



Royal College
of Nursing

Graft versus host disease

A guide for families





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of Nursing

What is this booklet about?

Graft versus host disease (GvHD) is a complication of allogeneic stem cell transplantation (SCT), in which the cells from the bone marrow or stem cell donor (graft) react to the cells in the patient (host).

This booklet has been written to give you simple, precise definitions of GvHD and to help you to understand the implications of GvHD and its possible treatments. The booklet is designed to compliment the information given by the nurses and doctors, who will be able to give you information specific to you/your child. You should never be afraid to ask questions.

This booklet has a glossary at the back to explain unfamiliar words.

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Graft versus host disease

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What is graft versus host disease?

GvHD can occur following a stem cell transplant whether cells come from bone marrow/peripheral blood or umbilical cord blood. The ‘graft’ is the donor cells and the ‘host’ is the bone marrow transplant (BMT) patient cells.

In GvHD, the donor’s T-cells fight the patient’s organs and tissue, reducing their ability to work normally.

T-cells are white cells that can identify “self” (cells that should be in our bodies) from “non-self” cells that should not be in our bodies for example bacteria and viruses. Once the donated bone marrow begins to grow in the patient’s body the donor’s T-cells become very active and identify the patient’s body tissue as “non-self”.

T-cells use human leucocyte antigen (HLA) to recognise “self” and “non self”. HLA is the inherited genetic material found on the surface of many human cells and tissue. The greater the difference between the patient’s and the donor’s HLA, the quicker and more severe the GvHD may be.

Who gets GvHD?

It is difficult to predict before the transplant exactly who will get GvHD and to what extent. When donors are matched to patients, whether related or unrelated, work done in the tissue typing laboratory aims to provide the best match possible. This work can attempt to predict the risk of GvHD. It is worth remembering that most patients will get some GvHD and it is a normal part of transplantation.

There are however some factors which may influence the possibility of GvHD:

- unrelated donor transplants
- mismatched related transplants
- female to male sex mismatch of donor and patient, due to female donor T-cells recognising male chromosomes
- age of donor, the older the donor the greater the risk of GvHD
- if the female donor has had pregnancies
- exposure to viral infection, particularly cytomegalovirus (CMV)

- the conditioning regimes used (pre BMT chemotherapy/ radiotherapy)
- racial mismatch.

Preventing GvHD

During and following the transplant drugs are given for GvHD treatment. These drugs help towards controlling the donor’s T-cell activity and may prevent/reduce GvHD. This will be discussed with you and your family by your individual team.

The main medications used to prevent GvHD are called immunosuppressive drugs in particular a drug called ciclosporin. There are other treatments used for GvHD these are discussed later on in the booklet.

Types of GvHD

Acute GvHD

This happens up to day 100 after the bone marrow transplant. This is graded from mild to severe (or grades 1 to 4). Please ask your doctor to explain.

Chronic GvHD

This occurs after day 100 and can be limited or extensive.

GvHD can occur in any body part but the most common sites are:

- skin
- gut (gastrointestinal tract)
- liver.

This booklet will describe each of these separately along with some less common sites.

Acute GvHD of the skin

Skin GvHD usually starts with a rash. It may be more obvious at certain parts of the day. It often starts on the palms of the hands and soles of the feet. The hands and feet can become sensitive. The rash may spread, come and go, or disappear.

Diagnosing acute GvHD of the skin

Often GvHD of the skin can be diagnosed by looking at the rash. Sometimes your team will get dermatologists (skin doctors) involved for advice, especially to rule

out drug reactions. A skin biopsy may be needed to ensure an accurate diagnosis; this allows a small sample of tissue to be collected so it can be examined in the laboratory.

Treating GvHD of the skin

Mild to moderate GvHD (grade 1-2) means the rash may cover 50% of the skin surface. Sometimes no treatment is necessary. The skin can become itchy, treatment usually involves emollient creams (special moisturising creams), medication to control the itch and/or steroid cream. It may be necessary to add in low doses of steroids by the mouth.

Moderate to severe (grade 3-4) GvHD means the rash covers more than 50% of the skin surface. Treatment will involve a combination – intravenous steroid infusions, steroid creams and emollient creams.

Other treatments can include additional medication and extracorporeal photochemotherapy or PUVA (see page 10).

