Handbook of Liver Transplantation for Children

2017 Edition

Organ Transplantation Center
National Center for Child Health and Development

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Greetings

In November 2005, the National Center for Child Health and Development (NCCHD) launched a live-donor liver transplantation program. Although the number of patients was initially limited, it grew every year, and the Center is now known to run the largest pediatric liver transplantation program in the world. Over the last 10 years, we have attempted to develop many new therapeutic methods. This has included the establishment of safe methods for liver transplantation in infants and newborns, the establishment of methods for extended hepatectomy and liver transplantation for hepatoblastoma, attempts at novel transplant applications to treat metabolic liver diseases, the establishment of intensive care for fulminant hepatitis, the performance of multiple organ transplants, the establishment of pediatric deceased donor transplants, split liver transplantation, cell transplants, and regenerative medicine, the construction of a national database for pediatric liver transplantations, the establishment of methods to operate donors through small incisions, the introduction of laparoscopic-assisted donor surgeries, and surveys of living donors' quality of life.

At the NCCHD, we perform transplant surgeries on children from all over Japan and overseas. As a national hospital, we are confronted with many patients who have extremely serious and rare diseases. To ensure that as many children as possible leave the hospital smiling and go on to attend school, build careers, and become fathers, mothers, grandfathers, or grandmothers themselves, the staff of the entire Center works as one to solve the problems of transplant medicine and to perform their jobs humbly.

This Handbook is based on the previous edition published in June 2010, but features a considerable amount of new content. It includes our latest findings, as well as useful information that can be applied by patients as they go through different stages of their lives.

In each section, specialists involved with transplant medicine at the NCCHD explain their area of expertise in accessible language.

The Handbook also includes interviews with four recipients and two donors, who generously shared their memories of the transplant process and described their current lives.

This Handbook contains all the knowledge on liver transplantation that we have accumulated here in Japan. We hope that it will help children and their families around the world to increase their understanding of liver transplantation.

March, 2017

Mureo Kasahara
Director, Organ Transplantation Center
National Center for Child Health and Development
Email: kasahara-m@ncchd.go.jp

1 Introduction

1 The transplantation medical care team

I specialized in organ transplantation in 1996. In my previous positions at Kyoto University and King's College London in the United Kingdom, I gained clinical experience on more than 1,200 organ transplant cases. Since joining the National Center for Child Health and Development (NCCHD) in June 2005, I have taken part in 442 liver transplantations (414 from live donors, 4 from domino donors, and 22 from deceased donors) and 2 hepatocyte transplants (as of the end of 2016). Outside the NCCHD, I have provided instructions and support for 600 liver transplantations performed at medical institutions both in Japan and overseas. My experience has taught me that collaboration and cooperation between various departments are essential to save the lives of children undergoing transplant surgery.

Children carry enormous potential within themselves as they grow and change. On May 1st 2011, the NCCHD established the Organ Transplantation Center to provide children with comprehensive support and to test promising new treatment options, including hepatocyte transplantation. The transplant therapies provided by the Center—including organ transplants of the liver, kidney, small intestine, lung, pancreas, and heart, as well as hepatocyte transplants—are made possible not only by the transplant surgeons and recipient coordinators, but also by the cooperation of many other physicians. At the NCCHD, a wide variety of departments and experts work together to create a coherent and enduring medical system for transplant patients. These various actors include the physicians involved in medical care, research scientists, the nursing staff, pharmacologists, the examination department staff, clinical engineers, radiologists, public health nurses, physical therapists, occupational therapists, and nutritionists.

We will continue to use the combined skills of these departments to offer our patients the best possible care.

Mureo Kasahara
Director, Organ Transplantation Center
National Center for Child Health and Development

2 The job of a transplant surgeon

Even in the United States and in Europe, the job of a transplant surgeon is extremely hard, and this specialty is particularly unpopular with new doctors in Japan. Although the liver transplantation survival rate has improved, it is still around 90%. Caring for patients and families as they deal with difficult post-operative complications is an important part of the job.

Diseases do not take vacations, which means that transplant surgeons work from Monday to Sunday. They start their day by taking blood samples from the patients in the general ward at 7 a.m. (and from the patients in the ICU at 5 a.m.), and by checking on the patients to see how they are doing. Rounds and ultrasound examinations of ICU patients begin at 7:30 a.m., followed by an ICU conference at 8:00 a.m. to confirm the daily plans for patients who have just received transplants. General ward rounds begin at 8:30 a.m. to confirm the plans for patients and to check what examinations are scheduled for that day.

Outpatient clinics are held on Tuesdays and Fridays. As part of organ transplantation, immunosuppressant therapy is required from the day of the transplant and throughout the patient's life. Therefore, regular outpatient examinations are extremely important. Transplant conferences are held every Tuesday. In these meetings, we not only talk about the patients who are receiving inpatient and outpatient care, but also check on the status of the roughly 50 people who are constantly waiting for liver transplantation, and consider how we can provide other forms of care for these patients. Liver transplantations are regularly performed on Thursdays and on the second and fourth Mondays of the month. We devote ourselves to our work every day to ensure that the transplant surgeries we perform are safe and successful.

Surgeons' skills can directly affect the patient's recovery process and prognosis. We take this responsibility seriously, and do not neglect fundamental skills such as knot-tying or the proper use of surgical instruments. We work hard every day to ensure that we make accurate decisions in every situation.

We also give presentations and lectures at transplant-related academic meetings and research conferences in Japan and overseas. At these meetings, we obtain the latest information on transplant medicine and exchange opinions with other specialists to apply to our surgery and everyday care. The main conferences we attend include those held by the Japan Surgical Society, the Japan Society of Hepato-Biliary-Pancreatic Surgery, the Japanese Society of Gastroenterological Surgery, the Japan Society for Transplantation, the Japan Liver Transplantation Society, the Japan Society of Pediatric Hepatology, the Japanese Society for Small Bowel Transplantation, the Transplantation Society, the European Society of Transplantation, the Asian Society of Transplantation, and the International Liver Transplantation Society. We prepare slides for these presentations and lectures, and practice our delivery when time allows. We also cooperate with researchers to develop new organ storage methods, and experiment with applications of regenerative medicine. The results of our work are published on the hospital's website.

Research achievements

Academic paper (English)
Conference presentation (English)
E-learning system (English)
Educational lecture on surgical instruction/cooperation (Japan, overseas)
Academic paper (Japanese)
Conference Presentation (Japanese)

https://www.ncchd.go.jp/hospital/about/section/special/transplant_surgery/gyoseki.html

We are blessed with good colleagues, friends, and families, and are motivated to do our best for our patients.

Mureo Kasahara
Director, Organ Transplantation Center
National Center for Child Health and Development

3 The job of a recipient transplant coordinator

In Japan, various coordinators specialize in different aspects of transplantation. These include recipient coordinators, who handle everything related to recipients; donor coordinators, who handle the provision of organs from deceased donors; and tissue and bone marrow transplant coordinators, who handle matters related to tissue and bone marrow transplants. Among these, our hospital employs two full-time recipient transplant coordinators certified by the Japan Society of Transplantation.

As these jobs involve a wide range of responsibilities, in the United States, the work is divided into different categories, including the duties arising before and after the transplant, as well as those related to children, adults, living donors, and data management. In Europe, there are specialized nurses called “transplant consultant nurses”. In Japan, however, recipient transplant coordinators handle all of these responsibilities. Moreover, as living-donor transplants are about 30 times more common than deceased donor transplants in Japan, coordination with living donors is an important part of the recipient transplant coordinator’s job.

As part of our coordination role, we are constantly striving to ensure that the children who need liver transplantation and their families are offered the best possible choices. As both of us have nursing backgrounds, we have a proper understanding of diseases, treatments, and children’s growth and development, which helps us in consultations and when making various arrangements or giving lifestyle guidance. We hope that our efforts will make people think, “I am so glad you were here.”

This section mainly discusses the responsibilities related to recipients.

1 Before surgery

Our involvement with patients who need transplant surgery or are looking for information on transplants starts at the first contact and involves coordination before surgery, information-sharing, and consultations. While all families are uneasy about the surgery itself, many other aspects can also cause them anxiety, including the donor selection, the child’s condition, the results of the surgery, the timing of the surgery, rejection responses, infections, and life after the transplant. Our job is to alleviate these concerns as much as possible. Moreover, the fact that liver transplantation requires a donor can create conflicts within families. We support families as they make decisions, while respecting their values, beliefs, and opinions.

2 From surgery to hospital discharge

On the day of the surgery, we explain the course of the operation. We also visit patients during their hospitalization to discuss various topics. As the hospital discharge approaches, we explain matters surrounding life after leaving the hospital. We make sure to tailor our explanations to the child's age and background so that both the child and family can live with confidence.

3 After leaving the hospital

Families can become anxious about many things after patients return home. Other life changes, such as starting school or moving house, can also cause worry. We provide support with all issues and problems, so please do not hesitate to contact us.

Start considering a transplant → **Liver transplant** → **Hospital discharge**

Coordinator's responsibilities

- coordinate interview schedule, understand patient's and family's condition, provide information on transplants, manage and coordinate schedules of examinations, hospitalization, and surgery day
- arrange donor examinations, organize consultations about the patient's condition and diet
- help with registration on the transplant waiting list
- coordinate deceased donor liver transplantations, and work with other institutions

Support after leaving the hospital

- discuss life after the hospital
- run post-discharge consultation desk
- follow-ups

Comprehensive transplant support

- Emotional support, coordination between medical professionals and child/family

People sometimes apologize for intruding on our work with their concerns. However, we strongly encourage you not to hesitate to approach us. We are available to talk about anything – not only about your troubles, but also about your joys and the things that make you sad. Our job is to give as much help as we can to the children who receive liver transplantation and to their families.

Masami Katono
Recipient Transplant Coordinator
National Center for Child Health and Development

4 The job of an internist

Many people reading this Handbook have already been examined and treated at other medical institutions, and have been told that medical therapy will probably not improve their child's condition. Others are trying to decide whether a liver transplant is the best option for their child.

The internal medicine team works with the department of surgery to care for patients based on the assumption that most of them have been referred for liver transplantation. In severe cases, the emergency transport team and intensive care department are the first to respond and to seek to improve and maintain the patients' general condition.

1 Final assessment of the need for a liver transplant

We rely on diagnoses from physicians in multiple fields to understand the effects of diseases of the liver and other organs. Our team includes specialists from the radiology, hepatology, and anesthesia departments, as well as experts on diseases related to infections, immunology, hematology, the endocrine system and metabolism, the brain, the heart, the lungs, the kidneys, and the digestive tract.

We not only have to consider whether the patient's condition will be improved by a liver transplant, but also to determine whether the patient can tolerate general anesthesia throughout a lengthy operation. In addition, we investigate any complications or existing diseases. After discussing the results, we decide whether a liver transplant is necessary.

2 Proceeding with medical therapies when transplantation is not an option

In many cases, even if a liver transplant is not indicated at the moment, it will be necessary later. It is important to improve the nutritional status of patients until surgery can be performed. Sometimes, a patient's condition can be improved with medical therapy alone. In these cases, we consult with a transplant surgeon to determine the extent to which we should pursue medical therapy. We then proceed with the treatment while bearing in mind the possibility that a transplant may be needed later. By contrast, some patients are deemed unable to bear the burden of general anesthesia and surgery. Medical therapy is therefore used to improve their condition until they can undergo a liver transplant.

3 Preparing for a transplant when one is indicated

A transplant requires complex preparations that involve the participation of many specialists. First, an infectious disease team plans the necessary vaccinations before a scheduled transplant. If the patient has a metabolic disease, a metabolic diseases specialist regulates his or her condition. Any other complicating

diseases are addressed, and the patient's nutritional status is improved until he or she is able to undergo surgery.

4 Support after transplant surgery

We are involved in addressing children-specific problems that cannot be resolved through transplant surgery. This includes the treatment of issues such as allergies, skin symptoms, and asthma.

The side effects of immunosuppressants require a long-term approach. Their effects on the kidneys, nervous system, and other areas are treated as issues of internal medicine.

Reiko Ito
Department of Hepatology and Internal Medicine
National Center for Child Health and Development

2

Liver transplantation

1 Understanding the liver and liver transplantation

1 What is the liver?

The liver is an organ that extracts energy in the form of glucose from nutrients absorbed by the stomach, the small intestine, and the large intestine through chemical reactions. The surplus energy is transformed so as to be easily stored by the liver itself, the muscles, and the fat cells. The liver plays an important role in the storage of nutrients absorbed by the stomach, the small intestine, and the large intestine. Moreover, it also produces bile juice. Bile juice travels from the liver through the bile duct to the duodenum, where it facilitates digestion and absorption.

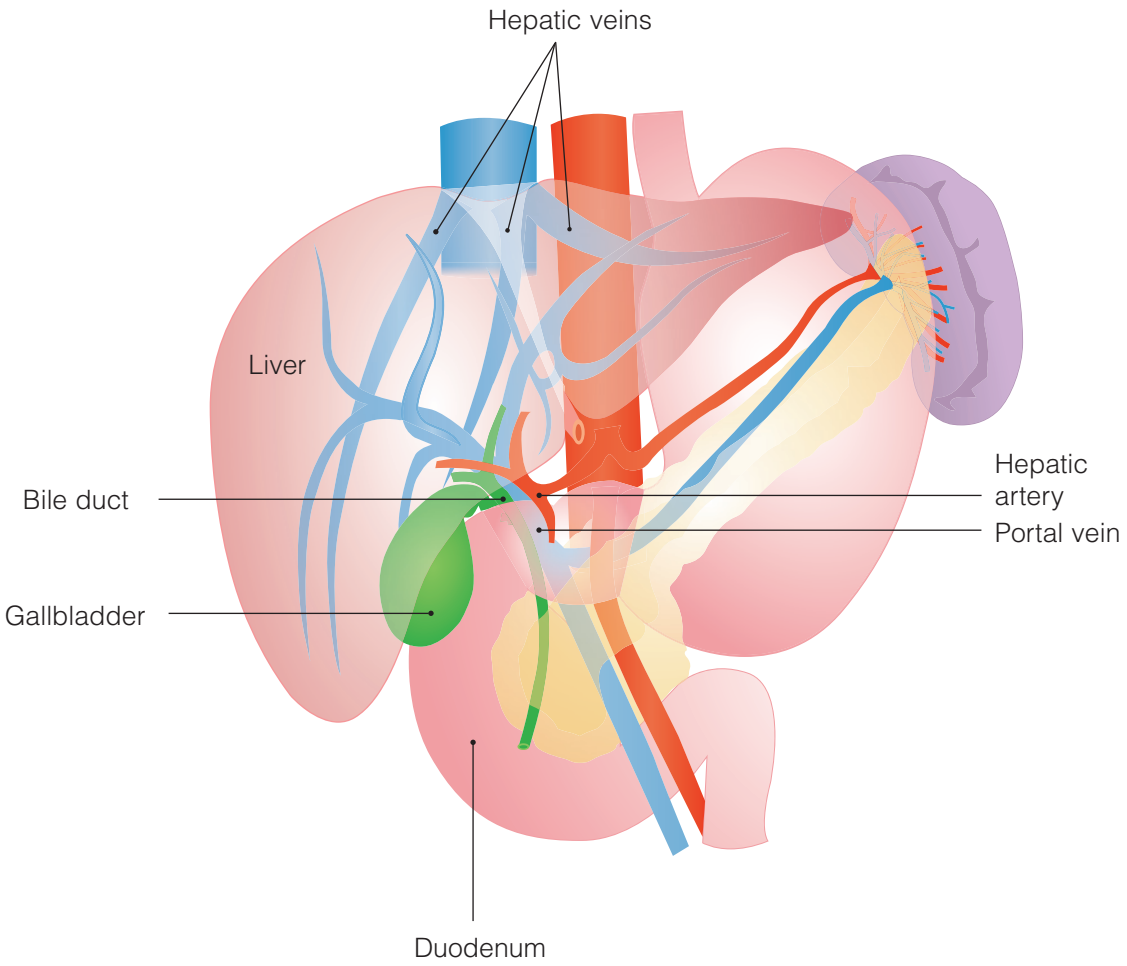


Figure 1. The liver, bile duct, gallbladder, and intestinal tract

According to a national survey by the Japan Liver Transplantation Society*, the primary diseases for which patients under 18 received living-donor liver transplantation between 1964 and the end of 2013 were cholestatic diseases (2,515 patients), mainly biliary atresia (1,869 patients – 74.3%), metabolic diseases (233 patients – 9.3%), and acute liver failure (222 patients – 8.8%). At our Center, we performed 442 liver transplantations (414 from living donors, 4 from domino donors, and 22 from deceased donors) and 2 hepatocyte transplants between November 2005 and the end of 2016. Figure 2 shows the primary diseases involved in these cases. In comparison with other institutions, we can note a higher proportion of patients with metabolic diseases and fulminant hepatic failure.

*Japan Liver Transplantation Society, Liver Transplantation in Japan – Registry by the Japanese Liver Transplantation Society. Ishoku 2014; 49:2.3:261–274

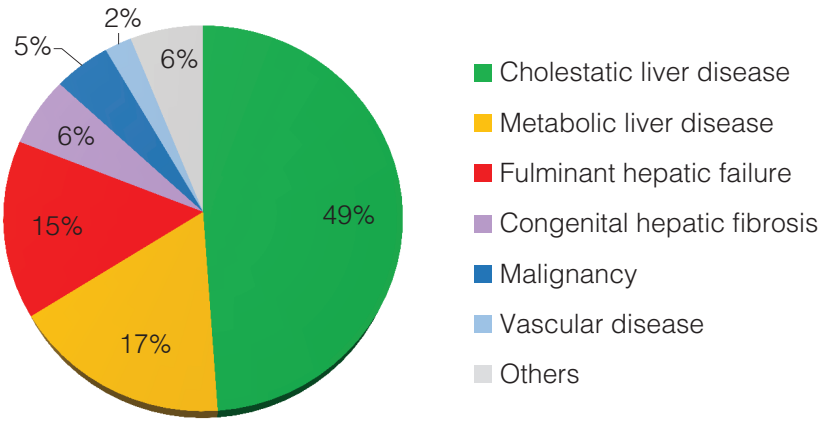


Figure 2. Original liver diseases at the NCCHD, Tokyo, Japan (2005/11 – 2016/12) n = 442

These conditions are initially treated with internal therapies such as medication, intravenous fluid infusions, and food and milk intake restrictions. However, the burden on the liver is severe, and when conditions such as cholangitis, ascites, hemorrhagic tendencies, growth disorders, and growth retardation due to frequent hyperammonemia appear, a liver transplant is considered as part of the treatment strategy.

2 Liver diseases

(1) Biliary atresia

Biliary atresia is a progressive disease of unknown origin in which the bile ducts outside the liver become obstructed. The bile's inability to flow can cause cirrhosis of the liver (Photo 1). This disease was first described by the British physician John Thompson in 1891. Although it was discovered more than 125 years ago, its cause remains unknown. We are currently working with the NCCHD's research institute to identify the causes of biliary atresia.

One in every 10,000 to 13,000 children is born with biliary atresia. In Japan, 100 to 120 children are born with this disease every year. The stool of children with biliary atresia is characterized by a pale color caused by the obstructed bile flow. However, as the change in color can be subtle, parents do not always notice anything abnormal. In addition to the stool color, ultrasound exams can be used to determine whether the gallbladder is visible, and hepatobiliary scintigraphy can be used to evaluate the bile flow. However, diagnosis through these methods is difficult. To reach a definitive diagnosis, a laparotomy is eventually needed in order to perform a cholangiography.

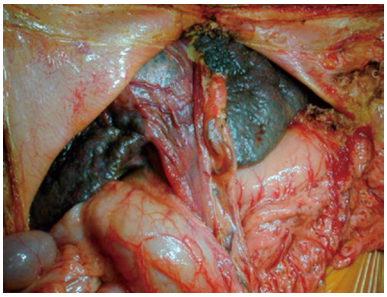


Photo 1
Liver of a patient with biliary atresia. The dark-green area shows cirrhosis.

When cirrhosis occurs, a great deal of pressure is placed on the portal vein that carries blood from the intestines to the liver, as well as on the intestines and spleen, causing abdominal distension (Photo 2).

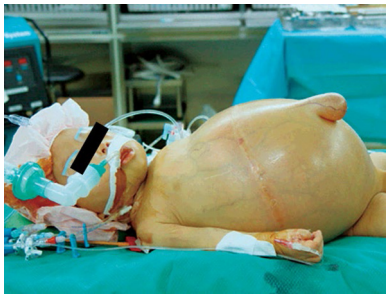


Photo 2
A 5-month-old boy with biliary atresia. His abdomen is swollen with ascites, and his liver looks dark-green and has developed multiple collateral vessels.

The liver's ability to produce clotting factors is also weakened by cirrhosis. Clotting factors play a crucial role in stopping bleeding, which means that bleeding is more difficult to stop in patients with cirrhosis. Biliary atresia is sometimes only discovered when children are examined for intracranial bleeding.

As early diagnosis is crucial, it is very helpful when parents notice changes in the color of their children's stool. In April 2012, a stool color card started to be included in mother/child health handbooks. Parents can use it as a reference to check their children's stool (Photo 3).

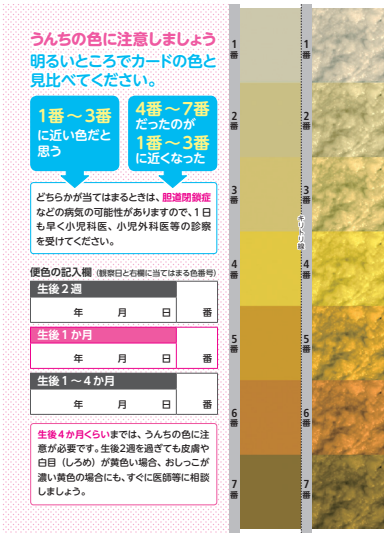


Photo 3
Stool color card

Biliary atresia is treated with what is called a portoenterostomy or the Kasai procedure, as named after Dr. Morio Kasai, a former Tohoku University professor who developed the procedure about 50 years prior. As this disease was untreatable before the Kasai procedure, its introduction has dramatically improved patients' survival prognoses. However, about 50% of children do not see an improvement from the procedure. Without a transplant, many children cannot survive for long with their own livers. Even when things go well after the Kasai procedure, a patient's condition can worsen if cholangitis appears in

adulthood. A liver transplant needs to be considered when signs of cirrhosis appear. These include jaundice (high bilirubin levels), ascites, frequent fevers caused by cholangitis, bleeding from esophageal varices, poor growth, pulmonary shunts, and pulmonary hypertension.

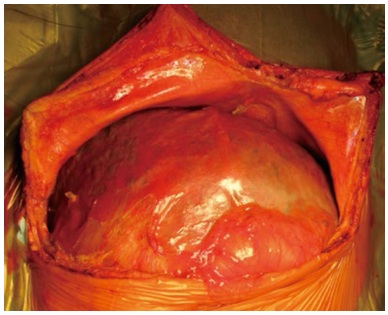


Photo 4
A 6-month-old girl with biliary atresia. After the Kasai procedure, she experienced repeated episodes of cholangitis, which caused adhesions between the liver and intestinal tract.

When liver transplantation is performed on biliary atresia patients who have undergone the Kasai procedure, the surgeries are sometimes complicated by the presence of strong adhesions in the abdominal cavity (Photo 4). The transplant procedure is even more complicated in children who have undergone several Kasai procedures or operations for other complications (such as splenectomy, esophageal transection, hepatic cyst jejunostomy, etc.).

With regard to liver transplant surgery, an early operation is preferable, as the patient will be in better condition. However, the patient's condition and the family circumstances should be taken into account when deciding when to perform a transplant.

As part of the Kasai procedure, a diagonal incision is normally made below the right costal arch in the child's abdomen. Although it is best to use the same wound for the transplant surgery, the Kasai procedure wound sometimes moves upward (above the ribs) when the child grows (Photo 5).

The same site is used whenever possible. However, when the wound is over the ribs, a new incision must be made for safety purposes. In the child in Photo 6, a horizontal incision was made slightly below the wound from the Kasai procedure for the liver transplant (Photo 7).

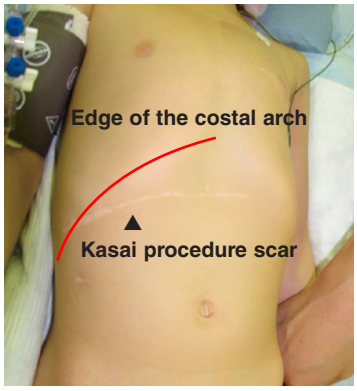


Photo 5
Scar from the Kasai procedure in a 10-year-old girl

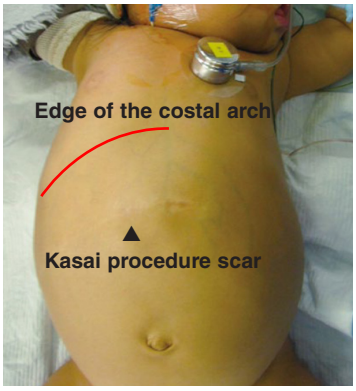


Photo 6
Scar from the Kasai procedure in a 10-month-old girl

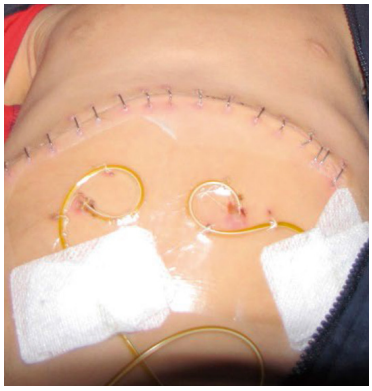


Photo 7
The girl in Photo 6 after a liver transplant

(2) Metabolic diseases

In the presence of metabolic diseases, some enzymes cannot be produced due to the poor condition of the liver, leading to an excess in harmful substances in the body. This may include high ammonia levels, a tendency to acidosis, etc. Liver transplantation can be indicated for metabolic diseases. There has been a long history of liver transplantation for congenital metabolic disorders, starting when Doubis and colleagues performed a liver transplant on a patient with Wilson's disease in 1971.

Metabolic diseases are classified into diseases in which cirrhosis occurs because of enzyme deficiency, and those in which the liver appears healthy but enzyme deficiency causes severe hyperammonemia or acidosis.

① Diseases in which cirrhosis is caused by enzyme deficiency or abnormality

These include Wilson's disease (Photo 8), hemochromatosis, hypertyrosinemia, progressive familial intrahepatic cholestasis (PFIC, a bile acid metabolism disorder), and neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD).

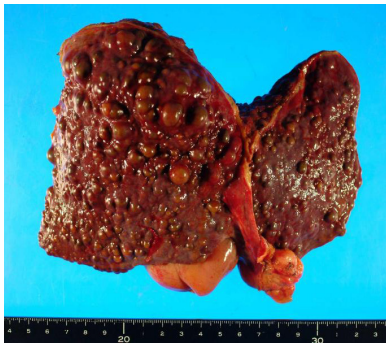


Photo 8
Liver of a patient with Wilson's disease

② Diseases in which there is no notable damage to the hepatic parenchymal cells, but serious, non-liver-related symptoms are caused by enzyme deficiency or abnormality

These include hyperlipoproteinemia, Crigler-Najjar syndrome, hemophilia, protein C deficiency, glycogen storage disease, protoporphyria, citrullinemia (type II), urea cycle disorders (OTCD, CPS1D, argininosuccinate synthetase deficiency), galactosemia, hyperoxaluria, and organic acidemia (methylmalonic acidemia, propionic acidemia).

Metabolic diseases require careful management, particularly before and after surgery. At the NCCHD, we work with the department of endocrinology and metabolism to treat children with metabolic diseases before and after surgery. Children with organic acid metabolism disorders such as methylmalonic acidemia require nutritional management and drugs after surgery. Therefore, they are regularly hospitalized for examinations even after the liver transplant.

(3) Fulminant hepatitis

Fulminant hepatitis occurs when the liver of a previously healthy child suddenly stops functioning. Although the liver appears healthy with a fresh, reddish color, the cells are dying and the liver becomes atrophic. This disease is believed to be caused by viruses or drugs. However, its origins are not clearly understood. We are currently working with the NCCHD's research institute to identify its causes. The disease occurs suddenly and requires a liver transplant, a drastic change in circumstances that can be incredibly trying for families and medical professionals alike.

Initial treatment modalities include steroids and immunosuppressants. When these fail, hemodialysis and plasmapheresis are performed (Photo 9). Children with this disease are treated by highly trained specialists from the nephrology and ICU departments.

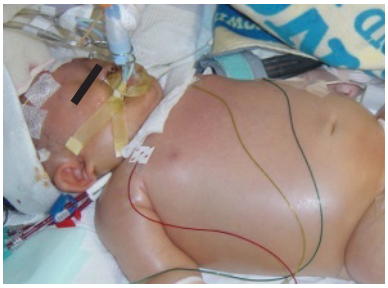


Photo 9
An 8-month-old girl with fulminant hepatitis being treated in the ICU

It is incredibly difficult to decide whether a patient with fulminant hepatitis needs a liver transplant. The decision is made by the clinical pathology department after discussing the findings from a liver biopsy with other departments. It is essential to avoid unnecessary liver transplantation. When liver necrosis occurs in children with fulminant hepatitis, the liver appears small and red (Photo 10).

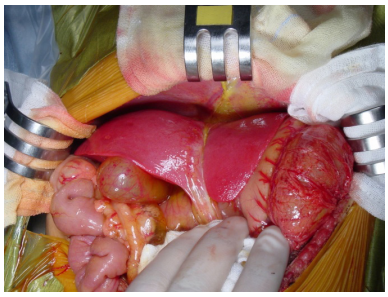


Photo 10
The atrophic liver of a 4-month-old boy with fulminant hepatitis

Liver transplantation for fulminant hepatitis often sparks severe rejection responses that are extremely difficult to treat.

For this reason, a 40% survival rate immediately after liver transplantation has been reported for fulminant hepatitis patients younger than 1 year. At the NCCHD, however, the efforts of our various departments have led to a relatively good survival rate of 90%.

3 History and current state of liver transplantation

The history of liver transplantation is relatively short, as the first transplant was performed by Thomas E. Starzl and colleagues in the United States in 1963. On March 1 of that year, a liver transplant was performed on a child (a 3-year-old boy with biliary atresia) for the first time. The donor was another 3-year-old child who had died during surgery for a brain tumor. Unfortunately, the recipient also died during the surgery. The news reports at the time covered the operation harshly. However, as the initial difficulties were gradually overcome by better surgical techniques, organ storage methods, immunotherapy, and perioperative care, the outcomes of liver transplantation improved dramatically. In the United States, about 6,000 deceased donor liver transplantations are now being performed each year, and the procedure is an established form of medical care.

1963	World's first liver transplant performed in the United States (by Dr. Thomas E. Starzl)
1989	First living-donor liver transplant performed in Shimane, Japan (by Dr. Naofumi Nagasue)
1990	Kyoto University and Tokyo University start performing living-donor liver transplantations
1997	Organ Transplant Law goes into effect
2004	Health insurance starts covering living-donor liver transplantations
2008	Declaration of Istanbul
2009	Organ Transplant Law revised

Table 1. History of liver transplantation

In Japan, the first living-donor liver transplant was performed on November 13, 1989, by the Shimane Medical University Faculty of Medicine on a child with biliary atresia. In October 1997, the Organ Transplant Law permitting deceased donor liver transplantation came into effect. Japan's first deceased donor liver transplant was performed on February 28, 1999, at Shinshu University. However, deceased donor liver transplantations remained exceedingly rare in Japan until 2006. The annual number performed nationwide did not even reach double digits. This caused a variety of ethical problems, encouraging people to go overseas and to purchase organs for deceased donor liver transplantation. In response to international criticism, the Transplantation Society issued the Declaration of Istanbul in 2008. The latter sought to restrict the practice of going to other countries for transplants, to ban the selling of organs, and to promote deceased donor transplants within national borders.

On July 13, 2009, the Japanese government revised the Organ Transplant Law to allow brain death to be recognized as a form of human death regardless of age, and enabled organ donations from deceased donor patients with the family's consent. Since the revision of the law, about 60 deceased donor organ transplants have been performed every year in Japan. The first deceased donor liver transplant was performed at our Center on August 29, 2010. By the end of 2016, we had performed 22 deceased donor liver transplantations. We have performed the highest number of deceased donor liver transplantations on child recipients of all institutions in Japan. In most cases, livers from adult deceased donors are split before being transplanted into child recipients. Although we have only performed a small number of deceased donor liver transplantations on children, we strive to pass on the baton of life to children with liver diseases while respecting the donors who have passed away from brain death.

4 Liver transplant surgery

Although humans only have one liver, it can be divided (Figure 3). While a liver that has been excised does not necessarily regain its original shape, it does regenerate. Therefore, excision is not a problem as long as it is done carefully. Up to 75% of the human liver can be excised safely. However, to guarantee the donor's safety, we do not excise more than 65%.

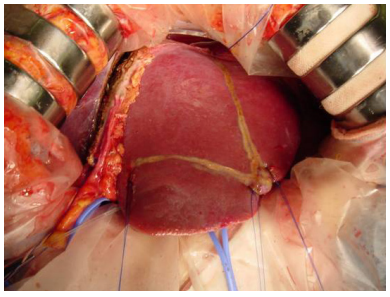


Photo 11
Part of a liver excised from a living donor

In living-donor liver transplants, we use a part of a healthy adult's liver (Photo 11).

At the NCCHD, a parent usually serves as the living donor. Anyone who is healthy and fulfills certain medical criteria for transplantation can become a voluntary donor. The amount excised from the liver during living-donor surgeries depends on the recipient's physique. For small children, about 20% of the living donor's liver is excised, while around 60% is needed for larger children.

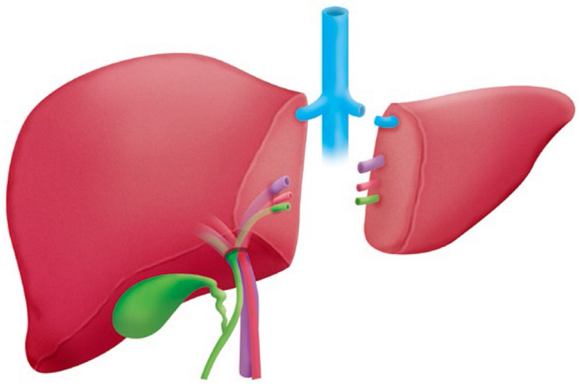


Figure 3. Split-liver transplantation
When the liver of an adult donor is divided, the smaller section on the left goes to a child recipient, while the larger section goes to an adult recipient.

5 Number of liver transplantations and their results

About 100 to 120 living-donor liver transplantations are performed on children in Japan each year (Figure 4). The NCCHD started performing liver transplantations on November 18, 2005. The hospital reached 100 transplants in August 2009, 200 in May 2012, 300 in October 2014, and 400 in April 2016. We currently perform about 70 pediatric liver transplantations per year, or about 70% of the totals number in Japan. We also perform the largest number of pediatric liver transplantations in the world. In the future, we hope to increase our rate to around 100 per year.

About three-quarters of the children who come to the NCCHD are from the Kanto region. However, we also see patients from all over Japan, from Hokkaido in the north to Okinawa in the south.

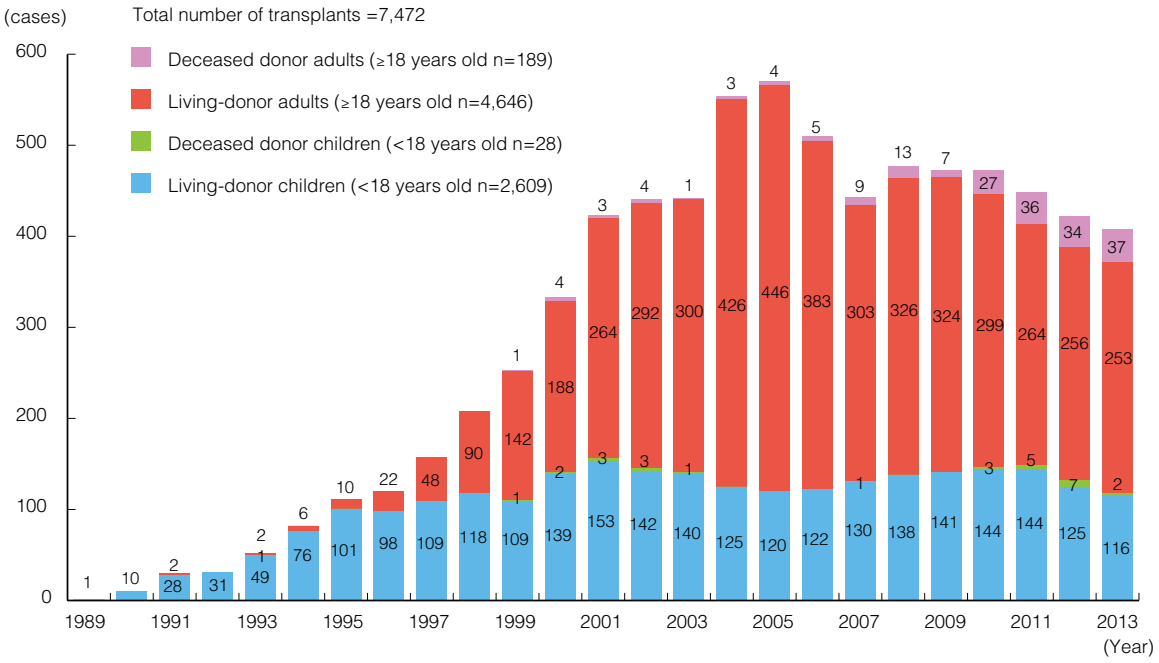


Figure 4. Number of liver transplantations in Japan (based on the Japan Liver Transplantation Society totals from 1989 to 2013)

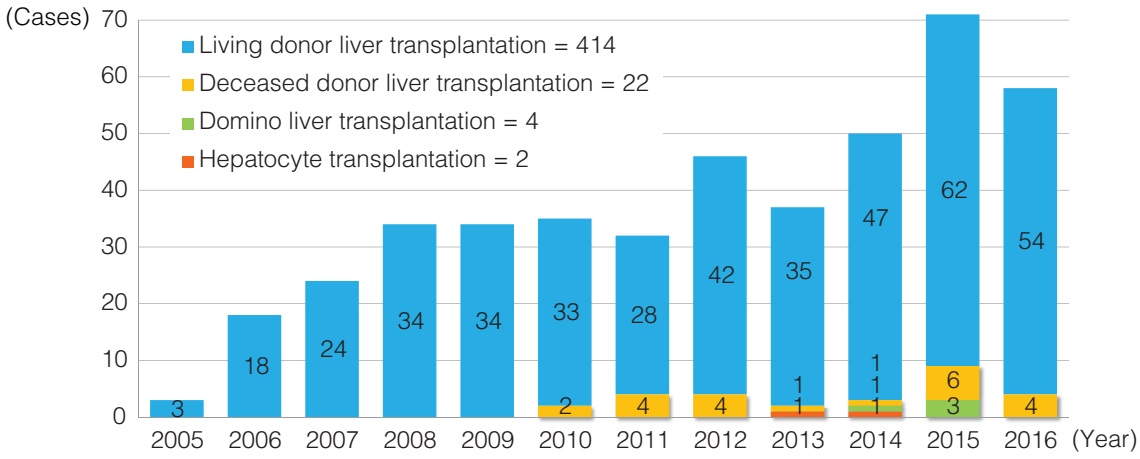


Figure 5. National Center for Child Health and Development, Center for Organ Transplantation Number of liver transplantations and hepatocyte transplantations Total: 442 cases (2005/11 – 2016/12)

Japanese children who live overseas also come to our Center for transplants. These patients often come with their families and stay in Japan for several months. We have also performed liver transplantations on children from Egypt, Indonesia, The Philippines, Taiwan, Russia, China, Korea, Mongolia, and the United States.

In December 2016, we reached 5-year patient survival rates of 91.8%/92.9% for LDLT/ DDLT at the NCCHD (Figure 6). These results were comparable with those of outstanding liver transplant institutions in the United States of America, the United Kingdom, other European countries, and Asia.

Pediatric liver transplantation	No. of cases		Patient Survival rates (%)						
			1 yr	3 yrs	5 yrs	10 yrs	15 yrs	20 yrs	25 yrs
Nationwide registry*	LDLT	2,897	89.4	87.8	86.8	84.4	82.6	80.9	79.6
NCCHD**		413	93.5	92.2	91.8	89.9	-	-	-
Nationwide registry*	DDLT	43	81.0	81.0	81.0	81.0	81.0	-	-
NCCHD**		14	92.9	92.9	92.9	-	-	-	-

* Japanese Liver Transplantation Society (1989-2015/12)
** National Center for Child Health and Development (2005/11-2016/12)

Figure 6. Patient survival rates for pediatric liver transplantation

Our transplant team has the youngest average age and is the smallest in the world. Nevertheless, we maintain the world's largest pediatric liver transplant program.

The liver transplant program at the NCCHD presents the following characteristics.

1. Many of the children referred to the Center have rather severe liver diseases that need systemic management. A high proportion of our children patients have fulminant hepatitis.
2. Many of the children are infants who experienced liver failure soon after birth.

3. We perform liver transplantation for rare diseases that are not treated with transplants at other institutions.
4. We make small donor incisions.
5. Our operation times are relatively short.

Our operations on liver transplant recipients last an average of 8 hours 30 minutes. As the Center's operation staff work extremely well together, our surgeries are about half as long as the national average. In September 2008, we switched to a method that creates a straight horizontal wound of about 10 to 12 cm on the donor. In some donors, we can excise the liver with a wound of only about 10 cm.

Photo 12
Liver transplant surgery

Thanks to the efforts of the physicians who came before us, liver transplantation has become a reasonably safe form of medical care. The department of transplant surgery staff strive every day to reach a 100% success rate. We will continue to work as one to ensure that the transplantations we perform are successful 100% of the time.

Mureo Kasahara
Director, Organ Transplantation Center
National Center for Child Health and Development

2 Indications for liver transplantation

While the liver has strong regenerative powers, it cannot return to a healthy state once it has been severely damaged. The same is true for minor damages that occur repeatedly over a long period of time. If the liver function is poor from the start, minor damages can cause it to stop functioning. We explain when liver transplantation is necessary for the diseases below, and when this type of therapy is difficult.

1 Liver diseases with disrupted bile flow (biliary atresia, Alagille syndrome)

Bile is an essential substance that breaks down the fat contained in food and beverages into small pieces easily absorbable by the intestine. It is produced in the liver and flows into the duodenum through the bile ducts. However, when this flow is disrupted, e.g. when the bile ducts are obstructed, too narrow, or too few, the excess bile gradually damages the liver cells. This causes fibrosis of the liver, which can turn into cirrhosis and prevent the liver from functioning properly.

In addition, the acids contained in bile can stimulate the peripheral nerves, causing itching.

Biliary atresia is one of the most common diseases involving a disrupted bile flow (Figure 1). In this disease, the biliary tract loses its ability to transport bile at birth, or a little before birth. With nowhere else to go, the bile flows from the liver into the blood and damages the liver. This causes cirrhosis of the damaged liver, which in turn increases the pressure in the portal veins that bring nutrients to the liver.

