurrent acute pain (≥3 in 1 year) or recurrent ACS, priapism, persistent anaemia.
- Primary or secondary stroke prevention – as a substitute for blood transfusions.

The current practice in many centres in LMICs is to give all patients with SCD from the age of nine months HU therapy. This protocol is supported by the HUSOFT Trials of HU therapy for the prevention of organ injury in very young children.[15] It should be noted that HU therapy is not just about pain prevention but also about the prevention of end-organ damage.

- Counselling and consent taking.
- Do baseline investigations: Full Blood Count, Renal Function Tests, Liver Function Tests, HbF level, Serological tests (hepatitis screening, HIV), and pregnancy tests for female adolescents.
- Treatment and monitoring algorithm: Patients will have a total of 13 visits, 13 FBC, 4 LFTs, 4RFTs and 2 HbF in the first year of therapy
- Identify toxicities during HU use.
-

Haematologic toxicities

The features include:

- Absolute neutrophil count (ANC) < 1,500/µL, or WBCC <4000/µL.
- Absolute reticulocyte count < 50,000/µL.
- Platelet count < 80,000/µL.
- Hb ≤ 4.5g/dl, or a fall of ≥20% in Hb concentration from the previous measurement

Non-haematologic toxicities

- Renal dysfunction - Serum creatinine doubles the baseline/ previous value.
- Hepatic dysfunction - ALT double the baseline value or is more than 2 times the upper limit of normal for age.
- Other side effects: skin dryness or darkening, rash, headache, dizziness, alopecia, nausea, vomiting, and constipation.

Management of haematologic toxicities

If Hb <4.5 g/dL, or,

Neutropaenia (ANC <1.5 x10^9/L)

Platelets <80 x10^9/L

Actions to be taken

- Withhold Hydroxyureahydroxyurea (i.e. temporarily discontinue).
- Monitor for signs of infection or bleeding.
- Repeat blood tests two-weekly until recovery

.

- Restart at the same dose or at 5 mg/kg/day less than the toxic dose.
- If recurrent or severe marrow toxicity occurs – reduce the dose to the last tolerated dose.

Management of non-haematologic toxicities
HU should be discontinued until:

- Toxicity resolves or is properly managed, or
- The suspected toxicity is determined not to be related to HU therapy.

Thereafter, resume HU at the previous dose.

Management of severe renal or liver toxicities - Decide whether to resume HU treatment or suspend it altogether.

Simplified protocol for HU therapy for children with SCD

Identify patients

All HbSS, Sβthal, SC, S-O Arab, S-D Punjab); age ≥9 months)
In LMICs: severe disease (recurrent pain ≥ 3/ year, anaemia or ACS, priapism, persistent anaemia, primary or secondary stroke prevention etc.)

Counselling and consent-taking

(Indication, benefits, cost, regular tests, potential side effects)

Baseline investigations

(FBC, RFT, LFT, HbF, pregnancy test for adolescent females, serology – Hepatitis, HIV)

Initiation of Hydroxyurea

(15mg/kg/day). Low dose of 10mg/kg/day can be used.

Laboratory monitoring

FBC: Two weeks after initiation, then monthly thereafter;
LFT/RFT three-monthly on two occasions after initiation, then six monthly;
HbF six monthly – yearly

Dose escalation

(5mg/kg/day every 2 – 3 months. Monitor for lab and clinical side effects)

Establish maximum tolerated dose (MTD): Dose beyond which the patient starts showing laboratory or clinical side effects of the drug: ANC <1500, WBC <4000, platelet count <80000, fall in Hb >20% of the previous value, renal or LFT (especially creatinine and ALT) values double the baseline.

No side effects: Up to 35mg/kg/day

With side effects: Withhold temporarily. Monitor clinically. Repeat blood investigations two-weekly until recovery. Restart at the same dose or at 5mg/kg/day less than the toxic dose on the last MTD.

The current state of prescription and use of HU in Nigeria

The current rate of HU prescription by physicians in Nigeria ranges between 44 and 74.3%. Isa *et al.* [26] in 2022 reported a physician prescription rate of 46.7% among 137 doctors. Ryan *et al.* [27] in a 2020 systematic review (two Nigerian studies and one Jamaican study), reported 44% of providers routinely prescribed HU and 40% of patients had used HU at least once. Okocha *et al.*[28] reported in 2020 that 74.3% of 120 physicians studied prescribed HU, while another study reported routine prescriptions among 44% of providers. [29]

Current rate of HU use in Nigeria

Rate of use: About 5.9 – 29.5% of children with SCD use HU routinely. The rate of use could be up to 33% in the adult population. Adewoyin *et al.* [30] reported that 40% of adults had used HU, 33% were currently using it, and 7% wholly adhered to its use. Chianumba *et al.* [31] from the 2022 study on outcome of HU use, showed that 378 (5.9%) of 6453 patients from 20 institutions were using HU or had ever used HU. Agumadu *et al.* [32] on Hydroxyureahydroxyurea in children with SCD in a resource-poor setting (2020) showed that only 116 (25%) of over 400 patients on their register were on HU at the time of the study. Isa *et al.* [26] showed that 15.6% of 237 patients were using HU, while Okechukwu *et al.* [33] reported that 29.5% of 88 children were using HU at the time of the study, with the majority of them belonging to the social class.

Barriers/Challenges to HU use in resource-poor settings

Challenges with the cost of the drug (affordability) - the high cost of HU is a major limiting factor. It affects initiation, compliance and overall effectiveness. Cost was identified as a barrier by 80% of surveyed doctors/patients in reports by Adeyemo *et al.*[34] and Okocha *et al.*[28]

Way forward

- Health insurance with good drug availability.
- Expanding local production.
- Free and all-inclusive health services.

Unavailability of HU—Poor accessibility remains a big challenge. HU is not available everywhere. Reports from a national study in 2015 showed that only 8 (44%) of the 18 clinics were prescribing Hydroxyurea.[29] Most likely, the proportions of SCD centres/facilities that regularly stock HU are still low.

The knowledge gap among managing health workers and patients on the safety, efficacy, availability, and cost of HU. Ofakunrin *et al*. in 2019 reported that 50.8% of 132 doctors had inadequate knowledge about HU use.[35]

Way forward

- Training and re-training of health care workers/ patients
- Advocacy for the routine use of HU in SCD patients
- Development of national guidelines on HU use

Challenges arising from the lack of paediatric formulation of HU. This is especially a problem for paediatric haematologists. Adeyemo *et al.* 34 and Isa *et al.* [26] documented that about two-thirds of physicians strongly identified this issue.

Way forward

- Institutions should enable pharmacists to prepare paediatric formulations /syrups.
- Advocate for smaller doses that are dissolvable in water (dispersible tablets).
- Encourage local manufacturers of HU.

