

**INFORMATION
BULLETIN**

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Guidelines for Diagnosis and Management of Haemoglobinopathies

Genetic disorders of globin including: α and β thalassaemias and variants such as HbS and HbE

Background

Genetic disorders result usually from a change in the hereditary (genetic) material contributed by the parents at the time of conception. Certain conditions occur more frequently in some families than others. Also, certain nationalities or ethnic groups may experience a higher incidence of certain inherited disorders. For example, cystic fibrosis and haemochromatosis are more prevalent in populations who have originated from Northern Europe. Haemoglobinopathies occur more frequently in populations who have originated from Southern Europe, the Middle East, Africa, Asian countries and the Indian sub-continent.

Haemoglobinopathies are recessively inherited blood disorders for which there is no cure. α thalassaemia major is fatal at birth. Those affected by β thalassaemia major have a severe anaemia. Affected children usually present in infancy with pallor, irritability and enlarged liver and spleen. They usually require regular (four weekly) blood transfusions throughout life. Although blood transfusion prolongs life, it also causes iron accumulation in the body that may result in diabetes, liver damage and cardiac problems. This may cause death in adolescence or early adulthood unless iron chelating therapy is used. The latter involves subcutaneous infusion of desferrioxamine for 10-12 hours most days of the week, usually overnight.

α and β thalassaemia minor may cause a mild anaemia. However, people usually have good health and their bodies function normally. People with the minor forms of thalassaemia are "genetic carriers" of a mutation in their α or β haemoglobin gene. They have one normal copy of the haemoglobin gene and one copy that is mutated.

During reproduction, if a couple are both carriers of the same thalassaemia mutation, there is a one in four chance in each pregnancy that a child will receive both copies of the mutant gene, ie one from each parent. Such a child will be affected with thalassaemia. In each pregnancy there is a 50% chance that the child will be a carrier of the mutant gene like the parents, and thus will have thalassaemia minor.

Distributed in accordance with circular list(s):

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If only one parent is a genetic carrier of thalassaemia the couple will not have a child with thalassaemia major. However, there is a 50% chance in every pregnancy that their child will be a genetic carrier of thalassaemia and have thalassaemia minor.

A conservative estimate of the genetic carrier frequency for haemoglobinopathies in NSW/ACT is about 60,000 genetic carriers.

Key Information

Detection of genetic carriers of thalassaemia

a) *Low MCV or MCH*

It is important to consider that an individual could be a genetic carrier for **thalassaemia or HbE** whenever a blood count shows a **low MCV or MCH**, particularly if an individual or their ancestors have originated from one of the at-risk groups identified below. The blood picture described is frequently mistaken for iron deficiency. It is also important to note that both iron deficiency due to other causes and thalassaemia can co-exist in the same individual. Therefore a low MCV or low MCH which appears to be refractory to iron treatment should be considered to represent thalassaemia minor until proven otherwise.

b) *Family history or at-risk group*

People who have a family history of haemoglobinopathies or whose ancestry is from Southern Europe, India, Africa, Middle East and Asia are considered to be in a higher risk group for genetic carrier status for thalassaemia. As Australia is a multicultural society, with a large degree of intermarriage, it is not always easy to identify at-risk groups. Therefore it is vitally important to consider all of the following in identifying risk for thalassaemia.

Target Groups

- Anyone with a blood count showing low MCV or MCH.
- People whose origins are from Southern Europe, Africa, the Middle East, Asian countries and the Indian Subcontinent where the incidence of haemoglobinopathies is significantly higher.
- All pregnant women when they are having routine antenatal blood examinations, and especially those with ancestry from the above groups who are at higher risk.

Reproduction issues for haemoglobinopathy carriers

Options are available for those who are either at-risk for being a genetic carrier or whose carrier status has been confirmed. These include laboratory detection, genetic counselling and prenatal diagnosis.

Further Information

1 Clinical and laboratory features

1.1 ***b*** *Thalassaemia*

Homozygous β thalassaemia, sometimes called thalassaemia major, is usually a cause of severe anaemia. β Thalassaemia is the most common type of thalassaemia in Australia, and occurs predominantly in people of South European, African, Middle-Eastern, Asian and Indian descent.

Genetic carriers of β thalassaemia are said to have β thalassaemia minor (or β thalassaemia trait). The β thalassaemia trait is asymptomatic. The red cells are smaller (low MCV) and paler (low MCH) than normal, and the haemoglobin level is normal or slightly reduced. Unlike other recessive disorders the carrier state in most cases is suspected on a routine blood count and can be confirmed by special studies (see also Diagnosis and Management of Haemoglobinopathies, 4.1).

