Platelets are the cells responsible for making blood clot so platelet disorders mean that injured blood vessels bleed more than usual and heal more slowly. This information from Great Ormond Street Hospital (GOSH) explains the causes, symptoms and treatment of inherited platelet disorders – including Bernard Soulier disease, Glanzmann’s thrombasthenia, Hermansky Pudlak syndrome, Jacobsen syndrome, Lowe syndrome, platelet release and storage pool defects, thrombocytopenia with absent radius (TAR) syndrome and thrombotic thrombocytopenic purpura (TTP) – and where to get help. Acquired platelet disorders – such as ITP or as a result of medication or as part of another condition – are not covered in this information sheet.

**What is a platelet disorder?**

Blood is made up of different types of cells (red blood cells, white blood cells and platelets) all suspended in a straw-coloured liquid called plasma. Platelets are the cells responsible for making blood clot. When a blood vessel is injured, platelets clump together to block the injury site. They also start off a complicated chemical reaction to form a mesh made of a substance called fibrin. This complicated chemical reaction always follows a strict pattern – with each clotting protein (known as a coagulation factor) turned on in order. When all of the factors are turned on, the blood forms a clot which stops the injury site bleeding any further.

**Platelets** – also called thrombocytes – are formed in the bone marrow from stem cells. Megakaryocytes (large bone marrow cells) are formed, mature and then die, which is when they release platelets. Over half of the new platelets circulate in the bloodstream and the rest remain in storage in the spleen. Platelets only live for just over a week, then the body destroys them and new ones are released.
What are platelet disorders?

There are lots of different groups of disorders affecting the platelets:

- **Thrombocythaemia** – where there are too many platelets in circulation
- **Thrombocytopenia** – where there are too few platelets in circulation
- **Dysfunction disorders** – where there are the correct number of platelets in circulation but they do not work properly

All of these disorders mean that the clotting process is disrupted so lead to abnormal clot formation and bleeding. Generally symptoms of a platelet disorder are similar, with bruising from minor trauma, bleeding from the mouth, nose or digestive system and excessive bleeding after injury or surgery. They may become apparent soon after birth when the umbilical cord is cut or later in childhood when teething or becoming more mobile.
What causes platelet disorders?

The majority of platelet disorders are caused by a genetic fault or mutation. Human beings have about 30,000 to 40,000 different genes, each of which has a function in making an individual person. The genes are arranged in pairs (one of the pair from each parent) on 23 chromosomes – inevitably some of these genes are faulty.

The exact manner in which this mutation is passed on from parent to child varies depending on the specific platelet disorder – see below for the main ways disorders can be inherited. Unless there have been other affected people in the family there may be no way of knowing whether someone is a carrier, as most carriers remain healthy. In some cases, the gene mutation occurs sporadically (out of the blue), with no family history of clotting disorders.

**Autosomal recessive inheritance**

In most cases a mutation in an autosomal gene does not cause problems if the equivalent gene on the other of the pair of autosomes is normal. However, if someone inherits a faulty gene from both mother and father, they may be affected. These are known as ‘autosomal recessive’ disorders, which means that a child has to inherit the faulty gene from both parents to have the condition.

Each pregnancy carries:

- A 25 per cent chance that the child will be unaffected and will not carry the mutation
- A 50 per cent chance that the child will not be affected but will carry the mutation
- A 25 per cent chance that the child will be affected

People who carry one copy of the faulty gene are said to be a ‘carrier’.

The majority of carriers are healthy but occasionally, ‘affected carriers’ may show mild symptoms of the condition, which may or may not need treatment.
Autosomal dominant inheritance
Some platelet disorders can be caused by a gene mutation being passed on in an autosomal dominant manner, which means that a child has to inherit the faulty gene from just one parent to have the condition.

Each pregnancy carries:
- A 50 per cent chance that the child will be unaffected and will not carry the gene mutation
- A 50 per cent chance that the child will carry the gene mutation and will have the condition

X-linked inheritance
The chromosome that determines the gender of the child will either contain ‘XX’ (female) or ‘XY’ (male). As females have two ‘X’ chromosomes, a fault on this chromosome can be completely or partially overcome by the other healthy ‘X’ in the pair. However, in males, who only have one ‘X’, there is not another ‘X’ to provide a functioning gene.