Concerns about safety

- Haematological - Leukopaenia, thrombocytopaenia, reticulocytopaenia, and anaemia.
- Reproductive - Temporary decline in sperm count, infertility (81.3% of physicians considered it a barrier)
- Birth defects, foetal growth problems (evidence is not strong)
- Skin: Hyper-pigmentation of nails and skin; Increase in superficial skin cancer (evidence is not strong)
- Leukaemia (85% of health workers considered carcinogenicity as a major concern) – reported by Adeyemo *et al*. [34]

Way forward

- Education.
- The effectiveness of the drug should be emphasized, along with its potential benefits for SCD patients. Also, the safety of HU treatment for children with SCA living in malaria-endemic sub-Saharan Africa should be discussed. HU use was not associated with increased severe malaria, infections, or adverse events – NOHARM trials.[18]
- Concern about growth impairment: Some physicians believe that HU will significantly retard growth in children. The fear is valid since HU inhibit DNA synthesis. However, previous clinical trials showed that height, weight, and BMI-Z scores were similar in both placebo and treatment groups after two years of HU use (BABY HUG Trial 2004). Similarly, the HUG-KIDS Study (2003) Phase I - II Pediatric HU trial concluded that HU

treatment had no adverse effect on height or weight gain in school-age children.[12,14]

Challenges with frequent monitoring during use (Tests and expertise): Expertise and resources to monitor patients on HU are limited. In many centres in Nigeria, the cost of baseline investigations has increased astronomically. There is a concern about whether it is advisable to start HU if HbF is not measured. Can HU therapy be dangerous in patients with high HbF levels? This is because high levels of HbF increase haematocrit and hence, blood viscosity, thus predisposing to thromboembolic phenomena and SCD-related complications such as osteonecrosis, retinopathy, acute chest syndrome and stroke. Also, should HU be stopped if there is no rise in HbF? It is better to consider the clinical or other haematological benefits of HU. It is known that about 25% of patients may not show any corresponding increase in HbF with HU therapy.

Lack of clear national guidelines on HU use: About 90% of the physicians believed that the inclusion of HU in SCD management protocol would motivate doctors to prescribe (Isa *et al*.). The protocol may improve physicians' expertise.

Other possible ways forward

Foundations/ NGOs are encouraged to raise awareness, funds and advocacy, and more implementation science research on how to improve the uptake of HU is desired. There is also a need to encourage studies on local alternatives to HU – there are local plants that can induce HbF. It is important to intensify collaboration with experts in pharmacognosy. Also, medical colleges and postgraduate colleges should embrace studies to test the safety and efficacy of identified plants that could induce HbF production, such as Resveratrol, a polyphenol found in grapes, red wine, peanuts and berries. *Boerhavia diffusa* root extracts showed similar HbF-inducing potentials when compared to HU.

Conclusion

HU is one of the approved drugs capable of modifying the pathogenesis of SCD. It is largely effective and safe and has transformed SCD management. Available evidence in LMICs showed that its adoption (provider prescription and patient adherence) is low despite the huge SCD burden. Provider expertise, poor knowledge, misinformation, fear of side effects, cost of drug and monitoring, drug availability, and absence of national policy are the major challenges. Although some protocols are available, the current reality calls for a renewed and harmonized protocol on HU use for Nigerian children.

Declaration

The author declares that he has no affiliation with any hydroxyurea-producing or sales company. This write-up reflects the current medical knowledge available at this time. It is a "snapshot in time" of the state of knowledge on HU therapy in resource-poor countries. It is important to note that new knowledge emanates daily through medical research.

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EXCERPTS FROM THE 2024 PAN WEBINAR SERIES

Paediatric Heart Failure: Management Options in the Past, Present and Prospects

Anah Maxwell U[1], Sadoh Wilson E[2]
[1]Department of Paediatrics, University of Calabar Teaching Hospital, Calabar, Nigeria.
[2]Department of Paediatrics, University of Benin Teaching Hospital, Benin-City, Nigeria.

Introduction

Heart failure (HF) in children differs from that in adults in many respects as our population is heterogeneous. For instance, the causes and clinical presentations differ considerably among children of different age groups and between children and adults. The time of onset of HF holds the key to the aetiological diagnosis. The clinical presentation of HF in younger children can be non-specific, requiring a heightened degree of suspicion.

Though HF in adults has been the subject of extensive research and the generation of evidence-based guidelines, there is a scarcity of evidence-based guidelines in paediatric HF. For better management options of HF in children, the diagnosis must be made with precision to know what and how to manage.

The prospects for management depend on the peculiarities of HF in children, as there are unique features from the foetal heart to the neonatal heart up to adolescence. Not many paediatric-focused trials on standardized HF treatment have been done. Therefore, validating a paediatric system of HF classification and accepting surrogate endpoints for HF studies are essential for the field to move towards reducing morbidity and mortality.

Definition of Heart Failure

It is difficult to define heart failure precisely because a consensus statement on paediatric HF is lacking. According to Dickstein Kenneth (2005), providing a mechanistic definition is difficult. The American Heart Association (AHA) states that 'the heart fails when it cannot pump enough blood to meet the body's needs for blood and oxygen'. It is, thus, the pathophysiological state in which the heart cannot pump blood to meet the body's metabolic needs despite adequate venous returns to the heart'. The weakened heart does not or cannot supply the cells with enough blood. Typically, the preload is maintained; this definition excludes poor venous return situations.

Definition of Heart Failure based on timing or duration

Acute - decompensation in minutes or hours followed by congestion, malperfusion, tachycardia and hypoperfusion

Chronic - a progressive, clinical and pathophysiological syndrome caused by cardiovascular and non-cardiovascular abnormalities that result in characteristic symptoms and signs such as oedema, respiratory distress, growth failure, exercise intolerance and is accompanied by circulatory, neurohormonal and molecular derangements.

Advanced – this requires special care,, including mechanical devices/transplantstransplants.

End-Stage - a final common pathway that may require a heart transplant.

Epidemiology of Heart Failure

This is globally difficult because of the lack of a standard definition and scoring system used for heart failure studies in children. The phenotype also differs in congenital heart disease (CHDs) and cardiomyopathies. In Nigeria, it ranges from 3 to 15.5% among paediatric emergencies, mainly as a result of severe anaemia and pneumonia. Both sexes are affected equally without seasonal variations.

In the United States, it accounts for 11,000-14,000 hospitalized children annually, while in Ethiopia, it is the 10th most common cause of paediatric admissions.

The incidence ranges from 0.97 to 7.4 per 100,000.

Causes of Heart Failure

- Congenital Heart Diseases
- Rheumatic Valvular Diseases
- Cardiomyopathies
- Myopericarditis
- Arrhythmias
- Anaemia
- Malnutrition
- Infection/sepsis

- Hypertension
- Endocrine diseases

Pathophysiology

Over circulation

Over-circulation failure includes conditions that result in volume overload of cardiac chambers. The left ventricular (LV) function is either normal or LV is hypercontractile. Pulmonary venous or arterial hypertension may be present to a variable degree.

