Anaemia, iron deficiency and infections: new perceptions of the interaction between hepcidin, iron biomarkers, anaemia and inflammation in Malawian children
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Chapter two

Severe acquired anaemia in Africa: new concepts

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Abstract
Severe anaemia is common in Africa. It has a high mortality and particularly affects young children and pregnant women. Recent research provides new insights into the mechanisms and causes of severe acquired anaemia and overturns accepted dogma. Deficiencies of vitamin B12 and vitamin A, but not of iron or folic acid, are associated with severe anaemia. Bacterial infections and in very young children, hookworm infections, are also common in severe anaemia. Irrespective of the aetiology, the mechanism causing severe anaemia is often red cell production failure. Severe anaemia in Africa is therefore a complex multi-factorial syndrome which, even in an individual patient, is unlikely to be amenable to a single intervention. Policies and practices concerning anaemia diagnosis, treatment and prevention need to be substantially revised if we are to make a significant impact on the huge burden of severe anaemia in Africa.
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Introduction
Severe anaemia in developing countries is a common syndrome with a high mortality\(^1\) which has received surprisingly little research attention. In Africa anaemia affects 68% of pre-school children, 57% of pregnant women and 48% of non-pregnant women\(^2\) but young children and pregnant women are particularly at risk of severe anaemia. Little is known about the complex interactions between the many factors that lead to severe anaemia so recommendations for preventing and treating severe anaemia are often not underpinned by evidence\(^3\). In this article we highlight recent research findings that provide new insights into the mechanisms and causes of acquired severe anaemia in Africa and which have the potential to generate novel approaches for its treatment and prevention.

Search strategy and selection of articles
There is no universally accepted definition of severe anaemia\(^2,4\) so for this review, unless otherwise stated, we have used the most frequently quoted haemoglobin threshold of <50 g/l. With assistance from a specialist clinical librarian, a search of the following databases and websites was conducted for information on ‘severe anaemia’, ‘sub-Saharan Africa’, ‘humans’ and ‘Africa (including the specific names of 57 African countries, nationalities and sub-regions: MEDLINE (National Library of Medicine, Bethesda, MD), EMBASE (Elsevier, Amsterdam, the Netherlands), the Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley InterScience, Hoboken, NJ), ‘ClinicalTrials.gov’, “National Guideline Clearinghouse”, “National Library of Guidelines” and “Guideline International Network”, as well as World Health Organisation (WHO), the WHO regional office for Africa and UNICEF websites. Information from 1990 to February 20th 2011 was collected and different spelling and languages of keywords were included if relevant.

Nine hundred and nineteen articles were identified through MEDLINE and 1110 through Embase. One thousand articles were retained for review after excluding 1029 articles because they were duplicate studies, case reports, letters or published prior to 1990. Using additional filters these articles were sub-categorised into “Epidemiology” (72 articles) “Aetiology/etiology” (425 articles), “Diagnosis” (82 articles), “Treatment” (123 articles), “Prevention” (45 articles) and “General” (253 articles). The ‘Clinical trials.gov’ search identified 43 trials related to severe anaemia since 1990 in Africa of which 31 had been completed and 12 were still recruiting.

Epidemiology
Anaemia is a moderate or severe public health problem in almost all countries in sub-Saharan Africa and has a significant morbidity and mortality. Severe anaemia features in the global policies of many programmes including those dealing with maternal, child and adolescent health, malaria, HIV, helminth infections, nutrition and tuberculosis. However population data on severe anaemia prevalence is scarce because it is generally documented in the context of a specific disease or in sub-populations (e.g. hospital in-patients)\(^5,7\). In community studies in Tanzania and Malawi 1% of children aged 6-60 months had severe anaemia\(^8,9\). 4% of children in primary level facilities In Ethiopia\(^10\), 11% of children in a rural Zambian hospital and 27% of children admitted to a tertiary hospital in The Gambia\(^11,12\) were severely anaemic. In Kenya 17% of pregnant
women had severe anaemia (Hb <70 g/dl). It is surprising that despite the extremely high prevalence of anaemia in pregnancy, international ‘general standards of care’ indicators for healthy pregnancy and childbirth do not include haemoglobin levels or anaemia.

