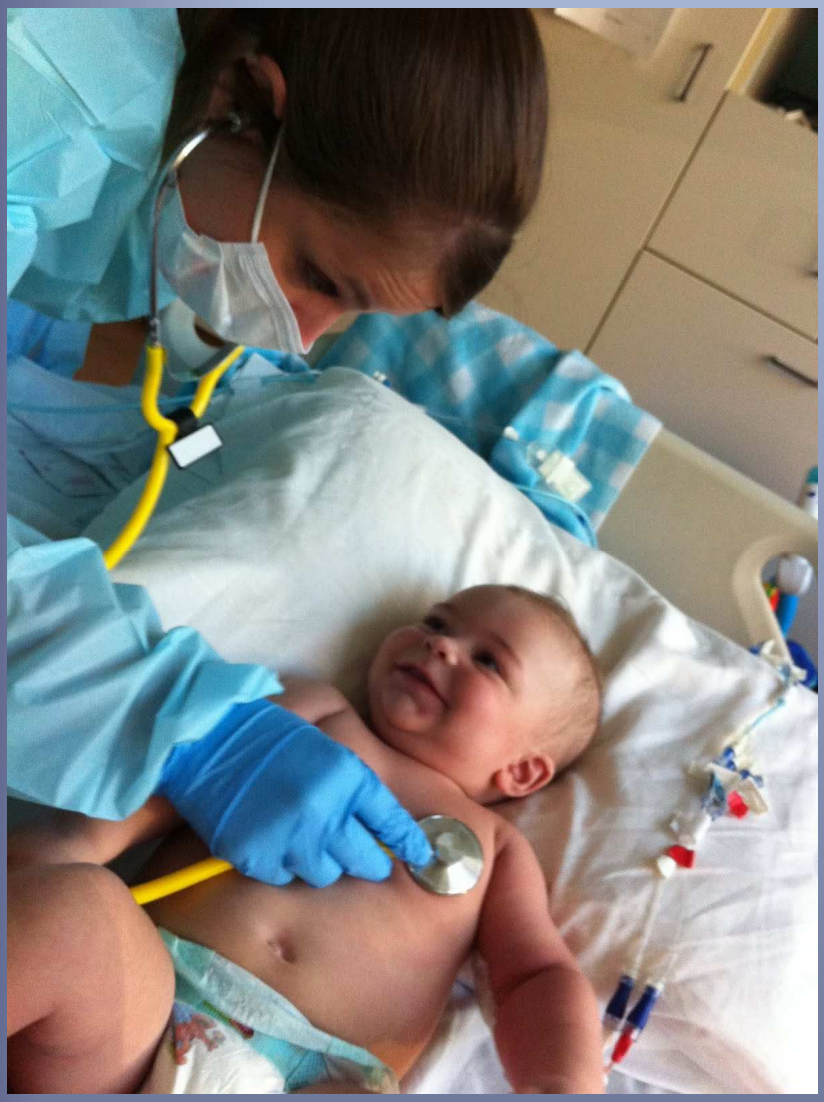

Wiskott-Aldrich Syndrome

A guide for patients and families

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Wiskott-Aldrich foundation™

www.wiskott.org

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This guide is designed to provide information about the current understanding of WAS. The content herein is intended to provide the reader with general information and is intended to be used for educational purposes. It does not address individual patient needs, and should not be used as a basis for decision making concerning diagnosis, care, or treatment of any condition related to WAS. Instead, such decisions should be based upon the advice of a physician or health care professional who is directly familiar with the patient and WAS. Patients and their families who read this information are warned against making any changes in their treatment based on this information without consulting their healthcare provider. While the Wiskott-Aldrich Foundation has made every effort to ensure the accuracy of this information, medical knowledge changes quickly and therefore practitioners and families of WAS patients are urged to continually seek up-to-date information. Some treatments discussed in these materials, while in line with accepted medical practice, may not be approved by the U.S. Food and Drug Administration for the described uses. Any reference to a particular product, source, or use within this publication does not constitute an endorsement of the same by the Wiskott-Aldrich Foundation. The Wiskott-Aldrich Foundation, its officers, directors, employees, agents, its Medical/Scientific Advisory Board, or their members, make no warranty concerning the information contained in this publication. They specifically disclaim any warranty of merchantability, fitness for any particular purpose, or reliability regarding the information contained herein, and assume no responsibility for any damage or liability resulting from the use of such information.

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INTRODUCTION

Wiskott-Aldrich Syndrome (WAS) is a rare but life threatening genetic disorder that mostly affects males. WAS is a challenging disorder affecting an estimated four out of one million boys worldwide. WAS affects the immune system, which is the defense mechanism of the body, protecting us from infection. WAS also affects the platelets, which are the blood cells that prevent excessive bleeding.

The disease is named after two physicians who first recognized the disorder. It was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who noticed a bleeding disorder due to low platelets that ran only in boys in a family. In 1954, Dr. Robert Aldrich, an American pediatrician, studied seven generations of an affected family and showed that this disease is passed on from mothers to their sons.

The disease varies in severity among patients. Severely affected patients typically have excessive bleeding, are at risk of serious infections, have eczema, and are at a high risk of developing autoimmune disorders and certain types of cancer.

Just a few decades ago, Wiskott-Aldrich Syndrome was considered one of the most serious of all immune deficiency disorders. Children with more severe forms rarely made it past five years of age. Thanks to advances in diagnosis and management of the condition, many children are now entering adulthood and raising families of their own. A bone marrow transplant is the only known cure. The earliest patients who received transplants are now in their third and fourth decade and are leading relatively normal lives.

From the early 2000's, gene therapy has emerged as a potential cure, and several clinical trials are in progress in Europe and in the U.S.

This guide answers the common questions asked by families of children with WAS. Included are the latest advances in medical care, clinical trials, and resources for families.

DESCRIPTION

What is Wiskott-Aldrich Syndrome?

Wiskott-Aldrich Syndrome (WAS) is a rare and life threatening genetic disorder that almost always affects boys. It is passed on from mothers to their sons. It affects the cells of the immune system, the body's defense against infection, and the platelets, which are the blood cells that help prevent excessive bleeding.

There is a wide variation in how severe the disease is for each patient. In its most complete or severe form, referred to as Classic WAS, patients exhibit the following symptoms:

1. An increased incidence of infections that may be recurrent and severe. Most commonly seen are ear infections, sinus infections, and pneumonia.
2. Prolonged and severe bleeding that can occur spontaneously or with minor injuries.
3. Eczema (atopic dermatitis) of the skin, including patches of inflamed, itchy, and dry skin.
4. A higher incidence of cancers such as leukemia and lymphoma as well as autoimmune disorders.

In milder forms of the disease, patients have low platelets and have a bleeding disorder similar to patients with Classic WAS but have mild or no immune-deficiency. This form of the disease is often called X-Linked Thrombocytopenia (or XLT for short), and the patients have mild or no increase in infections and mild or no eczema. XLT patients, however, have a higher than normal risk of developing autoimmune disorders and cancer.

The only proven cure for this disorder is a hematopoietic cell transplant (also known as bone marrow transplant or BMT). Starting from the early 2000's, significant progress has been made in gene therapy (GT) as a potential cure. The early results seem promising, and at present there are several clinical trials in progress in Europe and in the U.S.

What is the immune system?

The immune system is a network of organs, tissues, white blood cells, and protein that work together to protect us from diseases. In WAS patients, there is a dysfunction of many types of white blood cells (immune cells) such as T and B lymphocytes and the natural killer cells (NK Cells). These cells work together to help fight infection against bacteria, viruses, and fungi. Because the white blood cells (WBC) do not function effectively, WAS patients can have recurrent and sometimes serious infections with these organisms.

The white blood cells are also responsible for regulating the immune system and maintain its checks and balances. When this system of regulation does not function properly, the immune system may mount an attack on one of its own organs or tissues, which can result in what are called autoimmune disorders.

What are platelets?