Pump failure

Pump failure includes both congenital and acquired conditions. LV or systemic ventricle function is abnormal, and most patients have pulmonary venous hypertension in this group.

Peculiarities of heart failure in children

- The high output often describes cardiac or extracardiac conditions leading to volume overload or congestion.
- Compensated or stable heart failure is asymptomatic.
- Decompensated is symptomatic
-

HF is characterized by typical symptoms and signs associated with specific circulatory, neurohormonal and molecular abnormalities.

Clinical features of heart failure in children

Infancy

- The clinical features of HF in a newborn can be non-specific, and a high index of suspicion is required.
- Tachycardia > 150/minutes, respiratory rate >50/minutes, gallop rhythm, and hepatomegaly are features of HF in infants.
- The clinical features of HF in infants include tachypnoea, feeding difficulty, and diaphoresis. Feeding difficulty ranges from prolonged feeding time (>20 minutes) with decreased volume intake to frank intolerance and vomiting after feeds.
- Irritability with feeding, sweating, and even refusal of feeds are also common.
- Established HF presents with poor weight gain, and failure in linear growth can also occur in the long term.
- Oedema of the face and limbs is very uncommon in infants and young children.

Older children

The features of HF in older children and adolescents include fatigue, effort intolerance, dyspnoea, orthopnoea, abdominal pain, dependent oedema, and ascites. Others considered cardinal include:

- Tachycardia
- Tachypnoea
- Tender hepatomegaly
- Cardiomegaly

These features cause challenges in diagnosis because they are not specific.

Diagnosis of heart failure in children

The diagnosis of HF is necessary for treatment to reduce mortality, but it is challenging since no symptom or sign is pathognomonic.

The steps include history, physical examination, and investigation using the scoring systems.

Challenges of diagnosis heart failure in children

The signs and symptoms are similar to other pathologies, such as the problems of definition of HF delay diagnosis. The well-established New York Heart Association (NYHA) HF classification does not apply to most paediatric population, as it is only reliable in children ≥ 5years old.

The Ross HF classification was developed in 1987 to assess the severity of HF in infants, but it had to be modified to apply to all paediatric ages.

The Ibadan Heart Failure Index for children addressed some diagnostic challenges.

Investigations in paediatric heart failure

- No investigation finding is pathognomonic.
- Blood and urine tests.
- Chest X-ray may not show cardiomegaly.
- Electrocardiography (ECG).
- Echocardiography.
- Biomarkers.
- CMRI and CT.
- Catheterization and biopsy.

Challenges of definitions of hf medical terms in diagnosis

According to course

- Acute
- Acute on chronic
- Chronic

According to severity

- Mild - complete compensation
- Moderate - incomplete

- Severe - complete decompensation

According to cardiac output

- Low output
- High output

According to location

- Left ventricular failure
- Right ventricular failure
- Biventricular failure
-

According to function-impaired

- Systolic
- Diastolic
- Congestive

Challenges of Diagnosing Congestive Cardiac Failure

The American College of Cardiology/American Heart Association Task Force on practice guidelines published in 2005 that the term 'heart failure' was preferred over the older term 'congestive heart failure'. Unfortunately, there is no such consensus among paediatricians, so the terms are still used interchangeably.

Congestion of organs from heart failure will lead to backflow of blood and pooling of fluid in the lungs.

Diagnosis of heart failure using ventricular ejection fractions

There could be:

- Systolic failure (heart failure with reduced ejection fraction - HFrEF).
- Diastolic failure (heart failure with preserved ejection fraction - HFpEF).
- Combined HFrEF and HFpEF.

However, characterization is not necessary in children as in adults because of poor cardiac reserves. This has been incorporated into the age-based Ross scoring system.

Scoring systems in the diagnosis of heart failure in children

1. The International Society for Heart and Lung Transplant (ISHLT) stratified heart failure into stages: (a) to (d).
2. The New York University Paediatric Heart Failure Index (NYUPHFI) has an overall score of 30.
3. The Modified Ross Classification of Heart Failure in Children.
4. Age-based Ross classification 0-18 years.
5. The New York Heart Association Classification (NYHA).
6. The Ibadan Childhood Heart Failure Index (ICHFI).
7. New York Heart Association Classification of Heart Failure.

- There may be no limitations of physical activity.
- There may be fatigue, palpitations, dyspnoea, or angina during moderate exercise but not during rest.
- There may be symptoms occurring with minimal exertion that interfere with normal daily activities.
- There may be inability to carry out any physical activity because the symptoms of HF are present at rest and worsens with exercise.

Ross Scoring System for Heart Failure in Infants

Items assessed (scored 0-2)

- Feeding history
- Time taken per feeding
- Respiratory rate
- Respiratory pattern
- Peripheral perfusion
- Third heart sound diastolic rumble
- Liver edge

Scoring

0-2 - No heart failure.
3-6 – Mild.
7-9 – Moderate.
10-12 – Severe.

Modified Ross classification of heart failure

- No limitations or symptoms.
- Mild tachypnoea or diaphoresis with feeding.
- Infants with growth failure and marked tachypnoea or diaphoresis with feedings; older children with marked dyspnoea on exertion.
- Symptoms at rest such as tachypnoea, chest retractions, grunting, or diaphoresis.

The Ibadan Childhood Heart Failure Index 1

Items assessed (scored 0-2)

- Resting respiratory rate
- Resting heart rate

- Capillary refill time
- Presence of 3rd heart sound
- Tender hepatomegaly
- Allowing for age-related variations
-

Scoring
0–2 - No HF
3–4 - Mild HF
4–6 - Moderate HF
≥7 - Severe HF

Why the Ibadan Heart Failure Index should be adopted
The Ibadan Childhood Heart Failure Index (ICHHFI) is a clinical scoring system for the diagnosis of heart failure in children constructed using the resting respiratory rate, resting heart rate, capillary refill time, presence of a diastolic third heart sound, and tender hepatomegaly. It allows for age-related variations in some of these signs.

It was hypothesized that less severe forms of congestive HF would have lower respiratory rates, lower heart rates and less distension of the liver, while the more severe forms would have higher values as the body attempts to compensate for causes of HF using various mechanisms.

A study of the Diagnostic Accuracy of a Clinical Scoring Scheme in Childhood Heart Failure by Luke and co-workers in Ibadan in 2021, using B-type natriuretic peptide (BNP) as the gold standard on 45 consecutive hospitalized infants, reported that the mean plasma BNP was higher (3378.13±1114.54 pg/l) in patients with severe heart failure compared to those with moderate heart failure (826.46±282.89 pg/l) and mild heart failure (501.25±159.55 pg/l). The observed difference was statistically significant ($p<0.001$).