Aetiology and pathogenesis

Little is known about the aetiology of severe anaemia in Africa from a public health perspective as most studies have investigated anaemia in relation to specific diseases (e.g. malaria, HIV infection) or individual factors (e.g. folate or iron deficiency). However, many factors are potentially important in the development of severe anaemia and several factors may occur together in an individual patient.

Aetiology and pathogenesis | Infection
Malaria is considered to be the principal cause of severe anaemia in malaria-endemic areas in Africa. At the population level a clear association has been found between malaria and severe anaemia. However, the relationship between malaria and severe anaemia in individuals is highly variable with odds ratios varying between 0.8 and 3.5 depending on the intensity of malaria transmission. It is therefore important to consider non-malaria causes for severe anaemia in an individual even when their malaria test is positive.

Severe anaemia is common in individuals with HIV infection, particularly if they are co-infected with tuberculosis. 19% of hospitalised adults in Malawi had severe anaemia; of these 79% were HIV positive and 28% died in hospital. The association between HIV and severe anaemia can partly be explained by the potential of the HIV virus (especially X4 strains which use the CxCR4 co-receptor) to infect bone marrow stem cells and promote apoptosis. A strong association between bacteraemia, particularly non-typhoid salmonella, and severe anaemia has been described in both children and adults with a blood culture positivity rates of 15 and 27%, respectively. The association is strongest in areas where HIV infection is endemic probably because of increased susceptibility to bacterial infections.

In rural areas in Africa hookworm infection is a well recognised cause of severe anaemia. There are several interesting new findings concerning this association. In Kenya and Malawi, hookworm infection is common in children under 2 years old with severe anaemia. This is surprising as young children have traditionally not been thought to have a high burden of hookworm infection. In Malawi the less common but more virulent *Ascaris lumbricoides* hookworm species, occurs more frequently in children with severe anaemia compared to controls and in Malawian adults, heavy hookworm infections were found in 38% of HIV negative, but only 2% of HIV positive, individuals.

Aetiology and pathogenesis | Nutrition
The role that iron deficiency plays in the aetiology of severe anaemia has been the subject of debate for decades. Iron deficiency thought to be responsible for around 50% of all cases of anaemia. However this figure may not be reliable because anaemia has been used as a proxy for iron deficiency. It is difficult to determine the true prevalence of iron deficiency in Africa because serum ferritin is an acute phase protein and therefore not a helpful indicator where infectious diseases are common. Estimations of iron stores in bone marrow aspirates in Malawian children indicated that the threshold of ferritin should be raised almost 10-fold in order to detect iron deficiency. Bone marrow sampling is not a practical investigation to determine iron status so, based on available evidence, WHO policies recommend that serum ferritin and transferrin receptor are used to gauge the iron status of populations.
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Recently a negative association between iron deficiency and severe anaemia was found in Malawian children, which was partly explained by an inverse relationship between iron deficiency and bacteraemia\(^{17}\). This supports the hypothesis that iron deficiency protects against infection by creating an unfavourable environment for bacterial growth\(^{25, 26}\). Observations of increased morbidity and mortality in iron supplementation studies conducted where bacterial infections are common (e.g. in children in Tanzania) further corroborate this hypothesis\(^{27, 28}\).

Folic acid deficiency is uncommon in children\(^{17, 29, 30}\) and pregnant women in Africa\(^{31}\). In contrast, vitamin B\(_12\) deficiency occurs in up to 30% of African children and adults with severe anaemia possibly due to a lack of dietary animal products\(^{17, 31}\). Severe vitamin A deficiency occurs in about one third of severely anaemic African adults and children\(^{31, 32}\). Interestingly, it has recently been shown that the association between Vitamin A and severe anaemia could partly be explained by the effect of vitamin A deficiency on susceptibility to malaria and bacterial infection\(^{17}\). Although vitamin A supplementation can reduce the incidence of malaria it has surprisingly little effect on the incidence of severe anaemia in children\(^{33, 34}\).