If two genetic carriers have children, there is a 1:4 chance (25%) in each pregnancy that the child will have homozygous β thalassaemia.

The child who has homozygous β thalassaemia usually presents after the age of 6 months with pallor, irritability and an enlarged liver and spleen. Affected children usually require regular blood transfusion. Although blood transfusion prolongs life, it also causes iron accumulation in the body which may result in diabetes, liver damage and cardiac problems. This may cause death in adolescence or early adulthood, unless other steps have been taken to prevent iron accumulation i.e. iron chelation therapy. The latter involves subcutaneous infusions of desferrioxamine most days of the week. For those who cannot take desferrioxamine, there are trials underway to assess the efficacy of other medical treatments including oral chelating agents. However, these are investigative and should not be considered as alternatives for the well-proven subcutaneous treatment. In selected cases, bone marrow transplantation has been curative. Infection with hepatitis C is another complication of regular blood transfusion and those so affected need careful monitoring in case antiviral treatment is indicated (see also Diagnosis and Management of Haemoglobinopathies, 4.3).

1.2 ***a*** *Thalassaemia*

The genetic carrier for α thalassaemia, another form of thalassaemia, is also asymptomatic, and as with β thalassaemia, the red blood cells may be small and pale. Because there are 4 α globin genes compared to 2 β globin genes, there is greater variability in the types of α thalassaemias. The important one, from the point of view of children who might be affected with severe α thalassaemia, is the genetic carrier who has 2 α globin genes missing from the one chromosome (this is called α^0 thalassaemia or α thalassaemia-1 and is written as $\alpha\alpha/--$). This type of genetic carrier often originates from Asia, Southern Europe, Africa, India or the Middle East.

Like β thalassaemia, 2 parents with α^0 thalassaemia have a 1 in 4 chance (25%) that their children will be homozygous for a severe form of α thalassaemia (Hb Bart's hydrops fetalis, which is written as --/--). This is a fatal disorder with the fetus being stillborn or dying soon after birth. The mother in such a pregnancy is at greater risk for some pregnancy-related complications. HbH disease (written as $-\alpha/--$) is another form of α thalassaemia. In this case, the clinical and laboratory phenotypes are difficult to predict i.e. mild or asymptomatic to a severe disorder requiring regular blood transfusions. Determining the type of α thalassaemia present in an individual is more difficult than is the case with β thalassaemia. DNA studies are usually required (see also Diagnosis and Management of Haemoglobinopathies, 4.1).

1.3 Variant Hb (HbS and HbE)

There are over 200 variant haemoglobins (Hb). However, in Australia the common variant haemoglobins are HbS (sickle haemoglobin) and HbE. Like thalassaemia, genetic carriers of these traits originate from countries in which malaria is or was endemic. The reason for this is that thalassaemia and some of the variants (e.g. HbS and HbE) provide some protection from malaria. In Australia, HbS genetic carriers are predominantly individuals of Southern European, African, or Middle Eastern origin. HbE genetic carriers usually have a South Asian or South East Asian ethnic background. Like α and β thalassaemias, genetic carriers for both these variants are asymptomatic. The heterozygote (carrier) for the HbS trait has normal haematological parameters. Clinical complications arise in the case of: (1) a homozygote for HbS or (2) a double-heterozygote for β thalassaemia and HbS or (3) a double-heterozygote for β thalassaemia and HbE. In the first two cases, sickle cell disease develops. The individual with sickle cell disease can have a variable presentation but usually that person has an episodic disorder characterised by "crises" that may require hospital admissions for blood transfusion and/or pain relief. A female with sickle cell disease is particularly at risk for serious complications during pregnancy. The severity of sickle cell disease (just like homozygous β thalassaemia or HbH disease) cannot always be predicted and so counselling in the haemoglobinopathies can be difficult. A double-heterozygote for β thalassaemia and HbE can have a similar clinical picture to homozygous β thalassaemia.

2 Prevalence of the haemoglobinopathies in NSW

2.1 *β thalassaemia genetic carriers*

It is difficult to assess the number of people in Australia or NSW who are at risk of having one of the forms of thalassaemia or one of the above variant haemoglobins i.e. the carrier frequency for these disorders. A figure of at least 1.0% is estimated for NSW, based on the 1991 Census figures which calculated that 41% of the NSW/ACT population had one or more parents born overseas from a non-English speaking background. Thus, a conservative estimate is that there are about 60,000 genetic carriers of a haemoglobinopathy in NSW/ACT.

