Aplastic Anemia
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APLASTIC ANEMIA
A HANDBOOK FOR FAMILIES

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WHAT IS APLASTIC ANEMIA?

Aplastic anemia is a bone marrow failure syndrome. The bone marrow “shuts off” and stops producing white blood cells (WBCs), red blood cells (RBCs), and platelets. As a result, children with aplastic anemia are at risk for life-threatening infections, anemia, and bleeding. Children with aplastic anemia can become very sick and may require prolonged hospitalization, blood and platelet transfusions, intravenous (IV) antibiotics, and other medical tests and treatments.

WHAT IS BONE MARROW?

Bone marrow is spongy material located within the bones. It is like the “garden” for the body where the blood-forming cells (WBCs, RBCs, and platelets) grow. These cells are formed from a very young stem cell, which is like a seed. As the seed grows, it blossoms into fully functional and mature WBCs, RBCs, and platelets.

WHAT DO THE CELLS OF THE BONE MARROW DO?

White Blood Cells

WBCs help the body fight infection. They are part of the immune system and have a memory. This memory allows the body to help fight and control infections and to respond to childhood immunizations. If these cells do not work properly, very serious and life-threatening infections can develop.

Neutrophils, which are part of the WBCs, specifically fight bacterial infections. The absolute neutrophil count (ANC) is a calculated percentage of the WBCs that are neutrophils. This number tells you how well your child’s body is able to fight infection.

ANC is calculated using the following formula:

\[ \text{ANC} = \text{total WBCs} \times (\text{segs/polys + bands}) \]

Multiply total WBCs by the total of segs/polys + bands. (Segs or polys are mature WBCs that fight infection. Bands are immature segs or polys that cannot fight infections as well but do help. The segs/polys and bands are both neutrophils. Different labs may use different terminology to identify neutrophils. Your child’s nurse can show you how to calculate the ANC.)

Example: WBC is 5. This means 5,000. Your child has 20% segs (0.20) and 5% bands (0.05).

Calculate the ANC as follows:

\[ \text{ANC} = 5,000 \times (0.20 + 0.05) \]
\[ \text{ANC} = 5,000 \times (0.25) \]
\[ \text{ANC} = 1,250 \]

A child with a low ANC (less than 1,000) is considered neutropenic or not able to fight infection. A child with an ANC less than 500 is considered severely neutropenic.
Red Blood Cells

The RBCs carry oxygen to all parts of the body. Oxygen is food and nourishment for all the organs, including the heart, lungs, stomach, intestines, and brain, and keeps them working well. When an RBC attaches to oxygen, it is called hemoglobin.

Platelets

Platelets are sticky and help the body control bleeding by clumping together. An example of this is when a cut stops bleeding. As the bleeding slows, the blood cells stick together and form into a clot. If the blood has a low number of platelets, bleeding may be quick and spontaneous (without injury). When platelet levels are very low, a child could bleed into his or her head or another vital part of the body, which can be life threatening.

HOW DID MY CHILD GET APLASTIC ANEMIA?

Most cases of aplastic anemia are idiopathic, which means the cause is unknown. We do know that aplastic anemia is not caused by anything a parent or child did or did not do.

Aplastic anemia has been linked to exposure to radiation and some chemicals, such as benzenes. Some inherited diseases, such as Fanconi anemia, dyskeratosis congenita, Shwachmann–Diamond syndrome, and Diamond-Blackfan anemia, have been associated with the development of aplastic anemia. Infections such as Epstein Barr virus, hepatitis, and parvovirus (fifth disease) also have been associated with causing aplastic anemia.

WHAT ARE THE SIGNS AND SYMPTOMS OF APLASTIC ANEMIA?

Signs and symptoms of aplastic anemia occur as a result of bone marrow failure. If your child’s WBC count is low, he or she is at risk for developing fever and infection. It is important to monitor your child closely for fever and to contact your healthcare team immediately if a fever develops.

If your child’s RBC count is low, he or she may become pale, suffer from fatigue (decreased energy), and experience shortness of breath or headaches. If your child’s hemoglobin level becomes extremely low, he or she may receive a packed RBC transfusion.