Your skin can feel uncomfortable at this time. You can help this by:

- wearing loose cotton clothing and using cotton bed linen
- avoid highly perfumed washing powders and toiletries
- avoid getting hot and sweaty
- avoid very hot showers and use mild/non perfumed soaps or emollient bath oils
- patting rather than rubbing the skin
- keeping the skin well moisturised with emollient creams
- care to avoid trauma as the skin may be thin due to steroids.

Acute GvHD of the gut

Acute gut GvHD usually starts with diarrhoea, nausea and some tummy pain. Remember however, that these symptoms can also be caused by radiotherapy, chemotherapy, antibiotics or infection, so a specific diagnosis can sometimes prove difficult.

Small to large amounts of diarrhoea may be passed several times a day. Often the diarrhoea has a ‘mucus’ (jelly like) appearance and is green in colour. Sometimes small amounts of blood are present in the diarrhoea. This is caused by the GvHD inflaming the bowel lining and making it delicate. You/your child may experience tummy cramps, pain and sometimes nausea and vomiting with a loss of appetite, because attempting to eat often makes symptoms feel worse.

Diagnosing acute GvHD of the gut

Often the symptoms of acute GvHD of the gut and the type of diarrhoea is enough to make a diagnosis. Your stem cell transplantation (SCT) team may also want you/your child to be assessed by a gastroenterologist (specialist gut doctor). The gastroenterologist may want to view the inside of the bowel with a small camera, (a procedure called an endoscopy) and take a biopsy of the bowel wall. An accurate diagnosis ensures the correct treatment for acute GvHD of the gut is given.

Treating acute GvHD of the gut

Grade 1-2 (mid to moderate) will require low dose steroids (anti-inflammatory drugs) given by mouth or through a drip. Intravenous fluids may be required if the diarrhoea causes dehydration. Painkillers for tummy cramps and anti-sickness drugs will also be given.

Grade 2-4 (moderate to severe) will include all of the above treatments plus steroids through a drip in a higher dose (Methylprednisolone) and/or other immunosuppressive agents. As high dose treatment suppresses the immune system antibiotic/antiviral treatments may be prescribed.

Sometimes with GvHD the bowel will not tolerate food so you/your child won't be able to eat. In this case, feeding support may be given in one of two ways:

- naso-gastric feeding (NG feeding), where a tube is passed through the nose into the stomach, and liquid food enters the stomach directly via the tube
- total parental nutrition (TPN) is when nutrition is given directly into the bloodstream via the central line, allowing the gut to rest.

Essential measures for caring for you/your child include:

- good personal hygiene, ensuring that you/your child's bottom is kept clean and dry
- the use of barrier creams around the bottom to prevent skin soreness and damage
- regular inspection by the nurses to ensure the skin round the bottom is not broken, damaged or infected
- ensuring any sore area is left exposed to fresh air as much as possible
- any carer should ensure they wear disposable gloves when dealing with diarrhoea and thoroughly wash their hands afterwards
- painkillers for tummy ache
- anti sickness drugs to control nausea and vomiting.

Acute GvHD of the liver

GvHD of the liver affects the small ducts that allow the flow of bile out of the liver. These ducts become inflamed leading to mild, moderate or severe damage. If you/your child is thought to have early signs of acute GvHD of the liver, this may only show up as slightly abnormal liver function blood tests. If acute liver GvHD progresses, other symptoms may include:

- jaundice (yellowing of the skin and eyes and darkening of the urine)
- itchy skin caused by the jaundice
- swollen tummy
- altered bowel actions – stools (poos) may become pale and float
- the clotting mechanism of the blood is made in the liver. This system can become disturbed in acute GvHD of the liver, hence bruising and bleeding can occur more easily.

Diagnosing acute GvHD of the liver

The SCT team will monitor blood tests to see how well the liver is working. Results will change if liver GvHD happens. If they show that acute GvHD of the liver is occurring it may be necessary to ask hepatologists (specialist liver doctors) to assess any liver damage. A liver scan may be done and a liver biopsy may be taken to make an accurate diagnosis.

Treating acute GvHD of the liver

- Low or high dose steroids (anti-inflammatory drugs) depending on the grade of acute GvHD of the liver.
- Medication to help stop itching, which can be given either by mouth, or by injection or drip
- Painkillers if required.
- Blood product support, for example blood and platelets transfusions.
- Blood clotting factors.

