Background information on Sickle Cell Disease and the impact of interventions

This document gives a brief overview about haemoglobin disorders, their epidemiology and specific interventions that may reduce their burden. This background document applies to both Sickle Cell Disease and Thalassaemias, which are presented separately in the next stage of the Toolkit.

What are haemoglobin disorders?

Haemoglobin (Hb) disorders are single gene disorders resulting from abnormal changes in the production or structure of haemoglobin. They are recessively inherited from parents (often symptomless carriers themselves) and occur when both parents pass on the trait gene for a particular condition (e.g. Hb S, Hb C, Hb E, Hb D, alpha thalassaemia and alpha zero thalassaemia). The most significant are sickle cell disease (SCD) resulting from structural variant haemoglobins, and the thalassaemias, where there is a reduced rate of production of one or more of the globin chains. They are the most common and lethal single gene disorders, but many harmless combinations also exist. The Hb disorders can be treated effectively and are largely preventable. This topic focuses on SCD and thalassaemia.

What are the main risk factors?

The main risk factor is being a carrier of a significant Hb variant (5.2% of world population – around 323 million individuals) and this is related to ethnic origin because of the link with malaria. Hb disorders predominate in malaria endemic areas because healthy carriers have a survival advantage against the lethal effects of malaria. Consanguineous marriage increases the chance that a carrier will choose another carrier partner, although the effect is modest for Hb disorders because they are already so common.

Global epidemiology

Affected birth prevalence

There is considerable variation in carrier prevalence. Hb disorders are most common in sub-Saharan Africa with 60-70% of births occurring within this region. Globally, around 7% of pregnant women carry beta or alpha zero thalassaemia, or haemoglobin S, C, D Punjab or E, and over 1% of couples are at risk of an affected pregnancy. The global birth prevalence

is estimated as 21.8/1,000 (around 2.8 million) for any combination of Hb variants, with a global carrier prevalence of 3.0/1,000 for Hb variants of pathological significance. It is estimated that around 380,000 people are born with pathological combinations of Hb variants worldwide every year. SCD accounts for approximately 85% of these births, and thalassaemias for 15%.

Carrier prevalence

There are estimated to be around 1.7 billion people worldwide carrying a Hb variant although most will be unaffected healthy carriers. SCD is more common in sub-Saharan Africa while the thalassaemias are more prevalent in the Mediterranean, the Middle East, South and East Asia, and the Pacific. In countries where migration was high from these areas, initial small pockets of high prevalence have led to increased carrier prevalence in the whole population as the carrier status of the different Hb pathologically significant variants is the main risk factor.

Clinical Outcomes

Mortality

Haemoglobin disorders account for about 3.4% of under-five deaths[1]. Both SCD and thalassaemia are associated with significant morbidity and mortality, especially in developing countries. In the absence of diagnosis and care, in their severe forms both are approximately equally lethal in early life.

Sickle cell disease

Improved access to primary health care has resulted in an increase in the number of living SCD patients in many countries. Increased early mortality amongst children with SCD is mostly due to increased risk of infection, for example by malaria and bacterial infections such as Streptococcus. Provision of relatively simple services (such as information and education for parents, and prophylactic antibiotics and anti-malarials) leads both to greatly improved survival and quality of life. These services can be community-based but need to be supported by appropriate hospital facilities.

Childhood mortality is greatly reduced by early diagnosis, appropriate care and support. Early diagnosis can be achieved through carrier screening to identify reproductive risk followed by testing of newborns from ‘at risk’ couples, and/or newborn screening. Infrastructural requirements for screening are complex and need to be considered individually in each country.

Despite increased survival in childhood, SCD is a severe long-term condition with accumulation of complications such as sickle cell crisis, acute chest syndrome, or renal failure over time and high adult mortality.

Thalassaemia

For beta thalassaemia, survival generally depends on access to specialist care. Regular safe blood transfusions can dramatically increase life expectancy for transfusion-dependent thalassaemia patients. However blood transfusion alone can potentially lead to death from iron overload in adolescence or early adult life unless accompanied by iron chelation therapy. Where adequate iron chelation therapy and specialist care is available, life

[1] Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bull World Health Organ* 2008; 86:480-487.

expectancy approaches that of the general population. However, the necessary drugs are usually expensive (and normally need to be imported) and survival is often limited by cost even when transfusion is available. Bone marrow transplantation, where available, can be a cost-effective option.