If your child’s platelet count is low, he or she is at risk for bleeding and can have spontaneous nosebleeds, bleeding gums, excessive bruising, bruising in unusual areas such as the back or chest, and petechiae (pinpoint purple dots on the skin that are small hemorrhages). If your child’s platelet count is very low and he or she is experiencing bleeding, a platelet transfusion may be given.
HOW IS APLASTIC ANEMIA DIAGNOSED?

When a child develops signs of aplastic anemia, one of the first steps to making the diagnosis is a blood test. Blood tests are done by inserting a needle into the child’s arm or hand to draw blood that can be sent to a laboratory for analysis. Drawing blood can be difficult for the child and parent, but it is necessary to obtain an accurate diagnosis.

After the blood is drawn, a complete blood count (CBC) is done. The CBC measures the number of WBCs, RBCs, and platelets that are circulating in the blood. In a child with aplastic anemia, all of these numbers are low. A reticulocyte count, which assesses the number of young RBCs the body is making, may be low as well.

Your healthcare team also will draw blood to check your child’s electrolytes and to perform a chemistry panel to see how well the kidneys and liver are working. The blood sample also may be tested for recent viral infections. These tests will help your healthcare team look for other causes of decreased blood counts and help confirm the diagnosis of aplastic anemia.

The diagnosis of aplastic anemia is confirmed by a bone marrow aspirate and biopsy. During a bone marrow aspirate, a needle is inserted through the bone, generally into the iliac crest or hipbone, and a sample of the bone marrow from the spongy space in the bone is removed. The bone marrow is then examined under a microscope by a specially trained doctor (pathologist or hematologist) to see if WBCs, RBCs, and platelets are being produced. In children with aplastic anemia, the bone marrow is hypocellular, which means very few of the blood-forming cells are seen under the microscope. The pathologist also looks for any abnormal cells, such as leukemia blasts or dysmorphic (abnormal-looking) cells, which can indicate a different disease. The bone marrow is also assessed for protein expression of malignant cells, which can indicate leukemia, and chromosomal abnormalities, which can diagnose other diseases. In children with aplastic anemia, protein expression and chromosome tests are normal.

It also is very important that a bone marrow biopsy is obtained to help diagnose aplastic anemia. During the bone marrow biopsy, a needle is inserted into the hipbone and a “core,” or a cylinder-shaped piece of the bone, is obtained. The pathologist looks at this core and determines how hypocellular the marrow is. The degree of hypocellularity is graded as a percentage. That percentage helps determine the severity of the aplastic anemia.

The bone marrow aspirate and biopsy are performed at the same time. Children usually are given sedation or general anesthesia during the procedure to prevent discomfort. Upon awakening from sedation, your child may complain of bone pain at the bone marrow site; however, this pain is usually mild and resolves within 1–2 days. If your child is uncomfortable, a mild pain medication may be given.
HOW IS APLASTIC ANEMIA CLASSIFIED OR STAGED?

The International Aplastic Anemia Study Group has identified specific criteria for the blood and bone marrow values. This criteria is used in the staging of aplastic anemia.

The values in the blood are:
- ANC less than 500 (normal is greater than 1,000)
- Platelet count less than 20,000 (normal is 150,000–400,000)
- Reticulocyte count less than 1%.

The values in the bone marrow are severe hypocellularity moderate hypocellularity, with WBCs, RBCs, and platelets representing less than 30% of all cells.

Severe aplastic anemia (SAA) is defined by meeting at least two of the three criteria for blood and any of the marrow criteria. Very severe aplastic anemia (VSAA) includes the above diagnosis of severe aplastic anemia, but with an ANC less than 200.

HOW IS APLASTIC ANEMIA TREATED?

HLA Typing

Your child’s physician may order human leukocyte antigen (HLA) typing to determine if a bone marrow transplant is a recommended treatment option. HLA typing can be done through a blood sample or a swab on the inside of the cheek. This often is done on the child diagnosed with aplastic anemia, any siblings, and parents. This testing can determine if there is a family member who may be a possible donor or if a search for an unrelated person is needed. HLA is a system of proteins found on the surface of most cells in the body. A child generally receives half of his or her proteins from the mother and half from the father. Each sibling has a 25% chance of having the same proteins as the child. These proteins determine the sameness of the tissue of the two people. When the child and the sibling have the same protein, this is called a match.