Novel Biomarkers of Heart Failure in Children
These are based on the seven groups of pathophysiological mechanisms thus:

- Myocardial stretch
- Myocyte injury
- Myocardial remodelling
- Inflammation
- Renal dysfunction
- Neurohumoral activation
- Oxidative stress

Using biomarkers with different pathophysiological mechanisms improves the diagnostic and prognostic predictive value of HF in children

Biomarkers in Diagnosis
Accurate grading of the presence and severity of HF signs and symptoms in infants and children remains challenging despite using Ross criteria for over 25 years. New evidence has shown that in addition to signs and symptoms, data from echocardiography, exercise testing, and biomarkers such as N-terminal pro-brain natriuretic peptide (NT-pro BNP) are useful in stratifying outcomes for children with HF. It is also apparent that grading of signs and symptoms in children is dependent on age because infants manifest HF differently from toddlers and older children

Improving the accuracy of diagnosing HF has been the focus of research for a long time because diagnosing HF with CHDs is more difficult. For instance, Wu and co-workers used the modified Ross Classification, Qingado, NYUPHFI to recruit patients and reported a sensitivity and specificity of the NT-pro-BNP as 100% specificity and 47.9-88% sensitivity. It was suggested that using this biomarker with clinical criteria would improve its diagnostic accuracy.
Others have shown different values of NT-pro-BNP in cardiac or pulmonary causes of HF. Nevertheless, it correlates with the severity of HF in infants and small children.

Biomarkers used in diagnosing HF

- Brain Natriuretic Peptide and N-Terminal pro-BNP.
- Copeptin.
- Galectin-3.
- High sensitive cTnT.
- Mid-region pro-Atrial Natriuretic Peptide.
- Suppression tumorigenicity 2 (st2).

In children, NT-pro BNP correlates well with the stage of disease and is a better predictive factor of HF than BNP.

Cardiogenic Shock and Heart Failure in Children
Shock is an acute failure of the cardiovascular system to meet the metabolic demands of the tissues, namely, delivery of substrates and removal of metabolic wastes. Inadequate tissue oxygenation leads to anaerobic metabolism, acidosis, and

eventual loss of cellular functions. Cardiogenic shock is an acute state of end-organ hypoperfusion following heart failure. It occurs from various aetiologies leading to primary pump failure, with or without contributions from inadequate preload or afterload.

Conclusion

There are lots of challenges in the diagnosis of HF in children, though HF is a common paediatric emergency that causes high mortality. To reduce associated morbidity and mortality, the diagnosis of HF should be accurate. The use of biomarkers in suspected childhood HF is the solution to the problem of difficult clinical diagnosis arising from the non-specificity of the symptoms and signs of HF in children.

Paediatric Heart Failure Management Options: Past, Present and Prospects

Background

Most treatment options in children are offshoots of adult treatment guidelines.

Review of the pathophysiology of Paediatric HF

Features of HF in children are manifestations of compensatory responses to low cardiac output (CO). These include:

- Activation of the sympathetic nervous system.
- Increase in heart rate.
- Increase in inotropy.
- Diaphoresis, increase in CO and organ perfusion.
- Elevated catecholamines → cardiomyocyte injury, dysfunction and death.
- Activation of renin-angiotensin-aldosterone system.
- Angiotensin II causes vasoconstriction – and improves CO.
- Aldosterone causes salt and water retention – fluid accumulation.
- Angiotensin II and aldosterone promote cardiac fibrosis and apoptosis.

Compensatory mechanisms initially stabilize circulation but later cause the progression of HF.

Objectives of Paediatric Heart Failure Treatment

- Treat the underlying cause.
- Correct CHD.
- Blood transfusion for severe anaemia.
- Antibiotics for bronchopneumonia.
- Control of symptoms and disease progression.
- Reduce the preload.
- Enhance contractility.
- Reduce the afterload.
- Improve perfusion and oxygen delivery.
- Enhance nutrition.

Non-Specific/ General Measures

- Nutritional support - 150kcal/kg/day for infants; 25-30kcal/kg/day for children and adolescents.
- Give small energy-dense feeds frequently.
- Low salt intake in patients with oedema.
- Fluid restriction in patients with oedema.
- Daily weighing if admitted.
- Supplemental oxygen in severe cases.

Medical Treatment

Reduce the preload or the congestion

Diuretics

- Loop diuretic – Frusemide 1-2mg/kg/day
- Thiazides – 1-2mg/kg/day
- Metolazone - Acts like thiazide, more potent even with poor GFR (0.2 – 0.4mg/kg/day orally)
- Potassium-sparing diuretics –
- Spironolactone (0.5 – 1.5mg/kg/day), eplerenone
- Spironolactone counters the aldosterone-induced myocardial fibrosis and catecholamine release.
- Amiloride, triamterene

Afterload reduction

ACE inhibitors - Recommended in all patients with HF and systolic dysfunction

Captopril 0.1 – 0.5mg/kg/day

Enalapril 0.05 – 0.25mg/kg/day - Reverses myocardial remodelling

Angiotensin receptor blocker - Used with failure of ACE inhibitor or with contraindication to ACE inhibitor

Losartan – 0.5 – 1.5mg/kg/day

Nitrates

Nitropruside - 0.5-4ug/kg/minute infusion

Nitroglycerin - 0.5 – 10ug/kg/minute infusion

Epinephrine - 0.01 – 0.1ug/kg/minute infusion
Neseritide
Beta-blockers

- Antagonizes chronic sympathetic myocardial damage
- Reverses left ventricular remodeling
- Improved survival in some studies
- Carvedilol – 0.2 – 0.4mg/kg/dose

Enhances contractility
Digoxin

- Powerful inotrope, reduced chronotropic
- Problem with increased oxygen consumption
- Dose – 5 – 10ug/kg/day oral

Dopamine and dobutamine

- Weak inotropes and dose dependent vasopressor
- Good for patients with low CO
- Improved renal blood flow

Phosphodiesterase Type III inhibitors

- Example – Milrinone
- Has vasodilatory and inotropic effects
- Has proarrhythmic effects
- Calcium sensitizer
- Levosimendan – strong inotrope and vasodilatory effects
- Not proarrhythmic and reverses beta-blockade

Approach to the management of Acute Heart Failure in neonates

- Admit and assess the ABC
- Exclude duct –dependent CHDs via echo
- Prostaglandin E infusion
- Exclude tachyarrhythmias
- Pharmacological or electrical cardioversion
- Other causes of PHF including CHDs with significant left to right shunt lesions, LRTI
- With congestion, begin with diuretics
- Diuresis with frusemide/consider K sparing if failure persists
- In cases of severe hypotension: Dopamine infusion at 5-10mcg/kg/min

Managing acute HF in older children
Admit the child
Screen for congenital heart disease, dilated cardiomyopathies and lower respiratory tract infections.
Also, begin with diuretics to address congestion
IV Frusemide.
In cases with significant hypotension:
-Infusion Dopamine 5-10mcg/kg/minute.
-Infusion milrinone – 0.3-1mcg/kg/minute.
Consider nitroprusside, nitroglycerin or nesiritide with significant pulmonary oedema
In severe anaemia:
-Transfuse with blood along with diuretics.