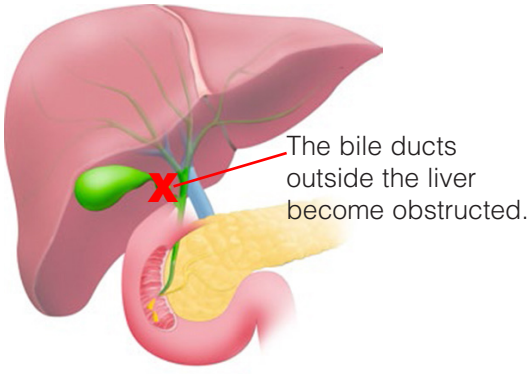


Figure 1. Biliary atresia

When biliary atresia is discovered, surgery is performed to create a pathway for the bile to flow from the liver to the intestines (i.e., the Kasai procedure). However, this is only a partial solution, and the cirrhosis can continue to progress, albeit at a slower pace. In addition, after surgery, the bacteria can flow in a retrograde direction from the intestines to the liver and cause a complication called cholangitis. For more details on biliary atresia, see "2-1 Understanding the liver and liver transplantation" and "2-4 Liver transplantation and pathological diagnosis."

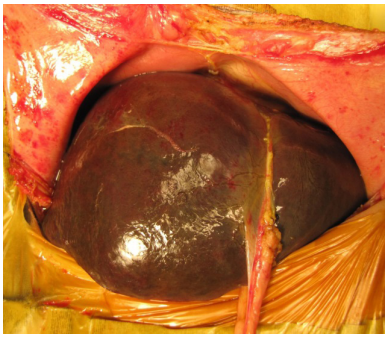


Photo 1 Alagille syndrome
In this disease, hypoplasia of the bile ducts in the liver disrupts the bile flow. The fibrosis is usually less severe than in biliary atresia.

In addition, abnormalities in the genes that contain codes for the building of the bile ducts can limit the number of bile ducts. This can lead to Alagille syndrome, a disease that causes jaundice.

As implied by the word "syndrome," this disease causes symptoms not only in the liver, but also in areas including the blood vessels, spine, and eyes, with different individuals exhibiting different symptoms. The small number of bile ducts in the liver associated with Alagille syndrome slows down the bile flow. If this leads to cirrhosis, the situation may require a liver transplant, as in biliary atresia.

[Times when a liver transplant is needed]

- When the child stops growing or gaining weight
- When the jaundice is not expected to improve
- When major hemorrhage, e.g. from vomiting blood or from blood in the stool, seems likely
- When the portal venous flow gets worse
- When cholangitis occurs repeatedly (such as when jaundice worsens or the patient cannot leave the hospital or eat)
- When symptoms of hepatopulmonary syndrome appear (low oxygen levels, clubbed finger, etc.)
- When pulmonary hypertension appears likely
- When itching is severe

Hepatopulmonary syndrome occurs when the liver disease causes low levels of oxygen in the blood. There is usually nothing inherently wrong with the heart or lungs, but the liver disease somehow causes the capillaries in the lungs to dilate, which increases the amount of blood in the pulmonary alveoli. In hepatopulmonary syndrome, the proper balance between the amount of air inhaled and the amount of blood flowing to the alveoli is disrupted, and the amount of air taken in is insufficient to match the increased blood flow. This makes it difficult for children to stand up, walk, climb stairs, and play. They find moving difficult, get tired easily, and are sluggish. In addition, their fingertips become thicker than the rest of their fingers and appear round, a condition called clubbed finger.

If the increase in the blood flow to the lungs persists, it can damage the walls of the blood vessels in the lungs, and cause them to thicken and harden. This causes the lumen of the vessels to narrow, leading to a condition called pulmonary hypertension that is not favorable to oxygenation. In children with cirrhosis, the liver does not manufacture albumin properly, which reduces the vessels' ability to draw in fluid, and causes the fluid to accumulate in the abdomen as ascites. The distended abdomen puts pressure on the chest, which prevents the lungs from expanding fully. This also causes breathing difficulties, albeit through a different mechanism than that involved in hepatopulmonary syndrome.

2 Acute liver failure (fulminant hepatitis) and hyperammonemia

Of all the diseases in this Handbook, if the reader is in the midst of urgent circumstances, it is probably due to this one. In many cases, life is normal until the symptoms suddenly appear within a few days. After going through examinations at several hospitals, families are told that a liver transplant may be necessary, and they scramble to learn about the disease and why it calls for a transplant.

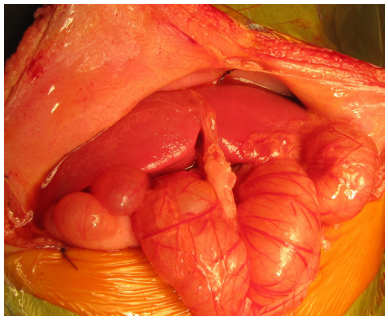


Photo 2
Acute liver failure

Acute liver failure occurs when the liver stops functioning. This can happen for many reasons, although the cause is often unknown. The condition often leads to severe hepatitis, with the liver cells disappearing almost as if the liver were dissolving. This disease often affects infants, and becomes rare once children reach school age. Table 1 shows the most common types of fulminant hepatic failure (see below).

This disease has a common clinical picture regardless of the cause. Hepatic encephalopathy is the most serious problem.

The liver is responsible for the metabolism, energy storage, the detoxification of harmful substances, and bile production. Although all are important functions, the effects on the body are particularly adverse when the ability to process and excrete harmful substances is damaged. A typical sign of this is hepatic encephalopathy,

which is a consciousness disturbance caused by the liver. The amino acids that are not used by the body are broken down by the liver, which converts them into ammonia (which is harmful to the body), and subsequently into urea (which is not harmful) to be excreted. If this process is impaired, the level of harmful ammonia in the blood increases, and this can lead to consciousness disturbances. The latter manifest in a wide variety of ways, from symptoms such as restlessness and absentmindedness to severe conditions such as unresponsiveness and comatose states.

Diseases often seen in newborns up to infancy

- Urea cycle disorders
- Methylmalonic acidemia
- Viral infections
  - Herpes simplex virus
  - Enterovirus
- Neonatal hemochromatosis
- Mitochondrial hepatopathy
- Citrin deficiency
- Progressive familial intrahepatic cholestasis
- Congenital bile acid synthesis defect
- Infantile fulminant hepatitis of unknown cause

Diseases often seen in and after infancy

- Hemophagocytic lymphohistiocytosis
  - Epstein-Barr virus
- Wilson's disease
- Autoimmune hepatitis
- Fulminant hepatitis of unknown cause

Table 1. Diseases that can cause acute liver failure (fulminant hepatitis) or hyperammonemia

Along with hepatic encephalopathy, coagulation disorders are another major problem. Under normal circumstances, when bleeding occurs, a large number of proteins (which are coagulation factors) organize to stop the bleeding. If the liver cannot produce these important proteins, the blood has difficulty solidifying to stop the bleeding, causing a coagulation disorder.

When both a coagulation disorder and hepatic encephalopathy are present, the condition is called fulminant hepatitis. A state of reduced liver function combined with a coagulation disorder that appears likely to turn into fulminant hepatitis is called acute liver failure. A situation with no coagulation disorder but with hyperammonemia caused by reduced liver function is also an emergency.

For more details on acute liver failure, see "2-1 Understanding the liver and liver transplantation" and "2-4 Liver transplantation and pathological diagnosis."

Congenital metabolic disorders often occur at the neonatal stage, as newborns lose the support they were receiving from their mother through the placenta. The metabolism is a way for the body to both create the molecules it needs and to break down unnecessary or harmful molecules. When milk, rice, vegetables, fish, and other food are consumed, they need to be transformed into structural elements of the body. The metabolism supports this process.

The metabolism also works in the background to help the body acquire nutrients and excrete urine and stool. There are many kinds of congenital metabolic disorders, some of which require a liver transplant.

Urea cycle disorders arise when the metabolic mechanism that breaks down unnecessary amino acids is disrupted. Normally, amino acids are metabolized into urea in the liver, and are then excreted by the kidneys as urine. This disease

causes problems with this process, leading to a large amount of harmful ammonia. There are several types of urea cycle disorders, including OTC, CPSI, ASS, ASL, and NAGS.

Methylmalonic acidemia is often discovered when a child is constantly tired or when hyperammonemia is detected. Although this condition does not necessarily lead to acute liver failure, the symptoms are problematic.

Mitochondrial hepatopathy is found when acute liver failure occurs due to problems with the liver mitochondria, which use oxygen to manufacture energy. There are several different types, including MPV17 and DGUOK.

Citrin deficiency is another mitochondrial disorder. It appears when the liver function declines due to a lack of protein citrin in the inner mitochondrial membrane. In severe cases, this can lead to acute liver failure.

A congenital bile acid synthesis defect arises when the bile acids that make up the bile cannot be synthesized properly. In this disease, the bile acids destroy the liver, which can also cause acute liver failure.

Wilson's disease is present when copper gradually accumulates in the body. It occurs after children reach school age. As there are few subjective symptoms, the disease is sometimes only discovered when acute liver failure occurs.

Many other diseases can cause acute liver failure.

Among viral infections, the herpes simplex virus causes an infection that leads to canker sores in the mouth or numerous small vesicles around the mouth in adults. Although it is a common virus, in some newborns it can lead to a serious infection called neonatal herpes that may cause acute liver failure.

Neonatal hemochromatosis is a form of cirrhosis observed in newborns that can occur in subsequent siblings. It is often discovered through the presence of jaundice or coagulation disorders, but can also be detected by metabolic screenings of newborns.

Progressive familial intrahepatic cholestasis type 2 involves problems with the protein BSEP, which transports the bile components. Acute liver failure can occur when bile secretion is severely reduced.

Hemophagocytic lymphohistiocytosis involves excessive immune activity triggered by a birth-related factor. This disease can cause severe hepatitis even in newborns. Infections from the Epstein-Barr virus resembling the neonatal herpes described above sometimes occur.

Autoimmune hepatitis occurs when for some reason the body itself attacks the liver, thereby causing hepatitis. Its acute form can lead to liver failure.

As the above shows, severe hepatitis can cause acute liver failure due to causes both known and unknown. Some of these causes are thought to involve unknown metabolic disorders or excessive immune activity. Even when the cause of the acute liver failure is known, the range of medical therapies is limited.

In severe cases, liver transplantation may be the only option. This is why many children with acute liver failure or hyperammonemia are referred to our Center.

[When to perform a liver transplant]

- When the liver is atrophied, with massive ascites
- In other situations, when the liver is unlikely to recover
- When cerebral edema appears likely to occur (hepatic encephalopathy that is expected to improve)

3 Congenital metabolic disorders

This covers a wide variety of diseases, including neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD), OTC deficiency, and Wilson's disease. In OTC deficiency (Photo 3), the liver can appear normal, but the restricted protein intake can lead to severe fatty liver. For more details on metabolic liver diseases, see "2-1 Understanding the liver and liver transplantation." The timing for the performance of a liver transplant depends on the disease. The following are some common principles.

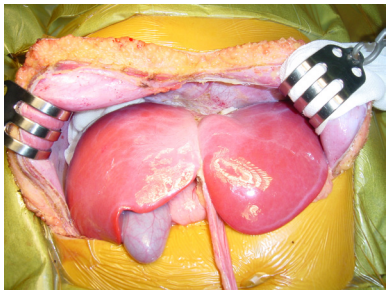


Photo 3 OTC deficiency
The liver in a case of OTC deficiency. Protein restrictions prior to surgery can cause fatty liver, although the liver often appears healthy.

[When to perform a liver transplant]

- When a child stops growing or gaining weight
- When dangerous hyperammonemia, acidosis, or other risky conditions occur or appear likely to occur
- When acute liver failure occurs
- When the quality of life declines due to severe dietary or other restrictions
- When infections occur repeatedly

4 Hepatic fibrosis

This disease is often accompanied by kidney disease. The timing of a liver transplant should be decided after a comprehensive evaluation. Most children who receive liver transplantation at our Center have autosomal recessive polycystic kidney disease. Despite being called a "kidney disease," it is characterized by concomitant hepatic fibrosis. Depending on the child's condition, a liver transplant is sometimes performed before a kidney transplant. Due to its long name, the disease is usually referred to by its acronym, ARPKD.

When a blood vessel ruptures and bleeding occurs, platelets gather to clog the hole. However, in advanced hepatic fibrosis, the number of platelets produced by the bone marrow declines, and

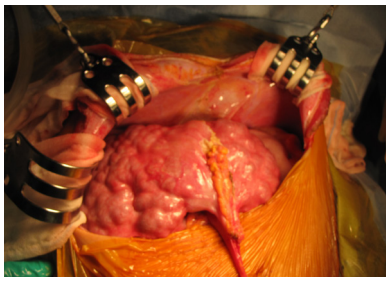


Photo 4 Hepatic fibrosis
The liver exhibits severe fibrosis and nodules on the surface. The complicating presence of kidney dysfunction makes immunosuppressant therapy after the transplant extremely important.

the number of those damaged increases. Thus, there is an overall reduction in the number of platelets.

[When to perform a liver transplant]

- When major hemorrhage, e.g. from vomiting blood or blood in the stool, may occur
- When symptoms of hepatopulmonary syndrome appear (low oxygen levels, clubbed finger, etc.)
- When it seems like pulmonary hypertension might occur

5 Cases that cannot be operated on

Liver transplantation is not always indicated for all liver diseases. First, the child must be able to withstand general anesthesia throughout the surgery. Moreover, the operation must be expected to lead to improvement. Cases that cannot be operated on are often characterized by the following.

- Septicemia
- Problems with the lungs or heart (e.g., heart failure, pneumonia, etc.)
- Severe pancreatitis
- Irreversible cerebral edema (hepatic encephalopathy, etc.)

Different children need liver transplantations for different reasons. Therefore, it is best to ask for a detailed explanation from the attending physician. While liver transplantation might not be the best choice for every child's disease, our job in the Department of Internal Medicine is to make sure that your child is in the best possible condition.

Reiko Ito
Department of Internal Medicine and Hepatology
National Center for Child Health and Development

3 Liver diseases and genetics

Families of children who received transplants often have questions related to heredity, such as, "Will our next child have the gene for this inborn disease?", "We were told it's a genetic disease. Why did it happen?", and "If our child has children, will they be fine?".

1 Liver transplantation and genetics

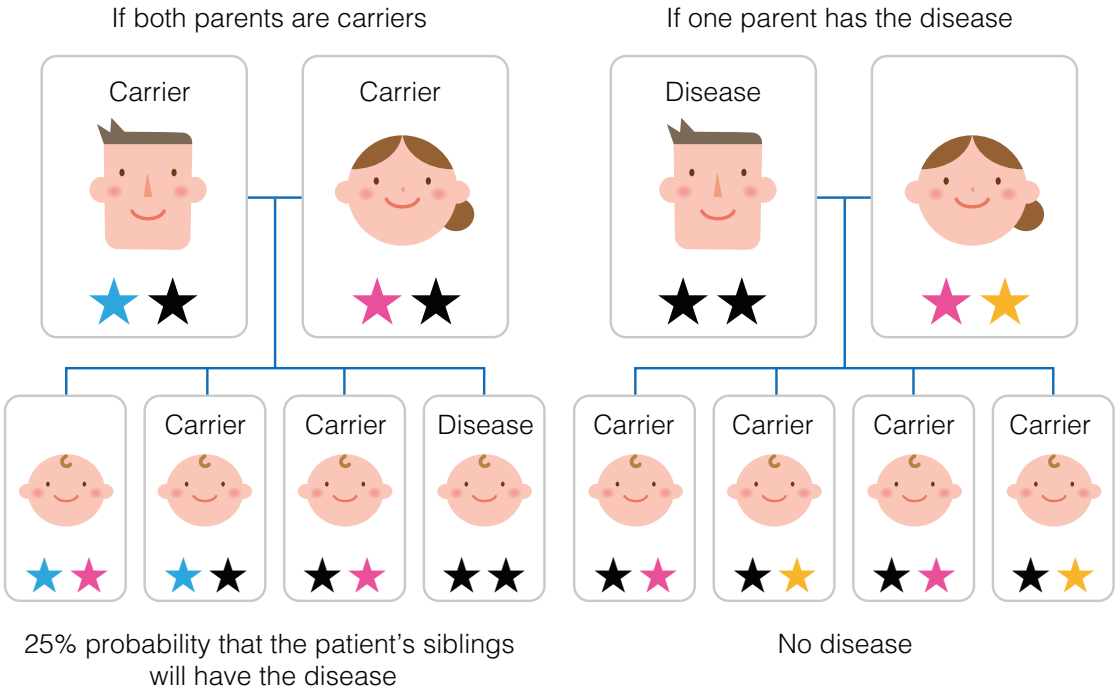
Diseases that require liver transplantation have a variety of causes, some of which involve genetics. Genes play a role in diseases that present abnormalities

in the body's ability to detoxify ammonia and other substances that accumulate in the body (metabolic liver diseases) or abnormalities in the liver's ability to discharge bile (cholestatic liver diseases).

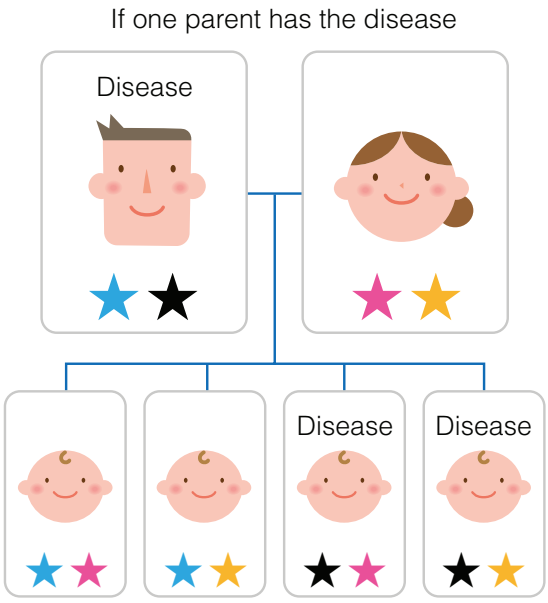
Abnormal gene functions are believed to be involved in the onset of these diseases. Depending on the gene, the same disease may be found in your next child or in your treated child's children. In other cases, there is nothing to worry about. While it is sometimes known what gene or genes are responsible, the cause is unknown in many cases. Therefore, no predictions can be made about genes.

Diseases involving genetics are broadly divided into three categories: autosomal recessive diseases, autosomal dominant diseases, and X chromosome-linked diseases.
The terms "recessive" and "dominant" do not imply anything about the inferiority or superiority of one's genes.

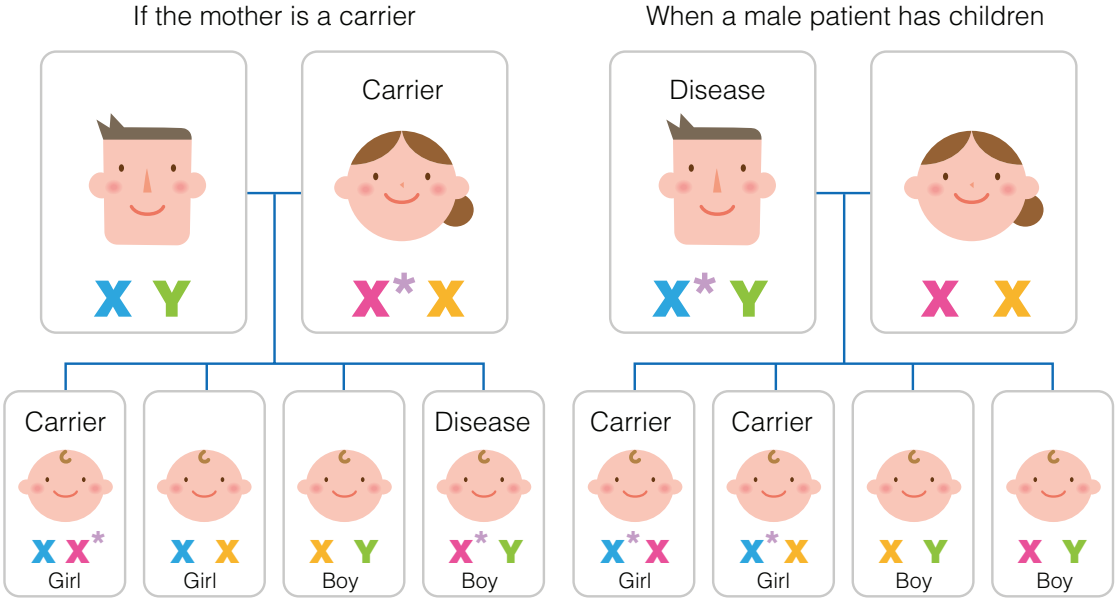
- In autosomal recessive diseases (e.g., Wilson's disease, methylmalonic acidemia, propionic acidemia, glycogen storage disease, carbamoyl phosphate synthetase deficiency, citrin deficiency, progressive familial intrahepatic cholestasis, etc.), there is a 25% probability that the patient's siblings will have the same disease. The probability that any of the patient's children will have the disease is nearly zero.



- In autosomal dominant diseases (Alagille syndrome, etc.), there is almost no risk that the patient's siblings will have the same disease, unless both parents have the disease (spontaneous mutation). If the patient becomes a parent, there is a 50% probability that his or her child will have the same disease.



- X chromosome-linked diseases (ornithine transcarbamylase deficiency) affect boys. Even if a girl has a genetic mutation (carrier), she will sometimes be asymptomatic. The probability that the next child will have the disease depends on whether the mother is a carrier or not. If she is, there is a 50% chance that a male child will have the disease. As a rule, any daughter born to a male patient will be a carrier.



The gene for the disease is on the X chromosome.

As men only have one X chromosome, if there is a mutation, the disease occurs.

As women have two X chromosomed, even if one chromosome has the gene for the disease, the other will compensate and the disease may not occur (but the woman will be a carrier). The disease can occur depending on the enzyme activity in the liver.

2 Genetic testing

If the gene that caused a disease is known, it is theoretically possible to investigate whether your child's symptoms are due to genetic changes – a process

known as genetic testing. However, these are highly specialized tests. It is not possible to investigate the genes involved in all liver diseases, and only a limited number of companies and institutions around the world are capable of conducting genetic tests. In many cases, this type of testing is carried out as part of research at universities and institutes.

Cost: Testing is not covered by insurance. The cost can vary from several tens of thousands of yen to several hundred thousand yen.

Time: The amount of time it takes to receive the results depends on the gene. It usually takes from one or two months to half a year, and sometimes longer.

Testing: Genetic tests search for differences between the DNA of a sick person and the standard DNA of a person without the disease. As there are approximately 25,000 types of genes, the test usually looks for one or a few genes that appear to be related to the patient's symptoms. As even healthy people have different DNAs, finding a difference between the patient's DNA and a standard sample does not necessarily mean that the cause of the disease has been found. A specialist needs to make this assessment. The genetic changes that cause diseases are called mutations or abnormalities. The technological limitations of these tests mean that even when the clinical diagnosis is correct, a genetic mutation is not found more than 30% of the time. The absence of mutations does not mean that a patient has normal genes, and it does not mean that you should worry about having received an incorrect diagnosis.

As genetic mutations are sometimes not found even when the diagnosis is correct, it is best to test the patient before the parents. Based on the results, it may be appropriate to test the parents. The prior identification of a child's genetic mutations will often save both time and money when testing the parents for the same mutations.

To test whether your next child will have the same disease, the enzyme activity in the pregnant mother's amnionic fluid can be measured, or genetic testing can be carried out to investigate the health of the fetus. As genetic testing takes a considerable amount of time, the genetic mutations of the child with the disease need to be identified before you become pregnant.

While a great deal of information on genetics is available on the internet, each family's situation is different. The NCCHD's Division of Medical Genetics is available to answer any of your questions or concerns about genetics in specialized consultations (please note that these consultations are not covered by health insurance). Our clinical geneticists can provide information on DNA, genetics, and other difficult topics in an accessible manner. If you would like to book a consultation, please speak with your doctor.

Rika Kosaki
Division of Medical Genetics
National Center for Child Health and Development

4 Liver transplantation and pathological diagnosis

1 Introduction

Pathologists perform cytodiagnoses, histopathological diagnoses, and pathological autopsies. For instance, in uterine cancer screenings or endoscopic stomach and intestinal exams, pathologists are the ones who look at cells and tissues under microscopes and make the final diagnosis. Although we work in hospitals just like physicians and surgeons, most patients never meet a pathologist, so they often do not know what we do. During liver transplant surgeries, we perform pathological diagnoses on the part of the liver that is removed from the donor and on the recipient's liver and gallbladder. After the transplant, we perform pathological diagnoses to check for rejection, infections, post-transplant lymphoproliferative disease, and other issues. If a patient dies, another important job of the pathologist is to perform an autopsy. We examine all the organs to discover what happened in the patient's body, investigate the reactions to the therapy and other issues, and determine whether the treatments were effective.

2 Transplant indications

Liver transplantation is indicated for a wide variety of diseases, including biliary atresia (Photo 1), congenital metabolic diseases, and liver tumor. Pathologists examine the tissue of the liver to determine the degree of fibrosis (is there cirrhosis?), the cause of jaundice, and the type and malignancy of any tumors.

A healthy liver　　A liver with biliary atresia

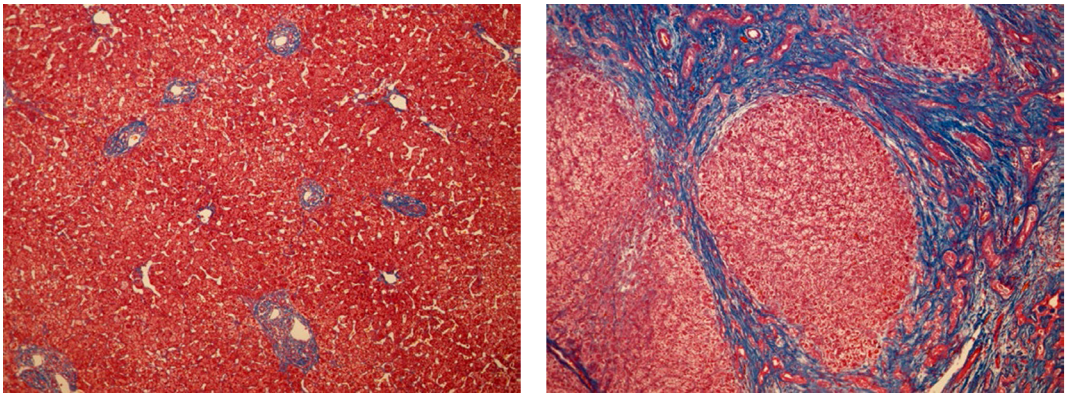


Photo 1 Liver with biliary atresia
The liver shows severe fibrosis (blue) indicating cirrhosis. The red areas are liver cells. There are fewer of them than in the healthy liver on the left.

The cause of fulminant hepatic failure (Photo 2) is often unknown. In this disease, the extremely poor liver function reduces the blood's ability to coagulate. Despite this limitation, at the NCCHD, we perform liver biopsies whenever possible to search for a cause and to investigate the reasons why a transplant may

be impossible to perform (i.e., be contraindicated). These reasons can include sepsis or lymphoma. One of the tensest duties of a pathologist is the liver biopsy performed immediately before the transplant surgery. Since the result of this biopsy is used to decide whether to perform the transplant, we cannot afford to oversee a disease that would contraindicate the transplant. As the diagnosis has to be made quickly, pathologists focus extensively on the examination of specimens under their microscopes.

A healthy liver

A liver with fulminant hepatic failure

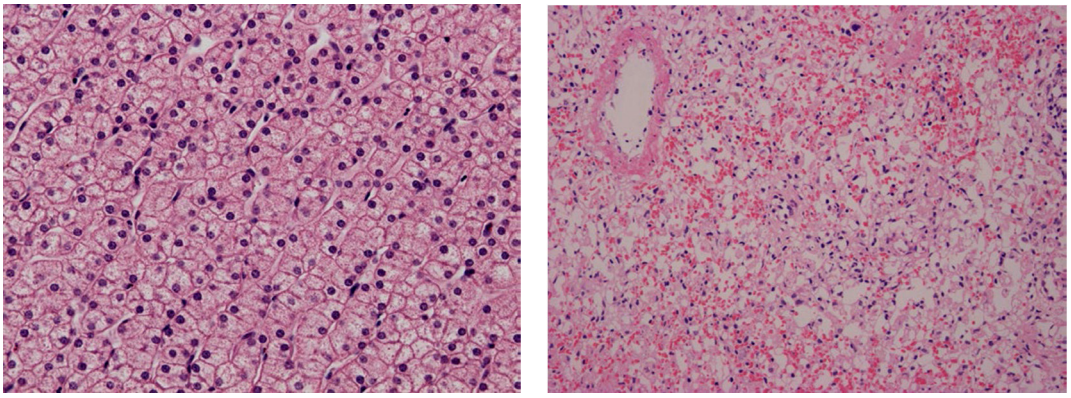


Photo 2 Liver with fulminant hepatic failure

In the healthy liver on the left, the liver cells are arranged in a closely packed, cordlike manner. In the liver with fulminant hepatic failure, almost all of the liver cells have disappeared and have been replaced by macrophages.

Several biopsies are performed to examine the tissue before the transplant, and if the liver cells are found to be regenerating, a transplant can sometimes be avoided. In cases of fulminant hepatic failure, tissue specimens are collected from several parts of the recipient's liver for rapid diagnosis before the transplant. While it usually takes two days to create paraffin embedded sections, in rapid diagnosis, the tissue is frozen to make sections within about 10 minutes. The samples are then examined under a microscope and discussed by the members of the transplant assessment committee to reach a final decision about whether or not to carry out the transplantation.

3 Donor's liver and recipient's liver

A "zero biopsy" is obtained from a part of the donor's liver. (When counting the number of days since the transplant surgery, the day of the surgery is day 0, which is when this biopsy is performed.) The liver is called the "silent organ", as abnormal pathologies of the liver can sometimes be found even when blood tests show no abnormality. The zero biopsy is performed to look for signs of fatty change and other hidden diseases.

After the recipient's liver is removed, it is brought to the pathology lab, where pathologists perform macroscopic observations, take images, and measure its weight and size (Photo 3). If consent is given to collect liver cells, the liver is split

and liver cells are extracted in another laboratory. Tissue specimen is collected for cell cultures. The liver is divided into 1-cm slices, and tissue samples are taken from it – usually from the right lobe, the left lobe, and the hilar area – and used to create paraffin sections. Pathologists need to be able to make diagnoses with their naked eyes. While dividing the liver, samples are taken from any area of even slight abnormality to create paraffin sections for pathological diagnosis. The tissue specimen is also frozen for the performance of genetic diagnoses and other tests, and tissue specimens are prepared for electron microscopic examinations. These tissue specimens are not only used for pathological diagnosis, but also kept to perform subsequent research into disease causes and treatments. The paraffin blocks that the pathological specimens are embedded into can still be used after one hundred years.

Photo 3
Examination of a liver removed from a recipient

4 Rejection

Another tense task for pathologists is the performance of diagnoses from liver biopsies when the liver functions deteriorate after a transplant. The liver biopsies collected after the transplant are examined to look for acute cellular rejection, antibody-mediated rejection, septic cholangitis, hepatic veno-occlusive disease, and other problems.

Since the treatment plan depends on the diagnosis, professional pathologists examine liver biopsy specimens in the same way as transplant surgeons examine patients. To determine what is happening in the patient's body, we consider the pathological findings together with the clinical findings for ascites, jaundice, and other symptoms, and the blood, imaging, and other test results. Post-transplant biopsies are performed with fine needles that collect tissue from the transplanted liver. These tiny tissue samples are the tools used by pathologists to explain a patient's condition. The immunosuppressants used after liver transplantation create an unusual mix of pathologies, making it incredibly risky for pathologists to make decisions alone. At the NCCHD, transplant surgeons and pathologists look into the microscope together, and decide on a diagnosis after discussing the case (Photo 4).

Rejection is a worrisome condition for patients and their families (Photo 5). The diagnosis of rejection is one of a pathologist's biggest responsibilities.

Photo 4
The entire staff looks at the microscopic findings to reach a pathological diagnosis.

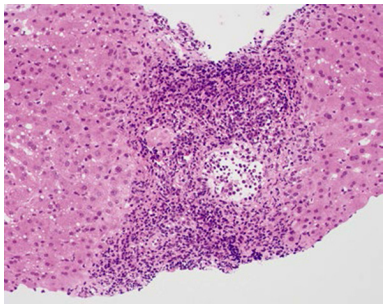


Photo 5 Liver tissue with acute cellular rejection
The portal area in the middle shows severe infiltration by lymphocytes and eosinophils. These are the recipient's lymphocytes attacking the donor's liver.

There are acute and chronic types of rejection. If either form worsens, it can cause the transplanted liver function to deteriorate. Therefore, rejection needs to be diagnosed early.

If a patient's symptoms or blood test results indicate rejection, a transplant surgeon inserts a fine needle into the liver to take a 15-20 mm-long and about 1 mm-wide tissue sample. The tissue section from this "needle biopsy" is sliced to create thin sections that are subjected to a pathological diagnosis to determine whether rejection is occurring. After the tissue collection, the sections can be created within about 5 hours. The pathologists and transplant surgeons decide on a treatment plan after examining the sections through a microscope and discussing the case.

5 Opportunistic infections

After a transplant, immunosuppressant drugs are used to ensure that the transplanted liver will not be recognized as "someone else's liver" and will avoid being "rejected". As patients in an immunosuppressed state have a lower resistance to infections than healthy people do, infections that are usually almost harmless can turn into severe illnesses. These are called "opportunistic infections." After a transplant, infections from the Cytomegalovirus (CMV) (Photo 6) and Epstein-Barr (EB) virus often cause problems. Once an infection becomes severe, it is much more difficult to treat. Blood tests are used to detect viruses early on so that they can be treated right away. As the EB virus requires a thorough DNA test that cannot be performed at regular laboratories, the NCCHD's mother-child infection research laboratory operates day and night to perform these tests. The EB virus infects the lymphocytes and is known to cause lymphoma in transplant patients (post-transplant lymphoproliferative disease). However, to this day, not a single NCCHD patient has experienced lymphoma caused by EB virus infection. The pathology department's liver tissue tests for viruses and increased lymphocyte levels and the cooperation of the laboratory have contributed to reducing the incidence of complications from EB virus infections.

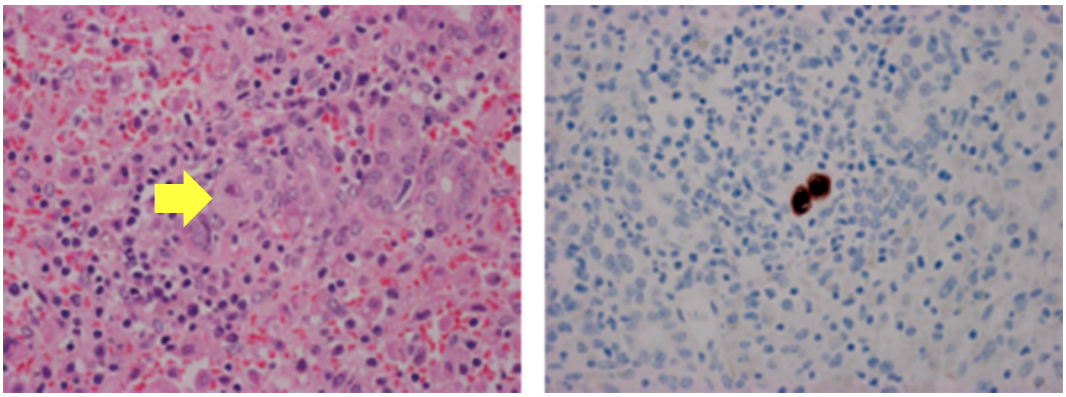


Photo 6 Cytomegalovirus (CMV) infection
Here, the CMV is infecting cholangiocytes. Deep-pink inclusion bodies (viruses) can be observed in the large nuclei. Many granular inclusion bodies (viruses) can also be seen in the cytoplasm (left). Immunohistochemical staining with anti-CMV antibodies showed the CMV in brown (right).

6 Outpatient pathological diagnosis

In April 2008, the NCCHD launched outpatient pathology visits to allow patients to talk directly to pathologists about pathological diagnoses. These consultations are sometimes attended by a transplant surgeon, a pediatrician, or a recipient transplant coordinator. Please contact us if you are interested.

The consultations are free for NCCHD patients (please talk to the doctor who handles your case in the transplant department). Patients from other institutions should apply for an outpatient second opinion consultation through the patient liaison office.

Conclusion

The information obtained from pathological diagnoses is the key to deciding what treatment to choose for your child. As pathologists, our job is to support children so that they can receive the care they need as early as possible. Pathologists and lab technicians work 24 hours a day to provide rapid and accurate pathological diagnoses.

Atsuko Nakazawa
Pathology Department
National Center for Child Health and Development

5 Liver transplantation and immunity/infection prevention

Infectious diseases are the most common risk faced by patients after transplantation. In the Department of Infectious Diseases, we try to minimize issues related to immunity and infection. Therefore, we form part of the medical team that supports the children from the preoperative stage.

1 Common infectious diseases

Immunosuppressants must be taken by patients to prevent rejection after liver transplantation. However, these drugs reduce the immune system's ability to fight bacteria, viruses, fungi, and other pathogens, thereby increasing the risk of infection. In addition, rejection, which calls for an increase in the immunosuppressant dose, can closely resemble the symptoms of an infection, which calls for a reduction in the immunosuppressant dose. The two can initially be difficult to distinguish. Moreover, as infections can occur during the treatment of rejection, it is sometimes necessary to both increase the immunosuppressant dose and to administer antimicrobial drugs. Transplant patients are susceptible to different infections at different times (Figure 1).

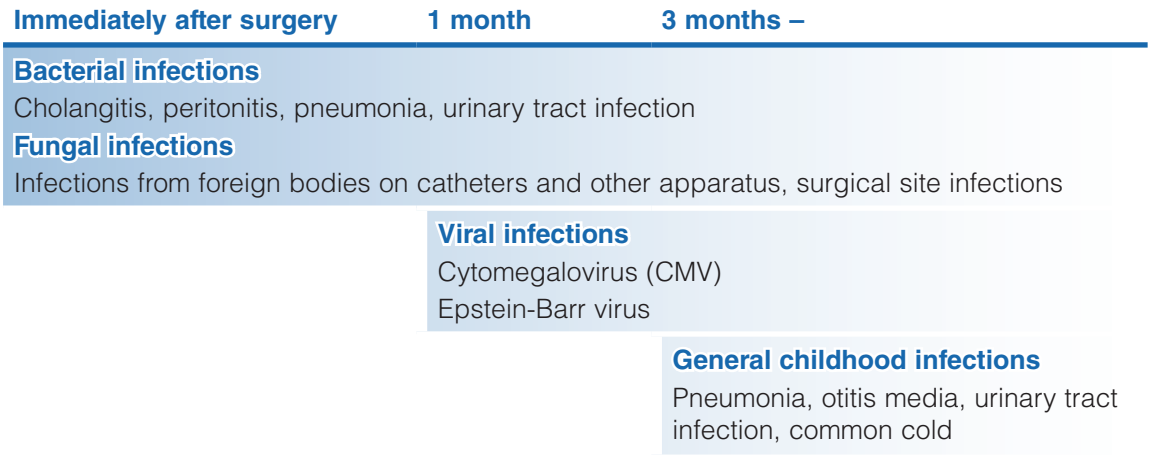


Figure 1. Onset of post-transplant infections

Immediately after surgery to 1 month later

Bacterial infections are most common during this period. They include cholangitis, peritonitis, urinary tract infections, infections from foreign bodies on catheters and other apparatus, and infections at the surgical site.

These infections can be caused by bacteria in the digestive tract, such as *E. coli*, *S. aureus*, or *P. aeruginosa*, which can become a problem when the body's resistance is lowered. These bacterial infections are treated with antimicrobial drugs. However, the long-term use of antimicrobials can lead to fungal infections such as candida. These then need to be treated with antifungal agents.

1 to 3 months after surgery

Viruses such as CMV and the Epstein-Barr virus start to present a risk about 1 month after the operation. Viruses that were already present in the body sometimes take advantage of the impaired immunity to proliferate, while other infections come from the transplanted organ itself. Regular blood tests are performed to check for CMV and the Epstein-Barr virus after transplantation. If an elevated viral load is found, the immunosuppressant dose is reduced. Although bacterial infections such as cholangitis may still occur during this period, they are less frequent than in the first month.

Furthermore, the use of immunosuppressants can lead to pneumocystis pneumonia (carinii pneumonia). To prevent this, patients are administered drugs such as Baktar®, Bactramin®, and Daiphen® for a while after the surgery.

3 months after surgery and onward

Although the frequency of infections gradually decreases, problems may still occur from bacterial infections such as cholangitis and viral infections caused by CMV, the Epstein-Barr virus, and others. In addition, transplant patients are more susceptible to common infections generally caught by all children. After leaving the hospital, patients and their families should be wary of pneumonia, otitis media, urinary tract infections, and the common cold virus. In particular, cases

of chickenpox and measles can become severe. Therefore, contact with infected people should be avoided, and a doctor should be consulted in that event.

2 Infections deserving special attention

(1) Chickenpox and herpes zoster

Chickenpox and herpes zoster are infections caused by the varicella-zoster virus. The initial infection from this virus causes chickenpox. When someone who has previously had chickenpox is in a poor condition or severely fatigued, herpes zoster may appear.

When people who take drugs to suppress the immune system after a liver transplant contract chickenpox, the symptoms are not limited to the skin, but can manifest even on the internal organs. For example, if the transplanted liver is infected or damaged, the infection can spread to other organs, such as the brain or lungs. These situations can be life-threatening. To avoid contracting chickenpox, transplant patients should avoid contact with infected people. If contact occurs, preventive antiviral drugs may be necessary.

Prevention through vaccinations is also important (see below).

How are chickenpox and herpes zoster contracted?

In herpes zoster, the virus lives in the area of eruption, so that infection can be caused by touching this area. The infected person will then experience chickenpox. People who have chickenpox can infect others from two days before the eruptions appear. Infections can be caught through the air by being in the same space, or by touching the eruptions. Herpes zoster can be passed on by touching the area of eruption. If a family member contracts herpes zoster, the eruption should be covered and the area should not be touched. Infections may also be caught through indirect contact, such as sharing bath water, using the same towel, or sleeping together. Therefore, people with herpes zoster should try to live separately as much as possible.

What to do after having contact with a person with chickenpox

If a liver transplant patient spends time around a person with chickenpox or touches herpes zoster eruptions, antiviral drugs should be administered to prevent chickenpox. If the drugs cannot be taken orally, they can be administered by intravenous drip. Immunoglobulin preparations can also be used for prevention. During chickenpox epidemics at daycare centers, kindergartens, primary schools, or elsewhere, try to find out who is infected and when the infection happened, before consulting a physician to determine whether antiviral drugs should be administered.

How long does it take for symptoms to appear after having contact with someone with chickenpox?

The disease may appear one to three weeks after the contact (latent period). If immunoglobulin preparations are used, the disease could appear up to four

weeks later. Watch carefully for fever and changes in mood or appetite. If a person is hospitalized for treatment during the latent period, he or she should be placed in a special room so as to not infect others, and should not be allowed to leave the room until the latent period ends.

Treatment for chickenpox

If a patient contracts chickenpox after a liver transplant, they usually need to be hospitalized and treated with intravenous antiviral drugs.