Platelets are blood cells that prevent bleeding and help maintain the integrity of blood vessels. Patients with WAS have a significantly reduced number of platelets, and the platelets do not function very effectively. Patients with WAS therefore bruise and bleed easily, even with minor injuries. They can have serious bleeds involving internal organs such as the brain, the intestines, lungs etc., sometimes even in the absence of traumatic causes.

SYMPTOMS

What are the symptoms of WAS?

The symptoms of WAS vary among patients. However, most patients show symptoms starting at birth to early infancy. Depending on the severity of WAS, patients may have few or many of the symptoms described below.

Bleeding: Bleeding is the most commonly noticed symptom and is seen in all patients with WAS. Most commonly seen are:

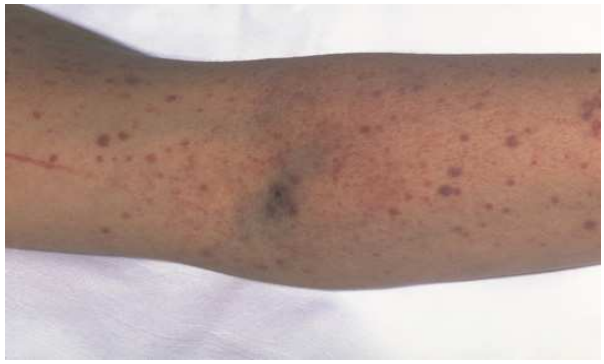

Figure 1: Petechiae and Purpura
Courtesy: National Heart Lung and Blood Institute

- Prolonged bleeding from the circumcision site or the umbilical cord in the first weeks of life.
- Skin: Parents frequently notice pin-head sized bluish red spots under the skin called petechiae or larger bruises. See Figure 1.
- Bowel movements: Bleeding in the stool, sometimes associated with diarrhea, is often seen in infancy.
- Bleeding from the gums
- Frequent or prolonged nosebleeds.
- Serious bleeding can occur, particularly if it involves the brain, lungs, intestines, spleen, or other vital organs and can be life threatening. Serious bleeds can also occur in about 14% of patients with XLT.

Infection: Infections with bacteria, viruses, and fungi are common, particularly in patients with severe WAS. They can be recurrent and severe at times. The most common infections that are seen are recurrent ear and sinus infections and pneumonia. Patients can have more severe infections with certain type of bacteria which cause sepsis (bloodstream infection) or meningitis. These infections can be severe, come on rapidly, and can be life threatening.

Patients with WAS are prone to infections with viruses such as cytomegalovirus (CMV), herpes virus, and Epstein Barr Virus (EBV, commonly referred to as Mono), pneumonia causing organisms such as Pneumocystis jirovecii (PCP), and skin viruses such as molluscum contagiosum.

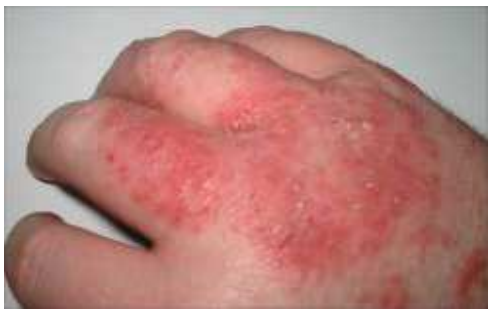

Figure 2: Eczema

Courtesy: Wikipedia

Eczema and Allergies: Most patients have or have had eczema, which is dry, inflamed, and irritated skin. This may be mild in some patients and more severe in others. Infants may have cradle cap, where flaky, oily patches are seen on the scalp and behind the ears. Eczema is usually seen on the insides of the elbows, the back of the knees and face, but can occur anywhere. There can be intense itching and a great deal of irritation. See Figure 2. These irritated areas tend to bleed easily and can get infected. Eczema can also lead to disturbed sleep and to social and emotional difficulties.

Patients with WAS have a higher incidence of other forms of allergy such as food allergies and hay fever.

Autoimmune Disorders: In some individuals, particularly those who are more severely affected, various autoimmune disorders may be seen. Among the ones more commonly seen are:

- Anemia due to destruction of the red blood cells.
- Further decrease in platelet counts due to platelet destruction (idiopathic thrombocytopenic purpura or ITP for short).
- Vasculitis: Painful raised spots on the skin due to inflammation of blood vessels.
- Arthritis: Swollen, painful joints.
- Colitis: Abdominal pain and blood in bowel movements due to inflammation of the intestine.
- Nephritis: Blood in the urine due to inflammation of the kidneys.

These autoimmune disorders may be mild and come and go over time, or they may be persistent and difficult to treat. There is a higher incidence of autoimmune disorders in patients with Classic WAS than in those with XLT. The reported incidence of autoimmune disorders in patients with XLT is around 12% as compared with a 40-70% incidence in patients with Classic WAS. Patients who develop autoimmune disorders seem to be at higher risk for development of malignancies later.

Malignancies: Malignancies are seen much more frequently in patients with Classic WAS and can occur at any age. The reported incidence of malignancies in patients with XLT is about 5% as compared to 13% in patients with Classic WAS. Most common are those associated with the immune system such as lymphoma (cancer of the lymphocytes) and leukemia (cancer of the blood cells).

CAUSE

What causes WAS?

WAS is a genetic disorder caused by a defective gene in the cell. *WAS is not infectious; other people cannot "catch it" from affected patients.*

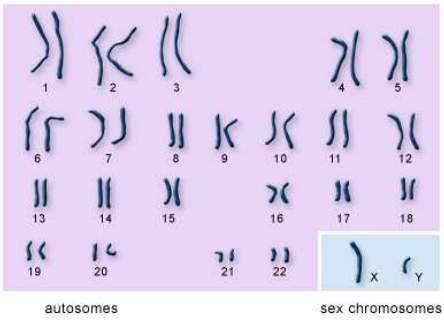

Figure 4: Chromosomes in a human cell
Courtesy: Genetics Home Reference

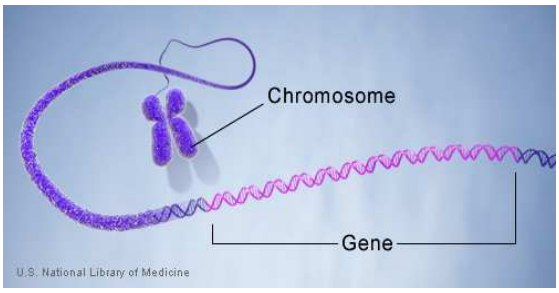

Figure 3: A single chromosome and gene
Courtesy: Genetics Home Reference

The genetic material that carries the information needed for the correct functioning of the organism is contained in the nucleus of each cell and is packaged in structures called chromosomes. See Figure 3. Each human cell has 23 pairs of chromosomes that include one pair of so-called sex chromosomes as they determine the sex of the child. These chromosomes are named X and Y. Girls have two X chromosomes and boys have one X and one Y chromosome.

Chromosomes are made up of long strands of DNA, which is the genetic material of cells. The DNA is organized into genes. Genes carry the code for the cell to make proteins that are important for the body to function normally. See Figure 4.

Patients with WAS have a defect in the *WAS* gene that is on the X chromosome. The *WAS* gene contains the instructions for the cell to make the WAS protein (WASp). WASp is essential for the normal functioning of white blood cells and platelets. When this gene is defective, the cells have absent, reduced or abnormal WASp, and this causes the symptoms of WAS.

How do patients get the abnormal gene?

A misspelling (mutation) in the *WAS* gene can occur at any time in the X-chromosome of the egg or the sperm of a mother or a father. If a boy is born and has inherited the abnormal *WAS* gene, then the boy will have WAS. If a girl is born and has inherited the abnormal *WAS* gene, then she will become a carrier. Girls who have inherited the abnormal *WAS* gene do not develop symptoms of WAS because their cells use the normal X-chromosome preferentially, which acts as a "back-up". Boys have one X and one Y chromosome and develop symptoms as they have no "back-up" or normal X-chromosome. A woman who has one X-chromosome carrying an abnormal *WAS* gene is referred to as a WAS carrier female. Because the WAS gene is on the X-chromosome, WAS is called an X-linked disorder. It is called a "recessive" disorder because the disease only becomes apparent when there is no "back-up" or normal X-chromosome, as it is with boys.