Homozygous alpha zero thalassaemia causes hydrops fetalis, which leads to intra-uterine or neonatal death and risks for the mother both during pregnancy and delivery. It is rarely possible to treat an affected newborn and so the principal approach is risk identification and termination of affected pregnancies (where legal and acceptable).

Disability and quality of life

Sickle cell disease

Disability and quality of life range from no problems throughout life to very severe problems from an early age. Affected people of African origin tend to have more severe disease than those of Middle Eastern or Indian origin. The most disabling aspect is the unpredictability and suddenness of many of the complications such as painful crises, chest syndrome, and priapism. These complications affect quality of life, disrupt life plans and can cause great anxiety. There is also often progressive physical deterioration causing increasing disability and risk of sudden death.

Thalassaemia

Treatment and care minimise disability and improve quality of life. Some individuals, for example many with Hb H, are clinically well and require little or no treatment other than occasional red blood cell transfusions. Others, for example those with transfusion-dependent beta thalassaemia major, may require regular red blood cell transfusions and iron chelation therapy. Most children born today with thalassaemia, who receive optimum expert care, may expect to be 'well on treatment' lifelong, although they remain at risk for complications such as osteoporosis and have a higher incidence of infections. Older patients often have more associated disability because of organ damage suffered before modern treatment was available. However, many and possibly the majority worldwide currently receive suboptimal care and treatment and are therefore likely to suffer some degree of disability.

Reducing prevalence, morbidity and mortality

Reducing birth prevalence depends on identifying at-risk couples and providing information on risk and options available for reducing it (genetic counselling). Prospective risk identification has a significant impact on birth prevalence unless the population total fertility rate is 3 or more. Prospective risk identification coupled with access to prenatal diagnosis can reduce thalassaemia major birth prevalence by over 90% and sickle cell disease birth prevalence by 13-30% in areas where termination of pregnancy is acceptable and widely available[2]. Figure 1 illustrates the determinants and interventions for the Hb disorders as they relate to key stages in life. The main specific interventions are briefly discussed below.

Interventions before pregnancy

Identifying at risk couples before any affected child is born (prospectively) involves preconception screening, cascade screening, and screening of population groups (e.g. school children) or the whole population in order to identify and inform carriers of their risk. Carrier screening can either be centred on the family or be population-based.

[2] ibid

With genetic counselling playing an integral part, at-risk couples may also be identified retrospectively (after diagnosis of the first affected child) and couples may use information on recurrence risk to avoid further affected pregnancies, by limiting family size and/or using prenatal diagnosis.

Interventions during pregnancy

These involve prenatal screening and diagnosis. A family history questionnaire may be the first step to identifying higher risk individuals, particularly in areas of low prevalence. Carrier screening of the pregnant woman (possibly using the family history questionnaire, a full blood count and a method to identify and quantify variant Hbs such as high-performance liquid chromatography) is followed by partner testing (if woman is a carrier) and prenatal diagnosis if both parents are carriers. Fetal DNA samples for prenatal diagnosis can be obtained by chorionic villus sampling or by amniocentesis and used for genetic testing for variant Hb genes. This may be followed by termination of pregnancy where this choice is available and acceptable, or by planning for the birth of an affected child.

Interventions after birth

Diagnosis shortly after birth allows appropriate care to be planned and put in place, leading to increased survival and reduced disability. Early diagnosis is particularly important for SCD. Most cases of thalassaemia present with severe anaemia needing transfusion and the reduction of mortality and morbidity depends on the availability and quality of services. Newborn screening involves testing of the neonate by obtaining a blood spot by heel prick and testing for variant Hbs. Laboratory testing methods include high-performance liquid chromatography or isoelectric focusing. A positive result requires confirmation testing using a different method. If SCD or any other clinically significant Hb disorder is suspected a further (confirmatory) test using a second blood sample may be conducted at the age of six weeks, followed by testing at the age of one year when the Hb F (fetal Hb) levels will have dropped. With neonatal diagnosis, mortality from the severe forms of Hb disorders decreases in the first few years of life. Treatment and care may involve chronic or sporadic blood transfusion, iron chelation therapy, splenectomy, regular clinical and haematological evaluations and monitoring, appropriate prophylactic antibiotics, vaccination against bacterial *Haemophilusinfluenza*e type b (Hib) and pneumococcal infection, folic acid supplementation, and possibly bone marrow or cord blood transplantation. These depend on setting, diagnosis and clinical severity.