Immune Suppression

Aplastic anemia is thought to be an autoimmune disorder in which the body’s own immune system attacks the blood-forming cells. Medications that suppress the immune system are used to try to stop this process from continuing. For children who do not have an available matched-sibling bone-marrow donor, immunosuppressive therapy is the standard recommended treatment.

Anti-thymocyte globulin (ATG) combined with cyclosporine is the most common first-line therapy. ATG is made from horse or rabbit serum. It is produced by injecting the animals with human lymphocytes (a type of WBC that participates in the body’s immune response), which produces antibodies (a protein made by the immune system) against these lymphocytes that are then harvested. The ATG is then infused into the child and suppresses (lowers) his or her immune system. While receiving ATG, your child will receive antipyretics (fever reducing medication,
such as Tylenol, antihistamines (such as Benadryl), and steroids. It is common for children to have fevers and chills during the infusion, and the medications are used to reduce these side effects. ATG is given very slowly through an IV, usually during a 4-day period. Because there is a risk for an adverse reaction to this treatment, children are hospitalized while receiving ATG. Serum sickness is another side effect that usually occurs 1–2 weeks after ATG is given. Symptoms include fever, rash, joint pain, and muscle aches. Serum sickness is treated with steroids and can last from several days to a couple of weeks.

The other medication that is used in combination with ATG is cyclosporine. Cyclosporine is a medication that can be given orally or via an IV. This medication is give twice daily and helps to suppress the immune system. It will be started at the beginning of treatment and will continue for 6 months or longer after your child has been discharged from the hospital. Your child’s healthcare team will monitor medication levels of this drug to make sure your child receives a therapeutic dose. This medication can have side effects including kidney damage, high blood pressure, low magnesium levels in the blood, seizures, and excess hair growth. It is important to discuss any side effects your child may be experiencing with your healthcare team.

After discharge from the hospital, patients frequently will be seen in the outpatient clinic to monitor blood counts and response to treatment.

Other immunosuppressive drugs have also been tried in place of cyclosporine, including tacrolimus (Prograf), daclizumab (Zenepax), mycophenolate (Cellcept), and cyclophosphamide (Cytoxan). These treatments usually are reserved for patients who do not respond to their initial course of immune suppression or for those who have a recurrence of aplastic anemia. Recently, the U.S. Federal Drug Administration (FDA) approved a new medication for the treatment of severe aplastic anemia. Eltrombopag (Promacta®) is indicated for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Immunosuppressive therapy is a very effective treatment for aplastic anemia. However, because of immune system suppression, patients are at risk for serious infection and need to be monitored closely. They also may require other supportive care medications to prevent infection.

If a child does not respond to the first course of immune suppression with horse ATG and cyclosporine, a second course of immune suppression may be considered.

**Hematopoietic Stem Cell Transplant**

**MATCHED-SIBLING DONOR**

For children with a sibling who is HLA matched, it is often recommended that they proceed to a hematopoietic stem cell transplant (HSCT), even if they have not received any other treatment for their aplastic anemia.

Children are admitted to the hospital for an HSCT. At the hospital, they have a central line placed (see page 7) to receive medications, IV fluids, and blood products that they will need during their HSCT. Two medications are used to destroy the malfunctioning immune system: ATG and cytoxan, a chemotherapy agent. After these medications have been given, new, healthy bone marrow that has been harvested (collected) from a sibling is infused into the patient. After approximately 10–20 days, the new marrow starts to
grow and repopulates the bone marrow. As a result, blood counts begin to return to normal. Children usually are hospitalized for 20–50 days after an HSCT. During this time, they are monitored closely for complications as they await the growth of the new marrow. When they are transitioned to the outpatient clinic, they are seen frequently and monitored closely for engraftment (growing of the new blood cells) and complications of HSCT, including graft-versus-host disease, infections, and organ toxicity. Matched-sibling HSCT is a very effective treatment for aplastic anemia; however, very serious complications can occur. The greatest risk for complications occurs during the first 2 years after HSCT; therefore, close monitoring is required during this time frame.