It is important to consider that an individual could be a genetic carrier for **thalassaemia or HbE** whenever a blood count shows a **low MCV or MCH**, particularly if an individual or their ancestors have originated from an at-risk group. The blood picture described is frequently mistaken for iron deficiency. It is also important to note that both iron deficiency due to other causes and thalassaemia can co-exist in the same individual. Therefore a low MCV or low MCH which appears to be refractory to iron treatment should be considered to represent thalassaemia minor until proven otherwise.

2.2. ***β* thalassaemia homozygotes**

In 1998, there were about 123 patients with a transfusion-dependent thalassaemia living in NSW or the ACT. Of these, 106 (86%) had homozygous β thalassaemia and 17 (14%) had related blood disorders. During the period 1989-1998 there were 23 new cases of homozygous β thalassaemia treated in NSW (figures provided by NSW Thalassaemia Centre). While it is difficult to be sure of the emerging trends it appears as though the numbers of cases of homozygous β thalassaemia detected are increasing, and the at risk groups are now predominantly those with a Middle Eastern or Asian background.

New thalassaemia major patients treated in NSW 1989 - 1998

Country of origin or ancestry	No of Diagnosis	Percentage
Middle East	8	34.5%
South East Asia	6	26.2%
Southern Europe/ Africa	6	26.2%
Indian Sub Continent (including Maldives)	3	13.1%
Total	23	100%

3 Target groups:

- Anyone with a blood count showing low MCV or MCH
- People whose origins are from Southern Europe, Africa, the Middle East, Asian countries and the Indian Subcontinent where the incidence of haemoglobinopathies is significantly higher.
- All pregnant women when they are having routine antenatal blood examinations, and especially those with ancestry from these geographic regions.

4 Diagnosis and Management of Haemoglobinopathies

4.1 *Homozygous haemoglobinopathies*

- Initial screening: This should include determinations of haemoglobin, red cell indices and examination of a blood film. HbEPG is essential if there is the possibility of HbS being present.
- Follow up tests: Blood samples showing a low MCV or MCH should have iron deficiency excluded. Iron deficiency should be treated and the individual followed to ensure that the MCV and MCH are corrected. Failure to do so usually means there is an underlying haemoglobinopathy. In some cases, the blood film might be suggestive of a haemoglobinopathy and so appropriate investigations should be started immediately. Haematological tests to confirm thalassaemia and the variant haemoglobins include: HbA₂, HbF, HbH inclusions and Hb EPG. These should be performed by experienced laboratories.

Laboratory detection of thalassaemia (or HbE, HbS) genetic carriers is readily available in NSW public hospital or private pathology laboratories. Specialised referral laboratories for the haemoglobinopathies are found at the Royal Prince Alfred and Westmead hospitals.

Further investigations, including DNA analysis, may also be necessary, particularly in the case of the α thalassaemias. Since the MCV or MCH is likely to be normal in the HbS carrier, the appropriate tests (HbEPG followed by the confirmatory HbS sickle test) will need to be requested in an individual whose ancestry includes an at risk group or whose pregnancy is at risk.

- Follow up: Where a person is a genetic carrier of thalassaemia (thalassaemia minor) it is imperative that the partner is tested if reproduction is an issue. Testing should also be offered to blood relatives.

4.2 *Genetic carriers of haemoglobinopathies*

It is important that females of child bearing age in the target groups are tested before pregnancy, or as soon as possible, if already pregnant. If the woman is a genetic carrier for thalassaemia, HbS, HbE or another less common but relevant haemoglobinopathy, the partner should be tested. If both are genetic carriers, genetic counselling and information regarding prenatal diagnosis can be provided.

- **Counselling:**

When couples are identified as genetic carriers of thalassaemia or other haemoglobinopathies, it is important that in-depth and experienced counselling is provided to minimise anxiety, to clarify risk, to avoid stigmatisation and dispel misconceptions about thalassaemia.

Because of the heterogeneity of abnormalities and the complex interactions that occur in the haemoglobinopathies, it is recommended that counselling is undertaken in conjunction with advice from a haematologist. Counselling services are available through the NSW Thalassaemia Centre at the Royal Prince Alfred Hospital, Clinical Genetics Units throughout

NSW. Information about counselling services is available from the NSW Genetics Education Program (Details in Appendix 1). It is Department of Health policy that a professional interpreter be used in such situations where the client is not fluent in English (see Appendix 1).

- **Prenatal diagnosis**

Prenatal diagnosis is an option that couples may wish to consider where pregnancies are at risk of producing a child who is severely affected with a haemoglobinopathy. Counselling sensitive to the issues concerning prenatal diagnosis should be offered by experienced counsellors.