Chronic GvHD (cGvHD)

cGvHD by definition occurs beyond day 100 from transplantation. It may be a continuation of acute GvHD or more rarely occur separately. cGvHD can affect almost every organ or system. The most frequently affected areas are the skin, mouth, liver and eyes. It can also affect the gut (gastrointestinal tract), lungs and musculoskeletal system.

How is chronic GVHD diagnosed and treated?

cGVHD can affect more systems than acute GvHD. The most common are shown on page 5. Treatment for cGvHD is often the use of steroids with continuing cyclosporin or similar drugs such as tacrolimus, though other drugs may be used to help other symptoms. Your SCT team will explain to you how you/your child will be treated if cGvHD develops.

How is chronic GvHD diagnosed and treated?

Body system effected	Signs and symptoms	Treatment
Skin	<p>Appearance</p> <ul style="list-style-type: none"> • red/flushed (erythema) • dry/flaky especially on knees, elbows and in skin creases • patchy in colour • patchy hair growth • hair and eyebrows may have streaks of white in them 	<ul style="list-style-type: none"> • daily skin care with soap free cleansers and regular emollient cream use • use of gentle shampoos
Mouth	<ul style="list-style-type: none"> • dry mouth • difficulty in tasting foods • inside of the mouth looks white 	<ul style="list-style-type: none"> • regular mouth care as recommended by your child's SCT team • a dentist will be involved in your child's care following SCT
Gut	<ul style="list-style-type: none"> • poor appetite • difficulty in swallowing • diarrhoea • poor weight gain • tummy pain 	<ul style="list-style-type: none"> • support with nutrition (NG feeds and/or TPN) • washing and using barrier creams after diarrhoea, to prevent skin breakdown and the risk of infection • pain killers for tummy pain
Lungs	<ul style="list-style-type: none"> • difficulty in breathing following exercise • wheezing 	<ul style="list-style-type: none"> • you/your child may be referred to a specialist lung/chest doctor
Eye	<ul style="list-style-type: none"> • dryness • sore eyes 	<ul style="list-style-type: none"> • eye drops and creams can help these symptoms • you/your child may be referred to an ophthalmologist (your specialist eye doctor)

The effect of GvHD on bone marrow function

Chronic GvHD and the immunosuppressive drug treatment used to treat it, means that you/your child will be at risk of infections. Information on how infection can be prevented will be given to you by your SCT team. During this time you/your child will not be able to form a response to certain types of immunisation/vaccination and therefore **NO IMMUNISATION / VACCINATION SHOULD BE GIVEN UNTIL INSTRUCTED BY THE SCT CONSULTANT.**

Vaginal GvHD

Vaginal GvHD is a rare complication that can present as vaginal discomfort and itching or may not be apparent until sexual activity commences. It can cause narrowing of the vaginal opening and dryness which may cause pain and/or discomfort during intercourse. If you wish to have further discussions with you SCT Team as you are concerned about this or you wish to have more information to give to your child then please contact us.

Graft versus leukaemia effect

Although GvHD is seen as a complication for some children, when children have a stem cell transplant because they have leukaemia or lymphoma, GvHD may actually be useful. As part of the process, donor T-cells may also recognise host blood cells, including leukaemia, lymphoma cells, and seek to destroy them. So if there are any leukaemic lymphoma cells left after the stem cell transplant, GvHD may destroy these cells and reduce the chance of the disease coming back.

Drugs used in stem cell transplantation (SCT) to prevent/treat GvHD

The following information on drug treatment is used as a general guide. Your own SCT team will discuss in detail the appropriate medication given to you/your child. These drugs are listed in alphabetical order, not their order of use.

Alemtuzamab

Purpose

An immunosuppressant used to prevent and treat graft rejection and GvHD, given before the transplant.

How is alemtuzamab given?

It is given through a drip in hospital, with the first dose given over four to eight hours.

Side effects

Reactions are most commonly seen during the first dose, less frequently with following doses. These may include:

- temperature
- chills
- rigors
- nausea
- rash
- hypotension (low blood pressure) may also occur
- low blood counts.