**ALTERNATIVE DONOR TRANSPLANT**

Children who do not have a matched sibling and do not respond to immune suppression are often referred for an alternative HSCT. Potential bone marrow donors can be an unrelated person that is identified from the National Marrow Donor Program (NMDP) or a partially matched family member, such as a parent. A member of the bone marrow transplant team will further discuss with you details of identifying a donor if this is needed for your child. This process is similar to a matched-sibling HSCT but may require different medications and possibly radiation for the new bone marrow to grow.

**Complications of HSCT**

Children who undergo HSCT are at risk for complications. However, the risks of transplant-related complications are higher with alternative donor transplants. Complications include the following:

- Nonengraftment occurs when the new bone marrow does not grow.
- Rejection occurs when the child's own immune system reacts with the donor's new immune system and the donor's cells do not grow. Rejection can sometimes be stopped by making changes to the immune-suppression medications.
- Graft-versus-host disease is a process during which the new bone marrow recognizes the child's body as foreign and attacks certain organ systems, such as the skin, gut, and liver. Symptoms include rash, nausea, vomiting, diarrhea, decreased appetite, and increased liver function tests.
- Infections develop as a result of the chemotherapy regimen and immune suppression. Children are at high risk of developing infections. Infections can be caused by bacteria, viruses (often as a result of reactivation of viruses that are already living in the body), fungi, or other organisms.
- Toxicity or damage to organs: Multiple organs in the body can be affected. The organ and the extent of damage are dependent on the type of HSCT the child has received as well as the complications he or she has experienced.

Additional written materials specifically addressing HSCT will be provided if a transplant is recommended for your child.
SUPPORTIVE CARE

Venous Access Device

A venous access device (VAD), sometimes called a central line, is an IV catheter that may be used for the duration of your child’s therapy. There are different types of VAD. Your child’s healthcare team will discuss the risks and benefits of the different types. The VAD is inserted surgically when your child is under sedation or general anesthesia. A VAD can be used to administer medication, blood products, IV fluids, or nutritional support when needed. It also may be used to draw blood for testing purposes. The VAD may remain in your child for the duration of treatment and will be removed during surgery when it is no longer needed.

Blood Product Transfusion

RBCs are the cells that carry oxygen to different parts of the body. When a child’s hemoglobin is low, his or her heart has to work harder to pump blood. Children with a low hemoglobin level often feel tired (especially with activity), have headaches, and may feel nauseated. Your child may receive an RBC transfusion to increase hemoglobin in the body and to ease the work of the heart by carrying oxygen to all parts of the body. This also may help him or her feel better.

Packed RBC transfusions consist of blood donated by healthy people. The blood is stored in a bag and infused into the child through his or her IV access, such as a VAD. Blood transfusion risks include allergic reactions such as itching, hives, or difficulty breathing. Your child will be monitored for a reaction very closely by the nurse.

Platelets are the parts of the blood system that prevent and stop bleeding. Children who have a low platelet count are at increased risk of bleeding. They may have bruising, gum bleeding, or little red spots on their skin called petechiae. Platelets can be infused to temporarily increase the platelet count.

The platelet transfusion process is similar to an RBC transfusion. The reaction risks are the same, and your child will be monitored closely during the platelet transfusion.

Although transfusions of blood and platelets may be necessary to help prevent serious complications, they should not be given if they are not needed. In the HSCT setting, getting more transfusions can increase the chance of your child rejecting the bone marrow.

WBCs help fight infection. Although children with aplastic anemia often have very low WBC counts, WBC transfusions are rarely given because WBCs only live a few hours, and serious side effects may develop. In certain situations, usually if there is evidence of a life-threatening infection, WBC transfusions may be recommended.

Growth Factors

Growth factors are medications that are given to help increase the body’s own production of various blood cells. They are generally given as a subcutaneous (under the skin) injection or as an IV infusion.

WBC growth factors are the most commonly used and include granulocyte colony stimulating factor
(G-CSF) or filgastrim (Neupogen), pegfilgastrim (Neulasta), and granulocyte macrophage stimulating factor (GM-CSF). These medications help decrease the risk of infection by increasing the ANC and the body’s ability to fight bacterial infections. Common side effects can include pain or redness at the injection site, bone pain, headache, and nausea.

There are growth factors that can stimulate RBC and platelet production. These are typically not used to treat patients with aplastic anemia. Your child’s healthcare team will discuss these options with you, if indicated.