(2) Influenza

The use of immunosuppressants after transplantation increases the potential severity of influenza infections. Understand what measures must be taken before flu season, what to do when people around you are infected, and how to deal with infections if they occur.

What to do before influenza season: vaccinations

At the NCCHD, we recommend that patients be vaccinated for influenza about six months after the transplantation, when their liver functions and general condition have stabilized. It is recommended for the entire family, and not just the patient, to be vaccinated.

Vaccines are not 100% effective, and even healthy children who are vaccinated may contract influenza. Vaccines may be even less effective in transplant patients taking immunosuppressants. Therefore, vaccinating the whole family before the transplant reduces the risk of contact with the influenza virus.

What to do during influenza season: hand-washing, masks, gargling

Washing hands, wearing a mask, and gargling are important measures. Crowds should also be avoided during flu season. If someone close to you contracts the flu, consult your doctor about taking anti-influenza drugs for prevention.

What to do if you contract influenza: anti-influenza drugs

As the flu often resolves on its own, healthy children do not necessarily need to take anti-influenza drugs. However, it is important for transplant patients to take

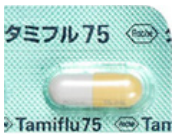
these drugs if they catch the flu. The early administration of anti-influenza drugs can prevent the infection from becoming serious.

It is important to check the patient's overall condition and whether he or she is eating and drinking. Depending on the severity of the infection, hospitalization may be necessary.

Anti-influenza drugs

Tamiflu® (oseltamivir)

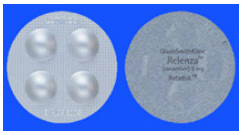
Dosage form: capsule, dry syrup
Regimen: therapeutic – twice per day for 5 days
preventative – once per day for 10 days



This drug is usually not used until 1 year of age, but is sometimes given to younger children. There have been reports of abnormal behavior after taking this drug in children aged 10 to 19 years. Therefore, as a rule, it is not very recommended for this age group.

Relenza® (zanamivir)

Dosage form: inhalant
Regimen: therapeutic – 2 inhalations per day for 5 days
preventative – 1 inhalation per day for 10 days

There are no age restrictions, but infants may not be able to inhale the drug properly. In general, children can inhale the drug properly from around 5 years old. In principle, this drug is not used in the presence of underlying respiratory organ diseases such as asthma.

Inavir® (laninamivir)

Dosage form: inhalant
Regimen: therapeutic – under 10 years, 1 inhalation of 20 mg
10 years and older, 1 inhalation of 40 mg
preventative – 10 years and older, 1 inhalation of 20 mg per day for 2 days

As the treatment is only one inhalation, you should make sure that a proper inhalation was performed. Use caution in the presence of underlying respiratory organ diseases such as asthma.

Rapiacta® (peramivir)

Dosage form: intravenous drip
Regimen: daily intravenous drip lasting at least 15 minutes
(administer on consecutive days depending on the symptoms)

As this drug has the same mechanism as Tamiflu®, it is not effective against viruses resistant to Tamiflu®. This drug can be considered in severe cases in which oral administration or inhalation is not possible.

3 Dealing with infections

(1) Preparing for and dealing with fevers

Get in the habit of measuring the body temperature regularly to watch for changes. It is convenient to keep ice packs in the freezer for use if a fever suddenly appears.

- **What to look for when a child has a fever**
  - When did the fever start?
  - Is the child drinking fluids?
  - Is the child eating?
  - Are there other symptoms? E.g., a cough, runny nose, vomiting, diarrhea, abdominal pain, red eyes, etc.
  - Is the child sluggish?

(2) How to care for a fever

- Give fluids often (Figure 2)
- Change clothes often in case of heavy sweating

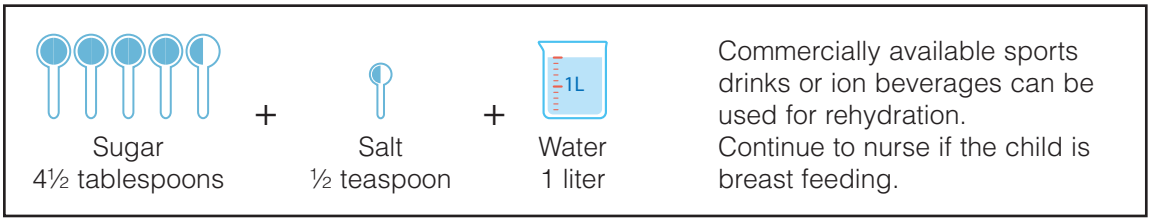


Figure 2. Recipe for oral rehydration fluid to prepare at home

(3) When to contact the hospital

- When a high fever (≥39°C) occurs
- When the child cannot drink fluids
- When the child is sluggish or appears to be in a poor condition

- When respiration is rapid or difficult
- When the child is in a bad mood or has an unusual facial expression

Dehydration can occur in the event of high fevers, and an infection may hide deep in the body. There are also risks of other infections such as respiratory organ infections, digestive tract infections, and cholangitis, so please do not wait to contact the hospital.

4 Basics of infection prevention

(1) Cautiousness in daily life

Wash your hands frequently

Washing your hands is the most effective way to prevent many infections. Get into the habit of washing your hands often and correctly.

Hand-washing pointers

1 When to wash your hands
After returning home, before eating, before and after using the toilet, before and after playing, before touching the mouth, eyes, or nose, before bed
2 Practice washing your hands
3 Carry alcohol gel or other quick-drying cleansers for when water is unavailable (Figure 3)

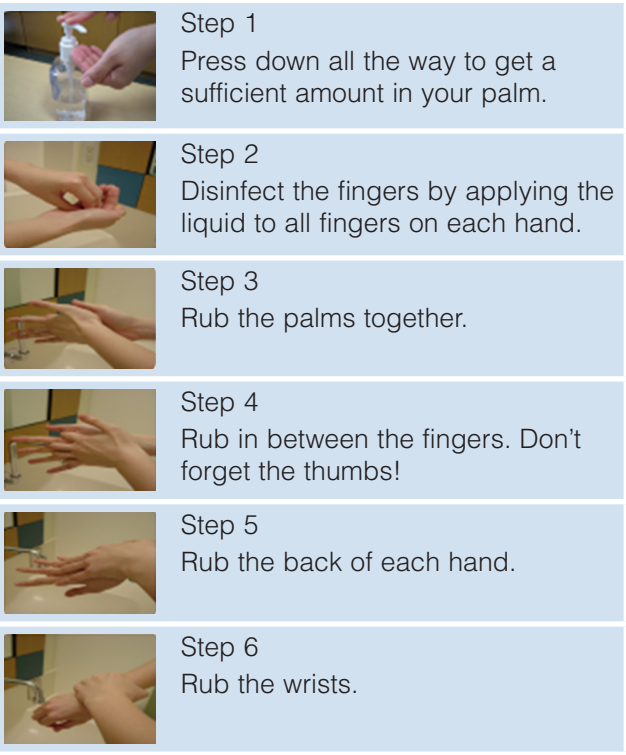


Figure 3. How to apply alcohol gel

Wearing a mask correctly

One of the reasons children should wear masks is to prevent them from touching their mouths with dirty hands. Although wearing a mask does not provide total protection against the pathogens in the air, it does help to prevent passing on infections to others through coughs and sneezes. When fitting a mask, make sure that it covers the nose and mouth completely.

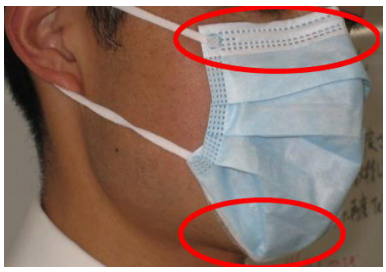


Photo 1
How to wear a mask correctly

Cavity prevention

Cavities can cause periodontal diseases, which can create opportunities for bacterial infections to affect the entire body. The best way to prevent cavities is

regular tooth-brushing. When seeing a dentist for a cavity, make sure to let him or her know about any immunosuppressants being taken.

Be careful in sandboxes

Bacteria can live in the sand of sandboxes and other play areas. Therefore, these places should be avoided when the child has cuts on his or her hands. Cut the fingernails so that sand does not get under them. Moreover, be careful that sand does not get into the mouth while playing. Wash the hands with soap and water immediately after play.

Avoid contact with infected people

Avoid direct contact with infected people who are in poor condition. If a family member gets an infection, try to live separately as much as possible (use different rooms, eat and bathe at different times, etc.).

(2) Living with pets

Pets are important members of the family. Being around pets can be mentally comforting and can provide opportunities for exercise. However, animals also carry a large number of pathogens, some of which can infect humans through what are called “zoonotic infections.” After a transplant, the patient may become vulnerable to new infections, and common infections may become serious. You should be careful of certain infectious diseases, depending on the species of the pet. The following URL will take you to a NCCHD website that offers information about living with pets for children undergoing organ transplants. (In Japanese only.)

* URL
https://www.ncchd.go.jp/hospital/about/section/special/transplant_surgery/images/110826-1.pdf

Two pointers to avoid catching infections from animals

1 Avoid infections from your own animals
Vaccinate your pets regularly.
2 Prevent pathogens from transferring to humans
Examples of “direct contact” with animals
- Being bitten or scratched by an animal
- Touching or otherwise coming into contact with animal feces or urine

[Examples]
- Rabies (from animal bites, extremely rare in Japan)
- Salmonella infection (from eating raw food, contact with turtles and other reptiles or chicks and other birds)
- Skin infections (from animal bites, scratches)

Examples of “indirect contact” with animals

- Touching soil contaminated with animal feces or urine
- Swallowing or inhaling bacteria or other pathogens in animal feces or urine

[Examples]

- Cryptococcosis pneumonia, meningitis, chlamydial pneumonia (from inhaling bird feces, etc.)
- Toxoplasmosis (from dog or cat feces, etc.)
- Dog roundworm (from dog feces, etc.)

Keeping animals after a transplant

1 Obtain the doctor’s permission to keep animals after a transplant.
2 The doctors will usually give permission about six months after the transplant.
3 If permission to have a pet is given, follow the precautions below.

Precautions for keeping pets

1 Keep the pet indoors as much as possible.
2 Always wash your hands with soap and water after touching the pet.
3 Never touch a pet’s urine or feces.
4 Never kiss a pet or let a pet lick you.
5 Dogs and cats are generally the only pets it is okay to have.

(3) Sexually transmitted diseases

Sexually transmitted diseases are often referred to by their acronym, STDs. These diseases can be contracted by anyone once they become sexually active. STDs cause a variety of symptoms, including pus discharge from the urinary tract, increased vaginal discharge, and rashes or ulcers on the external genitalia. Mild symptoms such as problems with the oral mucosa are common. If treatment is delayed because the infection is not detected, the reproductive organs can become infected, causing infertility.

The symptoms and complications of an STD may be more severe in transplant patients. For example, a gonorrhea infection that would normally only infect the sexual organs may infect the whole body, or a hepatitis B infection may cause fulminant hepatitis.

Preventing STDs

Prevention is the most effective way to avoid STDs. This basically entails getting the necessary vaccinations (hepatitis B vaccine, cervical cancer vaccine) and using condoms correctly.

Sex education can sometimes be put off at home in favor of treatment and recuperation after a liver transplant. Children should begin to be taught how life is created and the differences between men and women from primary school. In middle school and high school, they should learn about secondary sex

characteristics, the differences between men and women, STDs, and how to prevent infections.

When an STD is discovered

In addition to your own treatment, your partner should also be tested and treated. Be sure to continue treatment until the end, rather than quitting when things appear to be getting better.

(4) Vaccines

As the infections caught by a patient taking immunosuppressants after a transplant can become severe, vaccines (preventive inoculations) are administered aggressively at the NCCHD. When it is decided that a transplant is indicated, inoculations for infectious diseases that can be prevented with vaccines are administered. Although this depends on the child, several of the necessary vaccinations are often administered at once, a practice called “multiple inoculation”. The idea is to finish the course of vaccinations early so that the patient may acquire immunity before the transplant.

In general, live vaccines are not recommended when the patient is in an immunocompromised state after the transplant. However, at the NCCHD, we take the current epidemics occurring in Japan into consideration. Since our first priority is to protect transplant patients who have low immunity, live vaccines are sometimes used if certain criteria are fulfilled (Table 1).

	Before transplantation	After transplantation
Top priority inoculations	Measles-rubella (MR) Chickenpox	Measles-rubella (MR) Chickenpox
	Hepatitis B	Hepatitis B Hib, pediatric pneumococcus DTaP-IPV Influenza
Priority inoculations	Mumps	Mumps*2
	Hib, pediatric pneumococcus DTaP-IPV Influenza	Inactivated poliovirus 23-valent S. pneumoniae*3
Inoculations given when there is ample time	BCG*1	Japanese encephalitis Hepatitis A Cervical cancer
	Japanese encephalitis	
		Live vaccine / Inactivated vaccine

*1 Age 1 and older not inoculated
*2 Top priority if epidemic in people around the patient
*3 Top priority if at risk

Table 1. Priority levels for vaccinations before and after liver transplantation

Our center's vaccination criteria

[Before transplantation]

Live vaccines are performed up to 4 weeks before the surgery. Inactivated vaccines are performed up to 2 weeks before the surgery. However, there are some exceptions. Please ask about this during outpatient care or at any other opportunity.

[After transplantation]

Children with a good liver function can receive inactivated vaccinations from one year after the transplant (after six months for seasonal influenza) and live vaccines from after two years. However, this only applies to children taking a single immunosuppressant.

Assistance with routine vaccinations

Preventive inoculations cannot be administered until a certain amount of time has passed after the transplant. For this reason, children sometimes do not receive vaccinations at the recommended age.

In 2013, municipal governments began to grant extensions to the inoculation periods for routine vaccinations. In some situations, the vaccinations can be covered by public funds. Consult your local public health center after discussing the timing of the vaccinations with your doctor.

Vaccinations for family members

It is extremely common for infections to spread among family members. To protect children undergoing transplants, it is important for the family members to be vaccinated as well. Members of the family should be vaccinated against all diseases that can be prevented. Different families need different vaccines, so please speak to your doctor about this.

Each transplant patient's inoculation schedule is determined according to their treatment status and vaccination history. If you have doubts or questions about how to proceed with vaccinations after a transplant, please consult the outpatient vaccination team.

Subject	Recipient
Outpatient schedule	Tuesdays: vaccine consultations only Fridays: vaccine consultations, inoculations
Location	National Center for Child Health and Development Center for Clinical Research and Development, 1F

Kensuke Shoji, Takanori Funaki, Yoshiyuki Tezuka, Munehiro Furuichi,
Noriko Kinoshita, Yoshie Sugawara, Isao Miyairi
Division of Infectious Diseases/Office for Infection Control
National Center for Child Health and Development

6 Allergies after liver transplantation

1 Is it true that allergies can appear after a liver transplant?

Since the 1990s, there have been reports of recipients with no prior food allergies who developed some after receiving a transplant from a donor with food allergies. This has not only occurred after liver transplantation, but also after bone marrow, heart, lung, kidney, and a variety of other organ transplants.

Recently, there have been reports of new allergies developing in recipients even when the donor did not have food allergies. Particular attention has been paid to this increase in food allergies.

2 How frequent are allergies after liver transplantation?

Reports on the frequency of food allergies after liver transplantation differ widely, with rates ranging from 6% to 57%. Atopic dermatitis reportedly occurs in 5% to 8% of cases, bronchial asthma in 3% to 6%, and allergic rhinitis in 9% to 11%. While these reports offer conflicting evidence about the age distribution, making the results difficult to generalize, food allergies are clearly more common in transplant patients than in children who have never had a transplant. (In general, 5% to 10% of infants have food allergies.)

At the NCCHD, 22 of 149 patients (15%) who underwent liver transplantation between 2005 and June 2011 presented food allergies (Figure 1). Food allergies tended to appear about eight months after the liver transplant. About one-third of these patients (7 out of 22) could eat the given food without having an allergic reaction before the transplant. The others had not eaten the food before the transplant. A variety of factors have been thought to contribute to the appearance of allergies after transplantation. These are discussed in detail below.

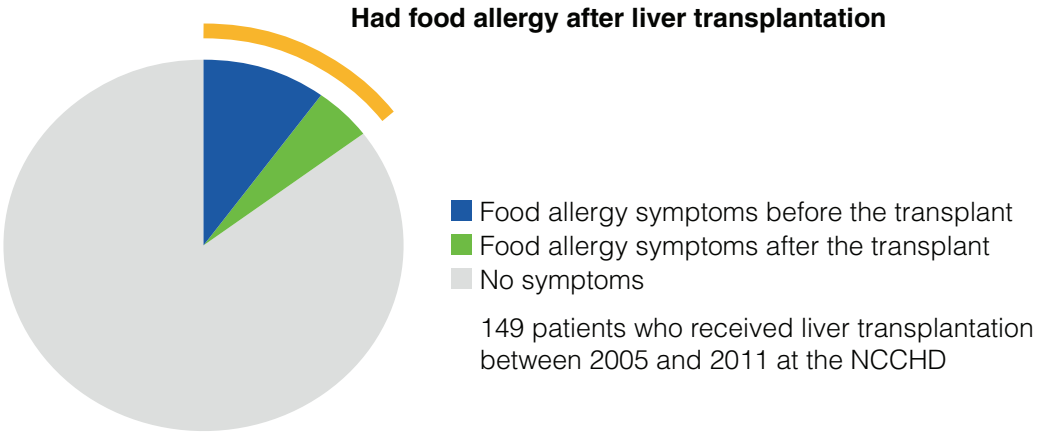
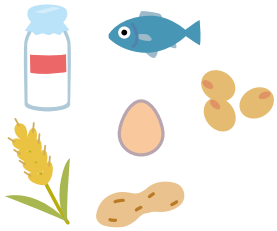


Figure 1. Food allergies after liver transplantation

3 What foods most commonly cause allergies?



Milk, eggs, fish, soybeans, wheat, and peanuts are said to be frequent causes of both immediate allergies (IgE-dependent) and gastrointestinal allergies (non-IgE-dependent) after transplantation. Among the 22 NCCHD patients who exhibited allergies, the most frequent allergens were eggs, milk, and fish, in that order. In about half of the children, the symptoms were caused by several foods.

However, the fact that these items frequently cause allergies does not mean that everyone should avoid them. It is best to avoid only the minimum amount of foods necessary. The symptoms, examinations, diagnostics, and treatments described below apply to food allergies in general. For more details, please ask your doctor at your next outpatient visit, or see *Children's Allergies* in the NCCHD Book Series published by the NCCHD.*

* Only available in Japanese.

Takashi Igarashi, supervising editor; Yoshihiro Ohya, editor (2013) *Children's Allergies – The NCCHD Book Series*, Medical Tribune ISBN-13: 978-4895894326

4 Things to watch out for to identify post-transplant food allergies

There are two broad types of food allergies: immediate allergic responses, and non-immediate allergic responses (gastrointestinal allergies). The former involve the appearance of symptoms within a few minutes to a couple of hours after eating the allergen, while in the latter, symptoms can take a few hours to a few days to appear (Figure 2).

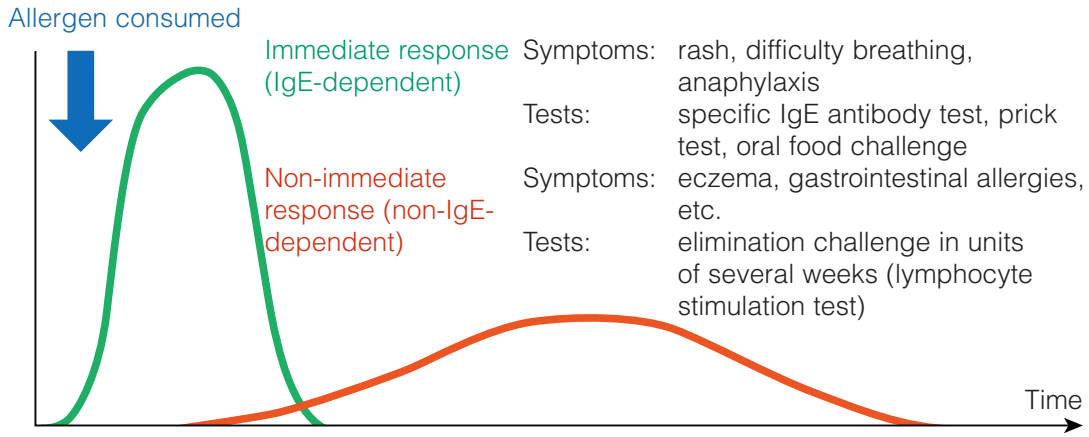


Figure 2. Immediate and non-immediate allergies

Immediate allergic responses

These responses are related to the IgE antibody. They can cause symptoms such as rashes, coughs, and stomach pain. A more severe reaction is called anaphylaxis.

Non-immediate allergic responses (particularly gastrointestinal allergies)

These have nothing to do with the IgE antibody. Although the mechanism is not clearly understood, immune cells called lymphocytes are believed to be the main entity involved. Non-immediate responses manifest as skin eczema and gastrointestinal symptoms such as vomiting and diarrhea. Non-immediate responses that mainly involve gastrointestinal symptoms are called non-IgE mediated gastrointestinal food allergies.

Immediate allergic responses and gastrointestinal allergies are two important types of food allergies that occur after liver transplantation. Therefore, we discuss both below.

5 What are the symptoms?

Immediate allergies

The symptoms include rashes, wheezing, coughs, vomiting, diarrhea, and listlessness. Rashes and other skin symptoms are the most common (Table 1).

Part	Symptoms
Skin	Itching, redness, rash
Nose	Runny nose, sneezing, stuffy nose
Mouth, throat	Swollen lips, discomfort in the mouth, throat discomfort, hoarse voice
Digestive organs	Nausea, vomiting, stomachache, diarrhea, bloody stool
Respiratory organs	Cough, wheezing, difficulty breathing
Circulatory organs	Low blood pressure, rapid pulse, cold hands and feet
Nerves	Lack of energy, listlessness, unconsciousness

Table 1. Symptoms of immediate allergic responses

Gastrointestinal food allergies (non-immediate)

Symptoms may include bloody stool, vomiting, diarrhea, stomachache, difficulty swallowing, and listlessness. Gastrointestinal allergies are sometimes recognized through chronic symptoms that can be difficult to notice, such as lack of appetite or poor weight gain.

Previously, families of children who had received liver transplantation at the NCCHD have brought their children in for examination after noticing swollen lips, skin symptoms, and digestive symptoms. If any of these symptoms occur, it is very helpful to take note of what your child ate and how much, the specific symptoms, when they appeared, and other relevant details.

6 What examinations are needed to make a diagnosis?

Immediate allergies

Blood tests (including an IgE antibody test) and the skin prick test* can be strong indicators of the presence of food allergies (immediate allergic responses). However, the ultimate diagnosis criterion is whether symptoms appear when a particular food is eaten. Therefore, even when a blood test is positive and the symptoms indicate an immediate allergic response, an oral food challenge needs to be performed. This involves administering certain foods to see if allergic symptoms appear.

* Skin prick test

In this test, a drop of a substance that can cause an allergy (an allergen) is placed on the skin. The skin is then pricked slightly (not strongly enough to cause bleeding) with a needle like the one pictured on the right so that the skin absorbs the allergen, and the area is observed to check for a response.

Gastrointestinal food allergies (non-immediate)

Since blood tests (IgE antibody tests) cannot serve to identify these allergies, an elimination test is performed. In this test, the suspected food item is not eaten for two or three weeks to see whether the symptoms improve. The stool can also be checked for an increase in eosinophil cells. When the diagnosis is difficult, the patient can be examined by gastrointestinal endoscopy. If the patient's general condition is good, an oral food challenge can be performed by making the patient eat increasing amounts of a food item over one to three weeks to see if the symptoms appear.

Gastrointestinal food allergies are difficult to diagnose, especially as several diseases that may occur after liver transplantation can cause the same symptoms. If you have any questions, please speak to your primary physician. Repeated episodes of symptoms occurring when the same food is eaten are extremely important. Therefore, please make a note of what was eaten, the symptoms that appeared, and other relevant information.

7 How are allergies treated?

Food allergies are treated with a dietary therapy on an everyday basis and with emergency responses when symptoms appear.

Immediate allergies

Dietary therapy: The basic principle is to eliminate the minimum number of foods possible based on a correct diagnosis. For a single food allergy, there is no need to eliminate other foods that tend to cause allergies, or foods that produced mildly positive results in the IgE antibody blood test. However, when strong allergy symptoms are caused by

small amounts of a food, this food should be eliminated for six months to a year, until the IgE levels and other markers decline. An oral food challenge should then be performed to see if the food can be tolerated.

Emergency responses: Antihistamine drugs can be used when only mild skin symptoms are present. If severe symptoms of anaphylaxis such as a continuous cough or repeated vomiting appear, an EpiPen® shot must be administered, and the patient should receive quick medical attention.

Gastrointestinal food allergies (non-immediate)

Dietary therapy: The allergenic food item must be eliminated. If the child is breastfeeding, in approximately half of the cases, the symptoms will resolve if the mother eliminates the allergenic food for at least three days. If the child continues to show an allergic response, the mother could compromise her health by eliminating more food items, so it is usually preferable for her to stop breastfeeding in these cases. The child will grow just fine drinking formula.

If the child is well enough, an oral food challenge can be performed after six months to two years to check if he or she can tolerate the food.

Steroids or intravenous fluid replacement may be administered as emergency responses.

8 Will the allergies ever disappear?

A few reports have indicated that one-third to two-thirds of patients could start eating the food that caused their allergy again after two or three years. However, information about this is still limited. At the NCCHD, approximately 70% of our patients are able to eat without restrictions after four years. This suggests that, as with regular food allergies, many patients gradually grow out of them.

9 Why do allergies appear after liver transplantation?

We do not have a clear answer to this question yet. However, there are several possible causes: ① a young age at the time of the transplant (younger than 12-16 months), ② the importance of the liver, ③ the use of tacrolimus (an immunosuppressant), ④ the degree of invasiveness of the surgery, and ⑤ the donor's food allergies. These are discussed in detail below.

① Young age at the time of the transplant

While children older than approximately 6 years of age and adults who receive liver transplantations almost never experience food allergies afterward, there have been many reports of food allergies appearing in children who underwent liver transplantation around 1 year of age. Food allergies generally appear sometime in the first two years of life, as the transplant patients may not have acquired immunotolerance to foods yet.

② Importance of the liver

Food allergies have been shown to appear more frequently after liver transplantations than after other organ transplants performed around the same age. After food is absorbed in the intestines, its first destination is the liver. This organ may therefore play a significant role in determining whether foods generate an allergic response.

③ Use of tacrolimus (Prograf® immunosuppressant)

The role of tacrolimus in allergic responses is still being debated by specialists. Tacrolimus is often compared to cyclosporine A. A report showed that the use of tacrolimus induced higher levels of total IgE and eosinophil counts – which are allergy markers in adults – in the blood tests of kidney transplant patients taking tacrolimus than in those who took cyclosporine A. This suggests that tacrolimus may predispose patients to allergies. However, food allergies very rarely appear in kidney transplant patients, including in those who take tacrolimus. Therefore, the role of tacrolimus may be smaller than that of the first two factors (i.e., a young age and the importance of the liver). Still, as other reports have not found a relationship between food allergies and tacrolimus use in pediatric liver transplant patients, we are still waiting to learn its true effects. At present, it is considered more important to select immunosuppressants based on a comprehensive assessment of rejection management and other factors than on any possible influence on food allergies.

④ Invasiveness of the surgery

Recently, there have been several reports of gastrointestinal food allergies appearing after surgeries in the neonatal period and in infancy. In many of these cases, gastrointestinal food allergies appeared after operations of the intestinal tract (i.e., from the esophagus to the colon). Children with biliary atresia, which is often an indication for a liver transplant, frequently undergo the Kasai procedure (an operation that connects the small intestine to the liver) before receiving a liver transplant. This may also contribute to the increase in food allergies, although further study is needed to confirm this.

⑤ Donor's food allergies

When the donor has a food allergy, the recipient can sometimes develop an allergy to the same food despite having no problem eating it before. However, some recipients who receive transplants from donors with allergies do not develop food allergies. Therefore, food allergies are not always passed on. The probability that a food allergy will be passed on is unknown. In certain cases in which a food allergy was passed on, the allergy disappeared after about a year, while in other cases, it remained even after seven years. This phenomenon is not well understood as there have only been a few studies on it.

If the donor has a food allergy, it is important to monitor the recipient when he or she eats the food after the transplant. Food allergies are not the most important consideration in selecting a donor, so please discuss your concerns with the transplant surgeon.

10 Prevention

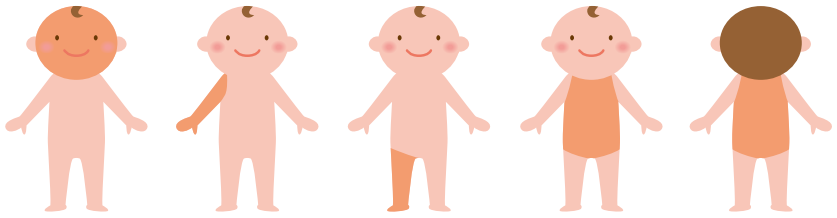
Unfortunately, the five possible causes described above are unavoidable. For allergies in general, the concept of "skin sensitization" has been receiving much attention lately. This refers to the idea that the risk of developing a food allergy increases if the food comes into contact with an inflamed area of the skin. Therefore, it is important to treat inflammation early and to keep the skin clean. This means that it is extremely important to bathe, to use soaps and moisturizers, and even to apply steroid ointment and other treatments if necessary. Figures 3 and 4 show the amounts of ointment to apply.

1 FTU
1 FTU = about 0.3-0.5 g

Equivalent to the size of an adult's palm

When using ointment in a container, 1 teaspoon (5 ml) = about 4 g

Figure 3. Amount of ointment to use Fingertip unit (FTU)



						Entire body
6 mo	1	1	1.5	1.5	2	9.5
1 yr	1.5	1.25	2	1.75	2.25	12
3 yr	1.5	1.75	2.5	2.5	3.5	16
7 yr	2	2.5	4.5	3.5	5	24.5

(units: FTU)

Based on Long C et al. J Dermatol. 1998; 138 (2): 293-6

Figure 4. Approximate amounts of ointment to apply

In addition, food allergy symptoms are more severe when a greater quantity of the food is eaten. Therefore, when your child first eats a suspect food item, do not allow him or her to eat a lot at once, but increase the amount little by little. This will reduce the risk of severe reactions such as anaphylaxis. At the same time, being too careful and avoiding many foods can prevent the acquisition of oral tolerance, which is the process by which allergies disappear as people become accustomed to foods. Best practices involve increasing amounts gradually and eating a wide variety of foods.

As allergies and their symptoms can vary greatly between individuals, we need to find a dietary therapy that is right for your child. For more details, please ask your doctor at your next outpatient visit.

Osamu Natsume, Tetsuo Shoda, Yukihiro Ohya
Division of Allergy
National Center for Child Health and Development

7 Liver transplantation and medication

1 Don't forget to take your medicine!

(1) Why do I need to take medication?

The drugs that you take support and treat your new liver and your body. They are prescribed by your doctor based on the present state of your liver and health. The liver is sometimes called the "silent organ," meaning that it does its job quietly. Even if it weakens slightly, you won't feel any discomfort, so you won't realize that anything is wrong. For this reason, doctors perform regular examinations and prescribe drugs adapted to your present condition. This is why you need to take your medicine.

Take care of the precious liver that has been given you by your donor: don't forget to take your medicine or decide to stop taking it arbitrarily. It is important to continue to take your medicine according to your doctor's instructions. Taking your medicine properly is an essential thing you can do to protect your health.

(2) What medication do I need to take?

Liver transplant patients take immunosuppressants, drugs to protect the liver, and important support drugs. We describe each of them below.

2 Immunosuppressants

(1) What are immunosuppressants?

Immunosuppressants are important drugs that suppress the actions of your immune system so that the donated liver can cooperate properly with your body.

Your immune system protects you from bacteria and from other things that are “not part of yourself.” When the immune system finds one of these foreign agents, it attacks it. However, since the body also sees the liver from a donor as “not part of yourself,” it tries to reject it, e.g., by having immune cells release substances to attack the liver. This is known as the “rejection response.” Without medicine to help both sides get along – that is, drugs that suppress the actions of the immune system –, the body’s immune cells will continue to attack the new liver, eventually causing it to stop functioning.

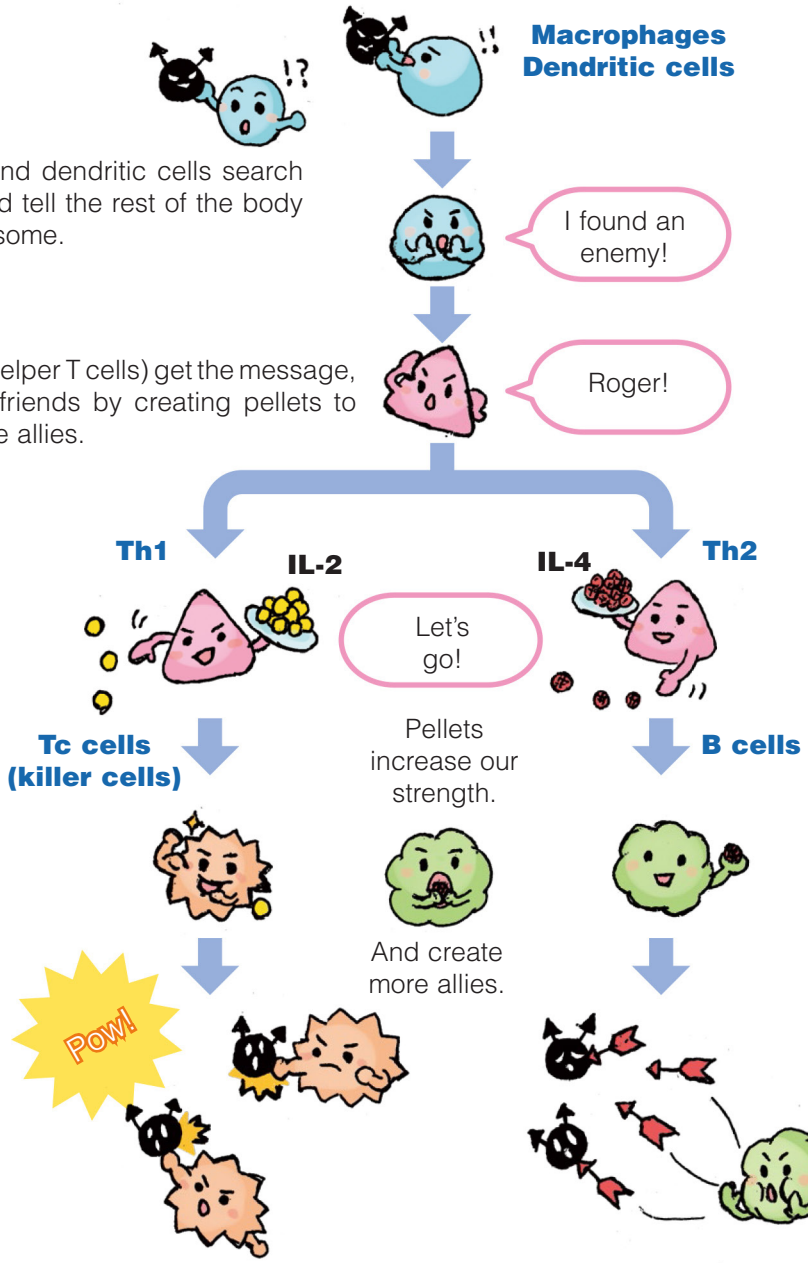
To avoid this unfortunate situation, patients need to protect their livers by taking immunosuppressants.

However, since immunosuppressants also weaken the body’s resistance against external enemies, it is important to develop good habits (such as regular handwashing) to protect yourself from bacterial, viral, and fungal infections.

Members of the immune system

These substances work together to protect the body from external enemies.

Name	Job
Macrophage	I search for enemies, then attack them and tell my friends about them.
Th cell (helper T cell) Th1 and Th2 cells	We receive messages and make special IL-2 and IL-4 pellets to help Tc and B cells.
Tc cell (killer T cell)	I directly attack enemies and use IL-2 pellets to power up!
B cell	I use IL-4 pellets to power up! I also make weapons (antibodies) and use them to fight.



Macrophages and dendritic cells search for enemies, and tell the rest of the body when they find some.

When Th cells (helper T cells) get the message, they help their friends by creating pellets to make even more allies.

Tc cells (killer cells) use IL-2 pellets made by the Th1 cells to get stronger, then attack the enemies directly.

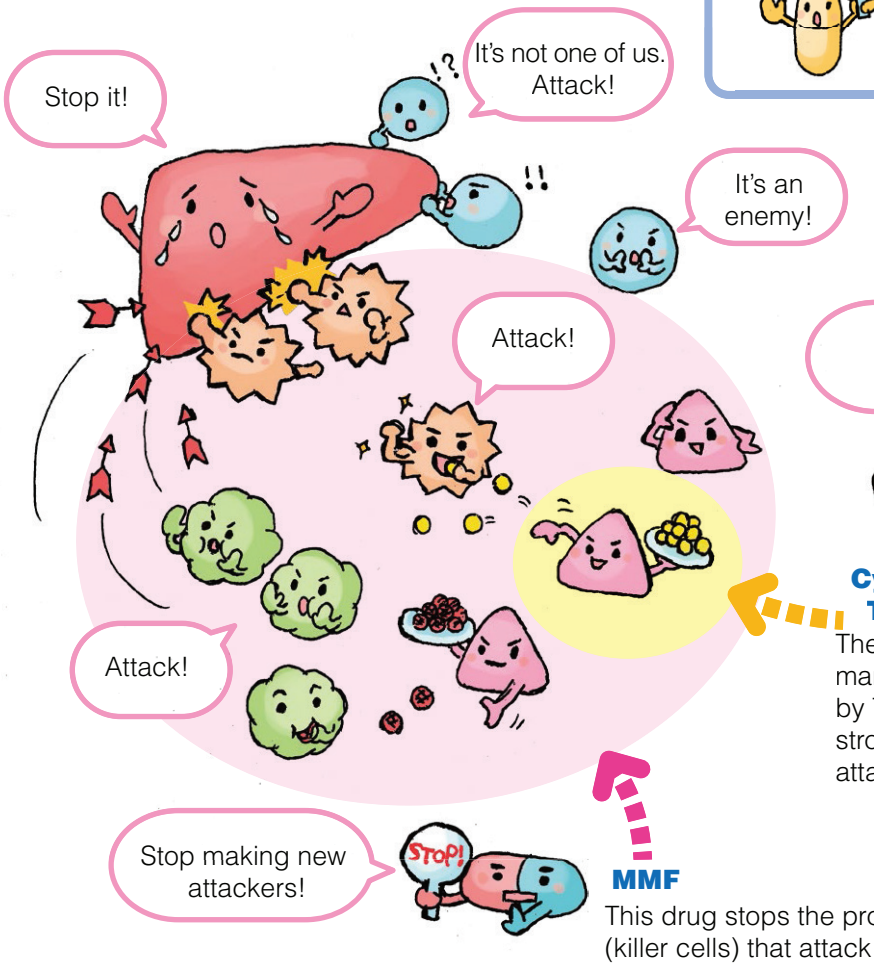
B cells use IL-4 pellets made by the Th2 cells to get stronger, then use weapons (antibodies) to attack the enemies.

After a liver transplant

When the immune system discovers a donated liver, it treats it as an outsider and starts attacking it. Immunosuppressants step in to protect the liver.

Immunosuppressants

Cyclosporine Tacrolimus **MMF**



Stop making power-up pellets!

Cyclosporine Tacrolimus

These drugs suppress the manufacture of IL-2 pellets used by Tc cells (killer cells) to get stronger so that they may attack the liver directly.

MMF

This drug stops the proliferation of the Tc cells (killer cells) that attack the liver directly and of the B cells that attack with weapons (antibodies).

What happens next?

The attacks on the transplanted liver stop, allowing it to stay healthy and to do its job in the recipient's body.

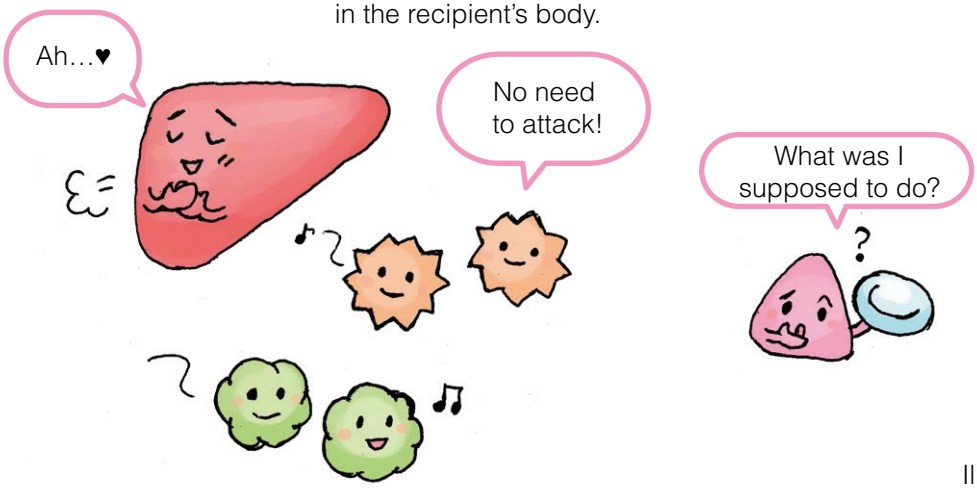
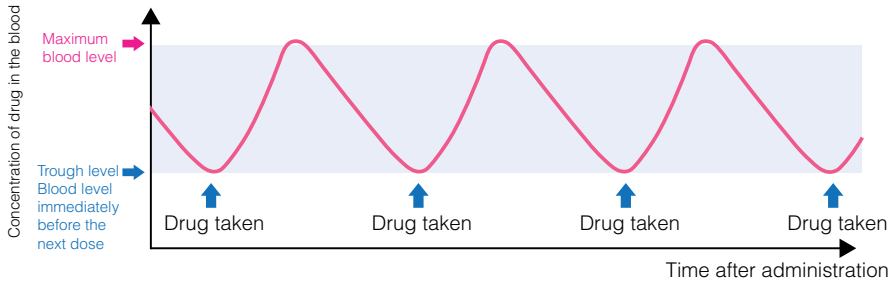


Illustration © M. Nagai

(2) Immunosuppressants used at the Organ Transplantation Center

Brand names	**Prograf®, Graceptor®**
Generic name	**Tacrolimus: Tac, FK506**
Characteristics	Tacrolimus is the most commonly used immunosuppressant for liver transplantation. It suppresses the immune system by inhibiting the ability of helper T cells (a type of immune cells) to release attack-promoting substances such as interleukin 2. Tacrolimus is the name of the effective ingredient in Prograf and Graceptor. The effects and side effects of these drugs depend on the amount of tacrolimus in the blood (blood level). If the blood level is too low, the effect won't be strong enough, and rejection may occur. If the level is too high, the risks of infections and of other side effects increase. Right after surgery, the blood level is kept high to ensure that acute rejection does not occur. We need to be wary of infections during this period. As the likelihood of rejection decreases with time, the blood level is lowered to reduce the risk of infection. If rejection is suspected, the situation can be controlled by raising the blood level. Doctors use blood tests and other examinations to adjust the doses. Changes in blood level after administration of medication (image)  **How to take tacrolimus (Prograf®, Graceptor®)** To ensure that the blood levels remain stable, Prograf must be taken every 12 hours, and Graceptor every 24 hours. As the level of tacrolimus in the blood increases more when the drug is taken before meals than after meals, doses should be taken on a set schedule. Since the dose is adjusted through frequent blood tests during your hospitalization, it is fine to take the medication at slightly different times. The level of tacrolimus in the blood is measured before the drug is taken, when levels are at their lowest (trough value). Therefore, do not take tacrolimus before outpatient visits. Bring your medication to the hospital and take it after a blood sample is taken. The examination will proceed after the results of the blood test are obtained.
Usage	**Combination with food or supplements**  Tacrolimus has been reported to interact with citrus fruits. As of December 2014, interactions have been reported with citrus varieties including grapefruit, banpeiyu, pomelo, and hassaku orange. The consumption of these fruits with tacrolimus should be avoided as they may cause the blood tacrolimus level to rise. For more details, see the Q&A section below. In addition, St. John's wort, an herb used in supplements and tea, may reduce the level of tacrolimus in the blood. Therefore, it should also be avoided.