A pre-medication can be given to reduce the severity of these reactions; drugs often used for this include paracetamol, hydrocortisone or other steroid and an anti-histamine (e.g. chlorphenamine).

Antilymphocyte/Antithymocyte Globulin (ALG/ATG)

Purpose

They selectively destroy T-lymphocytes. They are used before and during SCT to prevent graft rejection, or to prevent/treat GvHD.

How is ATG/ALG given?

A pre-medication is always given prior to the infusion of ATG/ ALG. It is always given as an intravenous infusion and is infused over a minimum of six hours. Regular observations take place throughout the infusion in order to detect side effects.

Side effects on the administration of ATG/ALG

- Temperature
- Rigors
- Skin rash
- Nausea and vomiting
- Headache
- High blood pressure

Very rarely patients can become shocked, causing a low blood pressure, high pulse rate, and breathing difficulties. While ATG/ALG is being used you/your child will be very carefully monitored for these signs.

Azathioprine

Purpose

Azathioprine helps to prevent graft rejection by suppressing the body's immune or defence system.

How is azathioprine given?

Available in tablet or injection form.

Side effects

- General feeling of being unwell
- Dizziness
- Nausea or vomiting
- Diarrhoea
- Fevers
- Shivering
- Muscle and joint pain
- Irregular heartbeat
- Rash
- Hair loss

Basiliximab and Dacluzimab

Purpose

They are antibodies used to prevent T-lymphocytes from reproducing. They are normally used alongside ciclosporin/mycophenolate mofetil and steroids.

How is it given?

By a 30 minute infusion twice a week on consecutive days. Both are given by intravenous infusion – sometimes used in combination.

Side effects

- Fever
- Rash
- Itching
- Headaches

- Dizziness
- Nausea

Budesonide

Purpose

Particularly used for gut GvHD.

How is budesonide given?

Only available in oral capsules. Usually three doses per day are given.

Side effects

- Tiredness, muscle weakness
- Roundness of the face, weight gain
- Heartburn

Ciclosporin

Purpose

An immunosuppressive drug used to prevent and treat graft rejection and GvHD.

How is ciclosporin given?

Usually twice daily, but can be more or less frequent.

In hospital it will be given through a drip, but changed to tablets or liquid given by mouth when you/your child can tolerate medicines and is free of diarrhoea.

Ciclosporin capsules should be swallowed whole.

Ciclosporin liquid can be taken neat or mixed by stirring well with water, chocolate powder, or orange/apple juice for preferred taste. If diluted with something, this should be done just before the drug is given.

Important

Do not use grapefruit juice to dilute ciclosporin or drink grapefruit juice or eat grapefruit within one hour of taking ciclosporin as this interferes with the action of the drug. Watch out for mixed fruit juice drinks, for example Five Alive, as they may contain grapefruit juice.

Do not rinse the measure with water or any other liquid. Wipe it clean with a dry tissue between doses.

How long will I/my child have to take ciclosporin?

Blood levels will be checked regularly. This is to make sure that the correct dose of ciclosporin is given to you/your child. You will need to delay giving the dose of ciclosporin until after a blood sample has been taken on days that you/your child has levels measured, as the doctors want to measure the ‘trough’ level. Your SCT team will discuss with you exactly how long you/your child needs to take it for; this will vary from one month to one year, or even longer if severe GvHD develops.

Side effects and precautionary checks

- Kidney and liver function may be affected. Regular blood tests will be taken to check these and determine if doses need to be altered.
- Hypertension (raised blood pressure). Regular blood pressure measurements will be taken and drugs to reduce the blood pressure prescribed if needed.
- Tremor or shaky hands. This can be due to high levels of ciclosporin in the blood and if so will reduce as the ciclosporin is reduced and stopped. Some children can develop excess shakiness, slurring of their speech, or unsteadiness on standing or walking even when the drug level is not high. Please inform your doctor of any of these side effects urgently, as the drug may need to be stopped.
- Burning hands and feet. This usually only occurs at the beginning of treatment.
- Abdominal pain, nausea, vomiting and diarrhoea.
- Low blood magnesium level. Magnesium supplements can be given to maintain normal levels and your dietician can offer advice about foods rich in magnesium.
- Increased hair growth, often around the neck and back and on the arms and legs. This will disappear as the drug is reduced.