Managing chronic or stable Congestive Heart Failure

- Manage on outpatient basis.
- ACE inhibitor is the cornerstone of treatment in CHDs, myocarditis, DCM.
- ARB can be used with ACEi adverse effects.
- May initiate low dose frusemide 1mg/kg/day
- May include inotrope (digoxin) or beta-blockers (carvedilol) for mild CHF
- In cases of moderate to severe CHF:
- Increase frusemide to 2mg/kg/day
- Or add a second agent: hydrochlorothiazide (HCT) or metolazone.
- Add simultaneously HCT or metolazone to frusemide for synergistic effect.
- To attenuate diuretic-induced hypokalaemia, add spironolactone or eplerenone.
- Beta blockers: metoprolol (selective) with carvedilol (non-selective).
- Useful in cardiomyopathies and chronic congestion.
- Decrease pulmonary artery pressure and cardiac non-epinephrine levels.
- Watch out for anaemia since anaemia aggravates CHF.
- May require blood transfusion to improve treatment.

Promising new medical therapies

- Ivabradine is used in children >6 months with CHF due to cardiomyopathy with tachycardia.
- Ivabradine is an “f” current inhibitor; it blocks the cardiac pacemaker "funny current."

- Neprilysin inhibitor with valsartan.
- Neprilysin is a neutral endopeptidase which degrades natriuretic peptide, bradykinin and adrenomedullin. Its inhibition causes less vasoconstriction, sodium excretion and remodelling.

Device therapies

- Blockade of potentially fatal arrhythmia
- Implantable Cardioverter Defibrillator (ICD)
- Prevention of sudden cardiac death in patients with aborted cardiac arrest
- Unexplained syncope in patients with surgically repaired CHD
- Improving ventricular contraction
- Cardiac Resynchronization Therapy (CRT)
- Improves contraction and cardiac output through biventricular pacing

Mechanical circulatory support therapies

- Extracorporeal life support (ECMO)
- Indication – HF Patients not stabilized on medical therapy
- Patients with cardiogenic shock not responding to medical treatment
- Interim period before transplant is short
-

Implantable Left Ventricular Assist Device

- A stop-gap treatment before transplantation.
- The period before transplant could be years because of difficulty with getting heart for transplant.
- Results in children are good.
-

Heart Transplantation

- Treatment for End-Stage/refractory HF in children.
- Advanced HF with restrictive cardiomyopathy and PAH.
- Children with end-stage cardiomyopathy.
- Outcome of paediatric transplantation is good.
- Survival for infants is over 20 years but decreases with increasing age at transplantation.

Conclusion

HF in children has its uniqueness in terms of the variety in aetiology and clinical presentation which are also related to age. Unfortunately, there are no international guidelines like in adults. Nevertheless, some treatment options and approaches have emerged as a result of extrapolation from adults' guidelines and from a few paediatric trials which led to some evidence-based approaches in managing this challenging condition.

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Questions

1. Which of the following is not a mechanism of heart failure in children with anaemia?
a. Increase cardiac workload
b. Increased cardiac dilation
c. Increased heart rate
d. Increased fluid overload

2. Which of these scores using the Ibadan childhood HF index indicates severe heart failure?
a. 0-3
b. 4-6
c. 7-10
d. 11-13

3. Which of these is not a biomarker for heart failure diagnosis?
a. Copeptin
b. Galectin -3
c. Suppression tumorigenicity 2
d. Atrial natriuretic peptide

4. A 2 -year old with repeated chest infections and small for age presented to you in the children outpatient clinic. He was dyspnoeic and tachypnoeic. He was found to be in heart failure with a grade III pansystolic murmur maximal at the lower left sternal boarder of the heart. What is the likely aetiology?
a. Mitral incompetence
b. Ventircular septal defect
c. Atrial septal defect
d. Aortic incompetence

5. Which of these causes of heart failure will not present with radiological evidence of cardiomegaly on the chest radiograph?
a. Endomyocardial fibrosis
b. Tricuspid atresia
c. Mitral stenosis
d. Coarctation of the Aorta.

6. Which measures will control the symptoms and progression of heart failure in children?
a. Increasing the preload
b. Enhance myocardial contractility
c. Reduce tissue perfusion
d. Enhance nutrition

7. About angiotensin receptor blocker, the best answer is
a. It is used in place of angiotensin-converting enzyme inhibitor (ACEi)
b. It is recommended for all patients with heart failure and systolic dysfunction
c. It reverses myocardial remodelling
d. Useful in cases of ACEi induced intractable cough

8. In managing a child with heart failure, the initial treatment is
a. A diuretic
b. Dopamine
c. Nesiritide
d. Milrinone

9. The cornerstone treatment in chronic heart failure is;
a. Beta-blocker therapy
b. Angiotensin receptor blocker therapy
c. Angiotensin-converting enzyme inhibitor
d. An inotropic agent

10. Which is the best option regarding Ivabradine?
a. Useful in children below six months,
b. It is an (f) current inhibitor

c. It enhances the cardiac 'funny current' pacemaker
d. Not useful in heart failure due to cardiomyopathy

Answers

Question	Answer	Question	Answer
1	D	6	B
2	C	7	D
3	D	8	A
4	B	9	C
5	C	10	B

Management of Coma in Childhood

Murtala M. Ahmad
Department of Paediatrics
Usmanu Danfodiyo University/Usmanu Danfodiyo University Teaching Hospital, Sokoto.

Goal of Management

For any critically ill child, the priorities include:

1. The goal is to stabilize life-sustaining functions (Airway, Breathing, Circulation).
2. Control life-threatening neurological signs (seizures, raised intracranial pressure [ICP], metabolic disorders, infections).
3. Preserve (or limit) further brain and other organ-system damage.
4. Restore normal body/ brain functions.

Principles of Coma Management

Irrespective of the cause, the general principle of management is to:

Protect the brain/prevent secondary brain injury by:

- Optimizing cerebral perfusion to prevent brain ischaemia.
- Maintaining appropriate ICP.
- Preventing herniation syndromes.

Identify and treat the underlying cause: infectious/inflammatory, metabolic, or traumatic)

Monitor neurologic recovery.

Initial Evaluation

- Immediate life support: Airway, Breathing and Circulation (ABCs).
- Quick identification of the cause: quick relevant history.
- Onset and progression may give a clue to cause (vascular, infectious, traumatic or neoplasms), recent illness, trauma, or toxic ingestions.
- Ask about allergies, medications, past medical history, last meal and events leading to presentation (AMPLE).
- Quick, focused physical examination: general and systemic examination including neurologic examinations.
- Prompt institution of specific therapy based on most likely diagnosis/identified cause.