This means that only boys are affected by x-linked disorders and the mother is a carrier of the disease. Each pregnancy carries a:
- 25 per cent chance of the child being an unaffected non-carrier girl
25 per cent chance of the child being an unaffected carrier girl
25 per cent chance of the child being an unaffected boy
25 per cent chance of the child being an affected boy

Unless there have been other affected boys in the family there may be no way of knowing whether the mother is a carrier, as most carriers remain healthy. In some cases, the gene mutation occurs sporadically (out of the blue), with no family history of clotting disorders.

How are platelet disorders diagnosed?

Doctors will usually start by taking a clinical history of which symptoms are present and when they appeared. They will also look at any other treatments or medications your child is having in case they could cause a platelet disorder. They will also carry out a physical examination to look for signs of any bleeding.

Platelet disorders can be diagnosed using a sample of blood for testing in the laboratory. The number and appearance of platelets in the blood will be checked. Clotting tests will also be carried out to record how long it takes a blood sample to form a clot. If an inherited disorder is suspected, doctors will try to identify the gene mutation as well, as this can be helpful for planning future brothers and sisters and for testing other family members.
Specific types of platelet disorders

There are a number of different types of platelet disorders. The most common types are:

- Bernard Soulier disease
- Glanzmann’s thrombasthenia
- Hermansky Pudlak syndrome
- Jacobsen syndrome
- Lowe syndrome
- Platelet release and storage pool defects
- Thrombocytopenia with absent radius (TAR) syndrome
- Thrombotic thrombocytopenic purpura (TTP)

Bernard Soulier disease

This is a type of macrothrombocytopenia, that is, there are some very large platelets in the blood that get counted on laboratory machines as bigger red and white blood cells. The platelets that are present are missing a protein on their surface that helps them stick together.

What causes Bernard Soulier disease?

Bernard Soulier disease is a rare condition – thought to affect around 1 in every 1 million people. It is an inherited condition, caused by a mutation (change) affecting a number of different genes. Most of the mutations are passed on in an autosomal recessive manner – see earlier section on inheritance.

What are the signs and symptoms of Bernard Soulier disease?

The symptoms of Bernard Soulier disease are very variable from mild to severe. Often symptoms become apparent in childhood, with frequent and heavy nosebleeds, as well as bleeding gums and easy bruising. Bleeding can be life threatening. In some females, symptoms are only noticed when menstrual periods start and/or during pregnancy.
Glanzmann's thrombasthenia

This is a condition where the platelets are present in the body but are dysfunctional, that is, they do not work properly because they are missing a protein on the outside of the platelets that makes them stick together.

What causes Glanzmann's thrombasthenia?

Glanzmann's thrombasthenia is a rare condition affecting around 1 in every 1 million people, although it is more common in certain ethnic groups. It is an inherited condition, caused by a mutation (change) affecting the ITGA2B and ITGB3 genes. There are a number of different types of mutations that have been reported. All the mutations are passed on in an autosomal recessive manner, which means that a child has to inherit the faulty gene from both parents to have the condition.

What are the signs and symptoms of Glanzmann's thrombasthenia?

Most symptoms of Glanzmann's thrombasthenia become apparent before a child is a few years old.

Symptoms can include bruising and petechiae (pinprick bleeds in the skin), bleeding gums, nose bleeds and heavy menstrual periods. Occasionally, there may be bleeding in the gastrointestinal tract or urinary tract. The most common symptom in children is frequent and heavy nosebleeds, which can lead to iron deficiency anaemia.

Hermansky Pudlak syndrome

This is also a condition where the platelets are present in the body but are dysfunctional, that is, they do not work properly. There are nine different subtypes of Hermansky Pudlak syndrome, some of which are associated with a particular type of albinism (lack of skin pigment) that affects the eyes and skin (oculocutaneous). One subtype of Hermansky Pudlak syndrome also affects the lungs, causing thickened tissue that leads to breathing difficulties. Hermansky Pudlak syndrome is thought to affect 1 in every 500,000 people.

What causes Hermansky Pudlak syndrome?