Side effects

Side effects may include hyperkalemia, kidney dysfunction, hyperglycemia (pancreatic dysfunction), and hyperuricemia. Regular blood tests are performed to check for these threats. Other side effects to be wary of include infections, high blood pressure, headache, flushing, trembling, consciousness disorders, encephalopathy, thrombosis, lymphoma and other malignant tumors, and various effects on the heart or liver. For more details on potential side effects, see the Q&A section below.

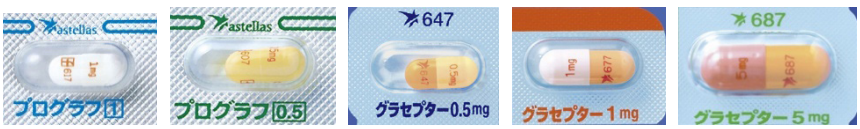
- **Drugs that should not be taken with tacrolimus**
  (contraindications for coadministration)

  Live vaccines, cyclosporine (immunosuppressant), bosentan (circulatory organ drug), potassium-sparing diuretics (as of December 2014)

- **Drugs that should be taken with tacrolimus with caution**
  (precautions for coadministration)

Immunosuppressants	Immunosuppressants, adrenocortical hormones, antirheumatic agents, etc.
Anti-inflammatory drugs	Non-steroidal anti-inflammatory drugs (NSAIDs)
Drugs that suppress gastric acid	Omeprazole, lansoprazole
Vaccines	Inactivated vaccines
Antibiotics	Erythromycin, josamycin, clarithromycin, aminoglycoside antibiotics, rifampicin, rifabutin, amphotericin B, sulfamethoxazole/trimethoprim, etc.
Antifungal drugs	Itraconazole, fluconazole, voriconazole, etc.
Antiviral drugs	Ritonavir, saquinavir, nelfinavir, telaprevir
Circulatory system drugs	Nifedipine, nilvadipine, nicardipine, diltiazem, eplerenone, amiodarone, etc.
Antiepileptic drugs	Carbamazepine, phenobarbital, phenytoin
Hormones	Ethinyl estradiol
Others	Danazol, tofisopam, bromocriptine

(as of December 2014)



Brand name	**Neoral®**
Generic name	**Cyclosporine: CsA, CyA**
Characteristics	For liver transplantations performed on infants, only a small part of the donor's liver is removed. In these cases, cyclosporine is sometimes selected as the immunosuppressant instead of tacrolimus. In addition, tacrolimus may be changed to cyclosporine if the former is thought to be causing side effects. This drug's characteristics, usage, and guidelines for combination with food or supplements are roughly the same as for tacrolimus, so please refer to that section for more details.
Usage and side effects	While cyclosporine is largely similar to tacrolimus, its effective ingredient has a different chemical structure that causes slightly different side effects. The side effects specific to cyclosporine include abnormal hair growth and thickening of the gums (gingival hyperplasia). For more details, refer to the tacrolimus section. • **Drugs that should not be taken with cyclosporine** (contraindications for coadministration) Live vaccines, tacrolimus (immunosuppressant), bosentan (circulatory organ drug), pitavastatin and rosuvastatin (drugs for hyperlipidemia), aliskiren (blood pressure drug), asunaprevir and vaniprevir (hepatitis drugs) (as of July 2016) • **Drugs that should be taken with cyclosporine with caution** (precautions for coadministration) Adrenocortical hormones, immunosuppressants such as Cellcept and Certican, NSAIDs, inactivated vaccines, antibiotics, antifungal drugs, antiviral drugs, diuretics, circulatory organ drugs, drugs to treat hyperlipidemia, anti-nausea drugs, theophylline, antiepileptics, antitumor agents, ultraviolet radiation treatments such as PUVA, etc. (as of December 2014)

Brand name	**Cellcept®**
Generic name	**Mycophenolate mofetil: MMF**
Characteristics	This is an important immunosuppressant that has a different action from tacrolimus. It may be added to the patient's drug regimen when rejection cannot be controlled with tacrolimus alone. If there are any concerns about the side effects of tacrolimus, the latter may be combined with Cellcept to reduce the tacrolimus blood trough level. Cellcept inhibits the proliferation of T lymphocytes and B lymphocytes (two types of immune cells). It suppresses immunity by causing the T lymphocytes to release fewer substances for the attack of foreign bodies, and the B lymphocytes to release fewer antibodies.

Usage and side effects

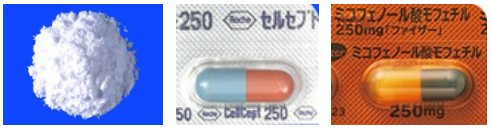
While its usage is largely the same as that of tacrolimus, there are important things to consider when taking Cellcept. (1) Women who may become pregnant should only take Cellcept after taking a negative pregnancy test, and they should avoid pregnancy before, during, and for six weeks after taking the drug. (2) Contact a doctor immediately when any of the following symptoms occur: signs of infection, unexpected bruises, bleeding, anemia, or severe diarrhea. (3) As this drug is associated with a risk of skin cancer, avoid ultraviolet rays from sunlight by wearing hats and other clothing and by applying sunscreen.

- **Drugs that should not be taken with Cellcept**
  (contraindications for coadministration)
  Live vaccines (as of December 2014)

- **Drugs that should be taken with Cellcept with caution**
  (precautions for coadministration)

Immunosuppressants	Azathioprine, mizoribine, cyclosporine
Drugs that suppress gastric acid	Lansoprazole
Vaccines	Inactivated vaccines
Antibiotics	Amoxicillin-clavulanate (combination drug), ciprofloxacin, rifampicin
Antiviral drugs	Acyclovir, valacyclovir, ganciclovir, valganciclovir
Antacids, laxatives	Antacids containing magnesium and aluminum
Drugs for hyperlipidemia	Cholestyramine, colestimide
Drugs for treatment of hyperphosphatemia	Sevelamer

(as of December 2014)



Brand name	**Predonine®**
Generic name	**Prednisolone: PSL**
Characteristics	Prednisolone is an adrenocortical steroid hormone and an essential immunosuppressant used in liver transplantation. It is usually administered by injection in the form of its close relative, methylprednisolone (mPSL: Solu-Medrol®, etc.). Steroids are hormones produced by your body to carry out a variety of tasks. As they have the same effects when used as medicine, they can cause a variety of side effects. However, as steroid therapy only lasts for about three months in successful cases, many patients experience no side effects. In the case of long-term steroid therapy, your body can come to rely on the drug, causing it to produce fewer adrenocortical hormones. Therefore, when stopping steroid therapy, it is important to reduce the dose gradually to allow the body to acclimatize. Stopping steroids all of a sudden can lead to withdrawal symptoms such as reduced blood pressure or fatigue. As with any other drug, it is important to follow your doctor's instructions.

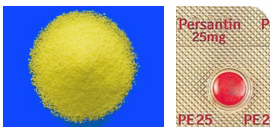
Usage	Steroid therapy starts during the transplant surgery. Steroids are injected once the recipient's blood vessels have been connected to the donor's liver, i.e., when the blood flow to the transplanted liver resumes. A high dose is used to prevent inflammation. After the operation, injections are generally given daily to prevent acute rejection. Over time, the dose is gradually lowered, and the patient is switched onto an oral drug. Therapy is expected to end about three months after the surgery. If a rejection response is suspected, higher doses of steroids may be administered for a short time, followed by a course of oral steroid administration. If a patient must continue steroid therapy, another immunosuppressant may be added to try to reduce the steroid dose, or control may be sought with multiple immunosuppressants.
Side effects	Possible side effects include infections that are difficult to cure, growth disorders, digestive ulcers, hypokalemia, high blood pressure, hyperglycemia, hyperlipidemia, thrombosis, increased appetite (Don't overeat!), abdominal obesity, moon face (fat accumulation on the face), excessive hair growth, hair loss, cuts that heal poorly, cataracts, glaucoma, osteoporosis, groin pain, acne, and menstrual irregularities. Although most side effects go away once the steroid therapy ends, some may be irreversible. If necessary, please consult with the department of ophthalmology, the department of endocrinology, or other relevant departments. 

3 Drugs for liver protection

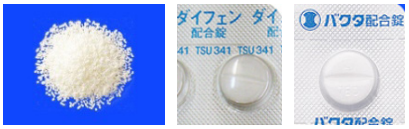
Brand name	**Urso®**
Generic name	**Ursodeoxycholic acid: UDCA**
Characteristics, usage	This important drug protects the liver cells by promoting the secretion of bile and improving its flow. Bile is produced by the liver, and is mainly used to digest fats. However, when it does not flow properly, it accumulates in the liver, where bile acids can damage liver cells. Urso protects the liver by weakening the bile acids' ability to damage liver cells, making gallstones easier to dissolve and discharging bile acids from the liver. Therapy usually ends six months to a year after the operation. However, as side effects are generally not a problem, some patients stay on it longer. 

4 Important support drugs

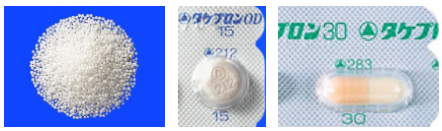
Drugs that prevent clogged blood vessels

Brand names	**Anginal®, Persantin®**
Generic name	**Dipyridamole**
Characteristics, usage	These drugs stop the blood from hardening in the portal vein, the hepatic artery, and the other blood vessels joined during the surgery to prevent thrombi from forming. Therapy usually ends about three months after the operation. 

Drugs protecting against bacteria

Brand names	**Daiphen®, Baktar®, Bactramin®**
Generic names	**Sulfamethoxazole, trimethoprim: ST combination drug**
Characteristics, usage	These drugs attack bacteria and other pathogens. They are used to prevent infections such as pneumocystis pneumonia. Therapy usually ends about three months after the operation. 

Drugs protecting the stomach from stress

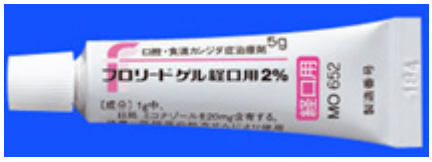
Brand name	**Takepron®**
Generic name	**Lansoprazole**
Characteristics, usage	This drug strongly suppresses the secretion of gastric acid in order to prevent steroids and the stress of surgery from disturbing the stomach and causing stomachaches. It comes in tiny pellets contained in a capsule. Each pellet is coated so that it can pass through the stomach into the intestines without dissolving. It should therefore be swallowed without chewing. Therapy usually ends when the patient stops taking prednisolone. 

Drugs for improvement of the intestinal function

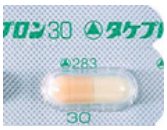
Brand names	**Biofermin®, Biofermin R®, Biolactis®, Bio-Three®**
Generic name	**Lactobacillus preparations**
Characteristics, usage	Lactobacillus is found in yogurt and is commonly used in probiotics that promote the growth of beneficial bacteria in the body. Increasing the amount of friendly bacteria in the intestines not only helps to clear up diarrhea, but it can also reduce the number of harmful bacteria, improve the habitat of bacteria in the intestines (called the intestinal flora), and strengthen the body's resistance to infections. As different bacteria thrive in different individuals, not every lactobacillus preparation is right for everyone. There are also differences between the products prescribed by hospitals and those available in stores. As the lactobacillus in Biofermin R® is resistant to some antibiotics, it is sometimes taken during a course of antibiotics. 

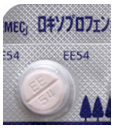
5 Drugs taken before surgery

Brand name	**Kanamycin®**
Generic name	**Kanamycin monosulfate**
Characteristics, usage	This drug attacks bacteria to prevent infections. 

Brand name	**FLORID® Oral gel**
Generic name	**Miconazole**
Characteristics, usage	This drug attacks fungi to prevent infections. 

6 Drugs taken by the donor

Brand name	**Takepron®**
Generic name	**Lansoprazole**
Characteristics, usage	This drug strongly suppresses the secretion of gastric acid in order to prevent the stress of surgery from disturbing the stomach and causing pain. It comes in tiny pellets inside a capsule. Each pellet is coated so that it can pass through the stomach into the intestines without dissolving. Therefore, it must not be chewed. If the patient does not have a history of stomach pain, gastric ulcers, or other issues, therapy usually ends after one or two weeks. 

Brand name	**Loxonin®**
Generic name	**Loxoprofen sodium hydrate**
Characteristics, usage	This drug suppresses inflammation and relieves pain. It is used during the recovery period to relieve pain and allow the patient to gradually start moving again after surgery. After two or three weeks, the pain has usually decreased enough for the patient not to need pain medication anymore. Enduring pain after surgery is unnecessary; this drug helps by providing relief during periods of severe pain. However, it should not be taken long-term, as it is hard on the liver. 

Brand name	**Mucosta®**
Generic name	**Rebamipide**
Characteristics, usage	This drug protects the stomach by protecting and repairing the gastric mucosa. Therapy usually ends when loxoprofen therapy ends. 

7 Q&A corner: questions about medication

Q. What are side effects?

A. Unfortunately, no drug is without side effects. The more effective a drug, the higher the risks of side effects. Patients may experience rashes, itching, dazedness, dizziness, headache, numbness, heart palpitations,

difficulty breathing, heaviness, pain, fever, cough, stomachache, nausea, diarrhea, constipation, abdominal distention, swelling, or bleeding that is difficult to stop. There may be changes to the color of the skin, the whites of the eyes, the stool, the amount or frequency of urination, and the amount of liquid consumed. However, as these changes are not always side effects of a drug, it is difficult to judge what is a side effect and what is not. A variety of information needs to be considered, including when the symptoms began, when they appear, when they disappear, and when they worsen. Although we need to be careful of side effects, this does not mean that major side effects always occur. In fact, most patients do not experience severe side effects. Depending on the symptom(s), your doctor might let you continue to take the drug while keeping an eye on your condition. It is important to follow the doctor's instructions regarding your medication. If you are concerned about side effects, keep a record of any minor changes in your condition and consult your doctor when you have the opportunity. If small children develop a bad temper and do not stop crying even when comforted, this may indicate an important physical change. If there is anything that concerns you, contact your doctor.

Q. What is the general schedule for medication after a liver transplant?

A. Although it depends on the person, a recipient's medication schedule is generally as follows. (Table 1)

Drug function and name		Day 1~14 after surgery	Day 15~28	~ 3 months	~ 1 year	2 years ~
Suppress the immune system	Tacrolimus Cyclosporine	The dose is gradually reduced, but basically taken continuously.				
	Prednisolone (methylprednisolone)	The dose is gradually reduced, ending after 3 months.				
Protect the liver	Urso	Therapy ends after 6 months to 1 year. May be taken longer if necessary.				
Prevent thrombi	Anginal, Persantin	Therapy begins on day 8 after surgery and ends after 3 months.				
Fight bacteria	Daiphen Baktar, Bactramin	Therapy begins on day 8 after surgery and ends after 3 months.				
Protect the stomach	Takepron	Therapy begins on day 8 after surgery and ends after 3 months.				
Improve the intestinal flora	Lactobacillus preparations	Therapy begins on day 8 after surgery and ends after 3 months.				

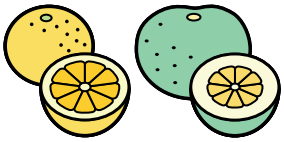
Table 1. General medication schedule after liver transplantation (recipient)

Q. What is the connection between medication and grapefruit? What about other citrus fruits?

A. Some adults have experienced issues from drinking grapefruit juice while on certain medications. Tacrolimus and cyclosporine are known to

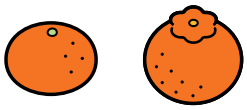
be affected by grapefruit. As of December 2014, tacrolimus has been reported to interact with citrus fruits including grapefruit, banpeiyu, pomelo, and hassaku orange. The pamphlet for Neoral also lists sweeties. Drinking or eating these fruits should be avoided as they may cause the tacrolimus and cyclosporine blood levels to rise. It was previously believed that only the bitter rind of the fruit (which contains naringin and other flavonoids) was responsible, and that it was safe to eat the pulp. However, the effects are now believed to be caused by furanocoumarins (such as bergamottin), which are found in the entire fruit. Furanocoumarins are organic compounds that are produced by a variety of plants. Although they are more concentrated in the peel than in the pulp, patients need to be careful even when eating only the pulp. Since citrus juice contains both pulp and endocarp, it can have a particularly strong effect. Furanocoumarins can inhibit certain enzymes that break down the medicine in the small intestine and block the pathway by which drugs exit the body, thus causing the blood levels to rise.

Do not eat or drink



Grapefruit, banpeiyu, pomelo, hassaku orange, sweetie, etc.

Probably ok to eat



Satsuma mandarin, orange, dekopon, hyuganatsu, etc.

These effects can last for days after consumption of the fruit, and may occur even if the medicine is taken separately.

Although research into the foods that contain furanocoumarins is making gradual progress, we do not yet know what foods affect medication. Some reports have identified foods besides citrus fruits. The citrus varieties that are known to have relatively high levels of furanocoumarins are grapefruit, sweetie (a grapefruit-pomelo hybrid), melogold (a grapefruit-pomelo hybrid), banpeiyu (a type of pomelo), pomelo, and hassaku orange (a hybrid pomelo). Juices that are thought to contain almost no furanocoumarins (from 1/100th to less than 1/1,000th the amount of grapefruit) include Satsuma mandarin, navel orange, sweet orange, hyuganatsu, ponkan, iyokan, dekopon, yuzu, kabosu, sudachi, lemon, and kumquat juice. Nevertheless, some reports have suggested that effects can occur from the peel even if the juice contains very few furanocoumarins. As fruit produces furanocoumarins naturally (and not in a set amount as in a drug), the levels can fluctuate depending on how mature the fruit is at the time of harvest and other factors. Different measurement methods can also yield different results. Therefore, please note that this information is included for reference purposes only (as of December 2014).

Q. Does my medication interact with any other foods or beverages?

A. The actions of some drugs can be affected by certain foods and beverages. Some examples are natto, green vegetable juice, milk, cheese, coffee, carbonated drinks, alcohol, and mineral water from overseas. When you pick up your prescription, please ask the pharmacist for the latest information.

Q. Are there any tips for getting children to take their medicine?

A. (1) Prepare efficiently. Extended preparations give the children who don't like taking their medicine time to realize what is happening and to put up resistance. Moreover, taking care of things quickly will help to maintain the child's attention. Have water or some other drink on hand, so that the child can rinse his or her mouth immediately after taking the medicine.

(2) Have a firm attitude about medicine-taking. If you give in when a child resists, the child will learn that, "If I refuse, they'll stop." Many parents lament that their child takes medicine easily when a nurse gives it. One reason for this is that nurses have a firm attitude and administer drugs efficiently.

(3) Giving what may feel like excessive praise ("Oh, you took your medicine so well!") will help make the next time go smoothly. Children can understand what is happening to them, so explain the importance of their medication in an age-appropriate way. Moreover, some children will behave well in front of medical workers, but will act spoiled, cry, and refuse to take medicine with their parents. It is important to draw a clear line between times when it is okay to act childish and times when proper behavior is necessary.

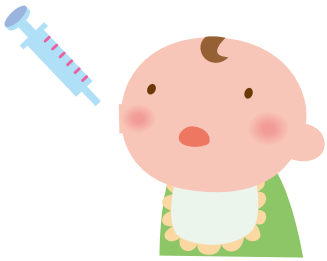
Q. How should infants take powdered medicine?

A. A single dose of powdered medicine can be placed in a shot glass or a small cup and dissolved in a teaspoon of water (about 2 cc). If too much liquid is used, the child may be unable to drink it all, so we recommend using as little water as possible. Use a dropper or syringe to squirt the liquid containing the dissolved medicine into the back of the mouth, along the inner side of the cheek. This will help the child swallow the medicine without choking. For infants, has the child started sucking on a nipple from

Give medicine through a nipple from a nursing bottle.

a nursing bottle, then gradually pour the dissolved medicine into the nipple. Children who are being weaned can drink medicine that has been dissolved in water from a shot glass or a small cup, or sip it from a spoon. After placing the powered medicine in a spoon, add a small amount of water to dissolve it. This method can be used to get a child to take their medicine with smaller and smaller amounts of water. Another tip is to use a special cup that the child likes only for the taking of medicine. If any medicine remains in the cup, add a little more water and have the child drink the rest. If the child does not take medicine well, a small amount of sugar can be added. Hospitals sometimes dissolve medicine in simple syrup, which resembles thick sugar water. At home, you can mix medicine with things like yogurt, mousse, jam, condensed milk, chocolate cream, or ice cream. Pudding or medical jelly can also be used. Give praise when a child takes medicine properly, and consider rewarding them with a treat. As cold numbs the sense of taste, some parents also have their children suck on an ice cube before taking their medicine. Around age five, many children start to prefer tablets or capsules. Powdered medicine can also be taken by wrapping it in edible paper (which comes in different flavors) or putting it in capsules. Some drug combinations can be problematic, so please check with your pharmacist.

Give medicine through a dropper or syringe.



Give medicine on a spoon.

Q. What if the medicine is thrown up?

A. Usually, if a person throws up within thirty minutes of taking their medication, it should be assumed that the medicine was also thrown up, so another dose should be taken. If more than thirty minutes have passed, the body has probably absorbed most of the drug. You should keep an eye on the person's condition, but there is no need to take another dose. However, continuous vomiting is a worrisome situation and diarrhea may cause the tacrolimus blood levels to rise. If vomiting, diarrhea, or other changes in the patient's condition occur, contact a doctor or a coordinator at the Organ Transplantation Center.

Q. Should medicine be taken if the patient has a high fever or cannot eat?

A. This is a worrisome situation, so please contact a doctor or a coordinator at the Organ Transplantation Center. Immunosuppressants should not be taken under fevers of 38.5°C or higher.

Q. Is it ok to take medication prescribed elsewhere, or over-the-counter cold medicine?

A. Over-the-counter cold medicine can be combined with most drugs. However, if you're concerned about a person's condition, please contact a doctor or a coordinator at the Organ Transplantation Center. When you

pick up your prescription, you should also ask the pharmacist for the latest information on drug combinations. Many over-the-counter cold medicines contain acetaminophen to bring down fevers and relieve pain. Acetaminophen can be hard on the liver, so be careful when taking this drug.

Q. What should I do if I lose my medication while traveling?

A. Please contact a doctor or a coordinator at the Organ Transplantation Center for instructions on what to do based on your condition and situation. When traveling by plane, keep your medication in your carry-on rather than in your checked baggage.

Q. What should I do if I forget to take my medicine?

A. First, take a dose as soon as you realize your mistake. Do not take a double dose the next time, as this could cause side effects. Medication taken three times per day should be taken at least four hours apart, and at least five hours apart for medication taken twice a day. In some cases, you may need to skip a dose. Please speak to a doctor or a coordinator at the Organ Transplantation Center about this. If you skip a dose or are late, make sure that you get back on track with the next dose. However, Urso, which is taken three times a day, and Prograf, which is taken twice a day, are incredibly important drugs. Forgetting to take Prograf could cause your blood levels to drop, putting you at risk of rejection. Meanwhile, if you take the forgotten dose too close to the next one, it could cause your blood levels to rise, increasing the risk of side effects. Therefore, please do not forget to take your medicine.

Q. What should I do if I take too much of a drug?

A. This is a worrisome situation, so please contact a doctor or a coordinator at the Organ Transplantation Center. You may be instructed to skip a dose. To avoid this, make sure that you store and handle your medication in a way that is easy to understand.

Q. How should medication be stored?

A. Keep medication in a cool place sheltered from direct sunlight, and where it cannot be reached by children. Store your medicine in its package so that you can remind yourself of how it should be taken, and only take it out of the package immediately before taking it. Some drugs, such as syrups, should be stored in the refrigerator. Others need to be kept away from light. Please check how to store your medication with your pharmacist.

Q. What is a regular pharmacy and a drug-history handbook?

A. Most people under outpatient care will get their prescriptions outside the hospital. Find a pharmacy in your neighborhood and let them know about any allergies you have, any side effects you have experienced, your disease, and other important details. If you go to the same pharmacy

every time, you don't have to repeat these explanations. They will also keep a record of your prescriptions, which will reduce the risk of mistakes. If you know when your outpatient examinations and prescription days are, it may be helpful to let your pharmacist know. If you choose a pharmacy near your home, you can drop off your prescription on your way back from the hospital, and pick it up the next time you go out. Having one regular pharmacy ensures that the pharmacist will consider your drug combinations comprehensively even if you receive prescriptions from several medical institutions. A drug-history handbook is a useful tool to keep track of what drugs you are taking, their doses, and how to take them. It is helpful to have a record of your examinations even if your prescriptions do not change. If anything should happen, these handbooks will be important sources of information. Therefore, we recommend that everyone keep one.

8 Drug price overview

Action	Drug name/form	Unit	Price (yen)
Suppress the immune system	Prograf Granules 0.2 mg	package	219.9
	Prograf Capsules 0.5 mg	capsule	458.1
	Prograf Capsules 1 mg	capsule	808.3
	Graceptor Capsules 0.5 mg	capsule	524.1
	Graceptor Capsules 1 mg	capsule	929.3
	Graceptor Capsules 5 mg	capsule	3434
	Neoral Oral Liquid 10% (100 mg/mL)	mL	928.6
	Neoral 10 mg Capsules	capsule	119.3
	Neoral 25 mg Capsules	capsule	252.2
	Neoral 50 mg Capsules	capsule	438
	Cyclosporine Fine Granules 17% (170 mg/g)	g	902.6
	Cyclosporine 10 mg Capsules (Pfizer)	capsule	84.4
	Cyclosporine 25 mg Capsules (Pfizer)	capsule	150.7
	Cyclosporine Capsules 50 mg (Pfizer)	capsule	266.1
	Cellcept Capsules 250 250 mg	capsule	293.3
	Mycophenolate Mofetil Capsule 250 mg (Pfizer)	capsule	184
	Predonine Tablets 5 mg	tablet	9.6
	Prednisolone Tablets 1 mg	tablet	8.1
	Prednisolone Powder (Takeda) 1% (10 mg/g)	g	8.9

Action	Drug name/form	Unit	Price (yen)
Protect the liver	Urso Granules 5% (50 mg/g)	g	7.7
	Urso Tablets 100 mg	tablet	11.8
	Glycyron Combination Tablets	tablet	5.6
Prevent thrombi	Anginal Powder 12.5% (125 mg/g)	g	25.8
	Persantin Tablets 25 mg	tablet	8.4
	Warfarin Granules 0.2% (2 mg/g)	g	9.3
	Warfarin Tablets 1 mg	tablet	9.6
Protect the stomach	Takepron OD Tablet 15 15 mg	tablet	89.3
	Takepron Capsules 30 30 mg	capsule	155.7
	Gaster Powder 10% (100 mg/g)	g	233.7
	Famotidine Powder 10% (Sawai) (100 mg/g)	g	89.8
	Blostar M Tablets 10 10 mg	tablet	10.6
	Mucosta Tablets 100 mg	tablet	16.4
	Rebamipide Tablets 100 mg (Tanabe)	tablet	9.6
Improve intestinal function	Gasmotin Powder 1% (10 mg/g)	g	37.3
	Tsumura Dai-kenchu-to Extract Granules (medical use)	g	9.6
Fight bacteria	Daiphen Combination Granules	g	17.7
	Daiphen Combination Tablets	tablet	15
	Baktar Combination Tablets	tablet	74.6
	Bactramin Combination Granules	g	59.8
	Kanamycin Capsules 250 mg (Meiji)	capsule	39.3
	Kanamycin Syrup 5% (Meiji) 50 mg (50 mg/mL)	mL	8.2
	Flagyl Internal Use Tablets 250 mg	tablet	35.5
Fight viruses	Valixa Tablets 450 mg	tablet	3027
Fight fungi	Florid Oral Gel 2%	5g	508
Improve the intestinal flora	Biofermin Combination Powder	g	6.2
	Biofermin R Powder	g	6.2
	Biofermin R tablet	tablet	5.8
	Biolactis Powder	g	6.2
	Bio-Three Combination Tablets	tablet	5.6
Relieve pain	Loxoprofen Tablets 60 mg (EMEC)	tablet	7.8
	Loxonin Tablets 60 mg	tablet	17.5
	Tramal OD Tablets 25 mg	tablet	38.6
	Adofeed Pap 40 mg 10cm×14cm	6 sheets	109.8
	Mohrus Tape 20 mg 7cm×10cm	7 sheets	198.8

Action	Drug name/form	Unit	Price (yen)
Mouthwash	Isodine Gargle Liquid 7%	30 mL container	99
Protect the skin	Propeto	g	1.63
Lower the ammonia levels	Monilac Syrup 65% (650 mg/mL)	mL	6.4
	Piarle Syrup 65% (650 mg/mL)	mL	4.8
	Monilac bulk	g	6.5
Reduce excess fluid through the urine	Lasix Fine Granules 4% (40 mg/g)	g	16.1
	Lasix Tablets 20 mg	tablet	9.6
	Aldactone A Fine Granules 10% (100 mg/g)	g	92.2
	Aldactone A Tablets 25 mg	tablet	21.8
Lower the blood pressure	Norvasc Tablets 2.5 mg	tablet	29.9
	Amlodipine Tablets 5 mg (Meiji)	tablet	32.2
	Sepamit-R Fine Granules 2% (20 mg/g)	g	37.5
Support mitochondria	L-Cartin FF Oral Liquid 10% (100 mg/mL)	mL	72.4
	L-Cartin Tablets 100 mg	tablet	97.3
	L-Cartin Tablets 300 mg	tablet	292
Vitamin B1	Benfotiamine Tablets 25 mg	tablet	5.6
Vitamin C	Cinal Combination Granules	g	6.2
Vitamin D	Alfarol Powder 1 μg/g	g	87
	Alfarol Oral Liquid 0.5 μg/mL	mL	75.7
	Alfarol Capsules 0.25μg	capsule	22.2
	Alfarol Capsules 1μg	capsule	77.9
	Caldemin Tablets 0.25μg	tablet	21.4
Vitamin H	Biotin 0.2% (whey) (2 mg/g)	g	7.6
Vitamin K	Kaytwo Syrup 0.2% (2 mg/mL)	mL	27.5
	Glakay Capsules 15 mg	capsule	34
Multivitamin	Panvitan Powder	g	6.2
Sweetener	Simple Syrup	10 mL	9.4

Japanese government's medical information service –
Example based on data revised on September 1, 2015
Urso Granules 5% (50 mg/g)
150 mg per day → 3 g per day → 23.1 yen per day

While transplantation does not always go exactly as planned, we want the donor, the recipient, and everyone involved to be healthy as possible. If you are not feeling well, we hope that you will come consult us.

Hidemi Tokunaga
Pharmaceutical Department
National Center for Child Health and Development

8 Eating after liver transplantation

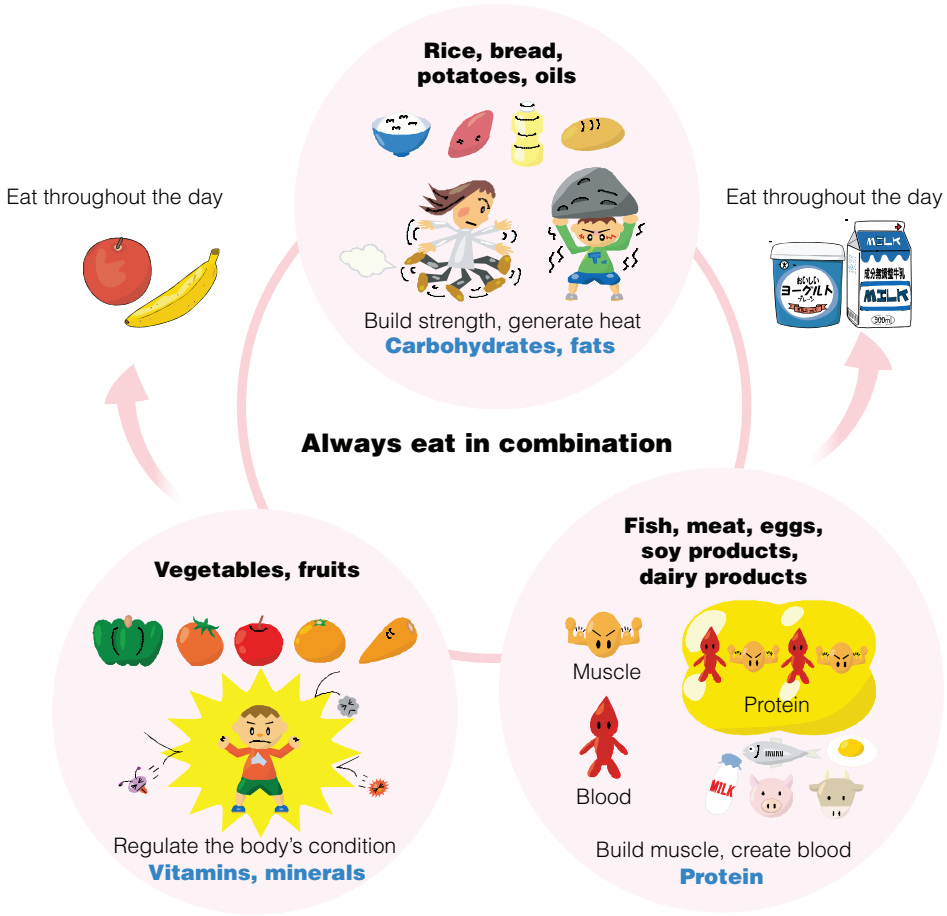
1 Basic pointers for recipients

- Unless the recipient has a metabolic disorder and apart from certain fruits and juices, there are no food restrictions. It is important to eat a balanced diet and to avoid eating too much of any particular food.
  * Recipients with metabolic disorders should follow their doctors' instructions about milk and diet.
- After leaving the hospital, there is no need to avoid raw foods (raw fish, sushi, raw vegetables, raw eggs, fruit, and tap water), unless a doctor says otherwise. Wash your hands regularly and make sure that your food and cooking implements are clean and hygienic.
- Do not eat fruits such as grapefruit, hassaku orange, pomelo, or sweetie (or drink juice made from them) as they can cause side effects by strengthening the action of immunosuppressant drugs (for more details, see "2.7 Liver transplantation and medication").
- As taking steroids can increase the risk of osteoporosis, make sure to eat food that is high in calcium.
- Steroids can increase the appetite, so be careful not to overeat.
- Transplant recipients should avoid alcoholic drinks, both in the short and long term.

2 What is a balanced diet?

Humans need nutrients from food to grow and stay healthy. When people only eat things they like, they may not get enough of certain nutrients. Each meal should include a combination of a staple food, a main dish (fish, meat, eggs, soy products), and side dishes (vegetables). A balanced diet also includes daily servings of dairy products and fruit. It is important to eat three meals a day. You should not skip meals.

Food is incredibly important
A healthy body is built on food



3 Daily amounts

Amounts for children aged 18 months to 2 years

Combine in every meal

Staple food	Rice: 1 small child's rice bowl (90 g) × 3 Equivalent to 1 serving of rice: Bread: 1 slice from an 8-slice loaf; Noodles: About 1/3~1/2 serving
Main dish	Fish: Fillet 1/3~1/2 slice (30 g) Meat: Thin slice 1~1.5 slice (30 g) Egg: 1/2 large egg (30 g) Soy products: Tofu 1/8 block (50 g) or Natto 1/2 box
Side dishes	Vegetables: 180 g (half should be colorful veggies) A suitable amount of seaweed/mushrooms Potato: 1/2 (50 g)

Eat throughout the day

Dairy products	Milk 200 cc Yogurt 50 g
Fruit	Apple 1/3 Or Banana 1 small one (100 g)
Oil	1/2~1 tablespoon 5~10 g (including in mayonnaise/butter)
Snacks	Snacks Eat foods that are not part of the other 3 meals

Daily amounts for children aged 3~5

Combine in every meal	Staple food	Rice: 1 child's rice bowl (120 g) × 3 Equivalent to 1 serving of rice: Bread: 1 slice from a 6-slice loaf; Noodles: About 2/3 serving
	Main dish	Fish: Fillet 1/3~1/2 slice (30 g) Meat: Thin slice 1~1.5 slice (30 g) Egg: 1 large egg (50 g) Soy products: Tofu 1/7 block (60 g) or Natto 1/2 box
	Side dishes	Vegetables: 270 g (half should be colorful veggies) A suitable amount of seaweed/mushrooms Potato: 2/3 (70 g)
Eat throughout the day	Dairy products	Milk: 200 cc Yogurt: 50 g
	Fruit	Apple: 1/2 Or 1 banana (150 g)
	Oil	1 tablespoon 10 g (including in mayonnaise/butter)
	Snacks	Eat foods that are not part of the other 3 meals, and other commercial food products.

4 Snacks for infants

As infants have small stomachs, they cannot get all the nutrients they need from just three meals. Snacks should form a regular part of their diet, and should provide the nutrients they may otherwise be lacking. Snack time is also an opportunity to drink fluids. Make sure that your child is getting enough to drink.

(1) When to eat?

Decide on snack times once or twice a day. A good time is around 3 p.m., as it will not affect other meals. However, anytime that is at least two hours before or after a meal and fits your child's schedule is fine. Feeding children only what they want could cause them to eat less or to develop cavities.

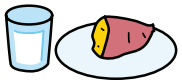
(2) How much to eat?

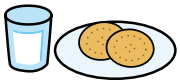
A good yardstick is one-third of a regular meal. About 10% to 20% of a child's daily calories should come from snacks. Depending on the child's physique or activity level, this is about 150 kcal for children aged one and two, and around 200 kcal for children aged three to five.

(3) What to eat?

Healthy snacks include milk, dairy products, potatoes, fruit, grains, and beans. If snacks are purchased from a store, they should be suitable for infants. For a child aged one or two years, 150 cc of milk provide 100 kcal, so this should be combined with about 50 kcal of other snacks.

Equivalent to 50 kcal	
Sweet potato	1/4 of medium-sized one
Potato	1/2 of large one
Banana	1/2
Tangerine	1
Apple	1/2 of medium-sized one
Biscuit	20 g


Milk with sweet potato


Milk with biscuits


Milk with fruit


Milk with steamed cake

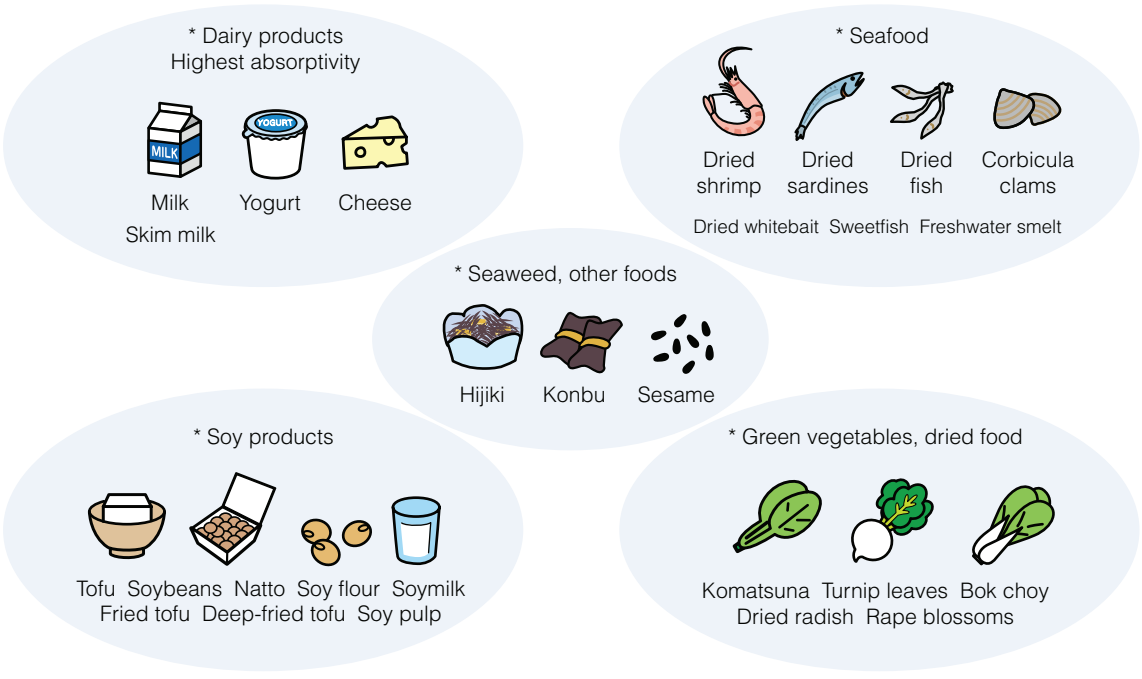
* Caution
Snacks high in sugar, salt, or oil can cause obesity. You should also make sure that your child does not drink too many cold drinks or have too much juice.

5 Preventing osteoporosis

(1) Eat foods high in calcium

Other foods besides dairy products are high in calcium. Try to eat one food from each group every day.

Foods high in calcium



(2) Eat foods that facilitate calcium absorption

① Foods high in vitamin D

Salmon | Saury, mackerel, sardine | Flounder | Tuna, bonito | Eel | Dried mushrooms | Egg yolk | Butter

② Foods high in protein

These include meat, fish, eggs, soy products, and dairy products. However, too much protein can affect the calcium absorption negatively.

(3) Be careful of foods that can harm the calcium absorption.

① Avoid excessive salt

Soy sauce | Salt

② Avoid excessive phosphorus

Instant foods | Snacks | Carbonated drinks | Frozen foods | Retort-pouch foods

(4) Other pointers

① Eating foods high in vitamin K can promote bone growth.

Natto | Ashitaba | Mulukhiyah | Spinach | Broccoli

② As proper exercise can increase the bone mass, frequent physical activity is encouraged.

③ Exposing the skin to ultraviolet light helps to create vitamin D. Therefore, some exposure to sunlight is a good thing (the amount that comes through lace curtains is enough).

6 Diet-related questions

Q. What should we be careful about in terms of food hygiene?

A. When barbequing meat, use different utensils to handle raw and cooked meat. (Don't eat with utensils that have touched raw meat.) When cooking steak, make sure that processed meat is thoroughly heated.

Q. My child's transplant was performed before he or she started eating solid food. What food is best for weaning? I'm worried about allergies, so should possible allergens be introduced later?

A. If your child has already been diagnosed with an allergy and has been instructed to avoid certain foods, he or she can start eating solid foods that do not include the allergen. It was previously thought that children should wait a while before eating potential allergens, but recent research has shown that this is not necessary. This is also believed to be true for children who take immunosuppressants. Please follow the regular methods for weaning.