**Infection**

Children with aplastic anemia are at risk for infection. The lower the ANC, the greater the child’s risk of infection. Children with an ANC less than 500 are at a high risk for infection, and those with an ANC of less than 200 are at very high risk for infection.

Children with aplastic anemia will have their ANC monitored closely. Those with a low ANC may require growth factors to increase their ANC. If your child develops a fever with a low ANC, he or she requires prompt medical evaluation no matter what time of the day or night. Medical evaluation includes laboratory tests, such as blood tests, exams, and other tests to determine the source of the fever. If a bacterial infection is suspected, your child needs to be started on antibiotics and may need to be admitted to the hospital for close observation.

Children with aplastic anemia also may require prophylactic or preventative medications to decrease their risk of developing an infection. Medication to prevent a specific type of pneumonia, called pneumocystic jirovecii pneumonia (PCP), is often needed. Although sulfamethoxazole/trimethoprim (Bactrim) is the best medication to prevent PCP pneumonia, a side effect of the medication is lower blood cell counts; therefore, it is not recommended in children with aplastic anemia. The use of this medication should be discussed with your healthcare provider. Other medications that may be used are pentamidine (given via aerosol or injection) or Dapsone (given orally).

Patients also may require medication to prevent fungal infections. Fluconazole (Diflucan) is a commonly used oral medication. For patients who no longer require transfusions, phlebotomy or withdrawing blood on a routine basis can be an effective method of decreasing iron overload.

**Iron Overload**

Iron overload can occur in patients who receive multiple RBC transfusions. Excess iron can build up in the liver, heart, and other organs of the body, causing the organ to not function as well as it should. Decreasing the number of transfusions a child receives is the best way to prevent iron overload from occurring. For children who develop iron overload, medications called chelators may be prescribed to decrease the amount of excess iron. These medications are either given through an IV, under the skin, or as an oral medication. Phlebotomy, or the removal of red blood cells, similar to donating a unit of blood, may be recommended to remove extra iron.
WHO WILL CARE FOR MY CHILD?
A team of professionals at a specialty clinic will be caring for your child. This team usually consists of specially trained physicians called hematologists. These are doctors who are trained to care for children with blood problems. Nurse practitioners, nurses, pharmacists, social workers, child life specialists, psychologists, and dieticians also may be members of your child’s healthcare team. You and your family are an important part of that team. You know your child better than anyone else. Be sure that you feel comfortable talking to your healthcare team members about symptoms you are noticing; questions you have regarding diagnosis, treatment, and medications; or any other concerns you may have.

WHAT RESOURCES EXIST FOR CHILDREN DIAGNOSED WITH APLASTIC ANEMIA AND THEIR FAMILIES?
Aplastic Anemia and MDS International Foundation
www.aamds.org
Blood & Marrow Transplant Information Network
www.bmtinfonet.org

HOW CAN I WORK WITH THE HEALTHCARE TEAM?
The care of your child requires a team approach. You are a key player on your child’s healthcare team. You know your child better than anyone else and your input is important.

Always communicate openly with the other members of your child’s healthcare team. Ask questions when there is anything you are not sure about. It may help to write down your questions as you think of them. This will help you remember all of your questions when you are talking to the healthcare team. Many families find it helpful to create a folder or binder in which they can store all of the information they have received about their child’s diagnosis including copies of laboratory results. This also can be a good place to write down any questions that arise between appointments.

Important questions you may want to ask include
• How severe is my child’s aplastic anemia, and what does that mean?
• What treatment choices are available?
• What treatment do you recommend and why?
• What are the risks or side effects during the treatment?
• What are the risks and side effects after the treatment?
• What are my child’s chances for survival?
• What are the chances for recurrence?
ARE MY FEELINGS NORMAL?

Hearing that your child has a serious illness is often shocking and overwhelming. Parents often feel numb and have a hard time believing the diagnosis. It is important to know that this is normal and expected. Most families have difficulty processing all of the information the healthcare team is providing to them. However, with time, information will be absorbed.

Many families feel somehow responsible for their child’s disease. Feelings of guilt because they could not protect their child from illness or about the amount of time it took to diagnose the child also are common. This disease is not caused by anything that you did or did not do. The cause of aplastic anemia is usually not known.