Hermansky Pudlak syndrome is an inherited condition, caused by a mutation (change) affecting a number of different genes. All the mutations are passed on in an autosomal recessive manner, which means that a child has to inherit the faulty gene from both parents to have the condition.
What are the signs and symptoms of Hermansky Pudlak syndrome?
The symptoms of Hermansky Pudlak syndrome vary depending on the particular type inherited but frequently include immunodeficiency and reduced numbers of white blood cells, leading to an increased risk of developing an infection. Almost all people also have an eye condition called nystagmus, where their eyes make up and down and side to side movements without them being able to control them. Other eye problems can occur, many of which can have an impact on vision, such as abnormalities of the optic nerve and how messages are interpreted by the brain, squint, cataract and astigmatism. Symptoms of the platelet disorder include bruising and petechiae (pinprick bleeds in the skin), bleeding gums and heavy menstrual periods.

Jacobsen syndrome
This is also known as Paris-Trousseau syndrome. It is a rare condition affecting around 1 in every 100,000 people. It is a condition where the platelets are present in the body but are dysfunctional, that is, they do not work properly. In Jacobsen syndrome, the platelets are oversized and cannot trigger the clotting process.

What causes Jacobsen syndrome?
Jacobsen syndrome is caused by a deletion affecting chromosome 11. The size of the deletion varies from person to person and the severity of symptoms increases as the amount deleted increases. In most cases, the deletion occurs sporadically (out of the blue), with no family history of clotting disorders. In around five to ten per cent of people with Jacobsen syndrome, the specific gene mutation they have is a ‘balanced translocation’. This means that two sections are swapped around but there is no loss of genetic material so the person has no symptoms. However, the gene mutation can be passed onto future generations.
What are the signs and symptoms of Jacobsen syndrome?
Children with Jacobsen syndrome have mild bleeding problems but it is associated with other symptoms including learning disabilities, attention deficit hyperactivity disorder (ADHD), heart problems and craniofacial (face and skull) abnormalities.

Lowe syndrome
This is a rare condition that only affects males, around 1 in every 500,000 males born. Lowe syndrome affects many areas of the body, including the eyes, brain and kidneys.

What causes Lowe syndrome?
Lowe syndrome is caused by a mutation (change) on the OCRL gene on the X-chromosome.

What are the signs and symptoms of Lowe syndrome?
Lowe syndrome affects many parts of the body, with cataracts forming in the eyes and glaucoma (raised pressure within the eye) being common. The kidneys are also affected with a condition called Fanconi syndrome, which reduces kidney function – that is, the ability of the kidneys to remove waste products from the blood to form urine. People with Lowe syndrome may have learning disabilities and weak muscle tone (hypotonia). Bleeding is usually mild with easy bruising and nose bleeds, as these children have learning disabilities they sometimes bruise more than expected as they don’t understand risk (and avoidance) of day-to-day activities.
Platelet release and storage pool defects

Inside platelets are ‘granules’ that play an important role in clotting. Platelet release and storage pool defects occur when the granules are either not released from the platelets properly or they are not stored correctly. In some forms, there are not enough granules within the platelets but in most forms, the release mechanism does not work.

What causes platelet release and storage pool defects?
Platelet release and storage pool defects can be acquired or inherited. If inherited, there are a number of ways that specific disorders can be passed on from parent to child.

What are the signs and symptoms of platelet release and storage pool defects?
The symptoms are similar to other platelet disorders in that they include easy bruising and bleeding from the gums and nose. There is also increased bleeding after injury and females may have heavy periods. The severity of symptoms varies but is usually from mild to moderate rather than life-threatening.

Thrombocytopenia with absent radius (TAR) syndrome

TAR syndrome leads to the radius bone in both lower arms being absent with the result that the arms are shorter than usual and bent inwards towards the body. Occasionally the ulna (the other bone in the lower arm) is abnormal as well, either affecting both arms or just on one side. In addition, people with TAR syndrome have a low level of platelets.

What causes thrombocytopenia with absent radius (TAR) syndrome?
TAR syndrome is a rare condition affecting around one in 100,000 people. It is caused by a mutation (change) on the RBM8A gene with or without an additional deletion affecting chromosome 1. These mutations are inherited in an autosomal recessive manner, which means that a child has to inherit the faulty gene from both parents to have the condition.
What are the signs and symptoms of thrombocytopenia with absent radius (TAR) syndrome?

The symptoms are similar to other platelet disorders in that they include easy bruising and bleeding from the gums and nose although this is quite rare. There is also increased bleeding after injury and females may have heavy periods, however the platelet count usually increases with age so this may not be a serious problem for most girls. Children with TAR syndrome may also have heart and kidney problems.