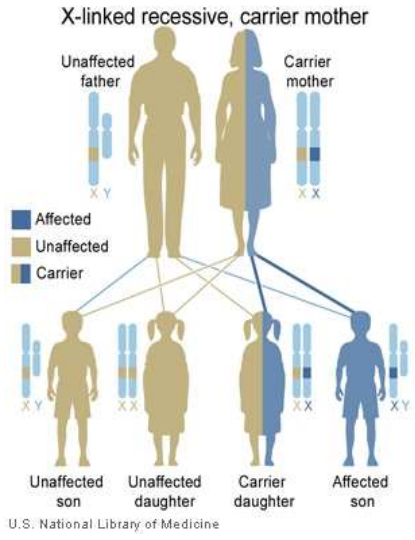

Figure 5: Inheritance of the WAS gene from a carrier mother
Courtesy: Genetics Home Reference

Once the first mutation in the *WAS* gene has occurred, mutated sperm cells from a father would give rise to carrier females, while mutated egg cells from the mother can give rise to boys who have WAS or girls who are carriers. WAS is inherited by one of two ways:

1. In most cases, the mother carries the abnormal gene on one of her X chromosomes, and the child inherits the abnormal gene. See Figure 5. The mother may be unaware that she is the carrier of the abnormal gene, or there may be a family history of brothers or maternal uncles being affected with similar symptoms on the mother's side of the family.
2. In some cases, the mothers are not carriers. The eggs in the ovary of the mother may carry the defective gene, or a spontaneous defect happens in the WAS gene very early during pregnancy. There is no family history in such cases.

DIAGNOSIS

How is WAS diagnosed?

The diagnosis of WAS should be considered in any boy with unusual bruising or bleeding, particularly if it is noticed soon after birth or in infancy. Suspicion is higher if the patient also has a history of recurrent infections in infancy and early childhood, eczema, autoimmune disorders, or lymphoma. There may be a family history of similar symptoms among brothers, cousins, or maternal uncles.

Lab diagnosis: Once the diagnosis of WAS is considered, the following lab tests are most often done:

Platelet count and size: This is a simple blood test in which the platelet count and size are checked. WAS is the only known disorder with low platelets where the platelets are smaller than normal. Normal platelet counts are from 150,000 – 450,000/micro liter. A platelet count of less than 70,000/micro liter along with platelets that are smaller than normal and a reduced platelet volume suggest WAS.

Tests that support the diagnosis of WAS:

- Immunoglobulins are antibodies that are made by the B lymphocytes subset of white blood cells and protect us from infections. In WAS, there may be a decrease in some types of antibodies in the blood such as Immunoglbulin M (IgM) and increase of IgA.
- Decreased response to vaccines, in particular to those made against bacteria that are coated with long sugar chains, such as the Pneumovax vaccine against the pneumococcal bacteria.
- Decrease in antibodies to red cells (isohemagglutinins), which is an antibody of the IgM class that is normally present in healthy individuals.

[1]**WAS protein level (WASp) in white blood cells*:** This is a blood test to determine WASp levels. If WASp is absent, decreased, or abnormal in the white blood cells, the patient most likely has WAS. The diagnosis should be confirmed using the genetic testing.

Genetic Testing*: This is a test that can be done on blood cells or other body tissue to confirm the diagnosis of WAS. It determines if there is an abnormality in the *WAS* gene. This test is essential to confirming the diagnosis. If the mutation carried by the family is known, it takes about a month to obtain the results. However the search for the mutation may be longer in the absence of prior family history of the disease.

[1] ***Tests to determine WASp level and genetic testing are specialized tests and should be done in centers with experience.***

TYPES OF WAS

What are the different forms of WAS?

Since the identification of the gene responsible for the disease in 1994, four forms of WAS are identified:

1. **Classic or Severe WAS:** The most severe form of WAS with severe immune deficiency, eczema, and low platelets. These patients have a significantly increased risk of developing autoimmune disorders and cancer.
2. **X-Linked Thrombocytopenia (XLT):** A milder form in which the platelets are affected but there is little or no immune deficiency. Patients have a bleeding disorder with mild or no increased incidence of infections and mild or no eczema. These patients appear to have a higher chance than the general population of developing autoimmune disorders and cancer.
3. **Intermittent X-Linked Thrombocytopenia (I-XLT):** The mildest form in which the platelet abnormalities are intermittent and there is no immune deficiency. Patients have a bleeding disorder without an increase in incidence of infections or eczema.
4. **X-Linked Neutropenia (XLN):** The platelets are normal, but there is a serious defect in the neutrophils (a type of white blood cell). Patients can have serious and recurrent infections but do not have a bleeding disorder.

This booklet provides information related to Classic WAS and XLT only. For more information on IT, please visit: Intermittent X-linked thrombocytopenia. For more information on XLN, please visit: Severe Congenital Neutropenia.

How can I tell if my child has Classic WAS or XLT?

Each child with WAS can be given a score from 1-5 depending upon the number of infections, severity of their eczema, and presence or absence of autoimmune conditions and malignancy. Your child's immunologist will guide you with your child's score. A patient with a score of 1-2 has XLT or mild WAS, and a patient with a score of 3-5 has Classic WAS (Scoring System adapted from Ochs, HD et al 2009 classification.

1. Low platelet count without eczema or infections.
2. Low platelet count + mild transient eczema and/or mild transient infections not resulting in complications.
3. Low platelet count + persistent but treatment responsive eczema + recurrent infections requiring antibiotics and often intravenous immunoglobulin for prevention of infection.
4. Low platelet count + persistent and difficult to control eczema + infections requiring antibiotics and often intravenous immunoglobulin prophylaxis and/or severe threatening infections.
5. Low platelet count + mild or persistent eczema + mild transient infections or recurrent infections requiring antibiotics with or without IVIG + autoimmunity, or malignancy.

Are there lab tests that can determine if my child has XLT or WAS?

Currently, there is no lab test to determine with certainty whether your child has XLT or Classic WAS. However, your immunologist can make a reasonable assessment by combining clinical history, physical examination, and the results of the following tests:

- **The type and location of mutation (abnormality) in the *WAS* gene:** Certain types of mutations are associated with the more severe forms and some others are known to be associated with milder forms of the disease.
- **The presence or absence of WASp in the lymphocytes:** Patient cells are positive (WASP+) or negative (WASp-) for the presence of WASp. Cells from patients with XLT usually have detectable WASp, whereas patients with Classic WAS usually do not have any WASp.

PROGNOSIS

What is the life expectancy of patients with WAS?

With advances in diagnosis and treatment, the life expectancy of patients with WAS has improved significantly over the last few decades. Successfully transplanted patients go on to lead normal lives, completely free from the disease. For patients with Classic WAS and no WASp expression who do not undergo a transplant, the reported average life expectancy is around 15 years.

A recent survey of patients with milder forms of WAS showed that 81% of patients reach the age of 60 years. However, most of these patients will experience at least one significant incident such as a significant bleeding episode, an autoimmune disorder, or cancer by the time they are 60 years old. Therefore the excellent survival in patients with XLT is associated with a high rate of severe disease-related events throughout life.

My child has XLT. Are there ways to predict whether my child will develop an autoimmune disease or malignancy?

Unfortunately, at this time there is no way of predicting which XLT patient will develop autoimmunity or malignancy.

RECENTLY DIAGNOSED

My son was recently diagnosed with WAS. Which specialists should he see?

WAS is a rare, complex disorder, and few physicians are familiar with it. Patients have the best outcomes when they are followed by physicians experienced with WAS. Once the diagnosis of WAS is confirmed, the first step is to obtain an evaluation of the immune system by an immunologist. However, because the various clinical manifestations of WAS involve many different organs and systems such as the joints, the kidneys, and the blood, you may find hematologists, rheumatologists, or oncologists who are familiar with WAS. Your pediatrician may be able to refer you to one, or you can find one at Find a Doctor. The evaluation of how well your immune system is working will help you decide on the best treatment for your child. Your immunologist will evaluate how well the immune system is working and help you decide on the best treatment for your child. Your immunologist can see your child on a regular basis and keep an eye on your child to make sure any problems or changes in condition are addressed promptly.