Emollients (moisturisers)

Purpose

Emollients prevent the skin from becoming dry. You would normally be asked to apply the emollients two to three times a day. However, this can be more if your skin is very dry.

Applying emollients can be hard work and tedious but is worthwhile in preventing skin from drying out.

Dry cracked skin can be a route for infection. Your SCT team will give you advice on how to apply your emollient regime.

How are emollients used?

Emollients are applied externally to the skin. You may be given a bath oil and/or cream/ointment to apply to your skin.

Side effects

It is uncommon to have side effects to emollient creams. However some people can become allergic to an ingredient. There are many different emollients. If you are concerned speak to your SCT team.

Extracorporeal photopheresis

Photopheresis is an “extracorporeal photoimmune” therapy. Whilst this may sound complicated, broken down it is simple to understand.

Extracorporeal – means outside the body

Photo – means light

Pheresis – a procedure in which the blood is filtered and/or treated.

Therefore photopheresis is light activated treatment taking place outside the body, where blood cells are treated by ultraviolet light as they pass through a special machine. They are then returned to the body where they tend to calm down some of the immune reactions, which cause GvHD to persist. This is only available in certain centres in the UK and patients may need to travel to these centres.

Infliximab

Purpose

Infliximab works by binding to and preventing the activity of a specific protein in the body called tumour necrosis factor alpha (TNF), a chemical that causes inflammation.

How is infliximab given?

Infliximab is given by intravenous infusion.

Side effects

- Fever
- Rash
- Itching
- Headaches
- Dizziness
- Nausea

Methotrexate**Purpose**

Used to prevent GvHD by killing the T-cells that are responsible for starting GvHD.

Often methotrexate is given with ciclosporin to prevent GvHD. It is given on certain days following the BMT (often some, or all, of days one, three, five and 11 post-transplant).

Occasionally it may be used on a weekly basis after transplant to treat acute GvHD, which is responding poorly to steroids, or in an attempt to aid faster reduction of steroid dosage.

How is methotrexate given?

As an intravenous injection through your child's central line.

Side effects

Although methotrexate is given in fairly small doses, it can cause significant mucositis, gut and liver disturbances and delayed engraftment.

Methylprednisolone**How is it given?**

By injection or drip.

Methylprednisolone is the intravenous equivalent of prednisolone and can be given in much higher doses.

Side effects of steroids

These will be discussed with your BMT team, but some general effects are:

- nausea and vomiting
- increased hair growth (hirsutism) particularly on the face
- puffy cheeks (a "Cushingoid" appearance – named after Cushing's disease where your body naturally makes too much steroid)
- increased appetite and weight gain
- high blood pressure
- risk of ulcers developing in the gastrointestinal tract
- mood swings/depression
- fluid retention
- higher blood glucose levels – in severe instances requiring insulin administration
- increased risk of infection – particularly CMV reactivation and fungal infections.

Important: If any of these problems occur you should seek medical advice. Do not stop taking or giving the drug suddenly.

Mycophenolate mofetil**Purpose**

This drug is used to treat and prevent graft rejection and GvHD.

How is mycophenolate mofetil given?

Two to three times daily via a drip in your arm/Hickman[®] line or by a tablet.

How long will I need to take this medication?

Usually as long as you have symptoms of graft versus host disease. It may be different from patient to patient.

Often used when ciclosporin and steroids don't appear to be working or when ciclosporin is not tolerated. May be used in conjunction with ciclosporin if you are having a cord stem cell transplant.

Side effects

- Diarrhoea and abdominal discomfort
- Nausea and vomiting

- Constipation
- Headaches
- Low blood counts

All of these side effects will be monitored and explained by your team.

Muronomab-CD3

Purpose

Very often used in steroid resistance acute graft versus host disease.

How is muronomab-CD3 given?

A fast intravenous injection.

Side effects

- Flu-like symptoms
- Headaches
- Chills and fever
- Nausea
- Diarrhoea
- Breathing difficulties

PUVA

PUVA is the name given to a skin treatment involving sensitising the skin with psoralens and then exposing it to ultraviolet A rays. Psoralens can be taken by tablet or applied to the skin in bath. The skin is then exposed to the UV light.

PUVA therapy is generally given two to three times per week as an outpatient – for a course of around 6-10 weeks.