We hope that this Handbook will help ease some of the anxiety and worries of families and children considering liver transplantation. As certified nutritionists, we aim to put a smile on the face of every child we work with. We are available for individual dietary consultations. If interested, please contact your doctor.

Miki Nakano
Department of Nutritional Management
National Center for Child Health and Development

9 Liver transplantation and pregnancy/childbirth

When parents first discover that their child is sick, all they can think about is fighting the disease. After the transplant, when the child's symptoms have stabilized, their thoughts turn to the future and to worries about school, work, marriage, and having children.

Although organ transplantation does not have a very long history, there have already been many reports from overseas of people getting pregnant and having children after transplants. In Japan, various initiatives are in progress, including the creation of guidelines for transplant patients who are considering pregnancy, and the establishment of a registry for post-transplant pregnancies and births.

In this section, we describe what is currently known about pregnancy after liver transplantation. We hope that it will be of help as you move forward and look to the future.

1 Data on pregnancy and childbirth after organ transplantation

The first woman to become pregnant and give birth after an organ transplant (in 1956) was a kidney transplant patient. Now, each year brings more and more reports of births after liver, heart, pancreas, and other organ transplants. In 1991,

the National Transplantation Pregnancy Registry (NTPR) was established in North America. By 2014, the NTPR had registered more than 3,300 post-transplant pregnancies. At that time, pregnancies after kidney transplants were the most common, with approximately 1,500 cases. Other countries, including many in Europe, have also implemented registries.

The NTPR reported the registration of 1,422 pregnancies from 886 kidney transplant patients and 292 pregnancies from 166 liver transplant patients by 2010. The report examined these women's pregnancies, deliveries, children, and other factors in detail. A 2011 survey by a Japanese transplantation society reported 38 pregnancies by 30 transplant patients in Japan, resulting in 31 births.

2 Secondary sex characteristics and fertility

Many patients who need liver transplantation begin treatment when they are young and continue therapy for many years. These patients often exhibit nutritional or growth disorders before the transplant. They also often develop secondary sex characteristics late. The Japanese Liver Transplantation Society surveyed the growth, bone density, and nutritional status of end-stage liver disease patients aged 16 and younger. They found a marked improvement in growth after liver transplantation in patients who had a low bone density and poor nutritional status before the transplant.

Many liver failure patients experience irregular menstruation or amenorrhea due to nutritional disorders and other causes. However, in approximately 80% of patients with irregular menstruation, the menstrual cycle returns to normal after the liver transplant. Larger studies have been performed on kidney failure patients. End-stage kidney failure is often associated with amenorrhea caused by anemia, hormone secretion disorders, or other issues, and with a decline in the pregnancy rate. However, in many patients, the secretion of sex hormones improves and the menstrual cycle resumes after a kidney transplant. Nevertheless, menstrual irregularities sometimes persist even after the liver or kidney functions have been improved by an organ transplant. For this reason, patients who wish to become pregnant should have their fertility evaluated early on through hormone tests and other examinations.

As some drugs used to treat kidney and liver diseases before transplantation can affect patients' fertility, their treatment and medical histories may also need to be checked.

After an organ transplant, complications may sometimes need to be evaluated and the patient's medication adjusted before pregnancy can occur. On the other hand, the fertility sometimes recovers naturally, and the patient may get pregnant unexpectedly. If you are considering getting pregnant, please talk to your primary physician early on to discuss how to prepare for it.

3 Impact of immunosuppressants on pregnancy and babies

After an organ transplant, patients generally have to take immunosuppressants continuously. Those who undergo a transplant at a young age will take

immunosuppressants for many years, so they may worry about the way these drugs can affect pregnancies and babies.

In Japan, the guidelines for calcineurin inhibitors (cyclosporin, tacrolimus) and azathioprine, which are often used after organ transplants, state that these drugs should not be taken by women who are or who want to become pregnant.

Package insert
Documentation that includes information about the drug, related warnings, and other important topics.

Congenital deformities reportedly occur in 3% to 5% of babies born to women who are not sick and who do not take medication during pregnancy. When considering the impact of a drug, the deformity rate associated with the use of that drug needs to be compared with the general deformity rate. Moreover, for various reasons, approximately 15% of pregnancies end in miscarriage. This should be considered when examining the miscarriage rate of women taking a drug.

Past studies have found that the congenital deformity and miscarriage rates of women taking calcineurin inhibitors (cyclosporine, tacrolimus) were not different from those of women in general. Regarding azathioprine, similarly, a large study of inflammatory bowel disease found no differences between the congenital deformity and miscarriage rates of women who took the drug and those of women in general.

In light of these findings, the guidelines on post-transplant pregnancy in Europe and the United States allow for maintenance doses of cyclosporine to be taken during pregnancy. To supplement package inserts, in 2014, the Japan Society of Obstetrics and Gynecology issued guidelines to state that some contraindicated medical products could be used during pregnancy if necessary. They recommended cyclosporine, tacrolimus hydrate, and azathioprine as substitute medications.

However, information from the aforementioned North American registry has shown that the immunosuppressant CellCept (mycophenolate mofetil) is associated with higher miscarriage and congenital deformity rates. The package insert for this drug indicates that pregnancy should be planned to occur at least six weeks after stopping the drug, and should be avoided while on the drug.

However, halting immunosuppressant administration may cause rejection, which could be dangerous for both the mother and the baby. If you are considering pregnancy, please speak to your doctor about adjusting your medication.

In addition, during pregnancy, patients may have to take a wide variety of drugs to deal with the infections and other complications that can occur after a transplant. The NCCHD's Japan Drug Information Institute in Pregnancy (an initiative of the Ministry of Health, Labor, and Welfare) gathers data on pregnancy and medical products, and provides outpatient consultations on matters such as drug use during pregnancy and breastfeeding.

Japan Drug Information Institute in Pregnancy

Address:
Japan Drug Information Institute in Pregnancy
National Center for Child Health and Development
2 Chome-10-1 Okura, Setagaya-ku, Tokyo, Japan 157-0074

Opening hours:
Monday to Friday (except holidays)
10 a.m. – 12 p.m., 1 p.m. – 4 p.m.

TEL: +81-3-5494-7845
URLs: http://www.ncchd.go.jp/kusuri/index.html (Japanese),
http://www.ncchd.go.jp/en/index.html (English)

* For more information, please visit the website of the Japan Drug Information Institute in Pregnancy.

4 Problems that may occur during pregnancy or childbirth

When taking calcineurin inhibitor immunosuppressants (cyclosporine, tacrolimus) after an organ transplant, side effects such as kidney dysfunction and high blood pressure may occur even before pregnancy. High blood pressure is an extremely common complication of pregnancy. A study of 450 pregnancies after liver transplantation and 4,002 pregnancies after kidney transplantation revealed high blood pressure in 27.2% of the former and in 54.2% of the latter. The presence of high blood pressure and proteinuria used to be called toxemia of pregnancy, but is now referred to as preeclampsia. If this condition becomes severe, it can slow the development of the fetus, and even threaten the pregnancy. Therefore, your blood pressure should be evaluated and treated appropriately before you become pregnant.

Moreover, the use of hypotensive drugs during pregnancy necessitates careful consideration. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been found to cause severe fetotoxicity in the second and third trimesters. These drugs should therefore be avoided as a rule.

In general, pregnant women are at a higher risk of urinary tract and other infections. As the effects of the immunosuppressants taken after organ transplantation can further increase the risk of infections and their severity, infection screenings such as urine tests and urine cultures should be performed regularly. In addition, viral infections such as cytomegalovirus infections and toxoplasmosis may affect the fetus. As transplant patients are at a higher risk of contracting these infections, they should be tested – and, if necessary, treated – before pregnancy, and should be tested regularly during pregnancy.

Past studies have shown that premature births occurring before the 37th week and low-birth-weight infants are more common after organ transplantation. However, these statistics included artificial premature deliveries, such as

Cesarean sections performed to deal with high blood pressure and other complications, making it difficult to assess the frequency of miscarriages. Premature births and low-birth-weight infants are more common after kidney transplants than after other organ transplants, possibly due to the greater impact of a high blood pressure. In any case, in pregnancy and childbirth after organ transplantation, the risks for the baby must be considered, and delivery should be performed at a medical institution that can respond rapidly to situations involving the baby.

Almost half of the births that have been reported involved Cesarean sections. However, the overseas guidelines for pregnancy after organ transplantation state that considering the risk of infections and other complications, vaginal births are the most advantageous.

5 Problems after delivery (breastfeeding, etc.)

Breastfeeding has many benefits for both the mother and the child. It lowers the risk of infection and promotes the intellectual development of the baby, and the mother also benefits as it promotes recovery of the uterus and reduces the incidence of diabetes. However, transplant patients must take immunosuppressants and a variety of other medications that can affect the baby through the breast milk. Unfortunately, in Japan, the package inserts for most drugs (and not only for immunosuppressants) state that the medications should not be used while breastfeeding as they can get into the breast milk.

Overseas studies on the use of cyclosporin, tacrolimus, and azathioprine—the main immunosuppressants used after organ transplantation—revealed that when nursing, only small amounts of these drugs were secreted in the breast milk, and that babies only ingested tiny amounts through breastfeeding. Moreover, there have been no reports of adverse events in babies breastfed by women taking these drugs. However, as the dose taken by the mother and the way the baby metabolizes medication can vary greatly between individuals, babies should be monitored and have their blood tested regularly. Furthermore, the mother should stop breastfeeding if any problem appears.

Past studies on the use of medication while breastfeeding have shown that many drugs could be used relatively safely by nursing mothers. However, more information is needed as not all drugs have been proven to be absolutely safe, particularly in the long run. More information on drugs is becoming available every day. Therefore, talk about your concerns. For example, you can discuss them in an outpatient breastfeeding consultation at the Japan Drug Information Institute in Pregnancy. Your treatment needs should remain your top priority when it comes to medication, so please discuss breastfeeding thoroughly with your primary physician.

When thinking about pregnancy and childbirth, you may also have concerns about how the process will affect the transplanted organ. Several long-term studies have compared kidney transplant patients with and without a history of pregnancy. No major difference in the transplanted kidney failure rate was found between these groups, and pregnancy was not thought to impact the long-term prognosis of the transplanted kidney negatively. Although only a few studies have examined pregnancy after liver transplantation, none have shown that it affected the transplanted liver negatively.

However, there have been reports of patients needing treatment for rejection during pregnancy and after delivery. Therefore, it is important to have the transplanted organ evaluated regularly, both during pregnancy and after delivery. In particular, if your immunosuppressants are changed or adjusted during pregnancy, they should be readjusted soon after delivery.

Although a variety of problems involving the management of pregnancy have been reported, most liver transplant patients give birth to healthy children. As a pediatrician, I have seen many children grow up to become excellent mothers, fathers, and members of society. Seeing them grow is one of the joys of our job.

Sachi Koinuma
Japan Drug Information Institute in Pregnancy
National Center for Child Health and Development

Ms. A began a new life after receiving a liver transplant at the NCCHD. She is now 24 years old, and cuts a stylish and slender figure with her chestnut-brown hair and long boots. Ms. A was a high-school senior when she received a liver transplant. She later became a wife, then a mother, and currently works as a licensed care worker. This summer will bring yet another member to her family. She spoke to us about her experiences of love, marriage, pregnancy, childbirth, and employment after undergoing a liver transplant.

“I have biliary atresia. I had jaundice when I was born, so I underwent phototherapy, but there were no problems with the color of my stool. When I was about two months old, my mother noticed that my stool was pale, so she brought me to the hospital. I was quickly referred to a university hospital, where I was diagnosed with biliary atresia. After I underwent the Kasai procedure (portoenterostomy), I was doing fine. I loved being active, but I was aware of my physical limitations, so I was careful not to go too far.

I had a scar on my belly from the Kasai procedure, but my mom told me, 'The scar is nothing to be embarrassed about. It's not a bad thing. It's like a medal. Don't let your friends tease you about the scar. And if they do, tell me about it.' So, I never worried about my scar. I wouldn't even hide it when I changed for the pool in primary school. As I grew older, I would sometimes hide it because it was annoying to be constantly asked about it (laughs), but I was never the least bit embarrassed by it. I love baths and I often go to hot springs. I'm totally comfortable. The Kasai procedure scar has turned white, but the scar from the liver transplant is still red and in a T shape. If someone I've just met asks me about my scars at a hot spring, I answer naturally. It's part of getting to know people, and can actually be fun. If a child innocently asks about the scars, their mother will often say something like, 'What are you asking something like that for?' It's funny to see a kid turn pale and look uneasy.

During the liver transplant, four wounds were made on my body for drainage. The lower two turned into keloids that looked like switches.

They were exactly where the waistband of my underwear sat, so when I changed, I had to be careful not to catch them with my fingernails, even if I cut them short. My mom suggested I get the keloids surgically removed so I could wear a bikini. A dermatologist at the NCCHD confirmed that surgery could fix it, so I had it done. That was about 18 months after the liver transplant.

I started thinking about my future in middle school. I chose the welfare industry because I wanted to help others and I knew there was always a shortage of workers in that area. I thought that if I got certified, I could find a job even with my physical disability. Therefore, I chose a high school with a welfare curriculum that would let me take the national certification exam when I graduated. I didn't play sports in high school, but I liked to jog because I could exercise at my own pace. However, around the summer of my final year in high school, I started having fevers about once a month. I was busy with school, so I put off going to the hospital. During the summer vacation, I even took a four-day course that would exempt me from the practical portion of the care worker exam. Coming home on the last day of the course, a friend of my mom's who works as a nurse told me that the whites of my eyes looked yellow. I looked in the mirror when I got home, and they did seem yellow.

As I saw my face every day, I hadn't noticed the jaundice. I decided to visit my primary care doctor, but outpatient visits with him were only available on certain days, so I had to wait a few more days. I expected to be hospitalized, so I packed a bag when I went to the outpatient visit. They immediately admitted me to the hospital and I had surgery after fasting for three days. They found atrophy and cirrhosis of the liver, and too many small stones to remove. My liver didn't recover after the surgery and I had fevers so high that they couldn't be measured with a thermometer. The fever finally went down in September, but as soon as I would start eating, my liver values would go up. 'You need a transplant,' they told me. At the time I thought, 'If that's the only way for me to live, that's how it has to be.' My primary care doctor contacted Dr. Kasahara at the NCCHD and we started talking about a transplant.

I was transferred to the NCCHD for transplant surgery that December. My mom decided to be the donor. I understood that I would be undergoing transplant surgery, but things were happening so fast, it didn't seem real. I was in a bad state, but my mom and the doctors only talked about how I was going to live. They never even mentioned death. So for me, the transplant was just another surgery. Still, since I was 18 years old, I had to sign the consent form myself. When they asked me if I was being forced to have surgery, that's when it started to feel real. Before the transplant I was anxious, not about whether I would live or die, but about the possibility of my mom dying. I was able to talk over so many things with the recipient transplant coordinator before the surgery. Afterward, I tried to be optimistic. My recovery went well and I left the hospital in January. It really surprised me how much I could do without getting tired after the transplant.

I graduated from high school in March, but since my hospitalization and surgery had overlapped with the job-hunting season and the preparation period for the national exam, I hadn't been able to get certified and to find a job like I'd wanted. Instead, I worked on building up my strength, and that summer I worked part-time in a convenience store for four days a week. I did it all—from working the register to stocking shelves. After that, I felt stronger, so I found a job at a day-service center for four days a week in the autumn. I worked there for a year, then for the next six months I stopped working to focus on studying for the national exam. I was so happy when I passed.

I wanted to find a job in which I could maximize the skills and knowledge I'd gained in school. That spring I was hired at a special nursing home for the elderly. I didn't tell my coworkers about my liver transplant or that I was taking immunosuppressants. I didn't want special treatment for having a disability. After working there for two years, I felt a lot stronger. I was healthy enough to start jogging again in order to relieve stress. When I'm feeling irritated, I have to run. I don't take a set course. I just run for as long as I can. I've even gotten lost before (laughs).

I met my husband on this job. During my second year there, a research team was put together to prepare presentations for academic conferences. My future husband and I were chosen to be on the team. Until then, we had a senior-junior relationship at work, but we became closer once we started spending more time together in the research meetings. Once, I asked him about a personal problem and I was really impressed with how closely he listened and the advice he gave. Nobody had ever given me advice after thinking so deeply about my problems before. 'He's a good person,' I thought. He was good at his job, passionate about what he did, and nice to the people at the nursing home—he's like me in those ways. We started talking about things besides research, and discovered we both liked going to movies. We decided to go watch one together, and that's how we started going out. I'd decided that I wouldn't date anybody who couldn't accept my disease and still be willing to marry me. So one day after eating out, I told him while standing at a crosswalk, 'Actually, I've had a liver transplant. I have a disability.'

In everyday life, I don't think of myself as a disabled person, but you end up in that category if that's how others see you. But I don't want pity for my disease. If telling him about my disability was going to make him pull back, I thought it was better for us not to get any closer.

I thought most families would want to steer clear of me once they learned I had a disability. I thought I'd live my life alone without ever getting married. But his response was just, 'Oh. So what?'

I was so surprised. I thought he would be taken aback. 'This person is amazing! I didn't think he'd react that way,' I thought.

'See you later. Work tomorrow, you know. Tell me more about your disease later,' he said.

His words were so unexpected. That night I told my mom, 'I met someone special.'

Sometime later, we decided to go see a local fireworks exhibition together. I wanted this time to be like a real date, so I planned it all out. During dinner I asked him, 'Will you be my boyfriend?'

'I was going to ask you the same thing!' he said.

'I should have waited a little longer then,' I said, laughing.

Eventually I introduced him to my mom. She was so happy. Did he propose? No, not formally, we just naturally moved toward marriage. Later, I heard that when I'd left them alone that day, he had told my mom he wanted to marry me. My mom got so excited and started asking about grandkids. I wasn't sure so we talked to the people at the NCCHD about pregnancy and I guess that clinched it.

I hadn't realized I could get pregnant. I didn't get my period until I was 18, the summer after the liver transplant. I was almost done with work one day when I started bleeding. I was so surprised. My family was so happy for me, they even cooked me a celebratory meal. I think my periods are heavy, but I don't have pain and my cycle is irregular. There was also the transplant to consider, so we went to the NCCHD to talk about it.

The doctors lowered the dose of the immunosuppressants I was taking and changed some others out of consideration for the fetus. About a year after adjusting my medication, I realized that I hadn't had a period in three or four months. I had been feeling bad around that time, experiencing stomach pain, so I thought maybe I was sick, but I was focused on other things. I felt better if I ate, so I started eating more. Now I realize it was morning sickness. But no matter how irregular my period was, it was strange for it not to have come for three or four months. I talked to Dr. Kasahara at the NCCHD, and he told me to go to the drug store and buy a pregnancy test. I did, and sure enough it was positive. When I went to the NCCHD for an appointment, they told me

I was five months pregnant. ‘Oh! There’s been a baby in my belly,’ I realized. My husband was worried about my health, but we were happy that our family would be gaining a new member. I’m the type that researches things in advance so I feel like I know what’s happening. For me, ‘I don’t know’ is a scary feeling. If I understand a situation, I feel comfortable moving forward. I wanted to talk to people who had similar experiences. I searched the social network Mixi for people who had given birth after a liver transplant for biliary atresia, but I didn’t find any. My husband told me, ‘Don’t worry about things alone. Talk to me.’ So we tackled things together. My husband was very supportive. He gave me so much strength.

My pregnancy was fine. Later in the pregnancy, I had some protein in my urine, but I didn’t have pre-eclampsia or anything. We were on a trip around New Year’s when my side started hurting and I developed a fever. Dr. Kasahara said, ‘You had that transplant, so why don’t you come to the hospital so we can keep an eye on you.’ At the NCCHD, they thought it might be pyelonephritis or cholangitis, or maybe the baby had grown and was putting pressure on my abdominal cavity, but my liver values were fine and the ultrasound was normal. They never figured out what had caused the fever.

I wanted a natural birth with my husband in the delivery room, but since my fever went up and down in a regular pattern, my doctors said it would be better to give birth when the fever was low. A balloon was inserted to induce labor, but a day passed and nothing happened. The next morning at 6 a.m. I had an intravenous inducer, but it only led to pain, nothing else. It was really hard. By 11 p.m., the baby’s head still wasn’t properly entering the pelvis, so a Cesarean section was performed to prevent any further strain on the baby. My husband stayed by my side through the whole thing. Once when the pain was bad, I dug my fingernails into his neck, but he never said a word.

Five minutes into the next day, our baby girl was delivered by Cesarean section. I was tired, but also happy she had finally arrived. They needed to investigate the effects of the immunosuppressants, so I couldn’t give her colostrum, but after three days of tests in the hospital I got approval to start nursing. I produced plenty of milk, enough to soak a towel that was against my chest. At first I had trouble getting my daughter to nurse, but I gradually got the hang of it.

After leaving the hospital I went straight back home, without spending time at my parents’ house, as some Japanese women do. My mom was working a night shift at the time, so I didn’t want to be a burden on her. I didn’t nurse every few hours or on any schedule, just every time the baby cried. My daughter was a good sleeper, so I tried to rest whenever she slept so I could take care of her properly. I was able to care for her and to take care of the house at my own pace. My husband was busy at work. He had to work nights about eight

times a month, but whenever he was home, he would happily change diapers and hold the baby when she cried, so I felt comfortable letting him handle things. Sometimes I got mad at him when he tried to pick up the baby after I'd finally gotten her to sleep (laughs). Now my daughter goes to daycare and I work the day shift at a special nursing home for the elderly four days a week. When my husband gets home, he watches our daughter while I make dinner. We make a good team. On my days off, I do housework or just whatever I want, although sometimes I don't feel well and need to rest. At times like these, my husband takes care of our daughter so I can be alone. Time has really flown by since the baby was born. The first year was over in a flash. Now my daughter likes to sing the chorus of the song from 'Frozen.' She loves to talk and laughs a lot. Lately she seems to want a lot of attention.

After giving birth, my period became more regular. I was told not to get pregnant for a year, and soon after that year was up, I discovered I was expecting again. My husband was happy. 'Now I've got to work!' he said. This time I went to the doctor early. The baby is due around the end of the rainy season, in early summer. I still need to talk to my coworkers about my pregnancy.

I want to keep working. I like having time to concentrate on things. When my husband and I have the same days off, we go to movies while our daughter is at daycare, and we enjoy our time alone together.

We named our daughter Akari. When she was born, Dr. Kasahara said, 'You're the first NCCHD transplant patient to give birth! It's like a second grandchild for me.' I chose a name that includes the character for 'star' because it felt like my daughter could be a 'star of hope' for other children with the same disease. I believe in a bright future, and that dreams are not just dreams, but can come true. My daughter is a symbol of that.

What do I want to say to children thinking about liver transplantation or who have had a transplant? I'd tell them to see the scars from surgery as medals, not something to hide. If you think of them that way, you won't be teased. Don't be timid. Life doesn't always go as planned. Don't close off paths for yourself. Some people draw a line on their future, but if you don't shut yourself out, you can build your own future. Believe that you can be happy."

While Ms. A was recounting her memories, she would often look affectionately at her husband when recalling certain events. They showed us several photos of Akari's smiling face on their smartphones. Her innocent and carefree smile reflects the warm home Ms. A and her husband have built. In meeting a partner who adores her and fully accepts and understands her disease and her liver transplant, Ms. A discovered a new form of happiness. Her experience shows that a liver transplant is not just a way to keep someone alive, but something that helps to create a new future. Ms. A's positive

attitude and willingness to work toward the future she wanted were a big help to her. While Ms. A was talking, her husband often looked at her fondly. These looks seemed a perfect reflection of the trust and support they offer each other as they work to create a happy family.

We hope that children and families thinking about a transplant will find happiness, and will achieve their own dreams just like Ms. A.

Organ Transplantation Center
National Center for Child Health and Development

10 The liver transplantation process

The process and schedule described below differ to a certain extent for foreign patients, who need to be referred by a registered government guarantor. This section describes the procedure for a regular liver transplant at the NCCHD.

From the start of the process to life after the transplant, patients and their families will have all kinds of questions and concerns. Although a lot of information is available online, you may sometimes not be able to find the information you need, or may encounter biased information that will only cause more anxiety. At the NCCHD, multiple departments and professionals work together to create a seamless support system for children who receive liver transplantation and their families. Please do not keep your worries to yourself: come to us with your questions at any stage of the process, and we will do our best to dispel your concerns.

In this section, we describe what is involved throughout the liver transplant process, as well as the follow-up terms for the child receiving the transplant and the family (including siblings), and we provide a general schedule. Donors can refer to “2.12 For people thinking of becoming living donors” for more details.

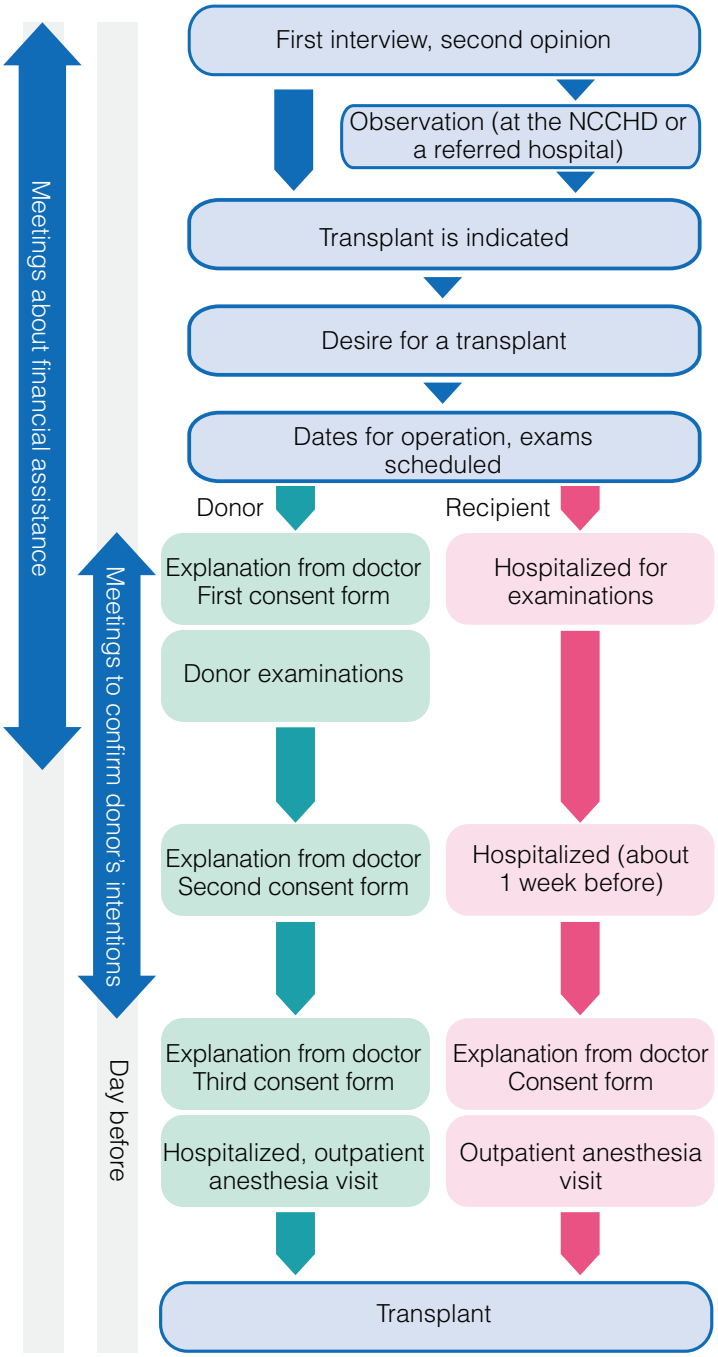
1 Thinking about a liver transplant

Regardless of why you are considering a liver transplant, the decision to undergo a major operation inevitably leads to much worry and conflict. The questions can be endless: Is a transplant really necessary? What is the difference between a living donor and a deceased donor? What will happen if we go ahead with the transplant? What will happen if we do not? What will life be like afterward?

At the first meeting, you will be asked many questions about your child, his or her medical history, and your family history. You will also be given a general

explanation of what a liver transplant entails, its benefits and risks, and the risks involved for living donors. This meeting usually lasts one or two hours. We will work hard to answer your questions and address your concerns. Therefore, please do consider what you want to ask before the meeting.

What happens in a liver transplant (up to the transplant)



That said, there is a huge amount of information to process, so you will not understand everything after one meeting. Things will be explained repeatedly as you prepare for the transplant. Depending on the situation, a schedule for the transplant may be drawn up at the first meeting. If a transplant is not necessary right away, a wait-and-see approach is sometimes adopted. In

other cases, follow-up will be performed by both your regular hospital and the NCCHD. Regardless of what is decided, people often think of more questions and concerns after returning home. Please feel free to contact us at any time. If necessary, we can schedule another meeting. We urge families not to keep their worries to themselves.

There are also financial issues to consider, such as how to pay for medical expenses and lodging for those who come from far away. The Center's medical social workers can help with these matters. For more details, please refer to "2.14 Liver transplantation and the medical expenses assistance system."

Parents may worry about how to talk to their child and any siblings about the surgery and the hospital stay. The NCCHD employs child life specialists who can teach you how to speak to your children in ways that are easy for them to understand. For more information, please see "2.11 Preoperative follow-up of children undergoing liver transplantation."

The NCCHD also has an association of families that have experienced liver transplantation, called the "Do-Re-Mi-Fa Club". As some difficulties can only be understood by families that have experienced them, the club's website can be a useful reference. In addition, it may also be possible to speak to some members of the club.

We seek to offer information about as many issues as possible while you decide whether to choose transplantation.

2 After the transplant is scheduled

* The recipient (child receiving the transplant)

The recipient needs to be hospitalized for approximately a week to 10 days to undergo tests, including blood sampling, abdominal ultrasounds, CT scans, X-rays, ECG, cardiac ultrasounds, dental examinations, etc. Depending on the underlying disease or the results of the initial examinations, additional tests may be necessary. Patients are usually hospitalized for tests one or two months before the transplant. However, in some cases, the tests are scheduled only a couple of weeks before the operation.

As the NCCHD is a pediatric transplant institution, approximately 80% of the transplant recipients are children who have not yet started school. For children aged 6 years and older, transplants are performed after explaining the procedure to them and obtaining their consent.

Explanations to children younger than 6 years of age are tailored to their development stage. Families can work with child life specialists to decide how to speak to their children, help them understand what is happening, and motivate them.

For older children, a proper understanding and acceptance of why the transplant is necessary, what it entails, and what life will be like afterward will help them to follow medication and other regimens after the transplant. As children

have their own thoughts and ways to prepare for things, it is important to use good communication and to respect their desires.

It is also helpful for families to share information about their children with us, including descriptions of their personalities and how they deal with difficult situations. If necessary, meetings can be arranged to deal with emotional matters.

*** The family**

In approximately 97% of the transplants performed at the NCCHD, one of the child's parents serves as the donor. It can be frightening to imagine two members of the family undergoing surgery at the same time. In addition to worrying about the recipient, donors have to think about their own surgery, their jobs, and many other medical and social matters. The other parent also plays an important role as he or she provides the donor with emotional support, takes care of the recipient, siblings, and other family members, and manages the household while possibly continuing to work as well. All of this can be incredibly stressful, and it can sometimes cause a great deal of tension within the family.

Family members who are physically unable to be donors may be consumed by feelings of guilt. While a transplant cannot happen without a donor, the presence of family members who can support the recipient and the donor throughout the process is indispensable. Donors have to follow dietary and exercise regimens, and refrain from drinking and smoking. They need encouragement and praise from their family to overcome these difficulties and to reach their goals. This can be done by helping them manage their diet or exercising with them.

As undergoing transplant surgery can create major problems within families, it is important to talk things out and to maintain good communication. An organ transplant is like climbing a big mountain. Therefore, it is best to have help from as many people as possible, e.g., by involving grandparents and other relatives in the process. After a transplant is scheduled, a number of explanatory sessions are held. It helps if these are attended by as many people as possible. Please talk to us about scheduling these meetings.

*** Supporting siblings**

The recipient's disease requires siblings to put up with a lot. Therefore, it is important not to burden them any more than is unavoidable. It may be necessary to ask the grandparents or other relatives to take care of the recipient's siblings. It can be emotionally difficult for young children to be away from their parents, and they may feel alienated when they see the adults around them focusing so much on the recipient.

If possible, bring the recipient's siblings to the outpatient explanatory meetings. Talking to and getting to know the child life specialists and recipient transplant coordinators can make them feel more like members of the family, and may help to alleviate their anxiety. Having strange things happen in an unfamiliar place can be unsettling. After the recipient is hospitalized, it may be difficult to make time to meet with siblings younger than middle school age. However, if time is available, a child life specialist or recipient transplant coordinator can

meet with them to explain what is happening. If you are having trouble speaking to the recipient's siblings or if they seem to be behaving strangely, please contact us.

After leaving the hospital, life will revolve around the recipient for a while. Therefore, make sure to spend time giving the siblings love and affection beforehand.

After leaving the hospital, the donor will recover at home for a while. This time can also be used to focus on the siblings.

3 Hospitalization and surgery

The length of the recipient's hospital stay before the transplant depends on his or her condition. If your child can live stably at home, you can wait until about a week before the transplant. The week the child spends in the hospital is used to get him or her physically ready by making him/her fast for two or three days before the operation, administering intravenous drips and medications, and making other preparations. If nutritional management or other care is needed to prepare the child for surgery, he or she may be admitted to the hospital about a month before the transplant. The hospital staff and transplant team work together to make sure that the transplant process goes smoothly.

The donor is hospitalized the day before the transplant. He or she will receive a final explanation from the transplant surgeon and will be asked to sign a consent form. Both parents should be there to hear the explanations, and other relatives are also welcome to join.

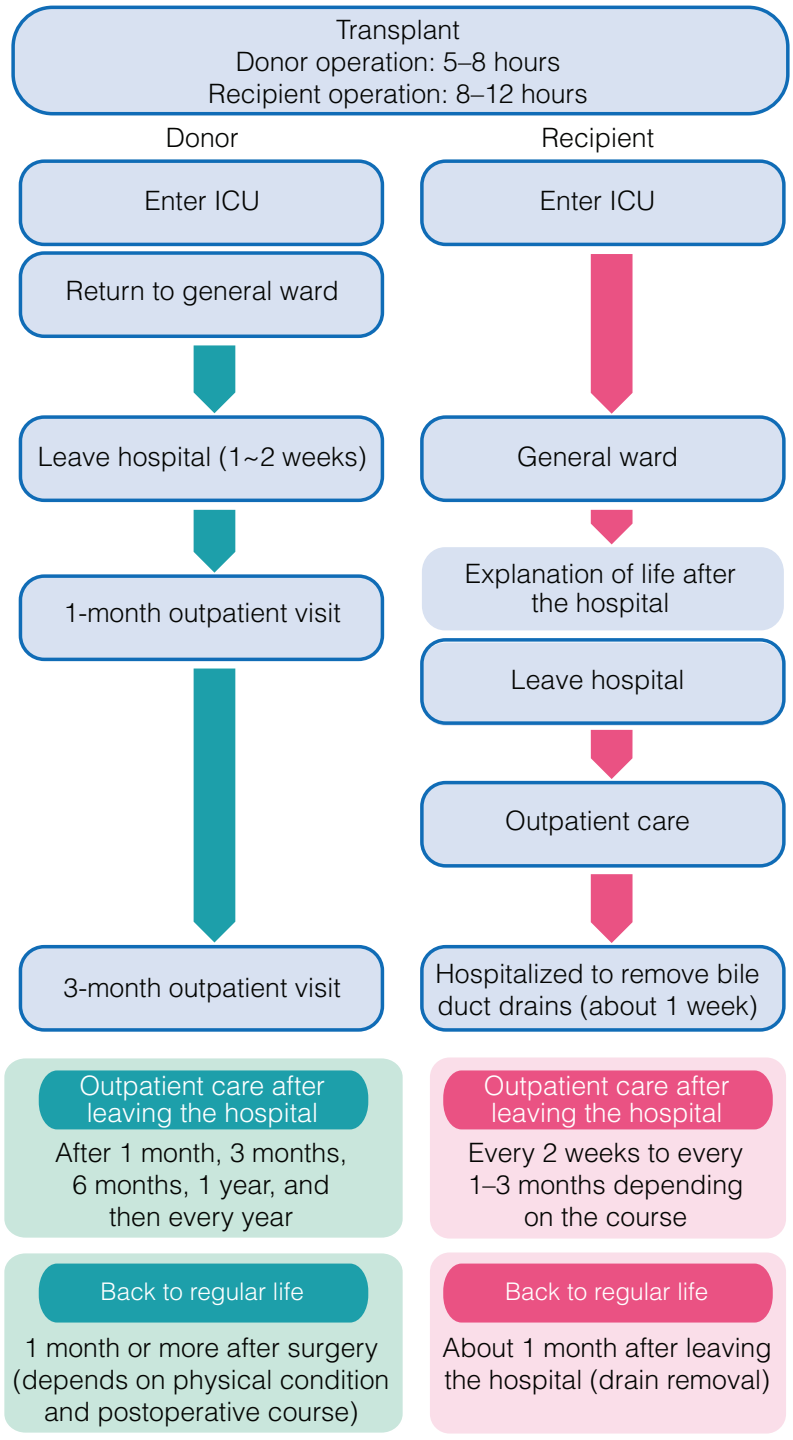
The day before the transplant, the anesthesiologist will also perform an examination and explain the anesthesic procedure, including the treatment for pain control, and there will be visits from the operating room and ICU nurses.

On the day of the surgery, we arrange for the donor, recipient, and family to meet for a short time before the patients enter the operating room. However, children younger than middle school age are not allowed in this area. As the operations are long, a waiting room is available for your use. Children of all ages are allowed in this area. As we sometimes need to speak to the family during the operation, please make sure that someone is in the waiting room at all times.

4 After the transplant

After the surgery, the recipient is usually taken to the ICU while he or she is still connected to a respirator. Even if the operation goes well, this is a period of both optimism and concern. It may be shocking or difficult to see your child connected to so many intravenous lines and drainage tubes. However, these all play important roles in your child's recovery. The ICU doctors and nurses work with the transplant team to give your child the best possible care. You will be updated on your child's condition and course, but please don't hesitate to ask if there is something you don't understand.

What happens in a living-donor liver transplant (after surgery)



Intensive care mainly involves providing respiratory and circulatory support, adjusting the fluid balance, and preventing infections. It is designed to help your child recover quickly. Once your child's condition stabilizes, rehabilitation starts as early as possible. Rejection is most likely to occur in the first week after surgery. If a severe rejection or infection occurs, your child may need to spend more time in the ICU.

Once the child's condition stabilizes, he or she is moved to the general ward. If things go well, this happens after about a week. In the general ward, the child starts rehabilitation and the oral intake (of milk) again. During this period, the immunosuppressant dose is adjusted to try to balance concerns about rejection with the need to prevent infections. Once the liver functions and the immunosuppressant dose are stabilized, the child is discharged.

The first outpatient examination is scheduled for about two weeks after leaving the hospital. However, the timing can change depending on the child's condition.

Approximately three months after the transplant, the child is hospitalized again to remove the bile duct drains. As this often causes a fever, intravenous drips and antibiotics are administered. The child is discharged once the fever goes away.

The postoperative course varies greatly between patients, and things often do not go as expected. The doctors, nurses, and recipient transplant coordinators will always be there to explain what is happening. Do not keep your worries and concerns to yourself; please come and talk to us so we can overcome them together.

5 Emotional problems after the surgery

Even when things go well, one in four adult recipients have been reported to experience anxiety or depression after a liver transplant. As most recipients at the NCCHD are small children, these responses can be difficult to recognize. However, bad moods, insomnia, and other physical responses, as well as infantile regression or tantrums, may occur. As patients often experience physical pain soon after the surgery, they need to be watched closely and should be made to feel both physically and mentally at ease.

Once children reach adolescence, their responses largely resemble those of adults. Pain after surgery can cause anxiety about the recovery. Even after things stabilize, the ups and downs of feeling better one day and worse the next can be stressful. This can create worries about the recovery process and lead to unstable emotional states. Not knowing what to expect in unfamiliar situations can also be a source of anxiety. For example, worries that the body will reject the transplanted liver, or about not being able to go back to school, are not limited to the early post-surgery stages.

Recipients who receive transplants in infancy might grow up not fully understanding what they went through. As they get older, they may feel somehow different from other children. They may ask, "Why am I the only one taking medicine?" or "Why can't I do such-and-such?" It is important to explain the transplant to your child in a way that is suited to his or her stage of development. This will help them to be more in touch with their bodies and their lives.

Different problems may occur at different stages of your child's life cycle—e.g., when starting school, getting a job, getting married, and so on. It is incredibly

helpful to have a clear understanding of one's body even before the surgery and to build trusting relationships with medical professionals.

Even in healthy children, adolescence is a time when emotions can fluctuate greatly. Difficult relations with adults may also develop during this time, particularly as adolescents have trouble expressing their feelings. An individualized approach is needed to deal with teenagers.

We will check in with the child periodically. However, if you notice or are concerned about anything in the meantime, please do not hesitate to contact us.

6 Getting ready to leave the hospital

Although leaving the hospital is a joyful event, the recipient has been through a major surgery and must continue to take immunosuppressants. Recipients and their families have to live with the constant possibility of rejection or infections. This can cause anxiety in many people. While in the hospital, you will receive instructions from a pharmacist and nutritionist about what you need to know before the child goes home, including how the drugs should be taken and tips for not forgetting to take them. If a patient leaves the hospital with the bile duct drains still inside, a nurse will explain how they should be taken care of and what to watch out for, and will have you practice the necessary tasks.

When your child is close to being ready to leave the hospital, a transplant surgeon and recipient transplant coordinator will discuss life after the hospital with you. For more information, please see "2.13 Q&A about life after a liver transplant."

We are here to address your worries and to support you as your child prepares to go back home. We will continue to provide support to make life as easy as possible for children who have undergone a transplant even after they leave the hospital. Please place your trust in us.

Tomomi Kubota
Recipient Transplant Coordinator
National Center for Child Health and Development

11 Child life services for children and families undergoing liver transplant

Child life specialists (CLSs) are members of the medical team who work with hospitalized children, their siblings, and the rest of the family to make the medical experience as positive as possible. CLSs help families go through their medical experiences, using a variety of interactions to meet the psychosocial needs of each child and his/her family. For example, they use therapeutic play

to encourage children to express their feelings and to help them cope with their stressful experiences in the medical setting. Moreover, they also use medical play to familiarize them with the medical equipment. In addition, CLSs provide developmentally appropriate explanations of each situation, including hospitalization, diagnosis, and upcoming medical events, to help children understand and adapt to these situations. CLSs believe that all children have specific strengths that carry them through life. The aim of child life interactions is to enable these strengths in each child, his/her family, and other medical team members.

How do you explain medical information to your child? Before talking to him/her, you had better consider that children understand things differently from adults. Indeed, children see and understand things according to their age and cognitive development. Even infants and younger children can be very sensitive to their families' anxieties or to changes in their routine and environment, and get stressed out. Older children can become anxious or fearful in unfamiliar or unknown situations, especially in a medical setting. Moreover, there is always a possibility that children may develop misunderstandings from overhearing casual conversations between family members and medical staff. If children are not given accurate information, fearfulness and misunderstandings can prevent them from coping with and adapting to new situations. Therefore, it is important that CLSs assess and provide appropriate interactions and interventions for each child and his/her family before surgery.