The next step is to meet with a BMT physician. Your BMT physician helps you understand more about transplants and will work with your immunologist to decide if a transplant is the best option for your child. Your transplant physician or a hematologist can address concerns with bleeding and advise you on safety measures for your child. They will outline a plan on what to do if there is a severe bleed or an emergency. A dermatologist can help manage eczema, particularly if it severe and resistant to treatment.

What questions should I ask the doctors?

WAS is a complex disorder, and you can make the best of your appointment by preparing. You and your family are an important part of the team taking care of your child and it is important that you have all the information that you need to understand your doctor's recommendations. Below is some information on how you can prepare for your appointment and what to expect.

Make a note of the symptoms your child is experiencing and have a list of medications and doses that your child is on. Please take all medical records including labs, test results, and notes from previous physicians. Write down a list of questions that you have. Take notes or make a recording (with the permission of the physician) of what the doctor says so that you can review it later. Encourage your child to make a list of questions and participate in the discussion. Below is a list of some basic questions that you can ask:

- How did you diagnose my child?
- Does he need any other tests?
- How sick is my child?
- What treatment would you recommend for my child and why?
- When can my child receive the treatment and what are the risks?
- How can I reduce the chances of my child catching an infection?
- How can I reduce bleeding?
- What should I do when my child is injured?
- Do other members of my family who need to be tested?
- Can you connect me to other families with WAS?

Should my child wear a Medic Alert bracelet?

Your child should wear some type of identification about low platelets, allergies, or splenectomy. This helps emergency medical staff quickly attend to your needs. For more details, please visit www.medicalalert.com or call 1-800-432-5378. Additionally, patients should carry a card with a list of medications that they are on and a list of important phone numbers to contact family and physicians.

TREATMENT

What is the treatment for WAS?

A hematopoietic cell transplant (HCT), also called bone marrow transplant (BMT), is the only proven cure for WAS. Other measures primarily provide relief from symptoms and decrease the risk of infections.

In the last five years, experimental gene therapy (GT) is emerging as a possible cure and several clinical trials are being conducted in Europe and in the U.S. More details are discussed below and in the section on Gene Therapy.

While BMT is currently recommended for most patients, particularly those with Classic WAS, it is not without risks and may not be suitable for all patients. Your immunologist and transplant physician will discuss the benefits and the risks of BMT and help with making this important decision on whether to transplant or not. More details about the process of BMT is discussed on this later in the guide.

In all patients, close attention should be given to the management of infections, bleeding and eczema and to treat complications that may arise during the course of the disease.

What is a bone marrow transplant (BMT)?

Bone marrow is the soft spongy tissue that is found in the center of bones. It is the "factory" where the white blood cells, platelets and red blood cells are produced. These cells arise from "mother cells" referred to as stem cells (hematopoietic stem cell).

The stem cells in the bone marrow of patients with WAS generate abnormal blood cells. To cure WAS the patients' stem cells in the bone marrow need to be replaced with stem cells from a healthy donor. The process by which the patient's stem cells in the marrow are replaced with healthy stem cells from a donor is referred to as a BMT.

What are the factors that decide which child receives a transplant?

Various factors such as the Clinical Score of your child, age, general health and the best donor available are taken into consideration when making the decision to transplant your child. Your immunologist and transplant physician will help you make the decision.

The decision is generally made on a case-by-case basis and, unfortunately, is often not straightforward, which may result in difference of opinions even among WAS experts. Some authors have recently published recommendations based upon the combination of Clinical Score and WASp expression (measured using sensitive methods):

Score of 3 to 5: Without definitive treatment, these children usually do not survive to adulthood. With a successful transplant, these patients can go on to leave healthy and normal lives. The current recommendation is to transplant these patients, regardless of WASp expression status at the earliest, with the best match that is available.

Relative contraindications to transplant include older age at transplant, pre-existing organ damage, such as lung disease, particularly if only mismatched donors are available. For these patients, GT can be considered.

Score of 1-2 and WASp negative: The recommendation is to strongly consider these patients for a transplant with a well matched donor. Some data indicate poorer results of HCT after the age of five, which, in view of the milder symptom of these patients, would support HCT if feasible in young age.

Score of 1-2 and WASp positive: These are patients with XLT who are relatively healthy and have detectable WASp. They have low platelets with few or no infections and little or no eczema. While most of the patients seem to be protected from cancer, there are reports of a few who have developed cancer. However, some patients do develop autoimmunity which, although at a lower percentage that those with Classic WAS.

The recommendation is to limit transplant consideration for patients with HLA identical sibling donors. Transplant with a non-sibling donor is considered if there is severe, transfusion dependent thrombocytopenia or serious complications such as intracranial hemorrhage.

How successful in BMT in treating WAS?

Results from about 200 WAS patients transplanted between 1980 and 2009 showed an overall five year survival of over 80%. With improvements in the field of BMT, 5 year survival rates have increased in the last decade and are now close to 90%. For patients transplanted from registry bone marrow donors, survival rates are higher if patients are younger than 2 years of age compared to patients older than 5 years.

Transplantation can cure the immunodeficiency, with normalization of T and B-cells in 70%-90% of cases and the thrombocytopenia in about 80% of patients. In about 30% of transplanted patients, long-lasting complications can occur. Five year survival results of BMT in patients with XLT have been reported to be similar to those in patients with classic WAS. More studies are needed to learn about the efficacy and complications of BMT in patients with XLT.

What is gene therapy?

In its currently available form, Gene Therapy (GT) is an experimental therapy aimed at introducing a copy of the normal gene to replace the function of the defective gene n the cell. In GT protocols, the patient's own stem cells are collected either from the bone marrow or the blood and allowed to multiply in culture dishes. Copies of the normal gene are then introduced into the stem cells and the cells are returned to the patient. This allows the stem cell to start producing normal WASp develop in corrected matured blood cells and platelets, thereby curing the patient.

The process is similar to that followed for a BMT. Gene therapy also requires a prolonged stay in the hospital and a period of isolation to prevent infection. The number of chemotherapeutic agents and the doses used for conditioning for GT are lower than those for a standard BMT. This reduces the toxicity from the various medications. As the patient's own cells are used in GT, graft versus host disease is not a problem.

How successful is GT in treating WAS? What are the complications of GT?

The first GT trials were started in Germany in 2008. Subsequently trials have started in several centers in Europe and one in Boston. GT is still a relatively new procedure and not all the complications are known.

Thus far, about 16 patients have received GT in all. A detailed report is available only for the first two patients treated in Germany, who derived clear benefit from the procedure, with the correction of the thrombocytopenia, autoimmunity, eczema and immunodeficiency. So far, there have been no deaths and

most patients seem to tolerate the procedure fairly well. The most significant complications that have been noted so far are:

- Failure to engraft with the repaired stem cell in one patient. This patient subsequently went on to receive a BMT and is reportedly doing well.
- Four patients from the trials in Germany developed leukemia, likely as a result of the GT. Researchers have concluded that this was likely a result of the type of vector used. The kind of vector that is currently being used in other trials is considered to be less risky.

MANAGEMENT OF INFECTION

How is infection managed?

Patients with WAS can have recurrent, serious and sometimes life threatening infections. Patients and the family should maintain a high degree of vigilance for infections, even while on antibiotics.

Patients with WAS will get colds and other viral infections like any other person. It can sometimes be difficult to identify infections that are "normal" from those that are a result of WAS. If in doubt it is best to ask! Patients with Classic WAS may need to be admitted to the hospital for intra-venous antibiotics if they develop an infection. Early treatment can be life-saving and can reduce the time needed to clear the infection. Therefore WAS patients should be on the lookout for and consult a physician if the patent has any of the following signs of infection:

- A fever of 38 C (100.4 F) or more
- Warm, tender or swollen areas
- Headache, neck stiffness
- Chills, general feeling of illness
- Suspected chicken pox
- Sores with pus or rashes
- Persistent cough or chest pain
- Night sweats
- Loss of appetite
- Weight loss

Are there specific vaccines that patients with WAS should receive?