In most cases prenatal testing for haemoglobinopathies is undertaken during the first trimester of pregnancy by a combination of chorionic villus sampling (CVS) and analysis of fetal DNA. However, to ensure that this type of prenatal testing is possible, it is essential to confirm the thalassaemia or variant haemoglobinopathy in both partners early in the pregnancy or preferably before the woman becomes pregnant.

Second trimester prenatal testing can be undertaken by testing fetal blood rather than DNA obtained at CVS or amniocentesis. However, the analysis of fetal blood has a higher rate of miscarriage related to the test and is now less frequently performed.

CVS, amniocentesis and, in some cases, fetal blood sampling can be obtained at the Royal Hospital for Women, King George V, Royal North Shore, Westmead, Liverpool, Nepean, John Hunter Hospitals as well as a number of country centres (see Appendix 1 for information)

4.3 *The birth of an affected child*

Children born with homozygous β thalassaemia should be referred to the thalassaemia units at the Sydney Children's Hospital or the Royal Alexandra Hospital for Children as soon as possible. Special centres to treat adults who have homozygous β thalassaemia are found in the Royal Prince Alfred Hospital and the Prince of Wales Hospital. It is important to ensure referral to appropriate support systems. It is also relevant to note that there may be stigmatisation of the affected family ("bad blood"), involving lack of support from blood relatives and avoidance by the community, and/or voluntary isolation by the family (see Appendix 1 - Thalassaemia Society of NSW and the NSW Thalassaemia Centre) .

<p>Treatment of the severe forms of the haemoglobinopathies is complex and involves the management of anaemia as well as potential complications of blood transfusion. Hence, treatment should be undertaken in a limited number of centres so that experienced health professionals are involved. With optimal treatment regimens in the severe forms of β thalassaemia, sickle cell or HbH disease, the life expectancy for a number of affected individuals is now considerably improved with some approaching normal. As indicated earlier, bone marrow transplantation in selected cases of severe β thalassaemia appears to be curative.</p>
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Treatment clinics for those with the severe haemoglobinopathies are held at the Sydney Children's and the Royal Alexandra Hospital for Children, as well as some of the major teaching hospitals in which adults are treated (Details – Appendix 1).

5 *Interpreter Service:*

It is Department of Health policy that a professional interpreter be used where the client is not fluent in English. This is mandatory when seeking consent for treatment or when informing individuals of the results of tests. Non-use of a professional interpreter may leave a practitioner open to legal liability. Appendix 1 gives contact details.

Interpreters can also provide valuable information on socio-cultural factors affecting patients' attitudes to health and medical conditions, and expectations for treatment.

6 *Educational Resources*

The NSW Thalassaemia Centre and the NSW Genetics Education Program have produced several educational resources. Some of these are available in a number of community languages. Titles are listed in Appendix 1.

APPENDIX 1

THALASSAEMIA RESOURCES

Health Information / Education Resources

NSW Thalassaemia Centre

Queen Mary Building
Royal Prince Alfred Hospital
Missenden Road
Camperdown NSW 2050.
Phone: 02 9550 4844.

NSW Genetics Education Program

PO Box 317,
St Leonards NSW 1590
Phone: 02 9926 7324.

Printed Information Material in Community languages:-

- **So you have the minor form of Thalassaemia** - available in English, Arabic, Greek and Italian - A pamphlet in question and answer format to be used as an adjunct for counselling individuals with β thalassaemia trait. This leaflet is available through the Thalassaemia Centre of NSW.
- **Thalassaemia - an information guide for people with the minor form of thalassaemia** - available in Arabic, Greek, Italian, Maltese, Vietnamese, Lao, Chinese, Kampuchean, Spanish, Indonesian and Turkish. Translations may also be available in other languages. This leaflet is available through the Thalassaemia Centre of NSW.
- **Thalassaemia - an inherited blood condition** – general introductory pamphlet - produced by the NSW Thalassaemia Group, the NSW Thalassaemia Centre, the NSW Thalassaemia Society and the NSW Genetic Education Program. At present the pamphlet is only available in English but it is planned to have it translated into appropriate languages.
- **Pregnancy Care** The 1998 booklet has a small section on thalassaemia and can be obtained through the Better Health Centre on 02 9816 0452.
- **Information on the Internet.** A useful site to obtain information about the haemoglobinopathies is: <http://www.chime.ucl.ac.uk/APoGI/>. Like all Internet-based documents the information provided should be viewed with some care although it originates from a reputable source.