Cost-effectiveness of interventions

In low-resource countries, the economic burden of treatment often falls directly on the family and unless covered by medical insurance, both health services and the families themselves are unable to afford the costs of long-term treatment. This cost is largely driven by the cost of the iron chelation therapy itself. This harsh reality increases the importance of prevention, which is relatively inexpensive due to low labour costs in these low resource countries, and can be significantly more ‘cost-effective’ than care. For example, in Hong Kong a universal prenatal screening programme for thalassaemia where both α and β thalassaemia were prevalent was found to be cost-effective with savings estimated at HK$40.4 million in 2002[3]. This point is further highlighted in Iran where the cost of treating 15,000 patients for thalassaemia in the year 2000 was estimated by WHO as costing US$200 million. However,

[3]Leung KY *et al*. Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong. *Prenatal Diagnosis* 2004; 24:899-907.

issues of cost-effectiveness are quite specific to each country as costs can vary tremendously and are also dependent on patient numbers. For cost-effectiveness cut-off points for different regions of the world, go to the following website http://www.who.int/choice/costs/CER_levels/en/index.html, and for costs for specific items by region and county, go to http://www.who.int/choice/costs/en/.

What are the main ethical legal and social issues (ELSI) to consider?

There are numerous ELSI raised by the Hb disorders, since multiple interventions to diagnose and treat these conditions are possible across a lifetime, ranging from screening of potential partners at the preconception stage, through to concerns about equity of access to treatment by blood transfusion and iron chelation for those with Hb disorders.

Carrier screening

Using population screening before pregnancy to determine carrier status in healthy individuals may be contentious (and its coercive use in the past has led to the stigmatisation and discrimination of affected individuals and distrust of population screening programmes by certain ethnic groups). The confidential nature of personal medical information, including information about carrier status and those affected by Hb S or certain types of thalassaemia, should be respected and safeguarded, particularly if information might be released to third parties such as insurers or employers (for which consent from the person being screened is usually required).

Prenatal population screening

The identification of fetuses that are homozygous for SCD or thalassaemia during prenatal screening may raise difficult choices about the course of the pregnancy and the ability of the family to support an affected child. Experience from countries which have implemented combined prenatal and newborn screening programmes suggests that participants need to be better prepared and informed about the consequences of screening, and the possible choices to be made (including choosing to terminate the pregnancy where this is legally and ethically acceptable).

Equitable access to care and treatment

Homozygous individuals often require repeated blood transfusions to manage their conditions. In some countries it might be difficult to ensure a reliable and safe source of blood which, combined with the cost of iron chelation therapy, and the high prevalence of the conditions, may pose difficult questions for health services: how are screening strategies to be implemented; how are resources to be distributed where resources are limited (such as the availability of iron chelation therapy and blood supplies)? Who should bear the cost of providing screening, services and treatment? These problems may be exacerbated in those with rare blood types.

Although life expectancy is increased by treatment, the treatments themselves may carry significant side-effects (such as iron overload) and those with homozygous disease may be very disabled. There is a need to provide appropriate social support for affected individuals.

Social, cultural and religious factors

Planning for prevention and treatment of Hb disorders often needs to take account of multiple social, cultural and religious factors such as a preference for consanguineous

marriage (for example in some populations in sub-Saharan Africa, the Middle East and parts of Asia), and social and religious attitudes to carrier screening, termination of pregnancy and medical factors.

KEY REFERENCES

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RELATED TOPICS

Preconception care and screening
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Figure 1: Needs assessment flowchart for haemoglobin disorders