As mentioned, the details given to each child about the intervention should depend on their age, cognitive development, and needs. Previous experiences with medical care and diagnosis also need to be considered. CLSs talk to children to assess what they know and think. If a child has any misunderstanding or confusion, they clarify the situation and provide accurate and appropriate information. They also encourage the children to express their feelings and acknowledge them. They then let them know that no behavior or thought causes their disease, for example by saying "What you do or what you think doesn't make this happen", and "I (as a CLS) am here to help you go through what happens in a hospital."

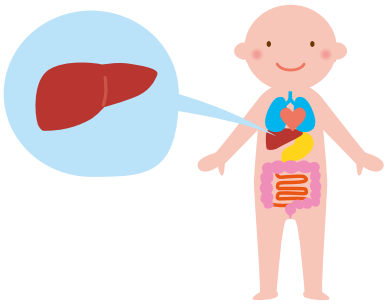
First, CLSs show where the liver is and how it works. They then explain why it is not working well, and why surgery is needed. Moreover, they explain what to expect after the surgery, including the tubes that will be placed in the children's bodies, where they will stay in the ICU, etc. CLSs focus not only on telling the children what will happen, but also on discussing how to deal with the situations they face.

In the case of school-aged children and teenagers, the role of the liver is explained in more detail, and some medical terminology is used. Drawing figures or taking notes during the explanation may help the child to process the information. It is important to be honest with children and adolescents. If they feel respected, they will be more motivated and will be encouraged to deal with their medical experiences.

Below are some examples of age-appropriate explanations:

1 Examples of explanations to transplant recipients

(1) Location of the liver



• Toddlers, preschool age

Your “liver” is in your tummy.

• School-aged children, adolescents

Your “liver” is in the upper-right part of your tummy.

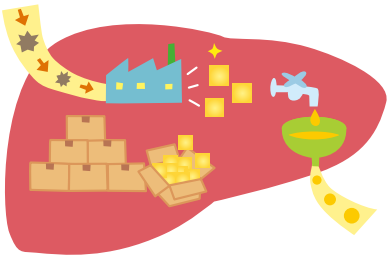
It is the largest organ in the body.

(2) The job of the liver

• Toddlers

The liver stores energy and sends it around the body.

• Preschool-aged children



The liver cleans your blood. It divides the good stuff from the stuff your body doesn’t need. The good stuff goes out to the rest of the body. The stuff your body doesn’t need goes out of the body through poop and pee.

• School-aged children

The liver makes a special liquid called “bile” that is used to break down the food we eat. Bile helps to give our bodies nutrients.

The liver also divides the good stuff from the waste stuff. The nutrients and good stuff are carried to the rest of the body through the blood. The waste stuff goes out of the body through poop and pee.

• Adolescents

The liver produces bile and cleans the blood.

Bile helps the blood to absorb fats.

The liver also stores energy in the form of sugars.

If a child has a subjective symptom (e.g., fatigue, swollen abdomen, etc.), it is explained that surgery is needed to make him/her feel better. Children become more positive when they see the operation as beneficial to them.

It is important for children to understand that surgery can improve their subjective symptoms (e.g., fatigue, swollen abdomen, etc.).

(3) Explaining the transplant surgery

• Preschool-aged children

When the liver gets sick, it can’t do its job. The doctor has decided to replace your liver that doesn’t work with a healthy liver, so you can play in many ways.

• School-aged children

When the liver gets sick, it can't do its job, so it makes you tired, turns your skin yellow, and makes your tummy swell up. The doctor has decided to have a surgery called a "liver transplant." The doctor replaces the liver that doesn't work with a healthy liver donated by another person.

* Some children may feel guilty about their disease, so it can be helpful to explain that it is nobody's fault that their liver got sick and isn't functioning.

* When children are scared, you can tell them that it is ok to be scared, and that a medicine called anesthesia will help them fall asleep during their surgery, so that it won't hurt at all during the surgery.

• Adolescents

Adolescents can have a better understanding of the details of their treatment, or may hope to learn more details, including unfamiliar medical terms. Figures and drawings can be useful to help teenagers understand unfamiliar medical terms.

It can be difficult for children to imagine staying in the ICU with IV and drains on their body. The ICU environment is very different from that in regular hospital wards. Waking up in an unfamiliar place with tubes after surgery without any previous explanation can be incredibly disturbing and frightening for a child. Therefore, it is important to explain what to expect after the surgery beforehand to allow the child to prepare for it.

(4) Explaining what happens after the surgery

• Toddlers

After the surgery, you will stay in the ICU, where the doctors and nurses will keep a close eye on you to make sure you're getting better. You will have a scar on your tummy after the surgery. It's a sign of how well you did.

• School-aged children

After the surgery, you will stay in the ICU for a while. This is a place where the doctors and nurses can keep a close eye on you to make sure you're getting better. After the surgery, some tubes will be placed on your body. The doctor wants you to leave these tubes there until he/she removes them. You will have a scar on your tummy after the surgery. It's a sign of how well you did.

• Adolescents

After the surgery, you will stay for a while in the ICU. Several tubes will be placed on your body when you wake up. These include intravenous lines, tubes in your chest and abdomen to remove excess fluid, and a urine catheter. You will also have a scar on your abdomen after the surgery.

* Many children feel anxious about pain after the surgery. It is OK to tell the medical staff about pain.
* If you have any question or concern, ask the hospital staff.

(5) Asking about feelings

Talking to children about their liver transplant beforehand gives them an opportunity to express their feelings. They may cry, get angry, or appear to accept things calmly. The next time you try to talk about their surgery, they may look away or try to avoid the conversation. When faced with a liver transplant, it is natural to feel anxious about changes to one's lifestyle and environment, or about the possibility of pain and discomfort. Regardless of your child's response or emotions, accept them without denying their validity. Sharing feelings as a family is part of the process of acceptance of the operation and liver transplant. After they have expressed their feelings, reassure your child that you will stay by their side throughout this important experience. It is helpful to talk to them about how to deal with things that they don't like or that they are worried about.

In addition, some children worry about their relationships with friends or about having a scar on their abdomen. It may be helpful to talk to the hospital staff about how children can explain their transplant to their friends, and how the scar's appearance will change as they grow. If you are confused about how to deal with something, please talk to the hospital staff. The NCCHD employs a wide range of specialists who can be of assistance.

2 Preoperative tour

CLSs provide a tour of the operating room beforehand. The aim of the tour is to help familiarize the child with the operating room and medical equipment.

CLSs use a photo book to show what the operating room looks like.

CLSs ask the children if they would like to see how to get to the operating room (Photo 2) and what it actually looks like.

If the patients are preschoolers or early school-aged children, the tour is conducted as a "stamp rally," in which the children collect stamps for a book from different places along the way (Photo 3).

CLSs use a doll to explain what the child will experience in the operating room, including anesthesia. They let him/her place a blood pressure cuff on the doll's arm, ECG electrodes on its body, and an oxygen mask over its mouth (Photo 4). These hands-on experiences can promote a better understanding.

Photo 1
Photo book of the operating room

Photo 2
The NCCHD operating room entrance

The family often joins the operating room tour. This preoperative program can help not only children but also other family members to feel more at ease.

3 Siblings

The experience of a liver transplant can also have a major impact on the rest of the family, particularly on the recipient's siblings. The hospitalization of family members can change the siblings' living environments and separate the family, which may increase their anxiety and stress level. They often have many questions about why their brother or sister is in the hospital, what is happening there, and how he or she is treated. This can generate anxiety and feelings of isolation. We encourage parents to talk to their other children in the same way as they do to the recipient.

Sometimes, siblings may feel responsible for the recipient's illness, or may say that they wished they were sick instead. Explain to them, "It's not your fault. Nobody did anything wrong." Siblings should be told that their presence is valuable.

Make sure to make time for the siblings, to hold them on your lap, and to listen to their feelings. Talk to them about ways they can relieve their worries and feel less lonely, and discuss how you will keep in contact (letters, phone calls, etc.) when you are apart.

Our job is to work with and support children and the families who know them best every step of the way.

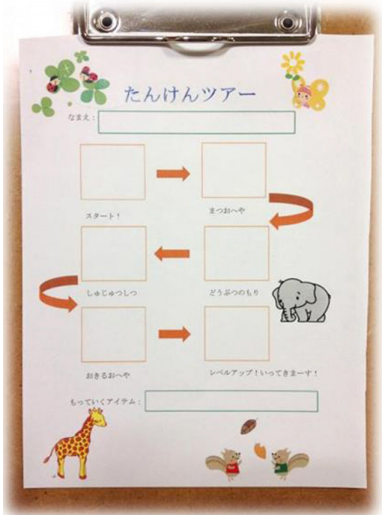


Photo 3
Stamp rally booklet for the operating room toure

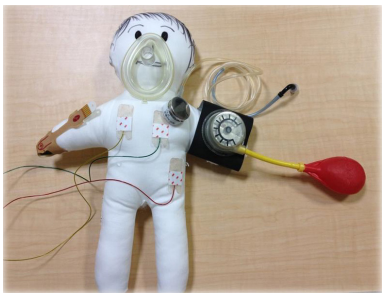


Photo 4
A Kiwanis doll is used to explain anesthesia

Mai Ito, Natsumi Kobayashi, Hiroko Yonemichi
Certified Child Life Specialist
National Center for Child Health and Development

12 For people thinking of living donation

1 What is a living donor?

A living donor is someone who voluntarily chooses to donate an organ, that is, a person who willingly undergoes organ-donation surgery out of a sincere desire to give another person a part of one of his or her organs. In living-donor liver transplantation, the concept of "choosing voluntarily to donate an organ" is incredibly important. It is essential that nobody—not a medical professional nor a family member—force a person to donate an organ.

2 Conditions for becoming a living donor

As stated above, at the NCCHD, all living donors must choose organ donation voluntarily. They must be at least 20 years old, younger than 65, and medically able to donate an organ. They must also be a blood relative of the recipient of at least the third degree of kinship. This means that the donor may be the recipient's father or mother (1st degree); grandfather, grandmother, or sibling (2nd degree); or uncle or aunt (3rd degree) (Figure 1).

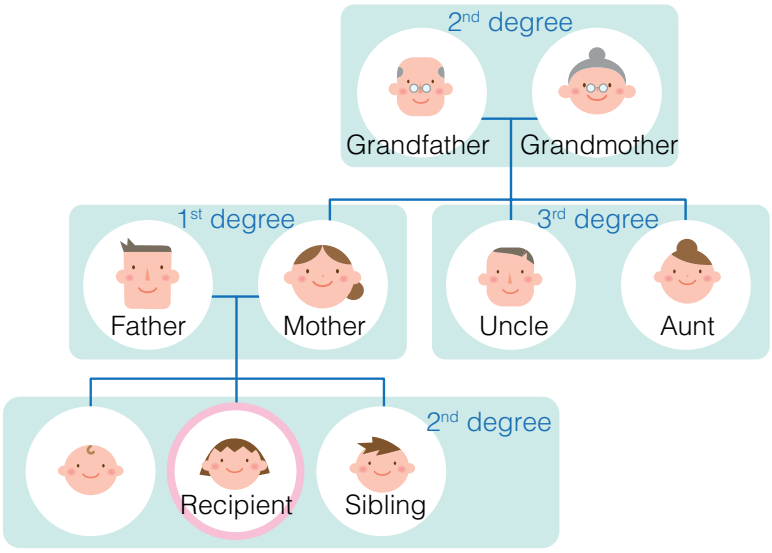
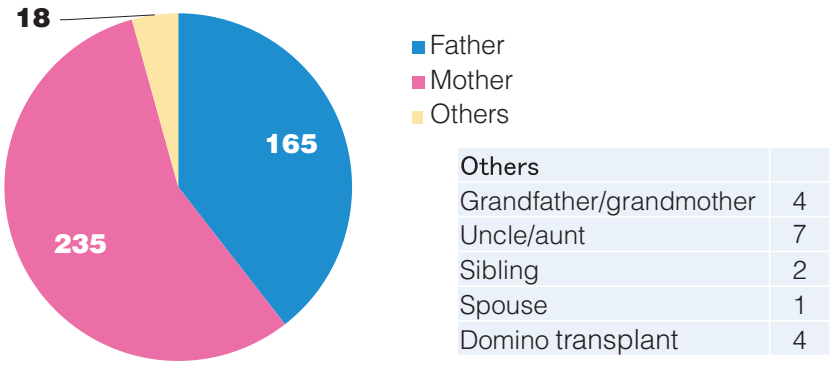


Figure 1. Relatives who can be donors in living-donor liver transplantation
* All living donors must choose organ donation voluntarily, be at least 20 years old, be younger than 65, and be medically able to donate an organ.

In most living-donor liver transplantations performed on children at the NCCHD, the donor is one of the recipient's parents. In rare cases, someone else serves as the donor (Figure 2). When a child younger than 1 month needs a transplant, the father is often considered as the donor candidate since the mother has recently given birth. If for some medical reason the father cannot be the donor, the mother may be eligible. In these cases, the mother must voluntarily choose to be the donor and must not have any health problems.



Others	
Grandfather/grandmother	4
Uncle/aunt	7
Sibling	2
Spouse	1
Domino transplant	4

Figure 2. Relationships between living donors and recipients at the National Center for Child Health and Development (N=418, 2005/11-2016/12)

Once a family realizes that their child needs a liver transplant, they start thinking of who will be the donor. This is an extremely important decision, since in a living-donor transplant, two members of the family will undergo surgery at the same time. The decision should be made after thoroughly discussing matters such as work, housework, and childcare. Unless there is a major medical contraindication such as hepatitis, fatty liver, specific HLA typing, or the size of the liver, the person chosen by the family is examined as the primary donor candidate.

Donor candidates need to take several days off work for examinations and other preparations before the operation. Afterward, the selected donor will need one month to recover from the operation before returning to work or to housework and childcare. The family should devise a system of cooperation that works for them. After the operation, the donor will need to attend outpatient examinations at the one-month, three-month, six-month, and one-year marks, and every year thereafter. At these appointments, blood tests and abdominal ultrasounds are performed to check on the liver.

Currently, the donor compensation systems operated by the national and municipal governments are not all standardized. Although employers offer various welfare benefits, it may not always be possible to receive sick benefits or life-insurance payments. Since donor surgeries are performed on healthy people, some employers will not treat the time off as sick leave. Donors should talk to their employers early on to address questions such as whether they can take paid vacation and if they will continue to be paid in their absence.

3 Examinations performed on donor candidates

The donor exam takes about half a day. The main examinations involve the blood type, general biochemistry, infectious diseases, tumor markers, occult blood, urinalysis, the respiratory functions, electrocardography (including an examination by the cardiovascular department if abnormalities are found), a chest/abdominal radiography, and contrast computed tomography (for fatty liver and lesions, and to estimate the vessel paths and the size of the liver).

If the person ends up having the operation and donating an organ, the costs of the donor exam and surgery will be covered by the recipient's health insurance. However, those who do not become donors will have to pay 100% of the cost of the exam (about 2,500 USD). Therefore, if both parents undergo donor exams, they will have to pay one of the exams out of their own pocket.

The donor exam considers the following items (Table 1).

Item	Exam details
HBc (Hepatitis B core) antibody positive	Liver donation is possible, but the recipient needs to be administered intravenous injections of antibodies for the hepatitis B virus.
Fatty liver	Depending on the severity, people with fatty liver may not be able to be donors, as this can cause liver dysfunction in the recipient after the surgery or may delay the donor's recovery. In the waiting period before the transplant, an effort should be made to improve fatty liver by refraining from drinking alcohol, dieting, and exercising.
Suspicion of Gilbert's syndrome	In most cases, any hyperbilirubinemia detected in preoperative tests is unconjugated hyperbilirubinemia, which indicates the presence of Gilbert's syndrome, a form of constitutional jaundice. People with this condition can be organ donors if their other liver function tests are normal.

Table 1. Test results that deserve attention

If the child receiving the transplant has any of the following diseases, additional tests are performed (Table 2).

Item	Exam details
Family members of children with Alagille syndrome	This condition can sometimes prevent a transplant, as the liver bile ducts of the donor candidate parent are too narrow. An additional magnetic resonance imaging exam (MRCP) and a liver biopsy are used to evaluate the bile ducts carefully.
Family members of children with metabolic liver diseases	Division of Medical Genetics may perform examinations and tests to determine if the family members are carriers of the same disease.

Table 2. Diseases that require additional testing

4 Confirming the donor's intentions

The donor's intentions are confirmed at least three times (except in emergency liver transplantations for fulminant hepatitis). Each time, a detailed explanation is given, and the donor must sign a consent form (Table 3).

Confirmation of donor's intentions	Timing of confirmation
1st Confirmation	When the donor exam is performed.
2nd Confirmation	After the donor exam, when it is determined that the person can be a donor.
3rd Confirmation	When the recipient's transplant has been scheduled and preparations have begun.

Table 3. Schedule for confirmation of donor's intentions

After all three consent forms have been collected, the donor is considered to have agreed to the operation. However, he or she is not obligated to go through with the surgery, as consent can be revoked at any stage of the process.

The recipient's condition, the donor's roles at home and at work, life after the transplant… These are not problems for the donor only, but for the entire family. Each of these issues needs to be considered and resolved. This is why the donor's intentions are confirmed at different stages. The process of confirmation of the donor's intentions is partially intended to keep donors safe, both physically and mentally. People's decision to become donors often sparks conflicts that only they can understand. The transplant staff is available to discuss these matters at any time.

5 Things families should talk about

Learning that a liver transplant is necessary can cause a huge amount of anxiety for families. They should first gain a proper understanding of the transplant process, before discussing candidate donors and how the family should cooperate. It is important to fully grasp that in addition to the child receiving the transplant, another family member will undergo surgery.

While becoming a donor is one way to help a child, the presence of other family members, who can provide many other forms of support to the child, is indispensable. The cooperation of all family members is needed for everyone to make it through the liver transplant.

The child's grandparents are welcome to attend the meetings at which liver transplantation is explained. Although people who live far away may find it difficult to attend, it is best to have as many family members present as possible. For the donor, the understanding of his or her family (i.e., the donor's parents, siblings, and relatives) and the knowledge that they will go through the surgery together can be greatly reassuring and encouraging.

Although a liver transplant is sometimes the only therapy available to a child, it unfortunately does not restore every patient to health. As of December 2012, the one-year survival rate (i.e., the percentage of recipients who were healthy one year after the transplant) for recipients under age 18 was 88% in Japan as a whole. In other words, this means that 12% of the recipients died in the first year after the transplant. The one-year survival rate for recipients at the NCCHD is 92%. While this is better than the national rate, it still means that therapy is not successful 100% of the time.

The incidence of complications in donors is not null either. In 2005, a national survey of 3,005 living donors who had undergone living-donor surgery (partial hepatectomy) found that 105 patients (3.5%) had experienced a complication that had required another surgery, endoscopic therapy, or some other treatment. One patient (0.03%) had died of liver failure after the operation. At the NCCHD, all patients who have undergone donor surgery are still alive. An August 2009 survey of the 100 NCCHD donors who had undergone donor surgery found that 3 patients (3.0%) had experienced a complication that had required another surgery, endoscopic therapy, or some other treatment. These included two cases of endoscopic therapy for duodenal ulcers and one case of bile leakage. A few patients had experienced complications that had not required surgery and had improved with drug therapy. These included four cases of infected wounds, three cases of wound hernia, and one case each of meningitis and duodenal ulcer (that had improved with drug therapy).

When donors were asked how much they had recovered from their surgery, 40% said they had fully recovered, 57% said they had almost fully recovered, and 3% said they had not recovered much at all. When asked if they were worried about their health, however, 40% said that they did feel worried (Figure 3).

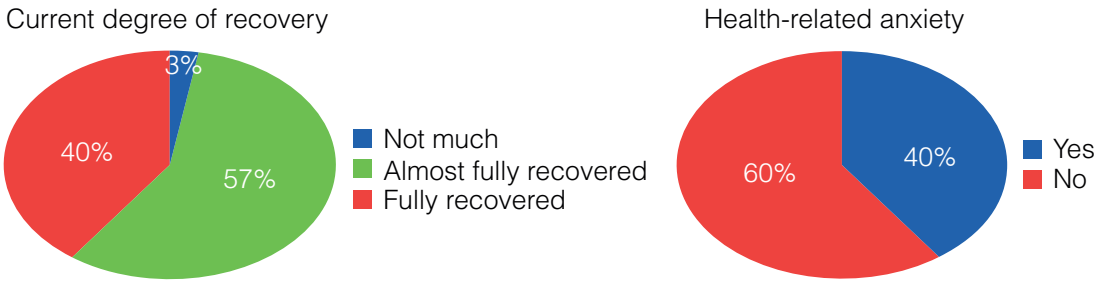


Figure 3. Physical condition and health worries after donor surgery (2009 NCCHD donor survey)

When donors were asked if they were currently experiencing any subjective symptoms, the most common response was fatigue. Unlike complications that occur immediately after surgery, this symptom is often chronic or continuous. It shows that even if one's body recovers from the operation, things do not always return to normal (Figure 4).

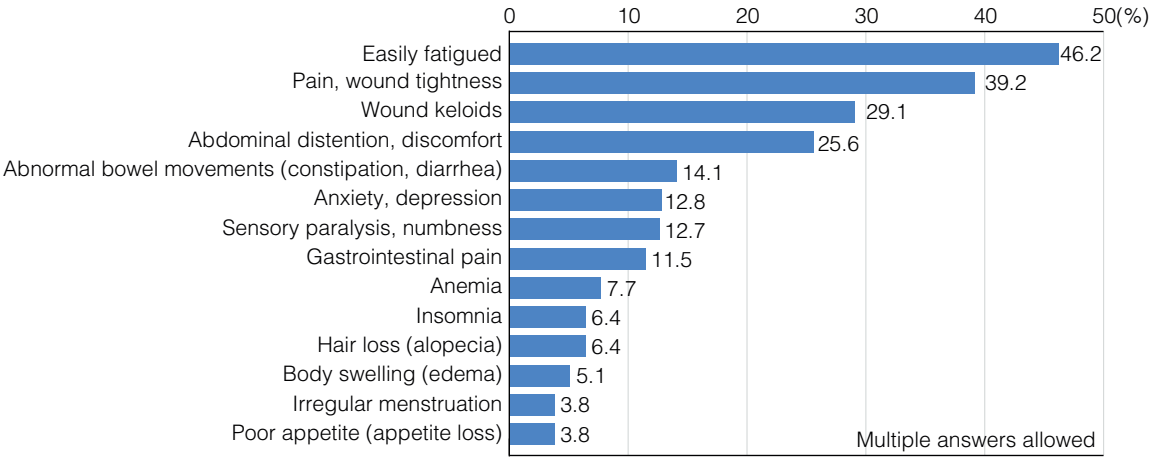


Figure 4. Subjective symptoms after donor surgery (2009 NCCHD donor survey)

We also used a 36-question survey (Short Form 36, Japanese Version 2) to estimate the donors' physical and mental quality of life (QOL). The responses showed that in the first year after surgery, donors' physical QOL was slightly below the Japanese average of 50 points. The mental QOL was slightly above average in the first year after the surgery. However, it decreased in the second year. After two years, the donors' mental and physical QOL scores were both higher than the Japanese average (Figure 5). These results show the importance of mental and physical support, and indicate that it takes about two years for both aspects of the QOL to recover.

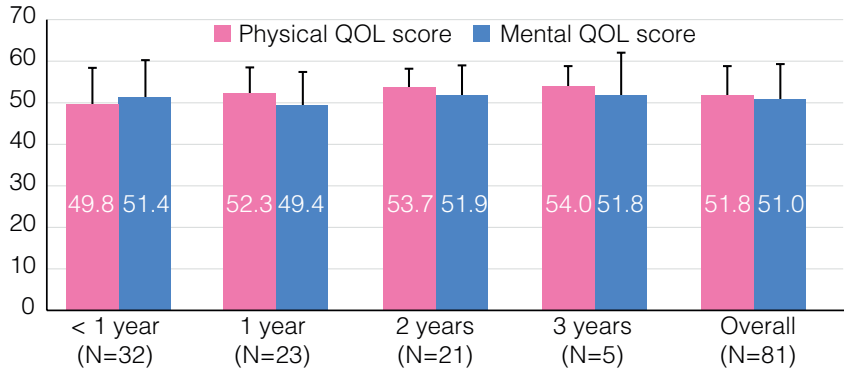


Figure 5. SF-36 scores against Japanese average of 50 points (2009 NCCHD donor survey)

6 Making it through the transplant

Most healthy donors will not need to be hospitalized for illnesses. Therefore, they can undergo the examinations and prepare for the surgery while helping out at home and going to work as usual. The timing of the transplant will be determined according to the child's condition. A variety of issues need to be resolved in the run-up to the transplant. It is particularly important to ensure that a recipient's parent does not think that he or she must be the donor and go through with the operation without fully understanding what changes it may cause. If you have any questions or concerns, please make sure to speak to someone.

The goal of transplant surgery is not merely to realize the transplant. We consider a transplant to have fulfilled its purpose when the recipient, the donor, and the rest of the family are able to return to a regular, healthy life. The doctors and other medical staff who provide transplant care strive to do their jobs in a way that takes the physical, emotional, and social characteristics of the recipient, donor, and other family members into consideration.

Akinari Fukuda, Seisuke Sakamoto
Organ Transplantation Center
National Center for Child Health and Development

13 Q&A about life after a liver transplant

[Recipient (the child receiving the liver transplant)]

Q. How long does my child have to wait to go outside after leaving the hospital?

A. After leaving the hospital, try to take your child out little by little while keeping an eye on his or her condition. Start with short outings at less-crowded times, e.g., to a local park, to the supermarket, or on a family outing. Although this varies between

individuals, it is usually fine to go out as normal after the bile duct drains are removed three months after the operation, as long as the child is well. Depending on the season, you should probably wait approximately six months before going on longer outings or to crowded places. Make sure to wear a mask when traveling on crowded trains, in winter and when the common cold is going around; also, wash your hands and gargle when necessary. Family and friends should also wash their hands and gargle. There is no need to stay cooped up in the house. Go out and live a normal life.

Q. Is it okay to exercise?

A. Your child can begin taking walks and doing mild exercise three months after the liver transplant. It is fine to let them dance, jump, and run around. If they feel well enough, mild exercise can begin a bit earlier. Just make sure that they drink enough fluids and that they rest when they are tired. As the transplanted liver is located under the solar plexus, it is relatively unprotected, and an impact to the solar plexus could damage the liver. Therefore, you should avoid hard blows to this area. Combat sports such as karate and boxing are not recommended. Don't let your child practice them. Hanging, spinning from the knees, and other moves on a horizontal bar are fine as long as they don't put pressure on the belly. Ball games are fine. Games such as dodge ball, in which there is a possibility of being struck in the belly, are also fine as long as the child is careful in catching the ball.

Q. Is it okay for my child to participate in physical education at school?

A. Basically, there is no problem as long as you heed the above warnings. If you have concerns, talk to your child's gym teacher about the planned activities. As long as the child is healthy, he or she can take part in swimming classes, ball games, dancing, and long-distance running events.

Q. Is it okay for my child to play in parks? When can we start going?

A. After leaving the hospital, start by taking short walks in the park at times when it is not crowded. As your child gets used to it, he or she can start playing in the sandbox and on the playground equipment. Just make sure that you watch your child in the sandbox to check that no sand gets into his or her mouth. With the playground equipment, just follow the same rules as for other children. After playing, make sure that your child washes his or her hands and gargles.

Q. Is it okay to go camping?

A. As long as it has been six months since the liver transplant, it should be fine. Be careful of insect bites, as the swelling and redness may be more severe than usual and last longer. Apply insect repellant before going out. Please contact us if you experience severe swelling or redness. If purulent inflammation spreads and causes cellulitis, the child may need internal medication, intravenous drips, or other treatments. Mosquitos are attracted to sweat, so use a sweat rag when needed.

Q. Is it okay to go to hot springs?

A. If it has been six months since the transplant and your child's liver functions are stable, it should be fine. Before you go, it may be helpful to talk to a doctor at the outpatient clinic. While rare, infections such as Legionnaires' disease may be caught from hot springs. Therefore, only bathe in hot springs that seem hygienic. When finished bathing, make sure to shower.

Q. Is it okay to swim in pools or in the ocean?

A. If it has been six months since the transplant and your child's liver functions are stable, it should be fine. Before you go, it may be helpful to talk to a doctor at the outpatient clinic. Going on waterslides is fine as long as no stress is applied onto the belly. Playing in sand at the beach is also fine. However, always rinse the child off with a shower after he or she plays in the pool or in the ocean. Mild sun tanning is not a problem, although steroid drugs can make the skin more sensitive to the sun. When swimming or playing outdoors on very sunny days, make sure to apply plenty of sunscreen.

Q. Is it okay to travel domestically?

A. If it has been six months since the transplant and your child's liver functions are stable, it should be fine to go on day or overnight trips. When you go, make sure to pack your child's medication, insurance card, drug history handbook (medication list), and the recipient card that was issued when your child left the hospital. Patients with blood type-incompatible transplants need to be careful of blood transfusions. Therefore, they are given a letter to explain their condition when they leave the hospital. This should also be packed when traveling. If your child starts feeling bad or is injured on a trip, you should go to the nearest emergency room. Make sure to mention the liver transplant to the hospital staff.

Please contact a doctor at the NCCHD's department of transplant surgery if you need to check your child's prescriptions or treatments. In some cases, the institution that examines your child will only provide initial treatment before transferring him or her to the NCCHD. If you cannot find anywhere to take your child at your destination, please contact us, and we will refer you to the closest hospital in the national network. If you are involved in an accident, do not hesitate to call 119 and ask for an ambulance. When explaining your child's symptoms to the emergency response team, do not forget to mention the liver transplant. Please contact us once you know what hospital your child is being taken to. We will contact the doctors there to give them the information they need.

Q. Is it okay to travel abroad?

A. If it has been six months since the transplant and your child's liver functions are stable, it should be fine. Before going abroad, please come see us to confirm that your child is well enough to travel. When you come,

please let us know where you will be going and how long you will be gone for. As for domestic trips, make sure to pack your child's medication, insurance card, drug history handbook, recipient card, and the explanatory letter for blood type-incompatible transplant patients. Although several days' or weeks' worth of medication do not usually need to be reported to immigration, make sure that you can justify it to them if you need to. If you would like a referral letter in English to use in case you need to visit a hospital at your destination, let us know early and we will be happy to prepare one. As the cost of medical care can be quite high in some countries, we recommend buying travel insurance in advance. At your destination, make sure that you have a good understanding of the hygiene situation, and be careful with unboiled water, uncooked food, and other foods to which your child is not accustomed. You may also need to adjust your schedule for immunosuppressant administration. Please consult us to make sure that this is done properly. Figure 1 shows an example medication schedule for a trip to Hawaii.

* Medication schedule for five-day trip to Hawaii

As the time difference between Japan and Hawaii is nineteen hours, a child who takes medicine at 8 a.m. and 8 p.m. in Japan would take it at 1 p.m. (the previous day) and 1 a.m. in Hawaii. Maintaining this schedule would require the child to take medicine in the middle of the night in Hawaii. Therefore, the schedule is adjusted. After arriving in Hawaii, the child skips the 1 p.m. dose (i.e., the next day's 8 a.m. Japan time dose). The next dose is taken at 8 p.m. (Hawaii time), returning the child to an 8 a.m., 8 p.m. schedule. After returning to Japan, a dose should be taken at 8 p.m. Japan time. As seen in the travel schedule below, although there is a gap after the first dose and before the last one, this allows the child to continue to take his or her immunosuppressants properly.

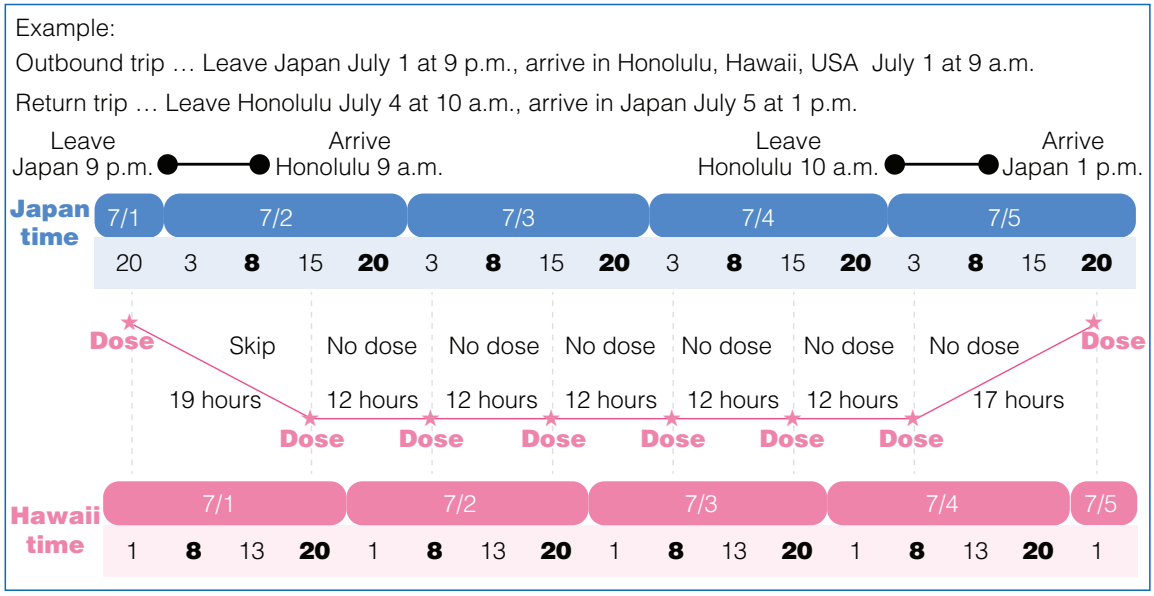


Figure 1. Adjusting the immunosuppressant schedule (Hawaii)

Q. When can my child start going to daycare or school?

A. It is best to wait for three months after the liver transplant (i.e., after removal of the bile duct drains). The post-transplant course, strength recovery process, and liver functions can vary between children, so please discuss this with us. Take things easy at first and see how your child does. If you wish, a recipient transplant coordinator can write a letter to your child's teacher to explain the things to watch out for. We also recommend that you explain your child's situation to his or her teacher. If more information is needed, a coordinator can call the teacher directly. It is helpful to let the coordinator know in advance what the teacher wants to discuss.

Q. There are so many types of medicine. What should I do if we forget to take one?

A. It depends on the medicine. For more details, please see "2.7 Liver transplantation and medication."

Q. Is it ok to receive vaccinations while taking immunosuppressants?

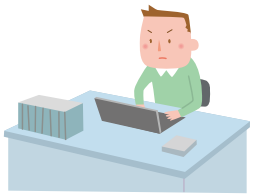
A. It depends on your child's immune status and age. A general vaccine schedule is provided in "2.5 Liver transplantation and immunology/infection prevention."

Q. Is it ok to have pets?

A. There are several things to be wary of with pets. For more details, please see "2.5 Liver transplantation and immunology/infection prevention."

[For donors (people who provide part of their liver)]

Q. When will I be able to return to work?



A. We will discuss your recovery in an outpatient examination one month after the donor surgery. We recommend that you ask for one month of leave from work. Depending on how your recovery goes, you may be able to return to work after one month. The amount of time needed will also depend on your job, e.g., if it involves desk work or manual labor. Please discuss the situation with your employer. If you need a medical certificate to ask for leave, please let us know.

Q. Is it ok to ride bicycles or motorbikes, or to drive cars?

A. After the donor surgery, the wound may feel tight. Although this will not prevent you from driving, it could be painful if you brake suddenly or perform other rapid movements. Please be careful on the road.

Q. Since I'm receiving outpatient examinations as a donor, should I still undergo regular health checks?

A. Please continue to have health checks. The outpatient examinations performed after the donor surgery only concern your liver. Although some items may overlap with the ones included in your regular checkups,

please bring the results on your outpatient visits. If a health check reveals something about your liver, please contact us.

Q. What kind of outpatient visits are required?

A. Donors undergo outpatient examinations one month, three months, six months, and one year after the surgery, and once a year thereafter. The cost of your outpatient visits is covered by the recipient's health insurance up to the three-month visit. After that, your own insurance will cover the examinations. A blood sample will be taken and an ultrasound examination will be performed each time. Both the donor and the recipient have their examinations on the same days. If you need to make a change, please speak to a recipient transplant coordinator.

Q. Can I drink alcohol after the donor surgery?

A. Please do not drink alcohol for at least six months after the surgery. Although your liver will return to its original weight within three months, it will take another few months for its functions to recover. Please avoid excessive drinking.

Q. Will I be able to get pregnant and have children after the donor surgery?

A. Yes. Although your belly will get quite large in the later part of the pregnancy, the scar from the donor surgery will not be a problem. It is also safe to undergo a Cesarean section for the first time after a donor surgery. However, as fatty liver sometimes occurs during pregnancy or delivery (a condition called "acute fatty liver of pregnancy"), you should wait until your liver functions have fully recovered before thinking about having another child. It is best to wait for about a year after the operation.

If you have any questions, please do not hesitate to speak to a recipient transplant coordinator.

Masami Katono
Recipient Transplant Coordinator
National Center for Child Health and Development

14 Liver transplantation and the medical expenses assistance system

Children and families from overseas who are interested in liver transplantation at the NCCHD should contact the Center for Patient Liaison and Services through a registered government guarantor.

https://www.ncchd.go.jp/en/hospital/outpatient/international_patients.html

Children and families who live outside Japan and do not have Japanese nationality must pay for the treatments themselves. They are also responsible for any additional expenses, such as travel and lodging. In this section, we give a general outline of the medical subsidy systems for domestic transplant patients. For the latest information, please contact the relevant department of your municipal government.

Figure 1 shows the ways liver transplant patients can apply for assistance.

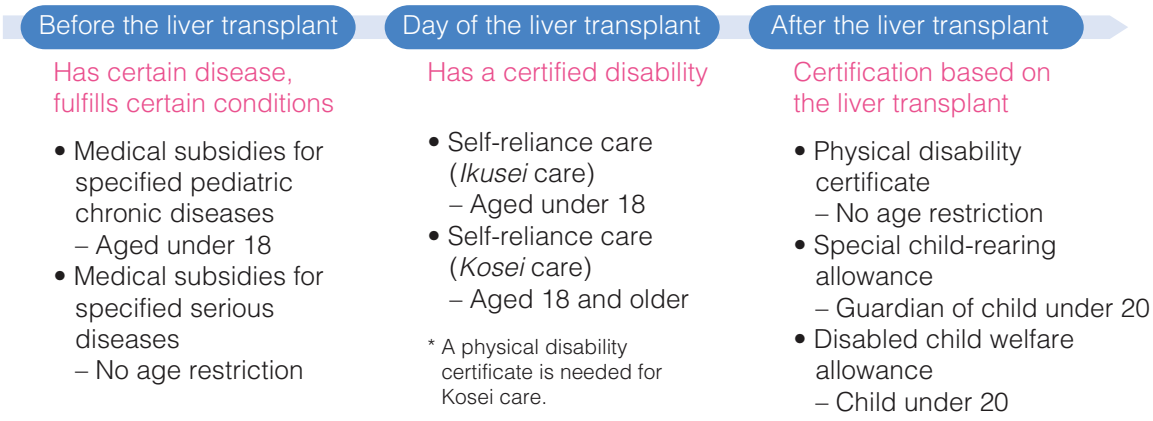


Figure 1. Conditions of liver transplant patients' application for medical subsidies

* If you do not fulfill the disease, disability, or certification criteria, contact the cashier's counter to apply for a fee reduction under the high-cost medical care benefit system.

Registered foreign residents in Japan may be eligible to receive government medical subsidies or to use the social welfare system. Please contact the Center for more details.

Figure 2 presents a general outline of the application process. The NCCHD will prepare the necessary medical certificates and recommendation forms. After obtaining the required forms from your municipal government's application department, bring them to the document counter on the Center's first floor.

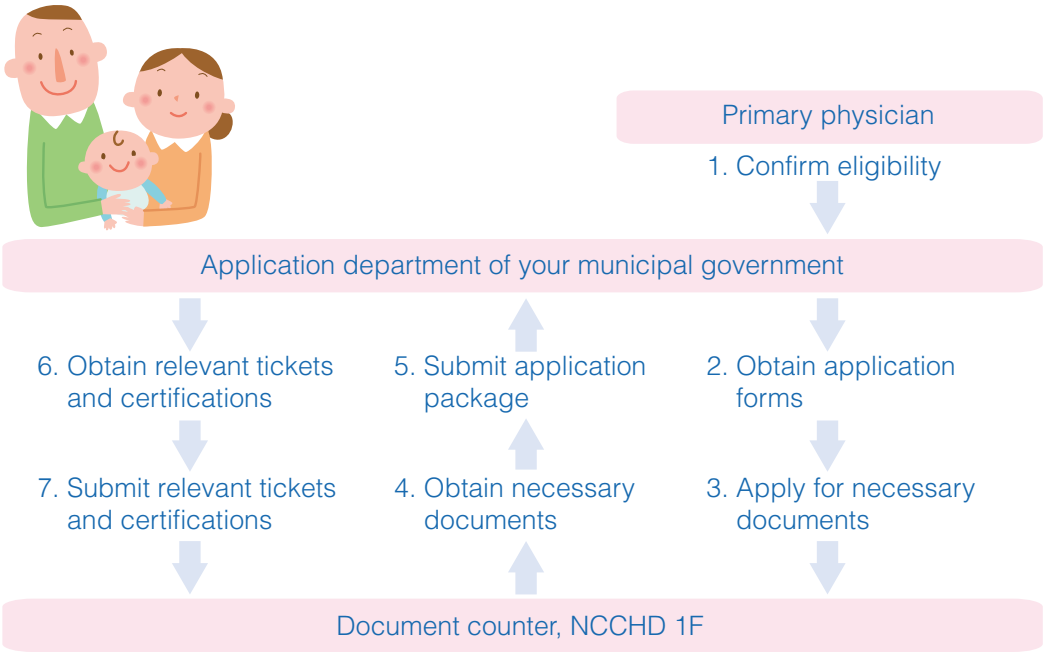


Figure 2. Application process for medical subsidies and allowances for liver transplant patients

1 After receipt of definitive diagnosis

Depending on your child's disease and condition, you may be eligible for medical subsidies.

(1) Medical subsidies for specified pediatric chronic diseases

Children under 18 years old who are receiving medical treatment for certain diseases and who fulfill the criteria set by the government are eligible for income-adjusted subsidies toward the individual contribution portion of their health insurance coverage.

(2) Medical subsidies for specified serious diseases

People who fulfill the certification criteria for certain diseases set by the government are eligible for income-adjusted subsidies for the individual contribution portion of their health insurance coverage. There are no age restrictions for these subsidies.

2 After setting the operation date

People with disabilities (as determined according to their condition before surgery) may be eligible for self-reliance care. You can apply for self-reliance care once the date of your operation has been set.

(1) Self-reliance care (*Ikusei* care)

Children under 18 years old who have a designated disability, or who are expected to develop a disability in the future if untreated, can receive government subsidies toward the individual contribution portion of their health insurance coverage for operations and other treatments expected to have a definitive effect.