The following translated documents were prepared by the Department of Health as Health Columns for the ethnic press, and are available in a range of languages from the Multicultural Health Communication Service (9382 8111) or from their website <http://mhcs.health.nsw.gov.au>.

- ***Why you should know about thalassaemia.*** Guide to understanding the inherited blood disorder thalassaemia, how it's inherited and what it's like to live with the disorder.
- ***How can genetic counselling help?*** Description of the role and benefits of genetic counselling to people at risk of genetic disorders, including thalassaemia.

Translated documents are also available from this website in relation to general procedures such as blood tests.

New South Wales Thalassaemia Group

This group comprises health professionals, both clinical and laboratory, who have a special interest in the haemoglobinopathies. The NSW thalassaemia Group can be contacted through:

- The Thalassaemia Centre of NSW 02 9550 4844 (see above)

The Thalassaemia Society of New South Wales

The Thalassaemia Society of NSW is an organisation for people with thalassaemia, their families and others who are interested. The Society's contact address and phone number is the same as for the Thalassaemia Centre of NSW – 02 9550 4844. The mailing address is:

The Thalassaemia Society of NSW
PO Box 80
Marrickville NSW 2204.

Interpreter service

The NSW Health Care Interpreter Service is available at all NSW public health facilities, **free of any charge** to patients/clients, 7 days a week 24 hours a day. Health Care interpreters cater for the communication needs of most communities. This includes Auslan and Signed English.

Area Health Service	Telephone Number
Central Coast	1800 674 994
Central Sydney	9515 3222
Far West	1800 674 994
Greater Murray	1800 247 272
Hunter	4924 6285
Illawarra	4274 4211
Macquarie	1800 674 994
Mid North Coast	1800 674 994
Mid Western	1800 674 994
New England	1800 674 994
Northern Rivers	1800 674 994
Northern Sydney	9926 7560
South Eastern Sydney	9515 3222
South Western Sydney	9828 6088
Southern	1800 247 272
The New Children's Hospital	9840 3456
Wentworth	9840 3456
Western Sydney	9840 3456

When Health Care Interpreters are not available, the following should be contacted:

Translating and Interpreting Service	131 450
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Multicultural Health Services

A range of services are available to assist health professionals to provide services to people from diverse cultural backgrounds. These services include bilingual counsellors, multicultural health workers, ethnic obstetric liaison workers and specialist services such as the Transcultural Mental Health Service. For information on your local services, contact the Multicultural Health service in your Area Health Service:

Area Health Service	Telephone Number
Central Sydney	9515 3273
Hunter	4924 6285
Illawarra	4274 6233
Northern Sydney	9926 7332
South Eastern Sydney	9382 8366
South Western Sydney	9828 5762
Wentworth	4736 0539
Western Sydney	9840 3940

SAFDA (Support After Fetal Diagnosis of Abnormality) network.

SAFDA was developed to help individuals, their partners and families at a time of crisis. SAFDA may be contacted through the NSW Genetic Education Program or the Head Social Worker at the Royal Hospital for Women Randwick (02 9382 6670).

APPENDIX 2

INFORMATION SHEETS SUITABLE FOR USE BY HAEMATOLOGY LABORATORIES IN COMMUNICATING WITH REFERRING DOCTORS

General details which should be provided to the referring doctor:

1. This patient's blood examination shows that α or β thalassaemia trait (or HbS or HbE trait) is present.
 - (A) Other blood relatives should be offered the opportunity of being tested for the condition.
 - (B) If the patient is likely to have children, the spouse should be tested. If both partners have a haemoglobinopathy (thalassaemia, HbS or HbE traits), they should be counselled on likely implications.
 - (C) If the patient is pregnant, it is essential that her spouse be tested as soon as possible because of the possibility of the child having a severe form of α or β thalassaemia (or HbS or HbE) if both partners have the trait. If both partners do show the trait, they should receive expert counselling as soon as possible so that they can consider the options available to them.
2. Thalassaemia carrier status is not associated with significant ill-health.
3. Information and pamphlets on thalassaemia trait (suitable for patients) and on thalassaemia and pregnancy (suitable for medical practitioners) are available from:

The NSW Thalassaemia Centre

Level 5, Queen Mary Building
Royal Prince Alfred Hospital
Missenden Road
Camperdown NSW 2050
Phone: 02-9550 4844

The NSW Genetics Education Program

PO Box 317
St Leonards NSW 1590
Phone: 02-9926 7324.

A reference to the laboratory testing of haemoglobinopathies:

The laboratory diagnosis of the haemoglobinopathies. British Journal of Haematology 1998;101:783-92.