Airway: Is the airway open?	Open, maintain and protect. Use techniques to open the airway (Head tilt-chin-lift, jaw thrust). Avoid neck extension if trauma is suspected. Suction, use of advanced airway.
Breathing: Is patient breathing? Is respiration adequate?	If not breathing or gasping, do CPR and establish breathing; take note of abnormal respiratory sounds. Check SPO_2 and give supplemental oxygen if needed, Use nebulizers etc
Circulation: Is circulation adequate? Check Pulses, capillary refill, skin colour, cold extremities, blood pressure.	-Establish vascular access (IV/IO). -If hypotensive /hypovolaemic/severe dehydration, give IVF (isotonic/colloid). -Do CPR if not breathing/gasping, use AED if there is a shockable rhythm (VF or pulseless ventricular tachycardia). Ensure adequate CO and cerebral perfusion.
Disability Is patient comatose? AVPU, GCS, BCS Quick, focused neurologic assess.	Evaluate for underlying cause of coma (infective, metabolic) check random blood glucose (RBG) and correct (if low), control seizures, look for signs of raised ICP and manage if present.

Always remember to follow this sequence:

Once a life-threatening issue is identified, immediate intervention should be provided before the next evaluation step.

Rapid assessment protocol
(Based on the guidelines of the African Federation for Emergency Medicine-AFEM)

ACTION	IMMEDIATE (0-5 mins)	EMERGENT (5-15 mins)	URGENT (15-60 mins)
History	- AMPLE History - Trauma, seizures, ingestions, neurol. Changes	Onset, evolution, duration, associated symptoms	- More detailed history, medications, past medical history (seizures, recent infection)
Physical examination	- Airway - Breathing - Circulation - D: AVPU, ↑ICP, focal neurol. Signs	Mental state, eyes, pupils, motor response, and fundoscopy	Exposure: Complete exam, survey for Non-accidental Injuries, repeat exam for evolving neurological signs.
Diagnostics	- Vital signs - O_2 saturation - Blood glucose - Malaria parasites	Repeat RBG if low (corrected)	E/U, CBC, urinalysis, tox screen, LFT, CT
Therapeutics	- O_2 therapy, IV Dextrose bolus, then intravenous fluid VF	- Antibiotics, antimalaria, antidotes, and intubation.	Osmotic diuresis, Dexamethasone, Antihypertensives

Signs of hypoxaemia

- Restlessness/ irritability
- Peripheral cyanosis
- Use of accessory muscles of respiration
- Flaring alae nasi
- Tachycardia
- Tachypnoea

Hypoxaemia may be related to:

-Respiratory diseases, cardiac diseases, neurologic (inadequate respiratory efforts)

-Confirmatory tests:

- Pulse Oximetry
- Capnography
- ABG
- HCT/HB

Indications for Endotracheal Intubation

To support breathing in apnoea. Intubation will facilitate oxygenation and ventilation reduce the risk of aspiration. It is indicated in:

- Respiratory failure (hypoxic/hypercapnic).
- Deep coma (GCS ≤8).
- Inability to maintain airway patency.
- Impending airway compromise/obstruction.
- High risk of aspiration/disruption of airway reflex.

D-Disability/Neurologic

Goal: To detect and halt ongoing brain insult and prevent secondary injury.

Perform a rapid neurologic evaluation:

Coma may present with or without focal neurologic /lateralizing signs (structural vs diffuse causes)

Abnormal posturing: Decerebrate, decorticate, opisthotonus, abnormal gaze, involuntary movements, seizures.

- AVPU level (GCS, BCS)

Assessing coma

- (4) or (3) response scale:
- AVPU (Alert, Verbal, Pain, Unresponsive)
- GCS/Modified GCS/BCS
- Stimulation methods:
- Voice: Talk, shout
- Tactile: light touch, deep/pressure
- Pain: Sternal rub, nail bed compression, supraorbital pressure, trapezius squeeze

- Signs of elevated ICP, dilated unresponsive pupils, bradycardia, elevated BP, respiratory irregularities or apnoea (suggest cerebral herniation)
- Brain CT provides the most rapid assessment.

Posture

This may suggest the level of the brain lesion:

- Decorticate posturing: supratentorial lesion
- Decerebrate posturing: brainstem dysfunction
- Fragment of celebrate (extended arms, flexed leg): pontine lesion
- Flaccidity: brainstem damage below the pontomedullary level

Pattern of respiration

Abnormal patterns associated with central lesions include:

- Cheyne-Stokes breathing (alternating hyperpnea and apnoea, may suggest brainstem or higher level extensive bilateral dysfunction),
- Central neurogenic hyperventilation (pontine or tegmental lesion),
- Apneustic breathing (pontine lesions),
- Ataxic breathing (medulla).

Pupillary changes

- May give additional clue about location of the cause:
- Small, reactive - metabolic, hypothalamic
- Pinpoint - pontine, narcotics poisoning, cholinergic agonists, phenothiazines
- Mid-position, fixed: midbrain.
- Ipsilateral fixed, dilated: CN III compression, uncal herniation
- Bilateral fixed, dilated: severe hypoxic-ischaemic encephalopathy (HIE), elevated ICP, anticholinergic poisoning, atropine effect.

E-exposure

- Expose and look for signs of trauma, fractures bruises, rash, petechiae, other cutaneous signs.
- May provide clue to the cause of coma and mechanism of injury.
- Odour: chemicals, ketone.
- Remember non-accidental injury as a possible cause too!
- Be sure to cover and maintain warmth during and after the diagnostic survey of the patient.

Fever

- Has deleterious effect on the injured brain.
- It increases metabolic expenditure, exacerbates neuroexcitation, and elevates ICP.
- Treat fever with a temperature greater than 38^{o}C: Tepid sponging, room cooling, exposure, parenteral antipyretics.
- Search for the cause and address it: CNS infection, pneumonia, urinary tract infection, sepsis.

Rapid diagnostic investigations

- Directed towards most likely aetiologies.
- Blood Glucose: Immediate correction if hypoglycaemia is detected.
- Urinalysis, Serum electrolytes, clotting profile, Liver Function Tests
- Blood gases (ABG)
- Toxicology screen if indicated (including drug/alcohol levels).
- Sepsis screen/infection biomarkers (full blood count, blood cultures, C-Reactive Protein, polymerase chain reaction)
- Lumbar puncture: If infection is suspected and there is no contraindication such as raised ICP.
- EEG (electrical status?).
- Brain Imaging: CT scan for suspected structural causes and raised ICP. CT is usually not necessary in coma caused by diffuse brain dysfunction, such as hypoglycaemia, infection or poisoning.
- MRI, PET, fMRI after stabilization (if indicated).

Contraindications to lumbar puncture in Coma

- Abnormal posturing.
- Lateralizing signs.
- Cardio-respiratory abnormalities.
- Signs of raised ICP, including anisocoria.
- Papilloedema.
- Seizures (prolonged, tonic).
- Suspicion of an intracranial space-occupying lesion.
- Deep coma.
- Overlying skin sepsis.

Treatment

- Definitive treatment of coma is ultimately disease-specific, based on the aetiology.
- Empiric treatment of suspected cause(s) must be given.
- Treating the underlying cause:
- Medical (specific treatment of causes)
- Surgical (burr hole, open surgery).

