Veno-occlusive disease (VOD) is one of the less common but still serious complications which can occur during stem cell transplant (SCT). Veno-occlusive disease is not another illness, but a complication that affects the liver.

This factsheet has been produced to help you understand more about VOD. The information given in this factsheet explains what VOD is and why it happens, how it is diagnosed, what the impact of it is, and how it is treated. It should give you a little more background and help you when you are asking questions to the SCT team.

VOD can range from mild to severe, and occurs in approximately 10 - 30% of children/young people who have received total body irradiation (TBI), busulfan, or high dose melphalan as part of their conditioning treatment before a stem cell transplant.

Although it is serious it is usually a temporary problem, but it can be more complicated or even cause long-term problems. Your SCT team will discuss this in more detail with you.

In VOD the chemotherapy causes damage to cells in the liver, so the veins within the liver become increasingly obstructed (occluded) by dead or damaged cells, causing the blood flow from the liver to back up.

The protein-rich fluid content of the blood leaks out into the peritoneal cavity (a space between the two membranes that separate the organs in the abdominal cavity from the abdominal wall). There will be an increase in weight as the fluid collects in this space.

As the tummy gets bigger it will become uncomfortable and may be quite painful requiring pain relief medicine.
The role of the liver and the impact of VOD

The liver is a large organ in the right upper part of the abdomen. You can’t usually feel it as it is under your ribs. It is made up of two lobes, each lobe consisting of 50,000 to 100,000 lobules.

Lobules are a series of liver cells in rows and beyond each row is a tiny channel or blood vessel, called a sinusoid. Blood flows through the sinusoids, bringing nutrients to be stored in the liver cells, and collecting products that need to be removed from the body. The sinusoids are lined with a type of cell called endothelial cells and these form the linings of the blood vessels. It is the endothelial cells that are damaged and cause VOD, and this damage stops the liver from working properly.

The liver helps the body in many ways:

Digestion
The liver helps in the breakdown of carbohydrates, proteins, vitamins, minerals and fats gained from food. You may not be able to eat or drink enough and may need support with this.

Detoxifies
Liver cells help to break down drugs so they can be used by the body. They also remove some drugs from the body once their job is done.

Breakdown of red blood cells
Red blood cells live for around 120 days and when they die, the liver is involved in their breakdown. Bilirubin (a yellowish pigment found in bile, a fluid made by the liver) is produced when red blood cells break down. Bilirubin is usually removed from the body in bile. In VOD it may not be removed from the body in this way. It may stay in the blood, and as your body tries to balance this, you start to look jaundiced (whites of eyes and skin become yellow).

Production of blood products
The liver produces vital blood products, including factors essential for stopping you from bleeding (clotting). If the cells of the liver are damaged these functions may be slower or not as effective as usual.

Risk factors
We know that some young people/children are more likely than others to develop VOD. If you fall into any of the categories listed below it does not mean that you will get VOD, but that you may be more likely to.

Before the transplant, your/your child’s SCT team will discuss your/your child’s care in more detail and will explain why this happens. Some of the circumstances which may trigger VOD include:

- children with osteopetrosis
- children with thalassaemia
- children with adrenoleukodystrophy (ALD)
- children with macrophage activating syndromes (MAS, i.e. haemophagocytic lymphohistiocytosis (HLH), Griscelli)
- evidence of previous liver damage (including prior abdominal radiotherapy)
- previous treatment with certain cytotoxic (anti-cancer) drugs (This generally affects patients aged over 15, but can also be seen in babies or children of any age.)
- any infection before or during the conditioning phase of SCT
- long-term treatment drugs that may harm the liver
- unrelated donor transplants
- second stem cell transplant
- the use of busulfan, high dose melphalan and/or total body irradiation in the conditioning regimen.
Signs and symptoms of VOD

Sudden weight gain
This may take place over a few days or, in extreme cases, hours. It is due to fluid collecting in the peritoneum rather than staying in the blood system. The fluid has collected in the wrong place, so it cannot be passed by the kidneys.

Ascites (fluid collecting in the abdomen)
As the liver swells, fluid is squeezed out of the liver and collects in the abdomen (tummy). This fluid contains a lot of protein which encourages more fluid to collect in the abdomen. As a result, the abdomen gets bigger and it may be uncomfortable or difficult to breathe especially when lying down.

Abnormal clotting
Abnormal clotting may require plasma or other clotting factors, e.g. cryoprecipitate or vitamin K. More frequent platelet transfusion may be required as platelets do not live as long in patients who have VOD.