(2) Self-reliance care (*Kosei* care)

People aged 18 or older with a physical disability certificate for a designated disability can receive subsidies toward the individual contribution portion of their health insurance coverage for operations expected to definitively eliminate or improve their disability.

3 If you are ineligible for government medical subsidies

Some people may be ineligible for the medical subsidies described above on account of their disease, condition, or age. These patients can use the high-cost medical care benefit system under their health insurance policy. (If the monthly medical bills from the hospital exceed the maximum individual contribution, the insurance association will pay for the excess portion.)

4 After the liver transplant

People who have received a liver transplant and who are taking immunosuppressants to prevent rejection are eligible for a class 1 physical disability

certificate. In addition to economic benefits, implements used in daily life and other benefits may also be provided.

5 Allowances

Although we have focused on medical subsidies, some people may also be eligible for allowances. For details on how to apply for and receive allowances, please contact the relevant program.

Special child-rearing allowance

The special child-rearing allowance is intended to promote the welfare of children with mental or physical disabilities. Parents or guardians of children under 20 years old with certain legally designated disabilities are eligible. Whether or not the child has a physical disability certificate is irrelevant to this program.

Disabled child-welfare allowance

The disabled child-welfare allowance is intended to improve the welfare of children with severe mental or physical disabilities who require constant care. Households with children under 20 years of age with severe mental or physical disabilities are eligible. (In general, this covers class 1 and some class 2 physical disability certificates, level 1 and some level 2 mental disability certificates, and certain other equivalent diseases and mental disorders.)

If you have any questions about medical subsidies or allowances, please contact a social worker through a recipient transplant coordinator. It is our job to inform children and their families of the medical subsidies, allowances, and other programs that they may be eligible for. As these programs can be difficult to understand, we strive to help children and families undergoing liver transplantation by explaining them in accessible terms. We are also available to discuss other matters related to life at and after leaving the hospital. Please visit us at any time.

Social workers of the Center for Patient Liaison and Services
National Center for Child Health and Development

15 Deceased donor liver transplant registration and surgery

In Japan, the performance of liver transplantations from deceased donors started in 1997. Since this kind of transplantation began at the NCCHD in 2010, 22 patients have received deceased donor liver transplantation (as at the end of 2016). This section explains the process of deceased donor liver transplantation. For the latest information on fees and other matters pertaining to deceased donor

liver transplantation, please refer to the Japan Organ Transplant Network (JOTN) homepage.

* http://www.jotnw.or.jp/index.html

1 Eligibility for deceased donor liver transplantation

Patients who express a desire to undergo deceased donor liver transplant surgery and who have been diagnosed by a doctor as needing the procedure are eligible. “Needing the procedure” means that the patient has an advanced liver disease that severely limits their everyday activities, that liver transplantation would be an extremely useful therapy, and that no other therapeutic method can improve their liver function. Note that liver transplantation cannot be performed on patients with severe infections or malignant tumors in areas beside the liver. Patients with hepatocellular cancer can undergo deceased donor liver transplantation, although this depends on the stage and size of the cancer.

Even for patients diagnosed as needing a liver transplant, the transplant may be canceled if the patient has a significant fever, is in an unstable condition, or is deemed to be at risk from the surgery on the day of the operation.

2 The deceased donor liver transplant process

Next, we explain the process of a deceased donor liver transplant.

① Registration for transplant

When a patient comes to the NCCHD, a transplant surgeon must first determine whether a deceased donor liver transplant is necessary. If it is, the Center’s assessment committee will discuss the case. If the committee decides that a deceased donor liver transplant is indicated, the patient can apply to register with the JOTN.

Registration costs 300 USD, which can be paid at any post office in Japan. The registration fee is considered a medical expense and therefore qualifies for income tax deduction. The registration fee is non-refundable. Households that are exempt from paying residential taxes can apply for exemption from the registration fee.

② Issuance of organ transplant registration card

About two weeks after the registration is completed, an “organ transplant registration card” will be sent to you by mail. Please store this card carefully as it contains your ID number.

③ Issuance of organ transplant registration card

The registration needs to be renewed every year. This costs 50 USD, which can also be paid at a post office. The renewal fee can also be deducted from your income taxes. Households that are exempt from paying residential taxes can apply for an exemption from the renewal fee.

④ Appearance of donor

The recipient is not given any information that could be used to identify the donor.

⑤ Selection of recipient

A liver transplant candidate is selected from the national waiting list after considering factors such as the waiting time, the disease severity (MELD and PELD scores), the blood type (match or compatible), the body size, and the age. The selection process is carried out by the JOTN in strict fairness.

The severity (medical urgency) of the patient's liver disease is rated based on the condition at the time of registration and the predicted life expectancy (Table 1).

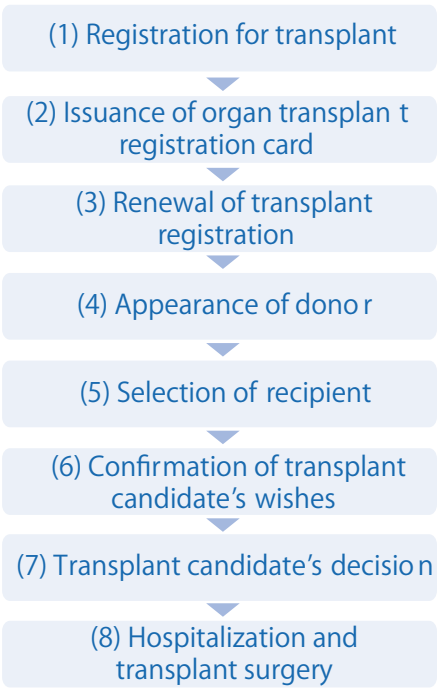


Figure 1. The deceased donor liver transplant process

Points	Condition	Predicted life expectancy
10 pts	The patient needs intensive care to stay alive.	1 month or less
8 pts	The patient does not need intensive care, but requires treatment and management in the hospital	1 – 3 months
6 pts	The patient is either hospitalized, or under home care with major lifestyle restrictions.	3 – 6 months
3 pts	The patient can go to work, attend school, or go on outings, although his/her condition is strongly expected to worsen.	6 months – 1 year

Table 1. Liver disease severity

The severity is reevaluated regularly after registration (at least once a year). If a patient's condition worsens, a revision can be applied for. Reevaluations are usually conducted through close communication between the patient's

primary physician and the NCCHD's department of transplant surgery. Note that the severity assessment methods may change. The assessment methods commonly used in Europe and the United States will probably be introduced to Japan.

⑥ Confirmation of transplant candidate's wishes

The JOTN contacts us when an NCCHD patient is selected as a recipient candidate. A transplant surgeon then telephones the candidate. If the candidate cannot be reached at the number listed in his or her registration profile, the liver will be offered to the next recipient on the list. In deceased donor liver transplantation, the name of the donor and other information about him/her are never revealed.

⑦ Transplant candidate's decision

An organ retrieval team is sent by the transplant institution to the institution providing the organ (i.e., where the donor is) to determine whether it can be transplanted. If so, the organ is removed and transported so that the transplant surgery may take place.

Sometimes, a transplant can be halted all of a sudden even after the candidate has been contacted. In some cases, the process is halted even after the candidate has been hospitalized and the surgery has begun.

Once a patient has been placed on the liver transplant waiting list, the phone call can come at any time, even during holidays or at night. You should always be ready for an urgent call, e.g., by keeping your cell phone with you. When you know you will be out of reach, e.g., at a wedding or a funeral, please contact a recipient transplant coordinator at the NCCHD in advance.

⑧ Hospitalization and transplant surgery

Once it has been confirmed that an NCCHD patient will be the recipient of a deceased donor liver transplant, a doctor of the Center will form a special team to go to the hospital where the donor is located. There, the team performs the operation to remove the liver from the donor. A preservation solution is perfused into the liver before the donor's heart stops, and the liver is then removed and stored so that it can be brought to the NCCHD.

As deceased donor liver transplantations are only performed as and when donors appear, the surgery cannot be scheduled in advance. Unlike living-donor transplants, which are planned in advance, there is very little time to prepare children for the surgery mentally and physically, or for the family to make arrangements. When the call comes, the patient must be hospitalized immediately. Therefore, patients and their families need to be constantly ready.

To ensure that recovery after the operation goes smoothly, be wary of infections and contact your primary doctor immediately should fever, a common cold, lymph node swelling, or any other symptoms appear. Patients

with severe infections may be unable to undergo liver transplantation. In your everyday life, watch what you eat and pay attention to your weight, how frequently you urinate and defecate, and any other changes.

Once the decision to perform a deceased donor liver transplant has been made, the patient is hospitalized for tests and preoperative treatment. As a rule, patients should not eat or drink anything (even tea or water) after being contacted about the surgery. Please record when the patient's last meal was eaten. If the surgery will not take place for a while, you will be contacted about how long you can continue to drink water. If your intestines are not empty when you arrive at the hospital, a laxative may be administered.

Although things go fast once the patient is admitted to the hospital, we still take the time to explain the procedure fully to the recipient and his or her family.

During the surgery, the recipient's liver, bile ducts, and blood vessels connected to the liver are removed, and are then replaced with the corresponding parts from the deceased donor. After the blood vessels of the new liver are connected to the recipient's vessels, the blood flow resumes and the transplanted liver starts working inside the recipient's body. The bile ducts of the transplanted liver are then sewn to the recipient's bile ducts or intestinal tract, and the surgery is over. The patient is then taken to the ICU for more treatment.

9 Costs related to deceased donor liver transplantation

- **Medical expenses**

  In deceased donor liver transplantations, health insurance covers the costs of surgery, postoperative hospitalization, and post-hospital care.

- **Cost of organ transport and dispatch of extraction doctor**

  Although the organ is usually transported by a public institution, livers that come from far away may need to be flown by helicopter or airplane. In these cases, an emergency transport cost of about 50,000 USD is charged. The patient will be billed for it separately by the NCCHD after the transplant.

- **JOTN agency fee: 1,000 USD**

  The patient will be billed for this directly by the JOTN rather than by the medical affairs department of the NCCHD.

10 Halting a liver transplant

Unlike those of living donors, the livers of deceased donors are not subjected to special examinations, and the donors have not engaged in dietary or exercise therapy to improve the condition of their liver. Therefore, nobody knows how healthy a deceased donor's liver is. After the liver is removed

and has undergone a special storage process, a final decision will be made at the institution where the operation is due to take place. Moreover, the transplanted liver may not always function properly even when the transplant surgery has gone perfectly. Although this does not happen frequently, it becomes apparent after one or two days when this is the case. The cause of this malfunction is unknown, and therefore cannot be prevented. If the transplanted liver is not functioning, another transplant may be necessary. Furthermore, it may take some time for the transplanted liver to start functioning properly, depending on the status of the recipient's disease. In these cases, the risk of infection is greater.

It is sometimes unclear whether a deceased donor's liver is suitable for transplantation until it is actually removed. Therefore, the operation is sometimes canceled even after the recipient candidate has been contacted and hospitalized. Note that in these cases, the patient is still billed the relevant fees.

(11) Results of deceased donor liver transplantation

According to statistics from the Japanese Liver Transplantation Society, as of 2014, the 1-, 3-, and 5-year survival rates for deceased donor liver transplantation were 81.8%, 78.7%, and 77.1%, respectively. These are not significantly different from the figures for living-donor liver transplantation (adults included).

Please do not hesitate to contact us about any concerns or worries you may have while awaiting your transplant.

Seisuke Sakamoto, Mureo Kasahara
Organ Transplantation Center
National Center for Child Health and Development

16 Interviews about undergoing a liver transplant (donors)

Many people, when a doctor explains that their child needs a liver transplant, must feel their mind going blank with anxiety. "What in the world is going to happen now?", they may wonder anxiously. Frequently, a healthy family member volunteers to be the donor for the liver transplant. The surgery to remove part of the liver can be incredibly frightening in itself.

Mr. N and Ms. K both donated parts of their livers so that their children could receive liver transplantations. They have agreed to speak to us about their

experiences. Although every disease course and every family situation is different, all parents want to help their children. What is it like as a father, mother, husband, wife—overall, a human—to be a live donor for a liver transplant? How does it feel? Mr. N and Ms. K agreed to be interviewed in the hope that their experiences would help other families who are considering a liver transplant.

First, we will hear from Mr. N, who was 30 years old when he gave part of his liver to his daughter.

"Our daughter was our first child, and my wife and I did our best to care for her. When she was a baby, the color of her stool seemed whitish with a little yellow mixed in, but we didn't have anything to compare it to. People at the hospital told us that sometimes a baby's stool is pale from drinking milk, so we thought that it must be normal. It's actually not true that milk can turn the stool white. This happens when the bile doesn't flow properly and fails to color the stool. Our daughter had health checks at one, two, and four months, but the doctor never suspected liver disease. We were a bit concerned about jaundice, but when we asked about it, the doctor dismissed the idea, saying that our daughter had naturally dark skin. Her skin did look dark as if she had a suntan, but it was actually jaundice that was causing the change in color.

When she was about four-and-a-half months old, her belly gradually became noticeably swollen. It looked to us as if there was something wrong, so we took her to a nearby hospital.

There, the doctor asked us, "How did things get to this point?" We were immediately referred to a pediatric hospital.

There, the doctors immediately admitted our daughter on suspicion of biliary atresia. She had severe jaundice and her swollen belly was caused by a great deal of ascites. The doctors said that she needed more specialized care, so we were referred to another hospital attached to a university. But it was far from our home, so we searched online for a closer hospital. This is how we learned about the NCCHD and found that it performed liver transplantation on children. We transferred my daughter there about a week after she was admitted to the first pediatric hospital. About a week later, she underwent the Kasai procedure. At the time we were told, "Things won't end with the Kasai procedure. You need to start thinking about a liver transplant. We'll see how things go for a week or ten days after the Kasai procedure, but if the jaundice doesn't improve, she'll need a liver transplant." The Kasai procedure was conducted a little before Christmas. Afterward, she was treated with steroids, but the jaundice didn't improve. About six weeks later, we started talking about a liver transplant.

I underwent donor screening. Even if my wife could have been the donor, I wanted to do it. Going through the screening and wanting to be the donor felt very natural. I didn't hesitate or feel any anxiety or fear. I was just worried about my daughter. When I need to decide something, I deliberate internally instead of talking it over with others. When I make a decision, I'm ready to move forward.

So when we started talking about a transplant, I didn't consult anyone in particular, I just thought hard about it. My willingness and desire to be the donor never wavered.

My wife was healthy, but the doctor said that we should consider her physical condition as she had recently given birth. As a father, I had a strong desire to be involved in my daughter's recovery process.

At the NCCHD, one of the parents is usually the donor. The other parent can have a lot of worries. After the surgery, I learned that my wife had been incredibly anxious, which makes complete sense. There's three of us in our family, and my wife had to watch two of us go into the operating room at the same time. She courageously faced all of these worries, anxieties, and other issues. I'm so grateful for the support she gave my daughter and me. Liver transplantation is not something that ends with the surgery. Patients have to take immunosuppressants afterward, and there are a lot of things to be careful about in relation to the child's growth and lifestyle. With all of this, it's a big challenge to raise our daughter healthily. My wife and I are doing the best we can.

While I was undergoing the donor screening and figuring out if it was medically possible for me to be the donor, I also had to sort things out at work. I was told I'd have to take about three months off. My company had never had an employee who had become an organ donor before, so the human resources department was not sure how to handle it. The issue was that it wasn't me who was sick. I was healthy, but I intended to take three months off for an operation. There were rules for taking time off for an illness, but nothing about being an organ donor. However, my bosses were helpful, and the company not only agreed to treat my situation as medical leave, but also continued to pay me during that time. As the date of the transplant approached, I was able to find people to take over my duties and prepare for my absence. This helped me to focus on my daughter's care and my surgery without having to worry about work.

The three months I was told I would need to recover from the donor surgery became a goal. "If the doctor says it will take three months, then I should be better after three months," I thought. The doctors explained everything I'd go through, both before and after the surgery. They talked about pain, about the wound, about the postoperative course. The reality differed from their explanations in a few respects, but I didn't worry about the small details. Whatever happened, I had a strong desire to recover within three months. It helped that I had the utmost confidence in the doctors.

I was able to return to work as planned. Now, I drink some alcohol when others are drinking. It doesn't feel like alcohol affects me differently. I didn't drink much even before the operation, so I'm not sure if others will have the same experience.

Eighty-two days after the transplant, which I think is a relatively long time, my daughter left the hospital healthy. We were finally able to return to life at home, living together as a family. My daughter takes immunosuppressants, so we were

really careful about preventing infections after she left the hospital. As we got used to things, we gradually started taking her outside to play in the park or with other children. My daughter is now in kindergarten, so being with other children inevitably increases the risk of infection. We decided to keep her home during overnight stays and outings, and we don't let her swim in the kindergarten's pool. If some kind of infection is going around at the kindergarten, we keep her at home for one or two weeks. We worried a bit that reducing her opportunities for contact with other children would harm her growth, but we have decided that preventing infections is the priority. She's had to be hospitalized a few times for colds, chickenpox, and infections from cuts in her mouth.

We asked each of the kindergarten teachers personally to let us know immediately if they noticed anything unusual about our daughter. If something happens, they contact us, and we go pick her up.

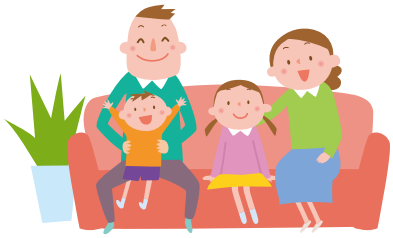
Our daughter has been hospitalized a couple of times for infections, so in that sense it's been harder than with a healthy child.

We are frank with our daughter about her disease. We tell her, 'Your liver had problems because of a disease you were born with. So we took it out and replaced it with half of daddy's liver.'

We don't treat this as anything special, just a natural occurrence. Our daughter also needs to understand that she has to be careful in her everyday life. For example, she is allergic to eggs, so we tell her, 'You can't eat eggs because you get a rash and it makes you feel bad.' We talk about the liver transplant in the same way, like it's an ordinary thing. As she gets older, we'll explain her disease more fully in ways that she can grasp, so she'll gradually get a deeper understanding of her condition. She's started to realize that the scar on her stomach is not something all kids have.

We are very concerned that our daughter will worry about or be teased for having had a liver transplant. As she grows up and becomes her own person, she'll eventually distance herself from us and build her own world. At first, the transplant was something for us parents to think and worry about, but as our daughter grows, it will become her own concern. We understand that she'll be confronted with all kinds of concerns. And we know that we can't solve all her problems. So it's important that we talk to her about her disease and her transplant so that she understands it clearly. We want her to be able to think about, decide, and deal with things on her own.

After our daughter's transplant, our family gained another member with the birth of our son. While we went through the big experience of the transplant with our daughter, our son has been healthy. We love them both equally and both are precious to us. Of course they are different, but everyone has different characters and personalities. As a father, I want both my daughter and my son to grow up naturally and free."



Next we will hear from Ms. K, who was 32 years old when she donated part of her liver to her daughter.

"There are four of us in our family: me, my husband, our son, and our daughter. When my daughter was three weeks old, we noticed that her stool was a pale yellow, almost lemon-colored. When we took her to the emergency room at a nearby general hospital, the doctor told us to come back if she continued to have pale stool. They didn't undertake any particular examinations that day.

When I saw the pale stool, I thought it might be biliary atresia. Unlike when I had my son, my daughter's mother-child health handbook contained a stool color card. The card had the name 'biliary atresia' on it, so I searched online for more information. Since my daughter's birth, I'd felt a discomfort in my heart and my physical condition hadn't been optimal. I searched frantically for information. I learned that if the initial surgery (Kasai procedure) didn't go well, she would need a liver transplant. So I also researched liver transplantation. A relative who is a doctor made light of my worries, 'Biliary atresia affects one in every 10,000 newborns, so it's not super rare. But a liver transplant? You don't need to worry about that now.' But I knew something was wrong.

I wanted to know how to deal with biliary atresia, so I started reading a blog. However, it was about a family whose child had unfortunately died. This created a strong image in my mind that a transplant equaled death. I even thought, 'It's such a heavy surgery for my daughter. If someone besides me bore the physical burden of donating part of an organ only to have an unfortunate result, maybe it would be better to accept that this is my child's lifespan.' It was incredibly difficult to have a positive image of biliary atresia.

At the same time, I continued to search frantically for a hospital where my daughter could quickly get access to the best care. Looking at the number of cases and the results of transplant surgeries, I narrowed it down to two hospitals in Tokyo. Three days after we first noticed her pale stools, nothing had changed, so we went in for another examination and asked for a referral to the NCCHD.

We immediately returned to Tokyo and admitted our daughter to the hospital for tests. About three weeks after the pale stools were first noticed, she underwent the Kasai procedure. This failed to improve the jaundice and we started discussing liver transplantation. I realized that a liver transplant was our only option for treatment. At that time, I felt so dark, so down. We had detected the problem early, but a transplant was still necessary. That was so hard to accept. Why was this happening to my daughter? I was anguished.

While I was caring for our daughter at the hospital, I was also spending time at home with our 3-year-old son. Time management was difficult with more than one child, but my son's innocent presence really cheered me up. He helped me to balance my emotions.

I wanted concrete information, so I asked the recipient transplant coordinator to introduce me to patients and families who had been through liver transplantation.

I was able to meet two families whose children had liver transplantations for the same disease as my daughter. That was a major turning-point for me. I had felt there was no hope for the future, but suddenly, there were healthy children running around after having liver transplantations before my eyes. As they say, 'Seeing something once is better than hearing it a hundred times.' I was also able to talk with people who had been donors. They encouraged me, and I started to have hope that our child could also get healthy again. I gained a lot of courage from the people who had gone through liver transplantation before me. 'It's a lot to deal with, but it'll work out in the end!' they told me. I also met families whose children had the same disease as my daughter on the social network Mixi and exchanged information with them.

My husband and I have a habit of gathering as much information as we can and thinking about things calmly. We're not the types to just believe things will be fine without any evidence. The reality that the Kasai procedure had failed to improve the bile flow in our daughter weighed heavily on our hearts. Whenever we talked about her disease, we would feel lost and depressed.

This feeling of helplessness was relieved by hearing about other people's experiences. Our attitude turned from negative to positive. We became determined to move forward and to take on this challenge.

We repeatedly talked to our 3-year-old son about his sister's illness. He was doing his best to cope with the situation, so we wanted to be honest with him about things. We bought a children's anatomy diagram and explained to him, 'The bile that breaks down fat in your sister's body isn't flowing right, so that's why her skin is yellow and she itches so much that she scratches until she bleeds.' We told him, 'We have to remove her liver. It's such a difficult surgery that she might even die; your mother believes she will get better.' He understood that his sister's disease was something serious, and started to feel a strong desire to protect her.

Still, my son has always demanded a lot of attention. When he's feeling sad, I want to be with him to make him feel better. So we constantly told him, 'Your sister is important, but you're precious too,' and, 'We love you so much.' At the same time, our son developed an awareness that his sister is precious. He would act as the big brother by telling us to make sure to bring back medicine for his sister. In his childish way, he would even admonish me, 'She's the cutest, so mom, you should give her affection.'

There were a lot of twists and turns before we decided who the donor would be. Both my husband and I are carriers of a certain virus, so initially we were told we couldn't be donors. We agonized over whether to ask my mother (the recipient's grandmother) to be the donor. We consulted the doctors about so many things. In the end, I decided to be the donor. As soon as it was decided, my resolve was set.

Maybe I did it because I felt guilty toward my daughter. After all, she grew inside my body. I had a number of regrets, such as 'I made a mistake by not bringing a mirror to a funeral I attended when I was pregnant,' or 'I didn't talk to

her enough or give her enough affection when she was in my belly.' I felt like I hadn't given birth to her properly, so I was susceptible to superstitions and my imagination. I felt that being the donor was a chance to give birth to her again. 'Take what is needed from my body and use it to help my daughter. I don't care what happens to me, just make my daughter's body healthy.'

Although the ECG they performed as part of the donor screening was normal, I still sometimes felt the discomfort that I'd had in my heart since giving birth. The doctor explained 'The donor's safety is the priority in living-donor liver transplantation, so if your condition suddenly changes for the worse, we will also halt your child's operation.' I worried about this until right before I went under anesthesia. 'If my heart stops, what will happen to my daughter?'

As the date of the transplant approached, our whole family, including both my and my husband's parents, all came together. My mother and I stayed at the Ronald McDonald House on the NCCHD grounds so that we could be close to my daughter. My husband and his mother took care of things at home so things could be as normal as possible for our son. My husband took two weeks off work around the time of the surgery, and my mom took three months off to help us. I felt confident and safe knowing that my family would be taking care of my daughter when I couldn't move around freely after the surgery. I feel that overcoming such a difficult situation brought us closer together as a family.

The night before the donor surgery, my period started. After the surgery, I felt a pain so strong I thought my shoulder was broken, and I had difficulty breathing and fevers. Now, I've totally forgotten about all that suffering, unless someone reminds me of it. My own condition was secondary, so all that has been completely forgotten.

Now, I'm sincerely glad we went through the transplant surgery. Our daughter did so well, going from the ICU to the general hospital ward then getting out of the hospital. People who meet her now are so surprised at the pink glow of her skin and how healthy she has grown.

She has spent a lot of time in the hospital for the Kasai procedure and the liver transplant surgery. At times, I worry about her development compared with that of other children, but considering how long her movements were restricted by intravenous lines and tubes, I've come to accept it. Other families have advised me not to make simple comparisons with other children of the same age, which has made me feel better. I have a belief that whatever happens, we'll make the best of it. I feel like I've become a stronger parent.

I would love to communicate with other families in similar conditions who have been told that a liver transplant is necessary. When you think that a transplant might be needed or are waiting for the transplant—I think these are the hardest times for families. At first, I was so worried and hopeless. "Why is this happening to our child?" But learning about other children and families who had overcome similar circumstances was a huge help. Diseases that require liver transplantation are not very common, but still, people should know that they're not alone. The feeling of isolation, that you are the only one who is suffering, is a powerful

enemy. There are many ways to take that first step away from the hopelessness that comes from isolation: researching things online, social networking sites, family associations. You can even ask for help at outpatient clinics.

The people I met through the family association helped me to gain hope for my daughter's life, so I'd like to repay that kindness. I'd be so happy if our difficult experience could help someone else. I've written about my experiences and I've started to become active on Facebook and other social networks. I want to give families who are feeling lost information that can be easily understood. I'd like to point out the way to hope.

Mr. N and Ms. K's stories show how strongly parents want to protect their children and help them get better. I am sure that other families who are considering a living-donor liver transplant found some of their feelings reflected in these stories. I also think that these stories can help people to see how certain obstacles can be overcome. No matter how healthy one is, going under anesthesia for abdominal surgery to remove part of one's liver is a big deal. To do this and still show so much concern for the child having the liver transplant and other family members is highly commendable.

Mr. N's daughter had a liver transplant when she was a baby. She is now in primary school. As she is their first child, they have to do so much to support their daughter's health by making sure she continues to take immunosuppressants and applying caution in other areas of her life. But it feels like all these hardships have helped their daughter grow. As Mr. N said, the liver transplant isn't everything. The important part is raising your child afterward.

Hearing a doctor say that a transplant is necessary can be a deep shock for families. Many have difficulties feeling any hope for the future. Like Ms. K initially, many become deeply depressed. I hope that Ms. K's words about "taking that first step away from the hopelessness that comes from isolation" will reach as many families as possible. Children who need liver transplantation are few and far between. It's easy to feel anxious and negative when you are thrown into an unknown situation. The families who are thinking about whether to have a liver transplant should start by getting the information they need. Both Mr. N and Ms. K sought to obtain as much information as possible, and processed it so as to understand the situation as best they could. Understanding what is involved helps people to be hopeful and gives them the strength to move forward. When this is added to a strong faith in recovery, I believe that it can help bring out a child's natural ability to heal.

At the NCCHD, most of the people who become donors are parents of the children involved. For a child, having a mother or father undergo surgery is a

big deal. Ms. K made sure to explain the situation thoroughly to her son, the recipient's older brother, and to give him plenty of love. I think it is incredibly important to explain what is happening to siblings so that they can take part in dealing with the transplant as a family. This not only creates a feeling of solidarity, but helps teach children about kindness to others.

After the transplant, Mr. N's family welcomed a new member, a little boy. Mr. N and his wife treasure both their daughter and her new little brother. They don't give their daughter any special treatment. They see both children as precious members of the family. The daughter and other children are all seen as cute. For the sake of the long-term health of the family, I think this is incredibly important.

Mr. N said, "We want her to be able to think about, decide, and deal with things on her own." Children will change and grow physically and mentally. They hold within them great possibilities. It is an immense joy to watch them define their personalities, become independent, and expand their world as they grow into adulthood.

The "Do-Re-Mi-Fa Club" is an association of families and children who have gone through liver transplantation at the NCCHD. It is run independently from the hospital, and currently holds events for families to get together and provides means to exchange information through a blog, website, and bulletin. Although every child's disease and family situation is different, all of the club's members have gone through the experience of a liver transplant and have overcome a variety of difficulties. If you would like to talk to people who have gone through this experience, please get in touch with the club.

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Email	office@doremifaclub.com

We sincerely thank Mr. N and Ms. K for participating in these interviews.

Interviews conducted by the Organ Transplantation Center of the National Center for Child Health and Development with assistance from the Do-Re-Mi-Fa Club.

17 Interviews about undergoing a liver transplant (recipients)

Parents probably worry about how a child receiving a liver transplant will grow up and what school life will be like. We spoke to three people about their experiences with liver transplantation. The first two are second-grade primary school students who received parts of their father's and mother's livers when they were babies. The third is a young man who received a transplant from a deceased donor in his final year of high school. He is now a university student.

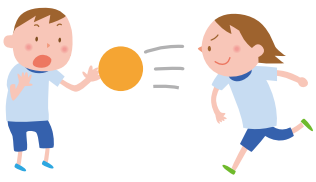
Ms. K underwent the Kasai procedure for biliary atresia, and received liver transplantation from her mother at seven months of age. Ms. R underwent the Kasai procedure for biliary atresia twice, and received liver transplantation from her father at eighteen months of age. Both are now seven years old and in second grade. They are also friends. They love to sing and dance, like vegetables, and enjoy collecting insects. They create an energetic, sparkling atmosphere. We spoke to them about school, their disease, and other matters.

Ms. K walks 20 or 30 minutes to school each day. Ms. R commutes to school by train and bus, which takes her about an hour.

Ms. K is in charge of helping her homeroom teacher pass out notices and printouts. Her favorite class is art. She loves making things, drawing with pens, and finger-painting. During recess, she likes collecting acorns from under a tree in the schoolyard. She takes them home and boils them to get rid of bugs, then uses them to make things.

Ms. R likes free time at school. She enjoys sleeping over at school in a sleeping bag, making curry, watering the tomatoes, carrots, okra, and corn in the garden, and taking care of animals. She attends a private school with students coming from different areas, so children from the same neighborhood go home together. This allows her to spend time with children from other grades, which she finds interesting. She's a bit mischievous, saying things like, "I love it when the teacher says there's no homework."

Many parents worry whether their children will be able to exercise or to attend gym class after a liver transplant, but Ms. K and Ms. R are very physically active.



"Sports Day at school is coming up, so we're practicing the relay. One time I had to sit out gym class, but that was because I ate too much breakfast (laughs)! It wasn't because I was sick. I'm fast and I love playing tag. Dodgeball doesn't scare me. I can play regular dodgeball or rolling dodgeball. I practice throwing the ball with my dad, to learn

when it's best to throw it straight or when diagonal is better. I can also perform a double-under. I did 33 jumps before. At morning physical education, we once did 104 jumps with a big rope. I'm also good at a game in which the teacher tells us to find something red and touch it," Ms. K said.

"During gym class, I don't do the things my mom tells me not to. And sometimes I don't go to class when I'm not feeling well. But I love to run. I can run and it doesn't hurt at all. When I play dodgeball, I'm fine as long as I watch where the ball is going. I practice with my dad and big sister. I'm terrible at jump rope. But when we did it with a big rope, we jumped 105 times. That's our record. It must have been hard for the teacher to count. I also play on the monkey bars and run the 50-meter race. I love competitions," Ms. R said.

The girls have a big world outside of school, too.

"I love playing at the park. I'm not scared of bugs at all. I like catching swallowtail butterflies and other insects. I played in the park yesterday with my friend," Ms. K said.

"I like doing cheerleader dances. My mom told me that if I imitated the people who dance behind the singers on TV, someday I'll remember it, so I do that. I want to be able to sing the song from the Disney movie 'Frozen' by myself. So when my family goes places in the car, we listen to that song," Ms. R said.

Next, we asked the girls how they felt about having had transplants, and about their scars from surgery.

"I don't remember the operation. It was when I was a baby, and I was asleep. My friends don't say anything about the scar from the surgery on my belly. People don't ask about the scar; they ask about my eyes because I have a little rash on my eyelids. But I put cream on it, so it's gotten better. Now people don't ask about it very often. When I wear clothes, people don't know about my belly, so they don't ask about it," said Ms. K.

"I also had surgery when I was a baby. I don't get asked much about my disease now. My teachers at school know about it, so they tell me to change in the changing room. I don't want people to see the scar when I take my clothes off, so I always use the changing room. But sometimes my friends follow me and ask me why I use the changing room. I tell them, 'Because I have a scar on my belly from surgery. I had a hard time when I was a baby.' Then they say, 'Oh, I see,' and that's it," said Ms. R.

As they grow, children gradually deepen their understanding of their bodies and are able to do more things on their own. Parents worry about preventing infections when their children are with other kids and about taking immunosuppressants, but how do the children feel about these things?

"I put on a mask if I think I might have a cold. When I'm healthy I don't use one. I don't only wear one when I have a cold, but also when my friends have one. If I can't practice dance like I love to, I know I'm feeling bad because I might have a cold. Every morning at school, we do a health check after the person on day duty's speech. One by one, everybody describes their condition, like, 'I'm feeling good,' or, 'I might have a cold.' I know how to take medicine very well. I always take one and I do it by myself. Grapefruit makes the medicine act too strong, so I can't eat it. Sometimes I take Biofermin® (Lactobacillus preparations) too," said Ms. K.

"In the other bag that I carry besides my backpack, I always have a new mask. I put it on if I feel like I need to, without anyone telling me to. If there's a disease going around school, my teacher will write a note to my parents. Then my mom will talk to the doctors at the NCCHD. We announce how we're feeling at the morning meeting at school. If you don't tell them, how will the teachers know? If someone says they have some kind of pain, the teacher tells us, 'Let's be nice to the person with a headache. I hope you feel better,' or, 'Let's help the person with a stomachache.' So if someone's not feeling well, everyone finds out at the morning meeting. I take three medicines. I put two of them in the packet for the third one and take them all together, by myself. My mom told me to try it on my own. So I tried, and I did it," Ms. R said.

Children don't just grow physically. How is their mental and emotional growth affected by their experience undergoing a liver transplant for a serious liver disease, being hospitalized for a long time, and taking immunosuppressants? Although parents might worry about these things, there is plenty to look forward to.

For example, Ms. K seems to have so many things she wants to tell us that her head is nearly overflowing. Sometimes it seems like her words can't keep up with her thoughts, and she gets derailed when talking. But when that happens, Ms. K realizes what she's doing. "Oops! Sorry. I'll talk about that later," she'll say, and get back on track. When she is asked a question and doesn't have an immediate answer, she'll think about it silently. She's not ignoring the question, just collecting her thoughts. She gives a proper response when she's ready.

At Ms. R's school, the class takes care of a rabbit. She does her best to make sure the floor of the rabbit's cage is clean. "It stinks, but it's so cute!" she says. It seems like Ms. R is kind to her friends and to animals and plants. During the interview, Ms. K dropped the straw from her drink on the floor. While someone was bringing a new straw, Ms. R waited to start drinking her own juice. When that was pointed out to her, she laughed shyly and looked at Ms. K. It was clear that she has learned how to show care and consideration for others.

When asked about their dreams for the future, Ms. K said she wanted to be a dancer, singer, or designer. Ms. R said she wanted to be a cheer dancer, singer, or nurse. They were so excited when they talked to each other about what they would do in the future. I hope that all of their dreams come true.

Next, we spoke with Mr. S, who is currently a sophomore in college. Mr. S has a metabolic disease, and has been on a restricted diet since he was a baby. He talked about living with his disease, about getting a liver transplant and the changes it brought, and about his feelings toward the deceased donor.

"My disease is called ornithine transcarbamylase (OTC) deficiency. Because of it, I wasn't able to metabolize protein properly since I was born. This meant I couldn't get rid of the ammonia in my body, which caused various symptoms. Ever since I was little, I was on a therapeutic diet that limited my protein intake. My parents explained my disease to me when I was young, so I saw the dietary restrictions as necessary, just the way things were. I don't remember feeling jealous of others for eating thing I couldn't. I go to a private school, so there's no school lunch; we bring our own. Sometimes a friend would offer me a hamburger from his lunch, but I knew I couldn't eat it, so I'd just say, 'Thanks, but I can't eat that. Sorry.'

In middle school, I started spending more time outside with my friends. We'd sometimes go to McDonalds. Of course, there were a lot of things I couldn't eat there, so I'd stick to what was allowed—french fries, salad, things like that. But even with french fries I'd have to get a small order. Or I'd have chicken nuggets, but only eat one.

My mom was great about managing my diet at home. She's a good cook. She would measure how many grams of protein in each ingredient, such as a carrot or a piece of meat. Normally, you can just estimate the amount when you cook, but day after day, my mom made sure she knew exactly how many grams were in each piece. I'm so thankful to her. She did an amazing job. For example, she would work really hard so I could participate in school events despite my dietary restrictions. When I went to camp, I couldn't eat what everyone else did. But my mom would stay at a lodge nearby and cook me the same items so I could eat them. I'm really grateful for that. For 18 years until I had the transplant, she cooked me a low-protein diet. When we ate at home, she cooked mainly vegetables so I could eat them. When she served meat, I would get a smaller portion. When we had rice, she made low-protein rice just for me. She would freeze individual portions and heat them up right before we ate. The rest of my family would eat regular rice.

Back then, I took medicine three times a day—morning, noon, and evening. I took sodium benzoate and Argi-U® (Arginine) to keep the ammonia levels in my blood from rising. Taking medicine became a habit, so it wasn't hard or anything.

I took part in physical education like everyone else. I didn't have any exercise restrictions, but I did feel I wasn't as strong as my friends.

I never thought, 'It'd be better if I didn't have this disease.' The dietary restrictions were always there, so it was just part of my life.

We started talking about a transplant during the winter of my first high school year. My doctor had warned me that I'd be more susceptible to health problems when I hit adolescence. From my second year of junior high through to my first year of high school, I often felt unwell. Each time, I'd go to a hospital emergency room and have an intravenous drip for about three hours, then get on with my life.

Gradually, I started missing more days at school. In the spring of my second high school year, I transferred to a correspondence school with a credit-based system. The classes at that school were recorded, so I could watch them on my computer back home. It was nice to be able to study whenever I felt well enough. At this school, each class is divided into ten portions, each of which lasts two weeks. In the first week you watch classes, study and review. Then, in the second week, you write a report and turn it in. This is repeated ten times. Once you pass a final test, you get the credit for that class. If you don't understand something, you look at the textbook or figure it out on your own. As I didn't have to commute to school, it was easy to just loaf around. To avoid this, I would wake up every morning and start watching classes and solving problems at 9 a.m. I took math, English, Japanese, chemistry, politics, economics, and world history. The school was associated with a university, so if you did well in the school's test you could get into the department you wanted. I did my best to study hard.

For the liver transplant, we first considered a living donor. For medical reasons, neither of my parents could be donors, so we started thinking about a deceased donor transplantation, and eventually I got on the waiting list for a deceased donor liver transplantation. I didn't feel impatient. It seemed that eventually my turn for surgery would come. I just had to wait.

Around that time, Professor Shinya Yamanaka won the Nobel Prize in Physiology or Medicine, so there were a lot of reports on iPS cells on TV and in the newspapers. I thought it would be great if iPS cells could be used to create a liver, so I cut out newspaper articles on the topic and put them in a scrapbook to have all the information in one place. I wanted to learn more about iPS cells, so I even signed up for a seminar by Professor Yamanaka.

Then one day at around 4 a.m., we got a phone call from Dr. Kasahara from the Organ Transplantation Center. That was four days before my eighteenth birthday.

My dad answered the phone, and after hanging up he rushed into my room to tell me the news. When he turned on the light, I had no idea what was going on. I was surprised when he told me they had found a deceased donor. I was so nervous. 'What should I do?' I kept thinking. Until then, I had just been living my life as a high school student.

I called Dr. Kasahara back right away. I was still nervous, but after talking to him for two minutes, I told him I wanted to get the transplant. At the time, I felt like I had to have it done. Like it was destiny. I packed for the hospital in a rush. As I was nervous on the way there, I listened to music to calm me down. I thought, 'You have to believe the surgery will be a success. Have hope!' So I listened to 'Kibo no Uta' (Song of Hope) by 'The Funky Monkey Babys' over and over.

We arrived at the hospital at 6 a.m. After being admitted, the doctors explained the surgery to my father, mother, grandfather, and me.

In the operation room at 8 a.m., they told me I could play any music I wanted, and by chance the same song—'Kibo no Uta' by 'The Funky Monkey Babys'—came on again. I was still really nervous, but I kept telling myself, 'Trust the doctor doing the transplant and it'll be a success.' until I went under anesthesia.

The surgery went fine, and the following day they removed the respirator tube and replaced it with an oxygen mask. After the operation, the pain medication worked well, so I didn't have any pain. However, I was incredibly thirsty. I really wanted something to drink, but I had kidney failure right after the surgery, so I was only allowed to melt one or two ice cubes in my mouth. Still, I didn't feel down. Afterward, my parents told me about the donor—a man from Nagoya. I felt so grateful to him. I thought, 'I want to live a full life for him.' Before the surgery, I didn't feel like I had given up on my dreams, but the transplant surgery helped me to broaden them even further. I felt like I was able to start a new life thanks to the donor.

About a month after the operation, my bile duct became obstructed, so I had to have another surgery to resolve that. There were a lot of difficulties, but 55 days after the surgery I left the hospital.

I am truly thankful to the donor.

About six months after the transplant, I started university. I decided to major in Northern European studies, with a minor in social welfare. My school is about an hour and a half away from my house, but I go every day I have class. When I was in middle school, I knew someone involved in elderly welfare. After hearing about it, I thought I'd like to study social welfare for the elderly. I chose to focus on Northern Europe because the countries there have incredibly advanced welfare systems for elderly people. I started studying the languages and all kinds of things about these countries. I chose to minor in social welfare because I also wanted to learn about it in general, not just in Northern Europe. This winter, I plan to study abroad in Denmark for a short time. I want to experience and see a lot of things so I can learn how social welfare works in practice.

I've always loved to be active, and since the transplant I've started doing sports. I mainly do jogging, weight training, and skiing. I started jogging in high school because I wanted to get stronger. Now I run five kilometers three times a week. I run with a friend, so it's fun. I'm about as strong as my healthy friends. I started weight training to develop

muscle strength during rehabilitation from the transplant surgery. As the training center at my university has a bench press, I started doing that in the spring of my first year. At first, I could only pump twenty-kilogram weights, but now I can do fifty kilograms. I've been skiing since I was small, so I'm pretty good at downhill and turns. I started snowboarding after the transplant. When I go to karaoke with my friends, we sing songs by my favorite band, 'Exile Tribe'. Music-wise, I also like 'E-Girls'.