It is important that patients with WAS receive routine vaccinations*[2] to minimize infections. Live vaccines should be avoided in WAS patients. These vaccines contain a weakened but live strain of the bacteria or virus and can cause a serious infection in WAS patients. Some live virus vaccines such as the MMR may be given to patients with XLT. The use of other live virus vaccine such as the chicken pox vaccine is still under debate. Let your physician know that your child cannot receive live virus vaccines. If family members receive live virus vaccines there is the theoretical possibility that they may transmit the virus to the child. Therefore it is advisable that they minimize contact with the child for a period of two to three weeks after receiving the vaccine, cover any rashes and maintain good personal hygiene for this period of time.

Some live virus vaccines that are currently in use are:

- Rotavirus,
- MMR
- Chicken pox vaccine,
- Live influenza vaccine (the nasal spray)
- Oral polio vaccine
- Oral typhoid vaccine
- BCG (tuberculosis)

[2] These recommendations are based on the recommended immunization schedule in the U.S. For patients from other countries, please contact your physician.

Patients with WAS are susceptible to serious infections with certain bacteria such as pneumococcus and meningococcus. Therefore, certain vaccines are recommended for WAS patients to provide protection against these specific pathogens. These additional vaccines are:

- Pneumovax (unconjugated)
- Meningococcal Vaccine
- Yearly vaccination with injectable influenza (Flu) vaccine

What can I do to prevent infections?

One of the most important things to do is to prevent exposure to infection. It is important to maintain good personal hygiene with regular use of soap and water to bathe and following good hand washing technique. If possible, avoid exposure to someone who is ill and encourage those who are ill to use good hygiene (using tissues etc.). Ask the school to notify you if there are outbreaks of communicable diseases at the school.

Most importantly, make sure that your immunization is up-to-date and that you keep taking your prescribed daily medication!

Prophylactic (preventative) Medications and Replacement Treatment to prevent infection:
Prophylactic medications to prevent infection is determined on a case by case basis depending on the presence or absence of WASp, the number and severity of infections, the plans for transplant etc. In general, the following medications are recommended for patients with Classic WAS. Some patients with XLT who have frequent infections may be advised to receive them as well.

- Antibody Replacement with Immunoglobulin given intravenously (IVIG) or subcutaneously – under the skin (ScIg) IVIG (Intravenous Immunoglobulin) or Subcutaneous Immunoglobulin: Immunoglobulins are proteins that are produced by the white blood cells that identify and destroy infectious organisms. IVIG is made up of antibodies that is collected and pooled from donors. Replacing the antibodies regularly boosts the body's ability to defend itself.
- Medications: The following are some of the medications that may be recommended to prevent infections:
    - Trimethoprim-Sulphamethoxazole (Bactrim, Septra) prevents infections with Pneumocystis jirovecii (commonly called PCP). This is started as soon as a patient is diagnosed with WAS and is continued if the patient has Classic WAS. Patients who have XLT do not usually need this medication.
    - Acyclovir: Patients with WAS are at risk of serious infections such as chicken pox and can have recurrent shingles. They can also have recurrent fever blisters. Acyclovir is effective in the prevention these infections.
    - Fluconazole: Patients who have shown recurrent fungal infections can also be given anti-fungal preventative medications such as fluconazole.

MANAGEMENT OF BLEEDING

What should I do if my child is bleeding?

If your child has a bleed:

- Wash your hands and put on gloves or use a clean cloth between your hands and the bleeding site.
- Elevate the bleeding area if possible and apply firm pressure for 5 minutes and check to see if the bleeding has stopped. If the bleeding continues, continue applying firm pressure for 10-15 minutes.
- If your child has a nosebleed, apply pressure on both sides of the nose below the bridge (the bony area) and keep his head raised.

If the bleeding is severe, call 911. If you are bruising or bleeding more than normal, or if you are unable to stop the bleeding in 10-15 minutes, call your doctor.

What can I do to reduce bleeding?

The lower platelet count predisposes the patient to spontaneous bleeding and unusually severe or prolonged bleeding with injuries. It is important to familiarize yourself with the symptoms of low platelets including easy bruising, petechiae, bleeding from the nose and gums, blood in the urine or stool and bleeding from cuts.

Encourage your child to lead as active and as normal a life as possible. Consult with your hematologist on activities that are appropriate for your child. In making decisions on what is okay for your child, consider permitting anything within reason where the child's feet never leave the ground. A helmet is recommended for infants and young children when they are active and mobile. Avoid contact sports, bicycles, skateboards and motorcycles. Avoid pointed and sharp edged toys and take extra care while using Popsicle sticks, drinking straws, sharp edged tools such as scissors and knives.

It is important to take precautions to prevent injuries as much as possible. Avoid slip injuries by using rubber mats in the tub and shower, wearing non-skid shoes around the pool and keeping the floor dry. Keeping floors clear of clutter helps prevent falls.

Good oral hygiene and care can help prevent gum bleeds. Use a soft toothbrush and maintain good oral hygiene. Keep your mouth and lips moistened with adequate hydration and lip balms. Use a humidifier to keep the nose moisturized to prevent nose bleeds. A small amount of water-based lubricant can be applied to inside of the nose to keep it from drying.

Avoid alcohol and medications such as aspirin (acetyl salicylic acid), ibuprofen, naproxen (NSAIDS), other medications and foods that reduce platelet counts or interfere with clotting. For a complete list of things to avoid please go to http://www.lowplatelets.com/lower-your-risk-for-bleeding.html.

Keep an emergency card and a letter from your hematologist or immunologist directing what should be done in an emergency with your child at all times. Take the time to build a strong and healthy relationship with your doctors.

What bleeding symptoms should prompt me to call my doctor?

Listed are some of the symptoms that could indicate a serious bleed that could require emergency care. Please call 911 without hesitation if you think that the bleed or the condition of your child is life threatening. It is better to be safe. If the situation does not require the intervention of paramedics, call your doctor right away or take the patient to the nearest Emergency Room.

- Significant head injury (anything that causes a hematoma) or have a serious accident
- Excessive bleeding in any part of the body
- Signs of bleeding in the brain such as a terrible headache or one that won't go away, dizziness, vomiting, increased sleepiness, confusion, changes in vision or hearing, eyes not moving together, slurring of speech or seizures.
- Blood is in the stool or urine or you have black stools
- Mild nose bleeds or gum bleeds if you cannot stop it after 10-15 minutes. Call immediately if the bleeding is excessive.
- Have an unusually large number of bruises or petechiae

Are there medications that can help control bleeding?

There are a few medications that can help control bleeding. Using these medications may help avoid platelet transfusions. Always consult with your doctor prior to starting the medication and keep them informed of the progress.

- Aminocaproic acid (Amicar) is a medication that reduces bleeding by stabilizing the clot that is formed. Physicians may use amicar to control a bleed and to avoid a platelet transfusion, or it may be used as an adjunct to platelet transfusion to help stop bleeding. A similar medication called tranexamic acid is used in Europe.
- Recombinant Factor VII (Novo 7): Factor VII is a naturally occurring protein that helps blood to clot. A recombinant form of human Factor VII has been approved by the FDA for uncontrolled bleeding in patients with hemophilia. Although though there have been no studies in patients with WAS, NovoSeven seems promising in studies involving other disorders where there was significant bleeding, decreasing the need for replacement blood products. It's off label use may be considered by your hematologist if there is life threatening bleeding.

My son has XLT. Is splenectomy recommended to increase his platelet count?

The spleen is an organ located in the upper left part of the abdomen and functions as a filter for removing old red blood cells and filters bacteria. In WAS patients, the spleen is thought to trap and remove platelets contributing to the decreased platelet counts.