Treatment of the underlying cause(s)

- Cerebral malaria: IV artesunate, Quinine
- Meningitis/para meningeal infections: IV antibiotics such as Ceftriaxone, Cefotaxime, Metronidazole, and neurosurgery.
- Encephalitis: IV Acyclovir (if indicated)
- Metabolic Disorders: Correction of electrolyte imbalances, hypo/hyperglycaemia, uraemia.
- Toxicology: Administer antidotes if available (e.g naloxone for opioid toxicity, flumazenil (BZD) physostigmine (anticholinergics) etc.
- Epilepsy: Control of seizures with anticonvulsants.

Ongoing Monitoring

- Review history: Unclear diagnosis, poor clinical response.
- Vital signs, including SPO_2.
- Neurological monitoring – GCS.
- Observing for new signs (neurologic and non-neurologic).
- ICP monitoring if indicated.
- Fluid and electrolytes balance and monitoring.
- Medications.
- Laboratory monitoring (Glucose, Packed Cell Volume, Electrolytes, Arterial Blood Gases, Electroencephalography (EEG) (when indicated).

Other supportive/ancillary care

- Nutritional support: NG feeding tube.
- Feedings should be calibrated to metabolic needs to reduce the risk of aspiration.
- Pulmonary management.
- Airway adjuncts for airway protection.
- Antibiotics when indicated.
- Regular turning and patient assessment.
- Observe for complications: Seizures, raised ICP.
- Good nursing care: hygiene, skin, eyes, bowel, and bladder care.
- Prevention of pressure sores, deep vein thrombosis and contractures.
- Family counselling and psychosocial support.

General Neuroprotective Strategies

Aims at preventing/limiting secondary brain injury.

Maintaining adequate O_2 delivery	**Modulating brain O_2 consumption**
Supplemental Oxygen PaO_2 (80-100mmHg) Adequate haemoglobin concentration Adequate cerebral perfusion: MAP, ICP Avoid hypo/hypercapnia PaCO2 (35-45mmHg) Maintain systemic haemodynamics	Maintenance of cerebral homeostasis. Prevent/treat seizures. Prevent/treat fever. Avoid agitations and noxious stimulation. Avoid hypoperfusion and worsening ischaemia.

Address any identified life-threatening condition such as raised ICP, Seizures, etc

Raised ICP as a Life-Threatening Feature

- ICP is raised when it is above 15mmHg.
- Diagnosis is made from clinical symptoms and signs.
- Confirmation by ventricular catheterization.
- Diagnosed with neuroimaging (CT or MRI), Transfontanelle ultrasound scan (for infants)
- Consequences of raised ICP include brain tissue compression, reduced cerebral perfusion, ischaemia. and brain herniation.
- All comatose patients with raised ICP require PICU care

Cerebral Oedema

1. Vasogenic oedema: Extracellular and increased permeability of BBB. This may be seen around brain tumours, trauma or haemorrhage. Treatment is mainly with corticosteroids.
2. Cytotoxic/cellular oedema: Intracelluar (neurons, glia and endothelial cells death) - caused by hypoxia/ischaemic stroke, CNS infections,

metabolic encephalopathies, and Reye syndrome. Treatment is with osmotic agents.
3. Hydrostatic/interstitial oedema: Extracellular, due to acute hypertension, obstructive hydrocephalus. Treatment includes acetazolamide and frusemide.

Consequences of Uncontrolled Raised ICP

- Reduced cerebral perfusion
- Cerebral Ischaemia
- Cerebral Oedema
- Brain herniation
- Increased mortality

Medical Management of ICP

- Management starts at the emergency room before transfer to the ICU.
- The primary goal is to reduce the ICP to <20mmHg or the maintenance of CPP > 60mmHg.
- To avoid factors that aggravate raised ICP (fever >38^{o}C, hypoxia, hypoglycaemia, hypotension and any noxious/excessive stimulation such as suctioning, and sudden head movement).
- To avoid fluid overload and monitor serum sodium levels.
- Treat the underlying cause, if identified.

Steps to prevent cerebral herniation syndromes and further brain damage

- ABC of resuscitation.
- 30^{o} Head elevation, neutral position (to promote venous drainage from the brain).
- Controlled hyperventilation (to maintain $PaCO_2$ to 30-35mmHg) to achieve cerebral vasoconstriction.
- Osmotherapy: 20% Mannitol 0.5-1g/kg over 15-20 minutes, q6-8 hours.
- Hypertonic saline (3%) infusion: 3-5ml/kg over 15-20 minutes to create an osmotic gradient.
- HTS: Phlebitis, hypernatraemia, hyperchloraemic metabolic acidosis.
- Steroids for vasogenic oedema: Dexamethasone 0.15-0.2mg/kg q6hours.
- Limited fluid restriction.
- Acetazolamide 5mg/kg (to reduce CSF production)
- Light sedation (midazolam infusion) to reduce metabolic demand and agitation.
- Other interventions for raised ICP
- For severe and refractory raised ICP, especially in traumatic coma, and to enhance brain tolerance to ischaemia by reducing cerebral metabolic rate and hyperadrenergic state.
- Therapeutic hypothermia (32-34^{o}C) reduces brain metabolic demand and oedema.
- Barbiturate coma (thiopental):
- Surgical measures – Decompressive craniotomy and CSF diversion.

ICP Monitoring

- <u>Non-invasive</u>
- Clinical symptoms and signs.
- Clinical monitoring using the Glasgow Scale (GCS).
- Pupillary asymmetry.
- Posturing.
- Optic Nerve sheath diameter.
- Neuroimaging.

- Invasive
- Ventriculostomy
- Implantable ICP sensors
- Fibre optic monitoring

How long does a coma last?

- Most patients with severe brain insult develop coma, but recovery rarely exceeds four weeks.
- Prolonged coma is that which lasts more than four weeks with no signs of recovery.
- Afterwards, patients may go into a spectrum of vegetative states: persistent or permanent (1-3mo or >3mo).
- The vital signs and brain stem functions are preserved; they appear ‘awake’ but unaware of self and the environment.

Treatment of Persistent Vegetative State is mainly supportive (medical & nursing care).
Neurostimulant medications (methylphenidate and amantadine) may aid recovery.
Cognitive recovery from a vegetative state is exceedingly rare after three months.
Ethical issues include consideration of the risks and benefits of continuous medical support or its withdrawal

Long term complications of coma

- Neurologic sequelae:

- Cortical blindness
- Developmental regression
- Learning disabilities
- Epileptic Seizures
- Movement disorders
- Cerebral Palsy
- Behavioural disorders/Hyperactivity
- Brain damage

Prognostic Indicators

- Underlying cause.
- Depth and duration of coma and neurologic findings.
- Age of the patient.
- Response to initial management.
- Presence of chronic co-morbidities.
- Neuroimaging findings/brain complications.
- Outcome: 15 - 58% mortality rate has been reported among African children with non-traumatic coma (depending on the factors listed above).
- Overall, good recovery with moderate disability may be expected.
- VS/Death

Residual deficits

- Long term follow-up.
- Neurorehabilitation: Physiotherapy, SALT, OT
- Psychological support for the family.
- Neurologic/developmental monitoring.
- Post discharge outcomes at 6months and 12months.