Side effects

- Flu-like symptoms
- Low blood pressure
- Nausea and Vomiting
- Allergic reactions
- Lowered resistance to infection
- Flushing

Rituximab

Purpose

Rituximab works by killing B-lymphocytes (B-cells), which make antibodies.

How is rituximab given?

Given as an intravenous infusion.

Side effects

The side effects of rituximab are generally mild and some of these can be reduced with medicines. Side effects can begin during the first dose of the drug and may continue for a few hours afterwards, but are usually milder with following doses.

They include:

- flu-like symptoms
- low blood pressure
- nausea and vomiting
- allergic reactions
- lowered resistance to infection
- flushing.

Sirolimus

Purpose

Used for GvHD prevention and treatment.

How is sirolimus given?

It is given as an oral solution or tablets.

Side effects

- Can drop the blood counts
- Can affect the kidney function
- Abdominal pain, nausea, vomiting
- TTP (thrombotic thrombocytopenic purpura)
- Cannot be used with voriconazole

Steroids (prednisolone)

Purpose

Steroids lower the production of white cells.

How is it given?

By mouth.

Prednisolone is available in tablets, dissolvable tablets or enteric-coated tablets.

Tacrolimus

Purpose

May be used to treat GvHD that does not respond to ciclosporin.

How is tacrolimus given?

Tacrolimus should be given orally if possible. Capsules should be swallowed with fluid, preferably water.

Remove the capsule from its blister pack immediately before taking. Once opened the pack must be used within three months.

Tacrolimus may be given via a nasogastric tube if not tolerated by mouth and may be given through a central line if necessary.

Tacrolimus may be given by intravenous infusion over a 24 hour period.

Tacrolimus is given in two doses per day, 12 hours apart and should be taken on an empty stomach for maximum absorption, i.e. one hour before, or two to three hours after a meal.

Side effects

- Hypertension (raised blood pressure). Regular blood pressure measurements will be taken and drugs will be given to reduce the blood pressure if required
- Tremor
- Headaches
- Poor sleeping

- Abnormal kidney function. Regular blood tests will be taken to monitor this
- Constipation, diarrhoea, nausea
- Abnormal blood electrolytes. Regular blood tests will monitor this
- TTP

Thalidomide

Purpose

This drug is used to treat chronic GvHD.

How is thalidomide given?

It is given orally.

Side effects

Main side effects are peripheral neuropathy and drowsiness.

GLOSSARY

Biopsy – the removal of a tiny piece of skin, liver or lining of the gut to examine it under a microscope. A biopsy may be used to help diagnose GvHD.

Chromosomes – a thread like structure in the nucleus of a cell that is made of genes.

Central line – a tube which goes into the child’s chest for drugs and feeding.

Conditioning – treatment before the bone marrow transplant used to get rid of the patient’s bone marrow. This may involve the use of chemotherapy, radiotherapy and/or monoclonal antibodies.

Dermatologist – a doctor who specialises in the skin.

Diarrhoea – frequent loose stools (poos).

Emollients – moisturisers.

Endoscopy – looking inside the body using a very small camera.

Enteric coated – a tablet covered in a sugar coating.

Gastroenterologist – a doctor who specialises in the stomach and gut.

Genetic – relating to something that is linked to genes.

Gastrointestinal (GI) tract – the mouth, throat, stomach and intestines are all from the GI tract.

Hepatologist – a doctor who specialises in the liver.

Immunosuppressive – reducing the effectiveness of the immune system.

IV/Intravenous – a method of giving medication directly into the vein, either by a drip, central line or an injection.

Hypertension – high (or raised) blood pressure.

Hypotension – low blood pressure.

Lymphocyte – a white blood cell.

Magnesium – an element needed for muscles and nerves to work.

Mucus – a slippery, sticky substance.

Nausea – a feeling of the need to be sick.

NG feeding/Nasogastric – where a soft, narrow tube is passed up the nose and into the stomach, through which liquid food and drugs can be given.

Ophthalmologist – a doctor who specialises in the eyes.

Steroids – a group of drugs used to reduce swelling/ inflammation.

TPN/Total Parental Nutrition – when the child’s nutrition is given directly into the bloodstream via the central line.

Tremor – shaking.



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