Removing the spleen (splenectomy) increases platelet count in most patients. However, there are important downsides to splenectomy. The benefits and risks of splenectomy are shown below. At the present time, there is no consensus on whether to recommend splenectomy or not and the decision is made on a case-by case basis.

- Advantages of Splenectomy:Results in an increase in platelet counts in most patients and reduces incidence of life threatening hemorrhages/decreased mortality from hemorrhage.
- Improves quality of life for the patient and the family.
- Reduces stress and anxiety for the patient and the family.

Disadvantages of Splenectomy:

- Increased risk of life threatening sepsis
- Lifelong need for prophylactic antibiotics.
- Increased post-transplant mortality

Can platelet transfusions be given to increase platelet counts?

Platelet transfusion can increase the platelet counts for several days and is used to control moderate to severe bleeding. Platelet transfusion may also be given prior to surgery to improve the counts and to prevent bleeding during surgery and recovery. However, platelet transfusions cannot be given on a regular basis to increase counts as the immune system will eventually start rejecting the platelets and the patient will become resistant to transfusions – that is, there will be little or no increase in platelet count even after a transfusion. As a general rule, it is better to keep platelet transfusions to a minimum to avoid the formation of antibodies to platelets. The presence of anti-platelet antibodies can complicate procedures such as BMT and splenectomy.

All blood products that are given to patients with WAS should be irradiated and be free of infection from CMV. This reduces the risk of infections in these patients.

Are there other ways to increase platelet counts?

Patients with WAS can develop ITP where their immune system destroys their own platelets. Medications that are used for these patients include steroids such as prednisone, high dose IVIG and rituximab. These may help control the ITP and increase the platelet counts.

Investigational trials are testing the use of platelet growth factors (Eltrombopag) that have been shown to be effective in ITP.

How do I treat eczema?

Eczema is a chronic and recurring skin disorder. The outer layer of the skin is not able to retain moisture, causing dry, itchy and irritated skin. Unfortunately there is no cure for eczema and it has to be controlled with good skin care. The skin of patients with eczema is more prone to infection. A dermatologist can be helpful in creating a care plan for the patient and should be a part of the care team, particularly for patients with moderate, severe or persistent eczema.

Good skin care is a three step process.

1. Avoid triggers that worsen eczema: Some foods, chemicals, cold weather, woolen fabrics and stress can make eczema worse. Cold temperatures, especially with low humidity as in a heated home, excessive sweating and excessive bathing can worsen eczema. Using mild, hypoallergenic soaps and detergents can help. Find products that do not irritate the skin and stick with them.
2. Moisturizing: Bathe daily for 5-10 minutes with soap and warm water followed by application of a moisturizer immediately. Addition of oatmeal, bleach or vinegar to the bath water has also reported to be effective. Frequent and liberal application of non-cosmetic moisturizing agents such as Aquaphor, Eucerin or CeraVe helps retain the moisture in the skin. Your dermatologist will be able to make recommendations.
3. Medications: Certain medications such as steroid creams and ointments can be used to control flare ups. Steroids help by reducing the inflammation in the skin. Steroids come in various strengths and some of them; particularly the stronger ones can cause thinning of the skin, stretch marks and growth retardation if used for a long period of time in the same areas. Therefore, they should be used for the least duration possible and directions on their use should be followed carefully.

   Occasionally medications that modify the immune system such as tacrolimus or pimecrolimus are used to help control the eczema. These medications should be used sparingly and directions on use should be followed very carefully. They are not used in children who are under the age of two years.

   Infections of the skin should be treated promptly with antibiotics and antiviral medications as needed until the infection has been resolved completely.

   Itching is a part of eczema and it is worsened by the itch-scratch cycle. It disrupts sleep and makes the skin more prone to infection. Good skin care and the routine use of moisturizers and oatmeal baths can be helpful in relieving itching. Keep nails trimmed and short. Medications such as Benadryl or Atarax at night relieve the itching and help the patient to get a good night's sleep.

My son has WAS. How do I know if I am a carrier?

By history: If there is a family history of the disease or you have maternal uncles or cousins who have WAS or who have a history of low platelets, bleeding, frequent infection etc. chances are that you are a carrier. However, a third of the cases are new mutations and there is no family history.

By testing: Genetic testing is done to confirm carrier status in women who are suspected of being a WAS carrier. This is a genetic test done on blood or other cells similar to what is done for the diagnosis of WAS in patients.

I am a carrier. What are the chances that my other children are be affected?

Each boy born to a mother who is a carrier has a 50% chance of inheriting the abnormal gene and having WAS. Each girl born to a mother who is a carrier has a 50% chance of inheriting the abnormal gene and becoming a carrier.

As WAS is a genetic disorder, it is a good to meet with a Genetic Counselor who can guide you and your family on who to test and when.

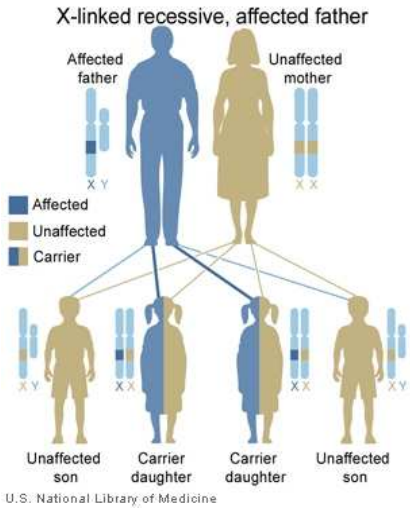

Figure 6: Inheritance of the *WAS* gene from an affected father

Courtesy: Genetics Home Reference

I have received a BMT for WAS and am now cured/I have WAS and have not had a BMT. What are the chances that my children are affected?

A boy born to a father with WAS does not inherit the abnormal gene and will not have WAS. All of his daughters will be carriers of the disease. Girls who are born to a father who has WAS are referred to as obligate carriers.

While a successful BMT cures the patient of WAS, it does not correct the abnormal gene that is present in the sperm. Therefore, even after a cure a father who had WAS will pass on the abnormal gene to all of his daughters. See Figure 6.

Why are girls not affected even though they carry the abnormal gene?

Girls have two X chromosomes. In women who are carriers, one of the two X chromosomes carries the abnormal *WAS* gene. The other X chromosome has a normal *WAS* gene. The woman's cells can use this normal *WAS* gene, which allows for normal production of the WASp and normal function of white blood cells and platelets. Therefore girls are usually not affected by WAS.

Boys, on the other hand, have one X chromosome and one Y chromosome. In patients with WAS, the single X chromosome carries the abnormal gene and the cells cannot produce normal amounts of the WAS protein. Therefore they have symptoms of WAS.

Can I find out if my child has WAS before birth?

There are at least two possibilities that can be done to determine if the unborn child has WAS. Between 10-12 weeks of pregnancy, tissue from the placenta is tested and is called Chorionic Villus Sampling or CVS for short. This tissue is tested to determine if the child has the abnormal *WAS* gene.

Another option is to wait until around the 16th week of pregnancy when the sex of the child can be determined with an ultrasound. If it is a male, fluid from the uterus can be studied and this procedure is called amniocentesis. The cells from the fluid are tested for the presence of the abnormal *WAS* gene.

I am pregnant with a child with WAS. Should I have a C-Section?

Under such circumstances, most experts recommend a C-Section as it could lower the risk of an intra-cranial hemorrhage during childbirth. It also gives the obstetrician the chance to deliver the baby at a time when neonatologists and hematologists are available in the event of an emergency. However, the decision will also depend upon on your health condition, facilities available etc. Discuss this with your obstetrician, who can weigh the various options and make the decision that is best for you and for your child.

Is there a way to have a child who does not have WAS?

Pre-Implantation Genetic Diagnosis can be used to avoid having a child with WAS. This technique involves using in-vitro fertilization treatment and can be used to enable couples to choose the sex of a baby, choose a baby who does not have WAS or to choose a baby who is not a carrier. This is a complicated process that involves the selection of an embryo that does not carry the abnormal *WAS* gene and is done at only a few specialized fertility centers. A genetic counselor is the best source of advice and information about this technique. Your physician will be able to refer you to a center that offers a PGD service.