Feelings of sadness, anger, and helplessness about your child’s diagnosis also are common. These feelings are normal. Each member of the family may express these emotions in different ways and at different times. Talking honestly with one another about these feelings, emotions, and reactions will help everyone in the family. Keep in mind that there is no right or wrong way to feel. Everyone needs the chance to express their feelings when they are ready and in their own way.

Talking to friends, family, and members of the healthcare team can be difficult at times, but expressing your feelings can help you cope. Your child will benefit from family and friends showing their care through communication and support.

HOW CAN I HELP MY CHILD?

Children often think that something they did caused their illness; reinforce that this is not the case. Make sure your child understands that your feelings of anger and sadness are directed at the disease and not at him or her. This will help to keep your relationship honest and to maintain closeness. Your child will need to share his or her feelings with someone whom he or she trusts. Sometimes, children choose to share their feelings with someone other than a parent because they are afraid they might upset the parent. Don’t be afraid to ask your child about his or her feelings—it may be what your child is waiting for. Also, don’t be afraid to share information with your child about what is happening and why it is happening. The things children imagine on their own often are more frightening than what is actually happening.

In spite of your child’s disease, keep in mind that he or she is still a child. All children need love, attention, the opportunity to learn and try new skills, and limits. As your child goes through treatment, keep in mind that he or she still has all the needs of a growing child. Do not avoid talking to your child about therapy; use direct terms and explanations your child will understand. Children tolerate treatment better if they understand it and are allowed to help make decisions about their care when appropriate.

As a parent, it may be difficult to watch your child go through a serious illness and treatment. Your child may sometimes seem sicker than before the therapy. Your feelings about what your child is going through during treatment must be balanced with the knowledge that treatment provides the chance of curing the disease and having your child live a full and meaningful life. Accepting the changes in your child that the aplastic anemia and the treatment may cause often is difficult, but keep in mind that many of these changes are often temporary. Always remember that, despite outward changes, your child is still the same person on the inside.
IS MY CHILD’S DIET IMPORTANT DURING THERAPY?

Your child’s diet is very important during therapy. Research has shown that well-nourished children tolerate therapy better. Offer foods that are high in calories, protein, and carbohydrates. Small frequent meals often are better tolerated than three larger meals. When possible, avoid junk foods and foods that are high in salt in favor of more nutritious foods.

Your child’s hydration status is also an important part of his or her well being. It is important to offer your child fluids to drink frequently throughout the day, or he or she may become dehydrated. Signs of dehydration include decreased urine output, dizziness, and a dry mouth.

Multivitamins, herbs, and medicines should be avoided unless approved by your child’s healthcare team. These medications may interact with your child’s therapy.

A dietician is a part of your child’s healthcare team. He or she is trained in the caloric and nutritional needs of children. The dietician can provide you with information regarding your child’s dietary needs and ideas about how you can meet these needs during treatment.

Your child’s healthcare team will monitor your child’s nutritional status, height, and weight during and after treatment to try to prevent problems. When there is a concern about nutritional problems, your child’s healthcare team will intervene.

CAN MY CHILD ATTEND SCHOOL DURING THERAPY?

Your child’s ability to attend school during therapy will depend on the intensity of the treatment, your child’s response to treatment, and how susceptible to infection your child is based on the ANC. There may be extended periods when your child is unable to attend school because of hospitalizations or treatments. However, it is important that even during these times your child keeps up with his or her schoolwork. Talk with your child’s healthcare team and school about arranging for homebound services, including a tutor, until he or she is able to return to school. Many children’s hospitals have school programs that allow patients to attend school while hospitalized. These programs often help coordinate home tutors and obtain homework and schoolwork.

Discuss your child’s ability to attend school with the healthcare team. Some children are able to attend school between hospitalizations or treatments and to use homebound services. The healthcare team can help coordinate the school services your child needs. When a child returns to school for the first time after starting treatment or at the end of therapy, many healthcare teams go to the school to educate teachers and students prior to a student’s return. Once your child does return to school, the healthcare team can continue to assist you with getting any special services your child may need.
BIBLIOGRAPHY


IMPORTANT PHONE NUMBERS


NOTES