Aetiology and pathogenesis | New concepts
Several distinct mechanisms, including haemolysis, blood loss and red cell production failure (RCPF), may lead to anaemia and individual factors (e.g. iron deficiency, malaria) may contribute to more than one mechanism\(^{16, 35}\). In Malawian children with severe anaemia 48%, 22% and 7% were found to have indications of RCPF, haemolysis and blood loss respectively; multiple aetiologies were common in individual children. RCPF, unlike haemolysis or blood loss, is likely to persist unless all of the factors contributing to its aetiology are corrected. The combination of factors that ultimately result in severe anaemia is likely to vary from region to region or between different age groups or populations within a region\(^{17, 18, 20, 36}\). For example, hookworm is an important cause of severe anaemia in rural but not urban areas, and HIV infection is important in adults in urban East Africa but not rural West Africa\(^{17}\). This new evidence concerning the variability of factors that contribute to pathogenesis of severe anaemia, and particularly to RCPF, may explain why the current ‘blanket’ approach to prevention and treatment has not been effective in reducing the burden severe anaemia in Africa\(^{35}\).

Diagnosis
There are inconsistencies in international strategies concerning the diagnosis of anaemia. For example policies concerning iron and folate supplementation in pregnancy, imply that clinical diagnosis is adequate to diagnose anaemia and monitor changes in individuals\(^{14, 37}\), whereas HIV policies require a diagnosis of severe anaemia to be confirmed by a laboratory test\(^{38}\). Clinical assessment remains the most commonly used method for diagnosis of anaemia but its effectiveness for identifying patients with severe anaemia (Hb <50 g/l) varies widely. In children the sensitivity and specificity of clinical examination for pallor (palms, conjunctivae, nail-beds and/or tongue), either alone or in combination with other clinical signs, vary from 53 to 96% and 57 to 91% respectively\(^{8, 10}\). In pregnant women with severe anaemia (Hb <70 g/l) the sensitivity and specificity of clinical diagnosis by midwives was 65% and 82% respectively\(^{39}\) though improvements were possible with training and close supervision.

Accurate diagnosis of severe anaemia is critical because the treatment may include blood transfusions which are a scarce resource, and risky and expensive in Africa. Clinical examination is not accurate enough for detecting the 10-20 g/l changes in haemoglobin level that are likely to occur in response to treatment and so
accurate laboratory test are required. The direct cyanmethaemoglobin method is the gold standard for haemoglobin measurement but it requires sample dilution, electrical power and cyanide buffer, which is increasingly difficult to obtain. Two other methods, the HemoCue and the Haemoglobin Colour Scale, have been used for field studies in Africa because they are simple and do not require sample dilution or a mains electricity supply. The HemoCue system® provides a reliable, rapid one-step haemoglobin determination with a sensitivity of 80-96.6% compared to standard laboratory methods. The main drawback is the cost of the disposable cuvettes which may make this technique expensive if the volume of tests is high. The HemoCue Hb301 version has been specifically designed to operate in humid conditions and at high temperatures, and uses cuvettes that are less expensive compared to earlier models. The Haemoglobin Colour Scale is a simple, inexpensive, semi-quantitative method but more studies are needed to evaluate whether it is superior to clinical diagnosis for detecting severe anaemia in routine use. Despite its variable sensitivity (24-63%) for detecting severe anaemia, the Haemoglobin Colour Scale is reported to be able to improve treatment rates from <10% to >65% for children with severe anaemia.

Management and prevention

Many policies concerning the treatment and prevention of anaemia have been based on the assumption that iron deficiency is the most common cause of anaemia. For example the current WHO recommendation for preventing anaemia in pregnancy is daily supplementation with iron and folic acid. However this strategy means that other potentially preventable or treatable co-morbidities, such as bacteraemia and other vitamin deficiencies may be missed. There is conflicting evidence about the value of the traditional approach of treating anaemia presumptively with iron and folate. In some studies, iron supplementation was effective for reducing anaemia, but in others it had no effect on haemoglobin levels and it has even been linked to increased mortality rates in children who are not iron deficient. Folic acid supplementation in Africa generally has very little effect on haemoglobin levels and there is some evidence to suggest that the efficacy of anti-folate antimalarial treatment may be reduced by folic acid supplementation.