We have a family history of WAS/I am pregnant with a child with WAS. Should I store the cord blood?

If there is a family history of WAS, it is a good idea to have the cord blood stored as it may be useful for a sibling or another member of the family for a BMT in the future.

If you are pregnant with a child with WAS, experts suggest that you consider storing the cord blood. At the present time, cord blood from patients is not being used. However, with the rapidly emerging field of GT and stem cell therapies, it may be of use in the future to cure the child.

CLINICAL TRIALS

What therapies/clinical trials are currently in development?

A great deal of research is being conducted on new treatments to find less toxic cures as well as better treatments to improve the quality of life. For a list of trials, go to: WAS Clinical Trials

The next several pages list some of the trials that are currently in progress.

What research is being done to improve BMT and where are these studies being conducted?

Research is being conducted on newer transplant treatments aimed at decreasing the acute toxicities and complications associated with standard treatment plans and to improve outcomes. For more details about each study and for contact information please visit: Transplant Trials

Are there trials of medications to improve platelet counts?

Eltrombopag is an oral medication being studied to see if it can create a sustained increase in platelet counts and reduce bleeding in patients with WAS. It mimics the action of thrombopoietin, the hormone responsible for maintaining normal platelet counts.

Eltrombopag has been shown to be effective at increasing platelet counts in a high percentage of ITP patients and in a few patients with XLT. The goal is to use eltrombopag to increase the number of platelets enough to lower the risk of bleeding and is not used to increase the number of platelets to a normal level. For details, please visit Eltrombopag Trial.

What studies are being done to improve immune function?

Administration of IL-2: Patients with WAS have a defect in the function of T-lymphocytes and natural killer cells, which are types of white blood cells. This results in an increase in the number of infections and puts these patients are at a higher risk of autoimmune disorders and malignancies.

IL-2 is a type of natural protein produced by the body. In the laboratory, studies have shown an improvement in the function of the immune system when exposed to IL-2.

This study is to determine if IL-2 therapy is safe and improves the immune system in WAS patients. Patients are given injections of IL-2 and observed to see if there is improvement in their eczema, infection rate, etc. This study is for patients with XLT who are not transplant candidates. For more information on the trial go to: IL-2 Trials

What non-pharmacologic treatments should be considered?

At the present time, there are no non-pharmacological treatments available to sure WAS or to increase the platelet count. As always, it is best for the patient to follow a healthy, balanced diet and exercise regularly. Meeting with a family therapist or child life specialist could help the patient and the family cope better with the complexities a chronic disease and BMT.

SUPPORT GROUPS

Where can I find a Support Group or Organization?

- Wiskott-Aldrich Foundation: Please e-mail us at info@wiskott.org to connect with us or call us at (919) 641-7134 if you wish to speak with someone right away.
- IDF Forums: Please register & join the Wiskott group
- Face book: Join the
  - Wiskott-Aldrich Foundation
  - Wiskott-Aldrich Syndrome Families
  - Children with Wiskott-Aldrich Syndrome

RESOURCES

What resources are available for families with WAS?

- WAS Organizations:
  - Wiskott-Aldrich Foundation
  - WAS Foundation
  - Israeli Wiskott-Aldrich Syndrome Foundation
- Immune Deficiency Organizations
- Financial Resources
- Get a Medical Alert Bracelet
- Genetic Testing in the U.S.. Genetic Testing outside the U.S.
- IDF School Guide
- Medical Supplies for WAS patients – helmets etc

FOR MORE INFORMATION

For more information on WAS

- Wiskott-Aldrich Foundation
- WAS Handbook from the IPOPI
- WAS Handbook from IDF
- WAS from Patient Plus UK

APPENDIX A: BONE MARROW TRANSPLANT

What is a bone marrow transplant (BMT)?

Bone marrow is the soft, spongy tissue that is found in the center of bones. It is the "factory" where the white blood cells, platelets and red blood cells are produced. These cells arise from "mother cells" referred to as stem cells (hematopoietic stem cell). See Figure 7.

The stem cells in the bone marrow of patients with WAS generate abnormal blood cells. To cure WAS the patients' stem cells in the bone marrow need to be replaced with stem cells from a healthy donor. The process by which the patient's stem cells in the marrow are replaced with healthy stem cells from a donor is referred to as a BMT.

Where do the donors stem cells come from?

The stem cells that are used in a transplant can come from three different sources. The transplant physician decides which one is best for the patient.

1. **Bone Marrow:** This is the most commonly used source of stem cells and the source with which transplant doctors have the largest experience as a treatment for WAS.
2. **Cord Blood:** This is blood that is collected from the umbilical cord after a baby is born. Cord blood is rich in stem cells that give rise to the blood cells and can cure WAS.
3. **Peripheral Blood Stem Cell (PBSC):** All of us have a low number of stem cells that are circulating in the blood. Growth factors can be given to the donors to increase these numbers so that the stem cells can collected from the blood and used as a source of stem cell for a transplant to cure WAS.

How will doctors find a donor for my child? Why is it important to find the right donor?

The first step in the transplant process is to find the best possible donor in order to improve the chances of success of the transplant and to reduce the possible complications from the transplant. A patient's immune system identifies and destroys cells that are not from his own body as foreign and is more likely to accept cells that are from a donor that are most similar to his own cells. Therefore, the donor is selected very carefully to closely match the patient. Human leukocyte antigens (HLA) are markers that are founds on cells and are used to find the best possible match for your child. A donor with HLA markers closest to the patient's own is identified.

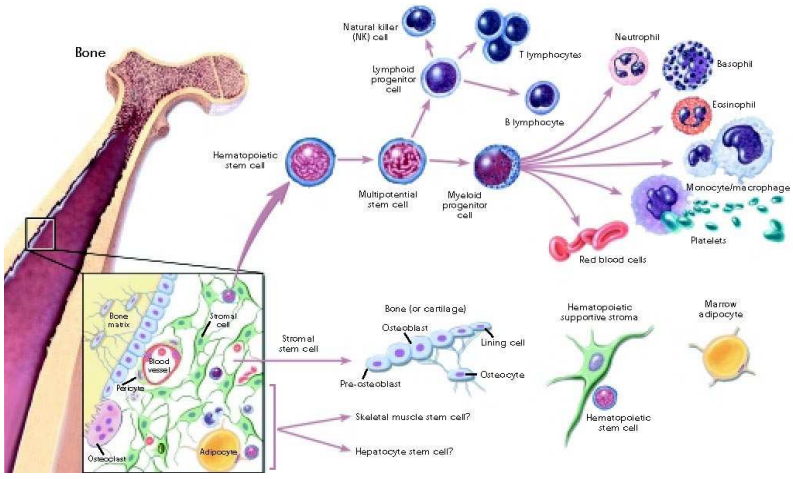

Figure 7: Stem Cells in the bone marrow. Courtesy: National Institutes of Health

To find a donor, a sample of blood is taken from your child to check his HLA type. Samples are also taken from siblings to see if they are a good match. There is a 25% chance that each sibling will be a perfect match for your child with WAS. Matched siblings are ideal donors for patients with WAS. If there is no sibling match, then a search is initiated to find the best match among bone marrow and cord blood registries worldwide. It may take up to two months to complete the search. In most, but not all cases, acceptable donors are found. If no match is found and the patient needs to have a transplant, then one of the parents or other relatives may be selected as donors.

Once a donor is found, testing is done to confirm that the match is good, that the donor does not have infection or disease that can be passed on by the transplant and that he/she is willing to donate. The first major step to a transplant is complete at this point! For more details on the matching process, please visit: ExploreBMT.org

What happens once a donor is found? What can I expect when my child has a transplant?