Pain
The liver is surrounded by a capsule. As it enlarges, due to VOD, the liver presses on the capsule and this can be painful. Older children and young people may complain of pain in their right upper abdomen. On examination of the abdomen the liver may feel bigger than usual.

Abnormal bilirubin
In the breakdown of dead red blood cells bilirubin is formed. The liver helps to eliminate this from the body. In VOD the liver is unable to do this as well as normal. Blood tests, (liver function tests LFTs) will also show the liver is not working as it should be.

Jaundice
If the level of bilirubin in the blood becomes very high the skin and whites of the eyes may look yellow. This is referred to as jaundice, which may also make your skin dry and itchy.

Feeling or being sick (nausea and vomiting)
Nausea and vomiting occur for many reasons in VOD: pain, ascites, or an enlarged liver pressing on the stomach are all possible causes.

Lethargy
The symptoms described above will all make you feel tired and generally unwell.

How is the diagnosis of VOD made?
Your/your child’s SCT team will be familiar with the signs and symptoms of VOD. Various investigations may be needed to make an accurate diagnosis. Some of the symptoms listed may be signs of other problems with your SCT, such as graft versus host disease or infection. However, it is only in VOD that there is unexplained weight gain and fluid retention.

There are two techniques available to confirm the diagnosis of VOD. The first is a procedure using ultrasound. This is done using a probe that is gently run over the skin to give a picture of what is happening in the liver. It shouldn’t hurt but may be uncomfortable if your/your child’s abdomen is already painful. A liver biopsy may be needed to confirm the diagnosis. Your/your child’s SCT team will discuss which is the best option for you/your child.

Treatment of VOD

Monitoring of busulfan levels
Monitoring of chemotherapy levels is routine in SCT. Monitoring of busulfan is aimed at reducing the risk of VOD.

Prophylaxis (preventative treatment)
Where there is a risk of VOD, prophylactic or preventative treatment is often given. An oral medicine called ursodeoxycholic acid or an intravenous (IV) medicine, defibrotide, may be given from the start of the chemotherapy conditioning,

Defibrotide (medication)
Defibrotide is commonly used for the prevention of VOD in children and young people undergoing SCT that are considered to be at high risk of developing the disease, or as treatment of suspected or established VOD.

Defibrotide is usually given as an intravenous infusion (over 2 hours, four times a day, directly into a vein). In severe cases of VOD, or poorly responding cases, the dose may be increased.
Defibrotide works in a number of ways; antithrombotic (anti-clotting), anti-inflammatory (reduce swelling) and anti-ischaemic (reduce the restriction of blood flow). Defibrotide appears to have a protective effect against endothelial cell injury caused by chemotherapy drugs.

**The management of medicines**

This can become a very difficult time as all the therapies required to support a child/young person through transplant have an impact on the liver, including IV feeding (TPN - total parenteral nutrition), analgesia (pain killers), antibiotic or antimicrobial treatments or blood products.

The SCT team will plan your/your child’s care on a daily basis to consider how to best manage your medication. Your/your child’s care will be discussed with you but remember you can always ask questions if you are finding something difficult to understand.

**Supportive care**

The management of fluid retention and ascites are an essential part of the treatment of VOD. The aim is to reduce the amount of fluid that has collected in the abdomen and elsewhere within the body.

This is achieved by giving diuretics (drug treatment) to encourage the passing of urine, and restricting the amount of oral fluids allowed within a day.

Restricting the amount you are allowed to drink within a day can often be very distressing if you are thirsty. Small drinks or ice lollies/cubes can occasionally relieve the distress.

To monitor the effects of this treatment regular blood tests will be done. The accurate monitoring of fluid input and output is essential, as well as weighing you/your child and measuring the tummy once or twice a day. In severe cases of VOD, fluid retention and a distended abdomen can have an effect on your kidney function. Occasional support may be required from the renal team (kidney specialists). Your/your child’s SCT team will discuss this with you should it be required.

VOD can cause you/your child to be very uncomfortable, occasionally leading to a painful tummy. Pillows and loose clothing may help you/your child get comfortable. Your/your child’s skin may also become dry and itchy. Continue to bath every day and use emollients (moisturisers) to stop your/your child’s skin itching. Drug treatments with antihistamines may also help relieve itching.

Do ask any members of the SCT team looking after you/your child if there is anything you don’t understand or if you have any questions.