Blood culture facilities are often not available in Africa and the high prevalence of bacteraemia, mainly non typhoid salmonella, in severe anaemia raises the question of whether antibiotic treatment should be recommended presumptively for severe anaemia. Currently in malaria endemic areas in Africa, severely anaemic patients are presumptively treated for malaria. Successful prevention of Plasmodium falciparum infections in endemic areas reduces the risk of severe maternal anaemia by 38% and this has led to the recommendation that pregnant women in malarious areas who have severe anaemia should be treated presumptively for malaria. However current malaria policies recommend that anti-malarials should only be prescribed for proven infections such as those demonstrated by rapid diagnostic malaria tests. In areas with a high incidence of hookworm infections, anti-helminthic treatment may need to be considered for patients with severe anaemia, especially children <2 years of age and HIV-negative adults.

Blood transfusion can be life-saving for patients with severe anaemia and is recommended for pregnant women of >34 weeks gestation with a haemoglobin concentration <70 g/l. WHO guidelines for treating children with uncomplicated severe anaemia and a haemoglobin <40 g/l recommend using 20ml/kg of whole blood (or 10ml/kg packed cells) but transfusions are not recommended for children with a haemoglobin of 40-60 g/l. Strict adherence to these guidelines has resulted in under-transfusion of a significant proportion of severely anaemic Kenyan and Malawian children (M. Esan personal observation) and may contribute to the high post discharge mortality rates observed in some children. There are concerns that this policy, and possibly also the recommendations concerning the volume of blood to be transfused, may be too conservative given the high rates of persistent severe anaemia, re-admission and death following treatment of severe anaemia.
Traditionally fluid resuscitation had not been given to children with severe anaemia complicated by shock whilst they were waiting for their blood transfusion. This because of concerns about dilutional anaemia or cardiac decompensation but recently it has been shown that fluid resuscitation is safe for severely anaemic children with circulatory failure.

Management and prevention | Global perspective
Our search strategy focused exclusively on evidence about severe anaemia from Africa. However, many of the issues we have highlighted relate to a lack of resources for fully investigating and treating patients with severe anaemia. Our findings, and in particular, the need to devise standard treatment packages based on knowledge of locally prevalent causes of anaemia, are therefore likely to be applicable to low-income settings beyond Africa. Clinicians in wealthy countries caring for patients from Africa with severe acquired anaemia, will need to consider causes such as malaria or infection with HIV or hookworm (see box) as well as the high likelihood of multiple factors operating in an individual, in addition to their usual list of differential diagnoses.

Over a decade ago it was recognised that a new multi-sectoral approach was needed to generate the evidence needed to address the complex aetiology of anaemia and to reduce the burden of anaemia. However, at global and national levels there is still a lack of agreement about strategies to prevent, diagnose and manage severe anaemia. Currently evidence to guide these strategies is fragmented and concentrated in just a few countries. More research is needed to establish whether this evidence is applicable to other low-income countries in Africa and beyond.

Table 1. Summary of recent research evidence concerning causes of severe acquired anaemia in Africa

<table>
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<th>Common causes</th>
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<tr>
<td>Malaria, especially P falciparum</td>
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<td>Bacteraemia, especially non-typhoid salmonella</td>
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<tr>
<td>HIV infection, especially in association with tuberculosis</td>
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<td>Hookworm (Necator americanus, and Ankylostoma duodenale)</td>
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<td>Vitamin A deficiency</td>
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<td>Vitamin B12 deficiency</td>
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<th>Uncommon causes</th>
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<tr>
<td>Iron deficiency</td>
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<td>Folate deficiency</td>
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Conclusions

Prevention and management of severe anaemia must be underpinned by a detailed knowledge of the aetiology but because the aetiology varies geographically, seasonally and between sub-populations, it is difficult to devise strategies that are universally applicable. Over the last decade it has become increasingly apparent that severe anaemia in Africa is a complex multi-factorial syndrome which is unlikely to be amenable to a single intervention. More research and strong partnerships between vertical programmes are needed to identify and address the causes of severe anaemia in a variety of settings and populations. In order to make a significant impact on the huge burden of severe anaemia in Africa this new evidence needs firstly to be replicated in other countries and then used to develop treatment and prevention packages that are tailored to address specific local causes of severe anaemia.

Acknowledgements and contributions

MBvH and FJ conducted the search for research literature concerning severe anaemia and IB conducted the search for policy documents. All authors made substantial contributions to the design of this review, and to the acquisition and synthesis of information. They all contributed to drafting and revising the paper and all approved the final version.
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