Since the transplant, I don't have to limit my protein intake anymore. Now when I go to McDonald's with my friends, I can eat hamburgers too. I take the immunosuppressant Graceptor once a day after breakfast, but it's not a big deal. I used to take medicine three times a day, so if anything it's easier now.

I'm 20 years old now. In the future, I'd like to have a job that's related to medicine so I can help people. I don't know exactly what that will be yet, but I'm contemplating a few professions. One is physical therapy. I went through rehabilitation when I was weak after the transplant surgery, using rubber bands to strengthen the muscles of my legs—it was really effective and I got interested in it. I've also thought of becoming a childcare worker. I'm good at looking after children. When a bunch of my four-year-old brother's friends came over, I took care of them. In the social welfare field, I'm interested in becoming a home helper. No matter what I end up doing, I want it to be something that helps others. I want to learn about social welfare broadly at university, and then study a specialized field at a vocational school to get certified in something work-related.

I'd like to tell kids who have the same disease but haven't had a transplant that the dietary restrictions aren't everything. Don't focus on the things you can't do or your limitations. Focus on the time outside meals. Have a lot of fun in your life. For example, think about the time you have for recess after finishing lunch at school. I used to play soccer or basketball during that time. Eating isn't everything in life.

For children who are on the waiting list for a deceased donor transplant, I hope that they can treasure and enjoy their current lives. After registering for a deceased donor transplant, you can't constantly be thinking about the transplant, 'When will I get to have the surgery? Why hasn't it come yet?' Instead, if you believe that someday the opportunity for a transplant will come and you just enjoy your life in the meantime, eventually that chance will arrive. In my first year of high school, I read a book about how to increase your luck. Of course, I didn't apply everything from the book, but I did start being more aware of certain things and implementing them. Not anything special, just parts of my daily life. Things like greeting teachers cheerfully, keeping my room clean, or talking to friends about things that might be uncomfortable. Doing these things gradually makes your heart clearer, and if you do them enough, I believe that you can bring yourself good luck. Someday you'll get the call to tell you that a deceased donor liver transplant is available. This can be nerve-racking, but be brave as you head into the surgery and everything will be fine.

I think it's important to have a positive attitude and to work toward achieving your dreams. If you do badly in a test, just think, 'Next time, I'll work harder!' My dad was a big influence on me in this regard.

When I was in my second year of middle school, my dad was working on his own dream. He was working at a construction company but had always dreamed of becoming a lawyer. To prepare for the exam, he would wake up every morning at 4 a.m. to study by himself. I really respected him for that, and it made me want to do my best as well. I decided to try hard and make continuous efforts to achieve my dreams. So I thought about what I could do, and I started waking up early to solve math problems or go jogging.

I was able to have the operation thanks to Dr. Kasahara and the rest of the transplant surgery team. Every day, I feel grateful to the transplant surgery team for giving me the chance to lead a healthy life. I want to live to 100 years old. But when I die, I want to meet my donor in heaven and give him a big 'Thank You.' I want to express my gratitude to him for giving me his liver so I could start a new life. Then, I want to tell him about all the things I was able to do after having the transplantation."

Many parents probably worry about how undergoing a liver transplant will affect their child's growth and development. But seeing how cheerful Ms. K and Ms. R are, I hope that parents will realize that these girls are no different health-wise from other kids. After the interview, Ms. R's mother spoke to us in another room. "I've seen that my daughter can deal with her disease and live her life," she said. Indeed, the way children who have had transplants deal with their disease is incredibly important. A liver transplant doesn't end with the surgery. We have to work to make sure that the transplanted liver cooperates with the rest of the body, which means taking immunosuppressants. Moreover, there are other things to take care of to make sure that the immunosuppressants are as effective as possible, such as watching what one eats. These things need to be kept up for the person's whole life, so teaching children how to deal with their disease is the best way to improve their quality of life.

It was also impressive to hear about the measures the parents put in place to raise their children healthily. For example, explaining how far they could go in gym class, practicing dodgeball so that they could play with their friends, or teaching them how to take multiple medications easily. The parents also taught their children how to answer their friends' questions about their surgical scars. This kind of parental involvement and advice is very helpful for children. I believe that it helps them to approach life independently.

Families are usually confronted with transplantation for the first time, and they don't know anyone else who has gone through it. This can increase the level of worry and anxiety. However, it was clear that Ms. K and Ms. R were not growing up in a constrained environment. Ms. K's mother said, "I'm

astounded at my daughter's ability to overcome her parents' preconceptions and what adults assume is proper." Children are able to think about things differently from adults in order to deal with situations and overcome difficulties.

In any family, parents have trouble understanding their children's feelings once they reach adolescence. Mr. S's story illustrates what it is like for a child who has been through adolescence and is nearing adulthood to experience a transplant. Since he was a small child, Mr. S had accepted his disease as a part of himself and lived his life to the fullest. To experience repeated health problems, miss school because of them, sign up for a deceased donor liver transplant, then undergo surgery—that must have been an incredible ordeal for a teenager. Yet for Mr. S, it is clear that each step was part of his growing process. While his consideration for others, feelings of gratitude, and serious attitude toward life are of course mostly down to his personality, I believe that his disease and experience of undergoing a liver transplant also played major roles. More than most children his age, Mr. S went through difficult experiences that forced him to face questions of life and death. Mr. S's words reveal the depth of his feelings and are an expression of his accumulated experiences.

Ms. K's mother said, "She is small, but has a powerful presence. Many times she's been the one to cheer me up. Actually, I'm thankful to her." I'm sure Ms. R's and Mr. S's parents feel the same way. Liver transplantation has allowed these three children to start new lives. I hope that they treasure these lives filled with possibilities. I sincerely hope they will enjoy their lives to the full.

Interview conducted by the Organ Transplantation Center
of the National Center for Child Health and Development
with assistance from the Do-Re-Mi-Fa Club.

3

Hepatocyte transplantation

1 From organ transplantation to regenerative medicine

1 Introduction

Our laboratory is connected to the Center's hospital by a bridge that crosses through a small park (Photo 1). We are currently working with the Organ Transplantation Center to develop a new form of transplantation, called hepatocyte transplantation (the officially approved research title is "Establishment of methods of hepatocyte transplantation to support or replace liver transplantation" – Shin Enosawa, National Center for Child Health and Development, Laboratory Representative, Division of Advanced Medical Sciences). As this research requires specimens from livers removed during surgery, our work would be impossible without patients' cooperation.

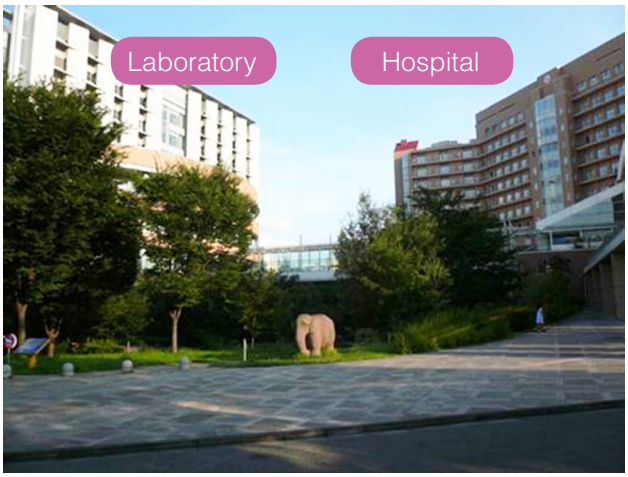


Photo 1
National Center for Child Health and Development laboratory and hospital

2 Advantages of cell transplantation

1. It is hoped that hepatocyte transplantation can help suppress the progress of diseases in babies until they are sufficiently grown up to be treated safely by liver transplantation. This is particularly advantageous for newborn patients

suffering from metabolic liver failure. The first pediatric hepatocyte transplant in Japan was performed at the NCCHD in August 2013. This case is described at the end of this chapter.

2. If only part of the liver function is not working properly, cell transplantation can be used to supplement the function instead of replacing the whole liver.
3. Liver cells from the patient's original liver can be transplanted into the transplanted liver to help it function.

Photo 2
Diagnosis by pathologist

3 Separation of the liver cells

We use the part of the liver that was not used by the pathologist for diagnosis, and isolate the liver cells. The separating procedure to obtain viable cells involves several steps and a variety of solutions (Photos 3, 4, and 5).

Photo 3
Beginning of the cell separation process. The red color in the liquid is a pH indicator.

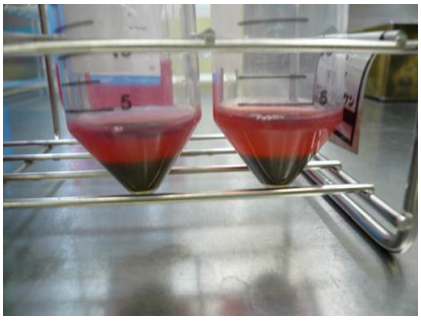


Photo 4
Cells obtained from the liver. The dark sediment denotes liver cells.

Photo 5
Machinery and equipment used in cell separation

4 Liver cells that have been working hard

Photos 6 and 7 show liver cells that have been separated from the liver of a patient with biliary atresia. The brown spots denote accumulated bilirubin, the substance that causes jaundice. Although these types of cells remain alive immediately after the separation, they do not survive in the culture medium ("culture" means "growth in an artificial environment"). However, recent research has found that some cells could turn into liver cells, i.e., stem cells. We are now investigating potential new therapies by transplanting hepatic stem cells into transplanted livers in animal experiments.

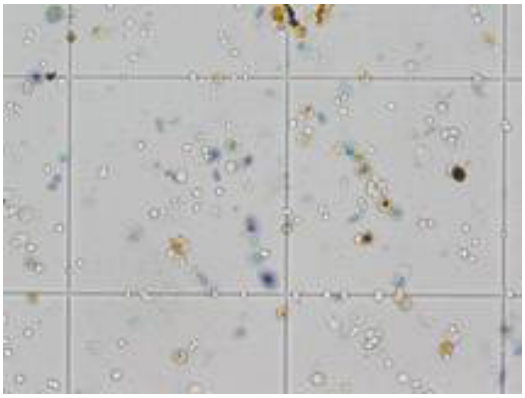


Photo 6
These liver cells were separated from the liver of a patient with biliary atresia. The white and brown spots are living cells. The brown spots are cells with accumulated bilirubin, the substance that causes jaundice. Although these types of cells remain alive after being separated from the liver, we have been unable to cultivate them. The blue spots represent cells that were killed or damaged in the separation process. Each square measures 250 microns (1/4th of a millimeter) on each side.

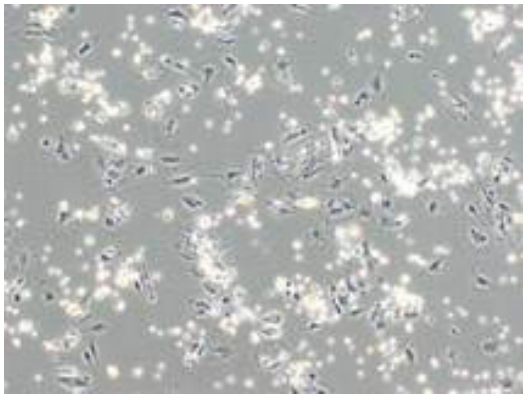


Photo 7
These are cultured liver cells (to "cultivate" means to "grow in an artificial environment"). In addition to the large liver cells, there are numerous fibroblasts, which are the cells that proliferate in liver cirrhosis.

5 Liver cells of donor's remnant liver (i.e., similar to those now living in the recipient)

These are liver cells that have been separated from the remnant part of a donor's liver (Photos 8, 9). They look very healthy. There are not only mature hepatocytes, but also other cell populations, including hepatic stem cells.

- Research by Dr. Kasahara, Director of the Organ Transplantation Center, has reported that the size of a liver graft should be adapted to the recipient's size – i.e., a small baby should receive a graft of an appropriate size, as the graft may otherwise burden the baby. However, for medical (anatomical) reasons, donors' livers must be excised along a given cutting-plane line. Therefore, the corners of the liver graft(s) must be removed. When this graft reduction

procedure is needed, the procedure is explained to the donor beforehand. The doctor also asks for the patient's consent to use the resected liver tissue for research. If the patient, donor, or family give their consent, we use the remnant liver tissue for research purposes.

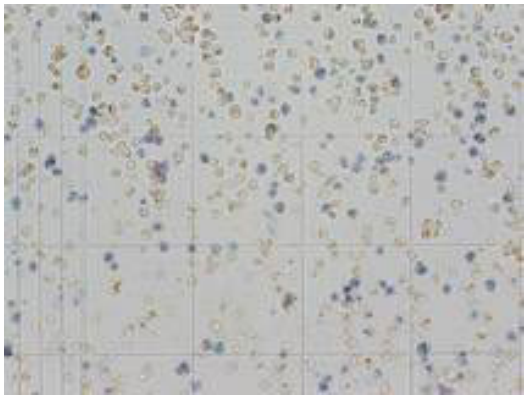


Photo 8
These are liver cells that have been separated from the remnant part of a donor's liver*. They look very healthy. Each square measures 250 microns (1/4th of a millimeter) on each side.

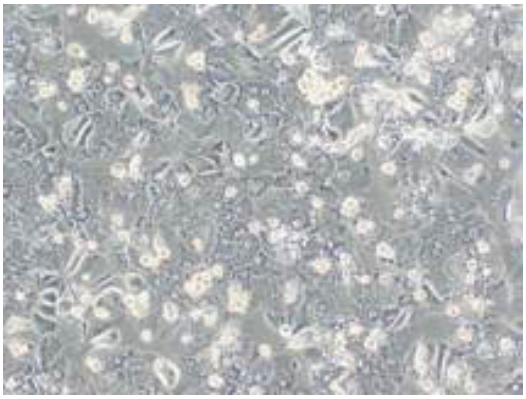


Photo 9
These are cultured liver cells (to "cultivate" means to "grow in an artificial environment"). They are packed together, with little space between them.

6 Searching for stem cells

This device, called a cell sorter, separates cells and examines the properties of each individual cell. It searches an enormous number of cells per second, and identifies the liver stem cells capable of forming liver tissue (Photo 10).

Photo 10
Searching for liver cells

7 Making hepatocyte transplantation a reality

Japan's first and second pediatric hepatocyte transplants were performed at the NCCHD in August 2013 and December 2014. In these clinical trials of hepatocyte transplantion for congenital metabolic disorders causing severe hyperammonemia led by Dr. Kasahara of the Organ Transplantation Center, cryopreserved third-person liver cells taken from the remnant liver tissue of living donor liver transplantations involving graft reduction procedures were transplanted into babies suffering from a urea cycle disorder with progressive hyperammonemia symptoms unresponsive to extensive conventional treatments. In both cases, the patient's condition was stabilized after the hepatocyte transplantation, and the

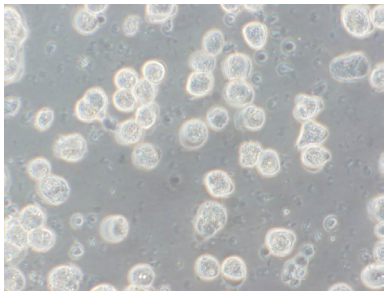


Photo 11
Transplanted liver cells appearing to be extremely healthy.
From Liver Transplantation. 2014; 20: 391-393

patients underwent safe liver transplantation 5 months later without hyperammonemia complications.

From 2008, we began to design a clinical hepatocyte transplantation program, which was launched in 2011. We sincerely appreciate the cooperation of the patients, donors, and families who donated their liver tissue for this research. We will keep striving to establish more effective therapies.

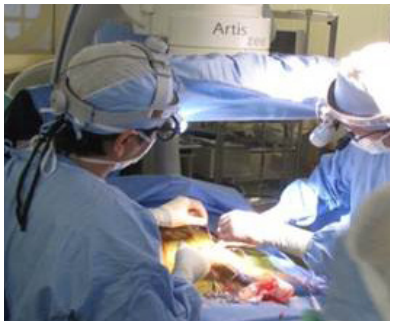


Photo 12
Transplanting liver cells in OR

Shin Enosawa
Division of Advanced Medical Sciences
National Center for Child Health and Development

2 The facts about liver cells (hepatocyte) transplantation

1 Introduction

The aim of hepatocyte transplantation is to compensate for defects in the liver function, which are often caused by inborn errors. The procedure is also hoped to provide temporal support in acute liver failure until the patient's own liver is regenerated (Figure 1).

Hepatocyte transplantation is more advantageous than liver transplantation as (1) it is less invasive, (2) it can be performed even on newborns, and (3) the

Inborn metabolic errors

- Crigler-Najjar syndrome type 1
- Familial hypercholesterolemia
- Factor VII deficiency
- Infantile Refsum disease
- Progressive familial cholestasis type 2
- Urea cycle disorders
  - Ornithine transcarbamylase deficiency
  - Argininosuccinate lyase deficiency
  - Carbamoyl phosphate synthetase I deficiency
  - Citrullinemia

Acute liver failure

- Drug-induced
- Viral
- Cause unknown

Acute exacerbation of chronic liver disease

- A1 antitrypsin deficiency
- Viral
- Alcohol-induced

Figure 1. Indications for hepatocyte transplantation
Based on Hughes RD et al. Current status of hepatocyte transplantation. *Transplantation*. 2012; 93: 342–347

liver cells can be frozen to be used at any time. However, it is problematic in that (1) it is difficult to assess the effects of the treatment, and (2) there are few sources of liver cells (hepatocytes).

Only a few medical facilities in Europe and the United States currently perform hepatocyte transplants. It is not yet a common form of medical care. Hepatocyte transplantation has been successfully performed to treat inborn diseases involving the ammonia metabolism (urea cycle disorders [UCD]) and to prevent fatal hyperammonemia before the patient could receive a liver transplant.

At the NCCHD1, we perform hepatocyte transplantation for UCD, ornithine transcarbamylase deficiency (OTCD), and carbamoyl phosphate synthetase I deficiency (CPSD). The procedure can reduce the risk of hyperammonemia by assisting the metabolism of ammonia until babies have grown enough (to a body weight of approximately 6kg) to undergo a liver transplant. At present, hepatocyte transplantation itself is not sufficient to maintain the metabolic functions for life, and the treatment serves as a "bridge to liver transplantation."

2 Steps to hepatocyte transplantation

In this section, we explain the steps to hepatocyte transplantation at the NCCHD (Figure 2). When UCD-related symptoms appear at the neonatal stage, the baby is initially treated with a protein-free diet, medication, or hemo-dialysis. Once a diagnosis of OTCD or CPS1D is made and the baby is a potential candidate for hepatocyte transplantation, he or she is immediately transferred to the NCCHD. Conventional treatment is maintained, and continuous hemodiafiltration is performed at the ICU if the condition becomes critical.

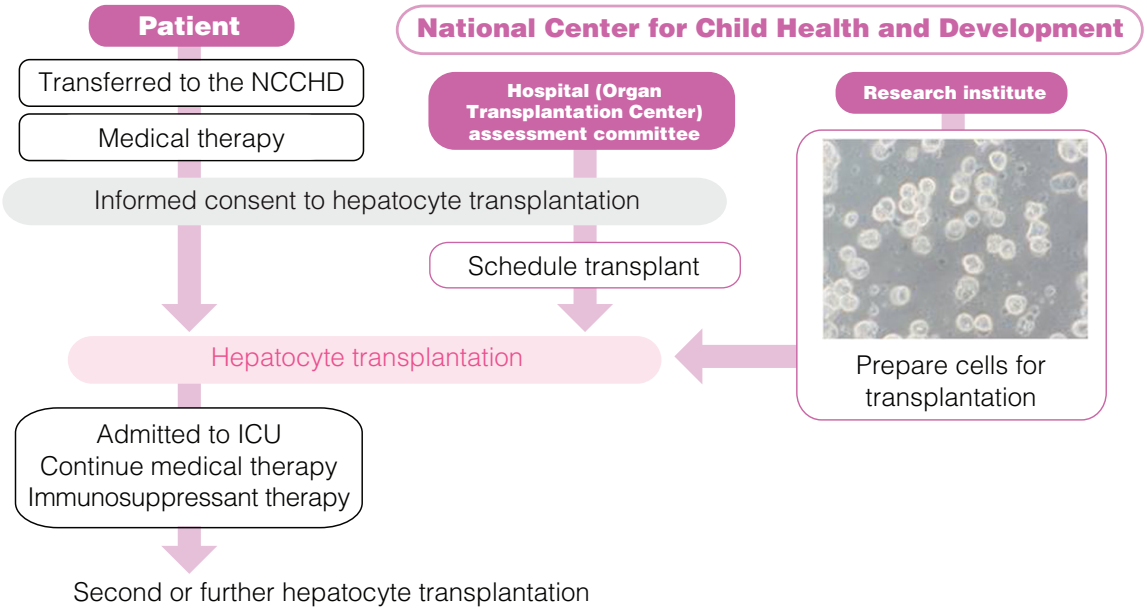


Figure 2. What happens in a liver cells transplant

When hepatocyte transplantation is indicated and parents have given their informed consent, the NCCHD Hepatocyte Transplantation Assessment Committee deliberates on the case and, if suitable, gives its approval. It must be difficult for families to make decisions within a short time. As medical staff, we do out best to help parents understand the options they have and to make informed decisions.

3 About hepatocyte transplantation

(1) Cells for transplantation

In most overseas countries, liver cells can be isolated from the livers of brain dead or cardiac dead donors. However, this practice is not legally allowed in Japan.

Therefore, we focus on the remnant liver tissue obtained from the graft reduction procedures performed as part of living-donor liver transplantations. In some cases, the lateral segment graft removed from the donor is too large for the recipient. The liver is therefore reduced to an appropriate size, which means that a portion is left over. If the donor agrees, liver cells from this excess portion are extracted in a laboratory, and are then frozen for later use in hepatocyte transplants (Photo 1).

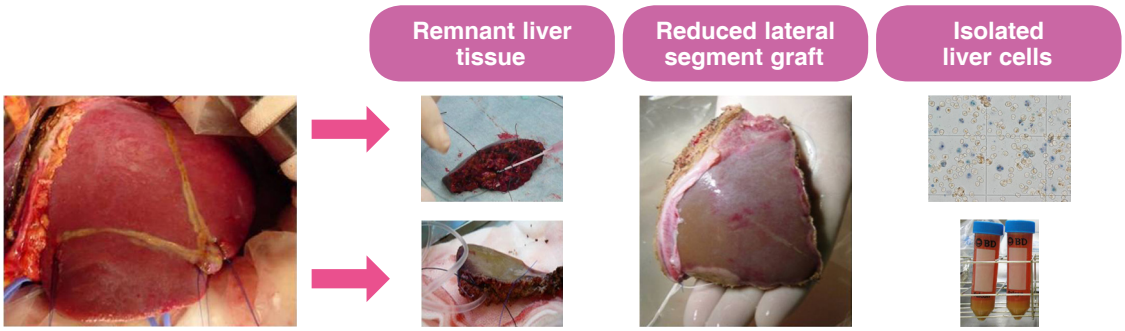


Photo 1
Isolation of cells from remnant liver tissue

(2) Hepatocyte transplantation

1) Inserting the catheter

Hepatocyte transplantation is performed in the angiography room. The first step involves the use of fluoroscopy to insert a catheter into the liver's portal vein (Photo 2).

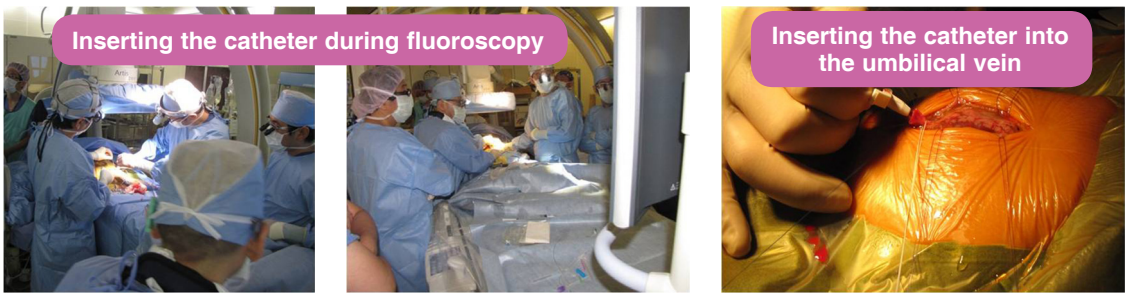


Photo 2
Hepatocyte transplantation (catheter insertion)

The catheter is inserted into the portal vein through the umbilical or mesenteric vein. The former is the vessel that carries nutrients from the mother's placenta to the fetus. As it is still open in the neonatal period, the catheter can be inserted into the umbilical vein by making a skin incision above the umbilicus. The mesenteric vein is used when the umbilical vein is not an option. The catheter is inserted into the mesenteric vein by making an opening in the abdomen. Whichever vein is selected, the wound is much smaller than that created by a liver transplant.

2) Injecting the liver cells (hepatocytes)

After thawing the liver cells (hepatocytes) at the laboratory, they are brought to the angiography room. The liver cells (hepatocytes) are injected very carefully, as they may obstruct the blood vessel during the injection. During the surgery, ultrasound is used to observe the blood flow and to monitor the pressure in the portal vein continuously (Photo 3). If the pressure rises or the blood flow weakens in the recipient's portal vein, the injection can be pursued safely by making short breaks of a few minutes each. It takes roughly thirty minutes to inject about 10 ml of thawed liver cells (hepatocytes).

Photo 3
Injecting the liver cells (hepatocytes)

3) After injecting the liver cells

After the injection is completed, the wound is closed and the catheter is fixed. As the catheter can be a source of infection, it is removed after about a week.

4 After hepatocyte transplantation

Just as in organ transplants, the transplanted liver cells (hepatocytes) are considered "someone else's," so immunosuppressant therapy is needed to prevent rejection. In liver transplantation, rejection is diagnosed with markers such as the AST, ALT, total bilirubin, and liver biopsy results. However, in hepatocyte transplantation, there are no markers of rejection. For this reason, different institutions administer immunosuppressant therapy differently. At the NCCHD, we use almost the same immunosuppressant protocol as for regular liver transplantation.

There are no definitive markers of how well the transplanted liver cells are functioning. In urea cycle disorders such as OTCD and CPS1D, their function is sometimes evaluated by whether the urea nitrogen levels increase. However, there are no established markers to assess the effect of the treatment. For this reason, patients need to stay on drug therapy even after hepatocyte transplantation.

5 Repeating hepatocyte transplantation

As a single injection of liver cells (hepatocytes) is not sufficient to have an effect, multiple injections are needed. If the recipient's condition is stable, further hepatocyte transplants are performed the week before the catheter is removed. If the patient's blood pressure, portal vein pressure, and portal vein blood flow can be monitored from his or her bedside, the second and subsequent hepatocyte transplants can be performed there (Photo 4).

Photo 4
Performing a hepatocyte transplant in the ICU

6 From hepatocyte transplantation to liver transplantation

After leaving the hospital, patients receive outpatient care from the departments of endocrinology and metabolism and of transplant surgery. Once a child reaches the weight at which a liver transplant can be performed relatively safely (i.e., at least 6 kg), a living-donor liver transplant can be scheduled. After the liver transplant, the patient is weaned off the drug therapy, and regular transplant care is provided.

7 Complications and problems

(1) Portal vein thrombosis

If a blood vessel becomes obstructed by the transplanted cells, it can cut off the blood flow to the liver. To prevent this, the catheter used to inject the liver cells (hepatocytes) is inserted toward the left side of the liver. If a thrombus forms, the blood flow will be maintained in the right side to avoid a life-threatening situation.

(2) Infection

The catheter is left in place for subsequent hepatocyte transplants. However, this creates a risk of infections. If an infection is suspected, the catheter must be removed.

The wound created during the hepatocyte transplant surgery may also become infected.

Moreover, the liver cells (hepatocytes) used in the transplant may also cause an infection. These cells are extracted by experienced researchers and physicians

in a special sterile room, and are subjected to bacterial tests before the transplant. However, there is always the risk that unknown bacteria undetected by these tests may cause an infection.

(3) Transplanted cells (hepatocytes) not working well

If too few liver cells (hepatocytes) are transplanted, or if the cells function poorly, the recipient will not metabolize enough ammonia, which could lead to severe hyperammonemia. One problem is that it is difficult to evaluate the functions of the liver cells (hepatocytes) after a transplant, making the risk of hyperammonemia unpredictable.

8 Conclusion

Hepatocyte transplantation is much less invasive than a liver (organ) transplant. However, evaluating the therapeutic effect of this type of transplant is difficult, and immunosuppressant therapy methods have yet to be established. Nevertheless, hepatocyte transplantation is believed to be efficient in reducing both the frequency and severity of hyperammonemia. In Japan, liver cells can only be obtained from the excess livers from living-donor transplants. However, it is hoped that the developments in regenerative medicine will provide a larger source of these cells. We expect that further research in this field will allow us to save even more lives with hepatocyte transplantation.

Seisuke Sakamoto, Mureo Kasahara
Organ Transplantation Center
National Center for Child Health and Development

4

Intestinal transplantation

1 Intestinal transplantation

1 What is the small intestine?

After food or drink enters the body through the mouth, it passes through the esophagus, the stomach, the small intestine, and the large intestine (also called the colon) before being excreted as stool by the anus (Figure 1). The inner surface of the small intestine is covered with fold-like tissue called villi, which would cover a large area if expanded (Figure 2). The villi allow us to properly absorb nutrients from the small intestine. The small intestine also protects the body from bacteria, viruses, and foreign bodies through immune responses.

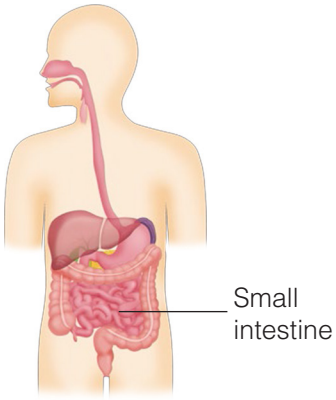


Figure 1. Gastrointestinal tract

2 What is an intestinal transplant?

(1) Diseases of the small intestine

Two important things are needed for the small intestine to absorb nutrients.

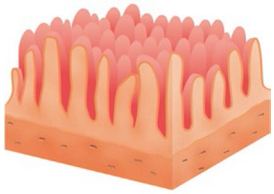


Figure 2. Normal intestinal villi

The first is a sufficient length. Children with short small intestines were either born with shorter intestines than other children, or were born with normal intestines but had most of their small intestine removed to treat a disease. Although these diseases have separate names, any child with a short small intestine is said to have “short bowel syndrome.”

The second requirement is to have a properly functioning small intestinal wall. In some children, although the small intestine is long enough, something is wrong with the intestinal wall (e.g., with the cells or the muscles). This is called “intestinal dysfunction.”

(2) Indications for intestinal transplantation

Children with short bowel syndrome or intestinal dysfunction cannot absorb the nutrients they need to grow through the small intestine. They are therefore

given high-calorie intravenous drips. These intravenous drips are highly concentrated, and strongly stimulate the fine blood vessels in the hands and feet. For this reason, they are usually administered to thick vessels with a high blood flow. Children undergoing central venous hyperalimentation for short bowel syndrome or intestinal dysfunction need to have a catheter (an intravenous drip tube) inserted in the neck, clavicle, or femor.

However, having a foreign body such as a catheter inside the body invariably increases the risk of infection. Once an infection occurs, the highly nutritious intravenous fluid helps the bacteria to proliferate, distributing them around the body through the bloodstream. If a person remains on central venous hyperalimentation for a long time, the catheter site will need to be changed several times. Eventually, there will be nowhere left to place it. In addition, the receipt of nutrients through intravenous drips for long periods can cause liver cirrhosis. When several of these conditions overlap, the continuation of high-calorie intravenous drips can be problematic. When such a situation puts the life of a child at risk, intestinal transplantation becomes an option.

(3) Difficulties with intestinal transplantation

Intestinal transplantation can be a very helpful therapy for children with short bowel syndrome or intestinal dysfunction who continuously have problems with high-calorie intravenous drips. However, it is not a common or widely performed procedure as yet. This is partly due to the fact that there tend to be stronger immune responses to intestinal transplants than to other organ transplants, which makes the post-transplantation management incredibly difficult.

The small intestine has an extremely strong immune response. If the body of the child receiving the transplant decides that the donor's small intestine is not one of its friends, it produces a natural immune response called "rejection". Rejection can damage the mucous membrane of the small intestine. To protect the transplanted small intestine, the child's immune system needs to be suppressed with immunosuppressant drugs.

However, problems with the intestinal bacteria also need to be considered. Normally, a large number of bacteria, called enterobacteria, live in the small intestine. Of course, a donor's small intestine is also filled with bacteria. If rejection after the surgery causes the mucous membrane to shed, the enterobacteria can enter the rest of the body through the blood, causing all kinds of problems. To protect children from these enterobacteria, we need to increase their ability to fight bacteria (immunity).

Therefore, the need to suppress a child's immunity must be balanced with the need to strengthen it, which is why therapy after an intestinal transplant is considered to be incredibly difficult. At our institution, we have conducted a great deal of research on this issue.

Although this is not an easy treatment modality, advances have been made in immunosuppressant therapy, and the situation has gradually improved. According to a 2015 report, as of February 2013, 82 facilities worldwide had performed a total of 2,887 intestinal transplantations (source: Intestinal Transplant Registry, http://www.intestinaltransplant.org/).

The first intestinal transplant from a living donor in Japan was performed in 1996. As of the end of 2014, 26 intestinal transplants had been performed in Japan, including 13 from living donors and 13 from deceased donors (source: The Japanese Society for Small Bowel Transplantation, "Report on small bowel transplants in Japan").

(4) The intestinal transplant procedure at our institution

Intestinal transplantation is considered an option once a transplant has been confirmed to be medically necessary, the child or his/her guardian has expressed a desire for it, and the transplant can be expected to improve the patient's life.

The first step is to contact a recipient transplant coordinator by calling the main switchboard. Next, the doctors of the Organ Transplantation Center assess the need for an intestinal transplant and its suitability through interviews, tests, and examinations. A third-party assessment is then obtained from the NCCHD's intestinal transplant assessment committee.

A patient can receive a transplant at the NCCHD once it has been determined that intestinal transplantation is an appropriate therapy. To ensure the reliability of our transplant care, we follow the "Criteria for intestinal transplant recipients" laid out by the special committee on intestinal transplantation of the Japanese Ministry of Health, Labour, and Welfare (issued on November 24, 1998).

(5) Organs from deceased donors

Small intestines can be obtained from deceased donors if the person has expressed a desire to donate his/her organs in their lifetime, or if the family grants permission. Patients who wish to receive an intestinal transplant from a deceased donor must first register with the Japan Organ Transplant Network.

As in the case of living-donor transplants, the NCCHD's intestinal transplant assessment committee will discuss the suitability of the transplant, and the patient or his/her guardian will need to sign a consent form. Only after undergoing all of the necessary tests and examinations will a child be allowed to register with the network as an intestinal transplant candidate.

However, registering with the network does not necessarily mean that the surgery will happen right away. When an organ from a deceased donor becomes available, a person on the waiting list will be selected only partly based on their level of medical urgency.

Therefore, this is not a surgery that can be undergone when one chooses. Please talk to your doctor and a recipient transplant coordinator about what to do until the surgery occurs.

(6) Conditions for living-donor intestinal transplant

People who wish to donate part of their small intestine for a transplant must fulfill the following conditions.

① **Be voluntarily willing to donate part of their small intestine**
The donor must fully understand what the surgery entails and its risks. The donor must not be coerced into having surgery.

② **Be a blood relative of at least the third degree of kinship**
This means that the donor may be the recipient's father, mother, grandfather, grandmother, brother, sister, uncle, or aunt.

③ **Have the same or a compatible blood type**
Same: child with type A, father with type A
Compatible: child with type A, mother with type O

④ **Be at least 20 years old but not over 65 years old**

⑤ **Not have or have had a history of the following diseases**
Liver disease, severe diabetes, malignant tumor, systemic bacterial, fungal, or viral disease, intestinal disease

⑥ **Have test results that are normal or within the acceptable range**
Blood test, X-ray, CT, echocardiography, electrocardiography, respiratory function, infectious diseases

(7) Informed consent

Regardless of whether the organ comes from a living donor or from a deceased donor, both the child and the donor must receive an explanation of the intestinal transplantation process to ensure that they understand the procedure fully and will not be overly anxious. This explanation should cover the examinations, operation, postoperative course, medical costs, drugs to be used, possible treatments besides transplantation, and the advantages, disadvantages, and risks of the surgery.

In addition, the patients must be asked if they want an intestinal transplant and must sign a consent form three times. They may decide not to have the transplant at any point. If this happens, they will be treated with the best non-transplantation option available.

③ Intestinal transplant surgery

(1) Surgery on a living donor

The blood vessels inside the donor's belly are examined with a CT to identify the vessels to excise. Then, 120-150 cm of the small intestine are removed, leaving a 30 cm portion on the mouth side of the ileocecum, which divides the small and large intestines.

(2) Surgery on the recipient of a living-donor or deceased donor transplant

The small intestine taken from the donor is connected to the child's intestinal tract. However, this is not simply a matter of connecting both ends and sewing up the abdomen. First, the upper end of the donor's small intestine (A) is sewn to the child's duodenum or jejunum. Next, the lower end of the donor's

small intestine (B) is taken out of the child's abdomen, and the child's large intestine is sewn to the donor's small intestine a little above the end (Figure 3). The end of the donor's small intestine (B), which sticks out of the child's abdomen, is called an "artificial anus."

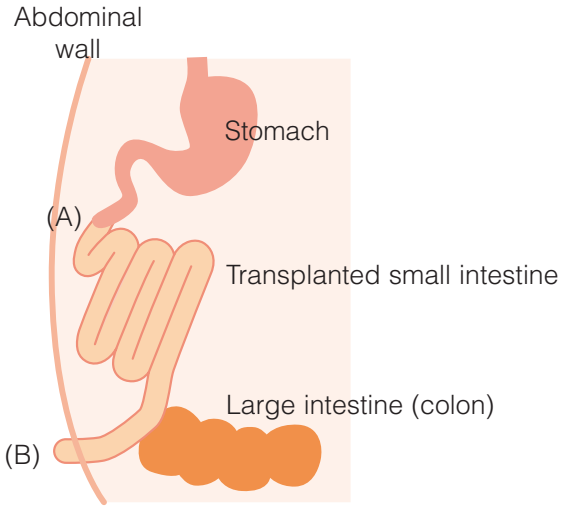


Figure 3. After an intestinal transplant

As the artificial anus is outside the child's abdomen, it plays an important role after the surgery. An endoscope can be inserted into it to examine the mucous membrane of the transplanted small intestine in order to check that it is working properly. Small samples of the transplanted small intestine can also be collected from this area in order to check for rejection.

As waste matter also comes out of the artificial anus, the kind and amount of secretions from the small intestine can be checked directly. The artificial anus is used to assess the recovery of the transplanted small intestine and to watch for abnormalities.

Rejection sometimes occurs for an extended period after surgery, causing the transplanted small intestine to malfunction (chronic rejection). If this happens, the artificial anus may be maintained for several years until the situation stabilizes before placing it back inside the abdomen.

4 Cost of intestinal transplantation

(1) Cost of living-donor intestinal transplant

Health insurance does not cover the costs of examinations or treatments either for the donor or the recipient of living-donor intestinal transplants. As a rule, patients must pay for the procedure themselves.

(2) Cost of deceased donor intestinal transplant

The following gives a general idea of the costs involved in a deceased donor intestinal transplant.

Category	Item and estimated cost
Registration with the Japan Organ Transplant Network	Tests, examinations for registration: about 3,000 USD Registration fee: 300 USD; renewal fee (once per year): 50 USD
Cost of extraction of the small intestine from the deceased donor	Organ transplantation intermediary fee: 1,000 USD Transport of extracted organ: from several hundreds of dollars to around 50,000 USD (if a helicopter or charter flight is used)
Cost of intestinal transplant surgery and preoperative/ postoperative care	150,000 USD or more Cost of transport when leaving the hospital: several hundreds of dollars for a private ambulance, around 50,000 USD for a helicopter

(based on prices in September 2011)

Table 1. Estimated costs of deceased donor intestinal transplant

The costs payable to the NCCHD will be billed separately by the Center's medical affairs department after the intestinal transplant. Note that health insurance does cover the medications needed after leaving the hospital, including immunosuppressants and antibiotics.

Caution: The costs associated with intestinal transplantation listed above are only estimates, and do not necessarily reflect the actual cost of the procedure. The costs may change in different circumstances. For details, please talk to a recipient transplant coordinator.

Hajime Uchida, Kengo Sasaki, Seisuke Sakamoto
Organ Transplantation Center
National Center for Child Health and Development

Conclusion

It has been eleven years since the National Center for Child Health and Development launched its transplant program in November 2005. When I first took this post, only a few solid-organ transplant surgeries had been performed on our Center. However, with our 400th liver transplant in April 2016, there was a feeling that liver transplantation had become a regular form of medical treatment at the NCCHD.

Every year, the NCCHD sees more and more children who need a liver transplant as a treatment option. Some of them have diseases so serious that they have been deemed untreatable by other transplant institutions. The parents of these children come to the NCCHD looking for something to help. However, the risks involved in surgery remain. Nevertheless, we consider it our mission to create a possibility of life despite these risks. I try to do my best as a transplant surgeon every day, and I never forget my initial passion for the job. For some patients, such as those with biliary atresia or metabolic liver disease, a liver transplant offers a way to dramatically improve their quality of life. For others, such as those with fulminant hepatitis, a liver transplant is the only chance to survive a sudden deterioration in their liver function. I hope that liver transplantation can create a better path for all these children and their families.

As few solid-organ transplants are performed from deceased donors in Japan, we still rely mainly on living donors. We have the utmost respect for the intentions and lives of donors who decide to undergo surgery to save the life of their child. We will continue to do our utmost in each and every surgery. We are constantly thinking about ways to guarantee the safety of living donors and to increase the number of deceased donors in Japan to levels comparable to those in Europe and the United States.

November 2016 marked the beginning of our program's twelfth year, and we will still be providing this service ten or twenty years from now. At the NCCHD, we not only seek to improve the results of our transplants and to save as many lives as possible, but we also assiduously research the causes of the diseases we see. Our ultimate goal is to develop new therapies to replace organ transplantation. We ask that you continue to understand and support the innovative medical care performed at the NCCHD.

We perform the largest number of pediatric liver transplantations in the world each year. Patients with severe organ failure come from all over Japan and from around the world. Our high survival rates are achieved by the efforts of doctors at the Organ Transplantation Center, including transplant coordinators, ICU staff, the emergency response team, the department of anesthesia, the department of endocrinology and metabolism, the department of neurology, the department of radiology, the department of pathological diagnosis, the department of nursing, secretaries, other hospital staff, researchers, and clerical staff. I would like to end this Handbook by thanking all of these people for their dedicated service.

Mureo Kasahara, MD. and Ph.D.
Director, Organ Transplantation Center
National Center for Child Health and Development
Email: kasahara-m@ncchd.go.jp

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National Center for Child Health and Development

2-10-1 Okura, Setagaya-ku

Tokyo, Japan

157-8535

Tel: +81-3-3416-0181

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101-0061

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