Pre Transplant Evaluation: Once the best donor is identified the pre-transplant evaluation begins. During the pre-transplant evaluation several tests are done to evaluate the function of the kidneys, heart, lungs etc. to determine that the patient will be able to withstand the rigors of the transplant process and to have a baseline recording for further evaluation. Financial planning is done at this time and measures are set in place for the support of the parents and siblings during the process. Going through a transplant is challenging and emotionally exhausting and the transplant team will be there to guide you through the process physically and emotionally.

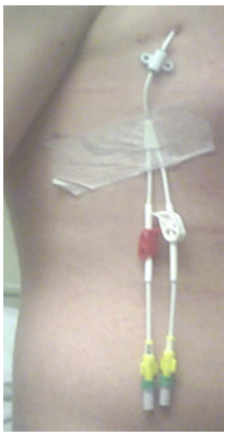

Figure 8: Hickman Catheter
Courtesy: Wikipedia

Patients are hospitalized anywhere from a week prior to the day before the preparatory medications are started. Some children may have to be hospitalized earlier to get them ready for the transplant. Several medications are given while the child is in the hospital and lab work is done frequently, up to every day at times. To prevent the child from having numerous pokes every day, sturdier, temporary IV lines (referred to as a Broviac or a Hickman Catheter) are implanted in a vein in the child's chest. See Figure 8.

The Transplant Process: Here are some of the basic steps that happen during a BMT:

Conditioning: This is the preparation process that gets the patient ready to receive the stem cells from the donor. Medications (chemotherapy) are given to destroy the patient's blood forming cells and to make place in the bone marrow for the donor cells. They also destroy the patient's immune system so that it does not reject the donor cells. This process is called myeloablation or conditioning and lasts for several days. For chemotherapy regimens that last for 8 days, the day that chemotherapy is started is referred to as Day -9. Chemotherapy is continued until day -2. Day -1 is a "rest day" when no chemotherapy is given. During this time, the patient is monitored closely for side effects from the chemotherapy and medications are given to prevent and treat the side effects.

Transplant Day: On Day "0" the donor cells are infused into the patient. The donor cells are infused into the blood in a simple process similar to a regular blood transfusion. The days after this are counted up as day +1, +2 etc.

Engraftment: Once the donor cells are given, blood samples are taken regularly to check for normal functioning of the body and to check if the donor cells are growing. Due to the chemotherapy, the patient will have a lower number of red blood cells, white blood cells and platelets in the blood and require transfusions to maintain normal levels of hemoglobin and platelets.

Over time the donor cells will populate the bone marrow and make new blood cells. This is called engraftment and is an important milestone in the transplant journey. Until the donor cells are well established patients have no immune system and they are very susceptible to infections. Patients are on several medications to prevent infection, to prevent rejection of the donor cells and to prevent the donor cells from attacking the body. Medications are given to control the pain and any complications that may arise. To decrease the chance of infection, patients are given rooms with special air filters, visitors are restricted, and several procedures are followed including a modification of the diet. It is important to

follow the reverse isolation procedures outlined by the BMT team hospital scrupulously as infections can be serious and cause significant setbacks in the transplant path.

Engraftment usually happens between Day +10 to Day +28, but could take longer (1-2 months). Patients are usually discharged once engrafted. How long your child stays in the hospital depends on several factors, but mainly depends upon how quickly his immune system begins to recover.
Once the patient is discharged, they are very closely monitored to make sure that steady progress is being made and to treat any complications at the earliest. Until such time that the donor cells grow and make enough cells, the patients are given transfusions of red blood cells and platelets as needed. This could take a few months. Replacement antibodies (Intravenous immunoglobulin, IVIG) are given on a regular basis, until such time that the donor's white blood cells are functioning well.

Visits to the hospital may be three times a week initially and reduced to once a week once the blood cell counts are more stable and the physician is comfortable that everything is going as planned. Patients are under close and regular supervision after the BMT until such time that the immune system has recovered completely. This usually takes 1-2 years.

What are the complications of transplant?

Great strides have been made in the last decade and there has been a significant improvement in survival rates. However, bone marrow transplant is not without risks. The five-year survival rate under ideal conditions is about 90%. This means that one out of every ten patients die in the first five years after BMT. Most of the deaths occur in the first year after transplant.

Complications are relatively common, particularly in the first year after transplant. Most commonly seen are infections, autoimmune disorders, graft versus host disease (GvHD) and rejection of the graft where the patient's own cells grow back. The situation where the patient has his own cells and that from the donor is referred to as mixed chimerism. Once again, complications are most frequent in the first year after transplant, and the number and severity of complications decrease after that.

Fertility Preservation: Some of the medications that are used during the transplant can cause infertility. In order to preserve fertility, there are options to freeze the sperm for adolescents and adults. Your BMT physician can coordinate this for you. More recently fertility preservation is being offered for infants and children. For details, please visit: Fertility Preservation for Infants and Children.

What factors determine the success of a transplant?

Over the last decade significant progress has been made in BMT and recent results for WAS patients have been very good. There are several factors that determine the success of a transplant. Overall, success rates are best and complications are the least when:

- Transplant is performed at an early age, especially if a registry donor is used
- When the child is still in good health without serious infections, autoimmunity, malignancy or damage to organs.
- Well matched donor.
- Although formal data are not available to support the notion, a common recommendation is that transplant is done at a center that is experienced in transplanting patients with WAS.

APPENDIX B: GENE THERAPY

What happens during GT?

Here are five basic steps in gene therapy. See Figure 9.

1. Doctors collect blood forming stem cells from the patient's bone marrow or blood. These cells are then grown in large numbers outside the body.

2. In the meantime, the normal, healthy *WAS* gene is obtained using genetic engineering in the laboratory. This gene is then incorporated into a virus. The virus is made incapable of replicating itself, which removes its capacity to infect the patient. The resulting defective virus carrying the normal *WAS* gene is called a "vector".

3. The patient's stem cells are mixed with the vector that incorporates the normal *WAS* gene into the stem cells. These stem cells that have the normal *WAS* gene in them are referred to as gene corrected cells.

4. Conditioning: The patient id then given chemotherapy in preparation for GT. This helps make space in the marrow for the repaired cells to engraft.

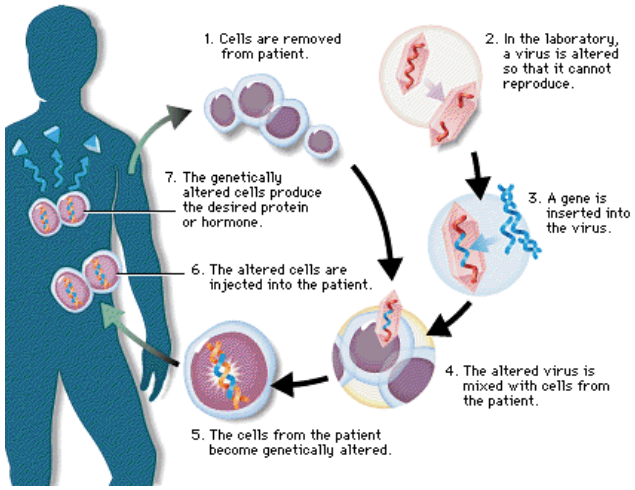

Figure 9: Illustration of Gene Therapy

Courtesy: Wikipedia

5. The repaired cells are now introduced into the patient in a process similar to blood transfusion.

After finding their way to the bone marrow, these repaired cells then continue to multiply, forming more numbers of normal cells. These newly repaired stem cells which have the normal *WAS* gene can now produce normal amounts of WASp and, if the process results in sufficient numbers of corrected cells the patient is cured.

When is gene therapy recommended?

Gene therapy is still in its early stages. So far the trials have had good success with significant increase in WASp levels and an accompanied improvement of symptoms. Not much is known about the long term success rates or complications. For this reason it is currently being offered only to a select group of patients for whom the benefit outweighs the risk.

In general, patients from the age of one month to 35 years who have Classic WAS (score of 3-5) and do not have a good match are eligible. For further details please go to Gene Therapy Trial Eligibility Criteria

Where are gene therapy trials being done?

Studies are in progress in several centers in Europe and in Boston in the U.S. For more details and contact information: Gene Therapy Trials.

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