**Thrombotic thrombocytopenic purpura (TTP)**

TTP is a rare condition where there is abnormal clotting affecting the small blood vessels, which leads to a low number of platelets in circulation as they are taken up by these blood clots. As blood clots affect blood flow through the blood vessels, this can lead to decreased oxygen reaching the internal organs. TTP can be inherited or acquired following an autoimmune reaction.

**What causes thrombotic thrombocytopenic purpura (TTP)?**

The inherited form of TTP is caused by a mutation (change) on the ADAMTS13 gene, which is involved in production of an enzyme that is vital for normal blood clotting. Instead of forming clots in response to injury, the blood forms clots inside small blood vessels instead reducing blood flow. This mutation is inherited in an autosomal recessive manner, which means that a child has to inherit the faulty gene from both parents to have the condition.
What are the symptoms of thrombotic thrombocytopenic purpura (TTP)?

If untreated, the symptoms of TTP can be life threatening and include neurological problems such as seizures and weakness, anaemia, fatigue and bruising. However, with treatment of congenital TTP with plasma products containing ADAMTS13 or with new recombinant ADAMTS13 products, the risk of severe symptoms is reduced. Plasma exchange is commonly used in acquired TTP, in conjunction with medications to damp down the immune system, may solve the problem by removing the autoantibodies and stopping the body from producing any more.
How are platelet disorders treated?

As platelet disorders are rare, treatment is best delivered by a specialist centre with input from other specialists as well as haematologists.

Treatment may be required as part of planning for an operation or treating an injury. The most common treatment is desmopressin (also known as DDAVP®) which increases levels of platelets in the blood by releasing them from storage. This is given as an injection under the skin or into a vein or as a ‘sniff’ up the nose. Alternatively, a medicine called tranexamic acid can be given to temporarily boost the proteins that stabilise blood clots. This is given by mouth, intravenously or topically (applied to the skin).

Platelet transfusions are only rarely needed as the body can form antibodies to the platelets so that they stop working. If bleeding is severe enough to require treatment, a man-made coagulation factor called Factor VIIa might be used.

It is important that people with a platelet disorder should not use Non-Steroidal Anti-Inflammatory Drugs (NSAIDs such as ibuprofen) as this greatly increases the risk of bleeding because NSAIDs reduce platelet sticking together. Other methods of pain relief should be used instead. Caution is needed for injections as well – immunisations for instance, should be given subcutaneously (under the skin) rather than intramuscularly (into a muscle) to reduce the risk of a painful bruised swelling (haematoma) developing.

Females may have to take additional measures to make their monthly periods manageable. Options can include taking tranexamic acid or DDAVP® before and during her periods, taking the contraceptive pill or having an intrauterine device (IUD) inserted. If anaemia develops due to heavy periods, an iron supplement may be needed. In many cases, pregnancy should be planned and monitoring throughout should involve the comprehensive care centre as well as midwives.

The only ‘curative’ treatment for some platelet disorders is a stem cell or bone marrow transplant; this is only offered for the most severe conditions.
What happens next?

The outlook for children with a platelet disorder depends on the type of disorder they have and its severity. Some have life-threatening symptoms which are manageable with good treatment whereas others only cause problems in specific circumstances, such as surgery, pregnancy, and childbirth. Most have mild symptoms or no symptoms at all so no adjustment to everyday life will be needed, although it is always helpful to be aware of their platelet disorder especially around dental intervention and other surgery. Good dental hygiene is important for everyone, especially to reduce the risk of bleeding gums.
Further information and support

Call the Haemophilia Comprehensive Care Centre at GOSH on 020 7829 8837. The Haemophilia Society offers support and advice to anyone affected by haemophilia or any other clotting disorder. Call their helpline on 020 7939 0780 or visit their website at www.haemophilia.org.uk

A wide range of resources is also available on the World Federation of Hemophilia website at www.wfh.org and UK-specific information regarding haemophilia, bleeding disorders and the National Haemophilia Database can be found via the United Kingdom Haemophilia Centre Doctors’ Organisation website at www.ukhcco.org. Useful details of Haemophilia Centres when travelling in Europe can be found at www.euhanet.org/centrelocator.