Conclusion

Coma is a common paediatric emergency (both traumatic and non-traumatic). Irrespective of the cause, it must be handled as an emergency. The management requires a systematic approach, including rapid stabilization, targeted evaluation, specific treatment and supportive care. The chances of good recovery are dependent on many factors, including the cause, depth, duration and initial response to interventions given. There is the need to follow-up all cases after recovery/discharge.

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Questions

1. Which of the following is correct about imaging in comatose child?
   a. CT scan is necessary for suspected structural causes & raised ICP
   b. CT is usually not necessary when there is deep coma
   c. MRI is superior to CT Scan in evaluation of acute coma
   d. Only C and D are correct

2. Which of the following is not a method of modulating brain oxygen consumption in coma?
   a. Maintenance of cerebral homeostasis.
   b. Treatment of fever.
   c. Avoiding noxious stimulation.
   d. Giving supplemental oxygen.

3. Which of the following is not an indication for endotracheal intubation in a comatose child?
   a. Light coma (BCS ≥8).
   b. Respiratory failure.
   c. Impending airway compromise/obstruction.
   d. Absence of protective airway reflex.

4. Which of the following is incorrect about the treatment of raised intracranial pressure?
   a. Hypertonic saline (3%) is an example of osmotic agent.
   b. Steroids are useful for vasogenic brain oedema.
   c. Mannitol is used for post-traumatic brain oedema.
   d. Hyperventilation reduces partial pressure of CO_2.

5. Prolonged coma refers to a coma that last …… with no signs of recovery.
   a. More than 4 weeks
   b. More than 2 weeks
   c. More than 2 months
   d. More than 3 months

Answers

Question	Answer
1	A
2	D
3	A
4	C
5	A

CLINICAL QUIZ

A clinical scenario and the corresponding clinical image are provided below. Please study the image and answer the questions.

A seven-day-old female infant was presented at a Teaching Hospital on referral from a private hospital with complaints of inability to swallow feeds noted soon after birth, excessive drooling, and episodes of choking. The mum booked at one month of pregnancy and was noted to have a twin gestation. She had a febrile illness in the first trimester and received some intramuscular unidentified injections. Thereafter, she developed bleeding par vagina which continued for two days. This culminated to a miscarriage of one of the twin foetuses. The index baby was eventually born at term via spontaneous vaginal delivery with a birth weight of 3 kg.

On examination, she had mild respiratory distress, mild flaring alae and excessive salivation. Attempts to insert a nasogastric tube failed. She also had fluctuating glycaemic levels. On further examination, the abdomen was distended, but the rectum was empty. Other systemic examinations revealed essentially normal findings.
Abdominal X-ray/baby gram showed a massively dilated stomach and dilated bowel loops and incidental total left lung collapse. Lung ultrasound scan confirmed the left lung collapse, with normal right lung and slight mediastinal shift. Intravenous fluids were infused to correct dehydration while glycaemic and serum electrolyte imbalances were corrected. Though SpO_2 was above 90% in room air, intranasal oxygen was administered to support the one normal lung. Initial surgical intervention to establish feeding was a gastrostomy procedure and this was successful. Unfortunately, baby died few days later.

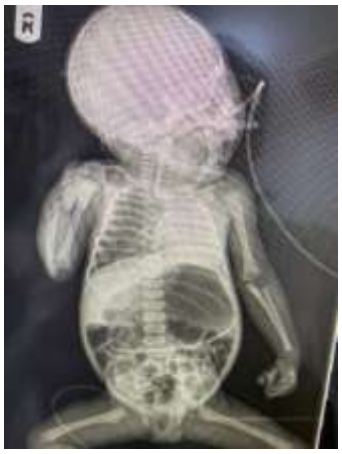

Figure 1: Initial X-Ray at presentation

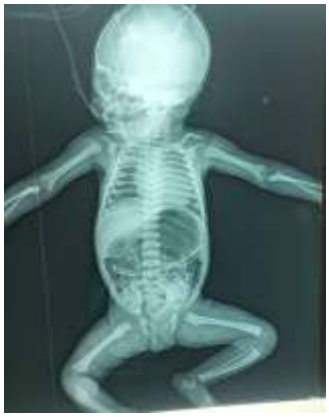

Figure 2: Follow-up X-Ray taken some days after hospitalization

Questions: Select the most appropriate answer to each question from the options A to D as provided.

1. What is the most likely diagnosis in the 7-day-old infant presenting with difficulty swallowing, excessive drooling, and episodes of choking?

a. Pyloric Stenosis
b. Oesophageal Atresia
c. Hirschsprung Disease
d. Intussusception

Correct Answer: B. Oesophageal Atresia
The symptoms of difficulty swallowing, excessive drooling, and choking from birth are characteristic of oesophageal atresia, where the oesophagus does not connect properly to the stomach.

2. Which imaging finding is most indicative of oesophageal atresia with tracheoesophageal fistula (TEF)?

a. Double bubble sign on abdominal X-ray
b. Air-filled stomach and proximal oesophagus on X-ray
c. Absence of gas in the intestine on X-ray
d. Enlarged liver on ultrasound

Correct Answer: B. Air-filled stomach and proximal oesophagus on X-ray
An air-filled stomach and proximal oesophagus on X-ray suggest the presence of a tracheoesophageal fistula, which allows air to pass get the stomach.

3. What is the initial management step for a newborn suspected of having oesophageal atresia?

a. Immediate surgical repair
b. Administration of oral feeds
c. Nasogastric tube insertion and intravenous infusion
d. Observation and wait for spontaneous resolution

Correct Answer: C. Nasogastric tube insertion and intravenous infusion.
The initial management involves stabilizing the infant by decompressing the stomach with a nasogastric tube and providing IV fluids to correct dehydration and electrolyte imbalances.

4. Which of the following complications is most likely in a newborn with oesophageal atresia and tracheoesophageal fistula?
a. Severe hypoglycaemia
b. Aspiration pneumonia
c. Bowel obstruction
d. Hepatomegaly

Correct Answer: B. Aspiration pneumonia.
Aspiration pneumonia is a common complication due to the abnormal connection between the trachea and oesophagus, allowing food and fluids to enter the lungs.

5. What is the purpose of the initial gastrostomy procedure in the management of oesophageal atresia?
a. To correct the anatomical defect
b. To provide a route for feeding
c. To decompress the intestines
d. To treat respiratory distress

Correct Answer: B. To provide a route for feeding.
A gastrostomy is performed to create an alternative route for feeding until the definitive surgical repair of the oesophagus can be completed.

Anarado Chika, Ayuk Adaeze
Department of Paediatrics,
University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu, Nigeria
E-mail: adaeze.ayuk@unn.edu.ng