



Bone Marrow Transplant: *A Chance for Health*

By Lauren Gerstmann, MPH

Step into Children's Hospital of Cincinnati, with its giant bright murals and its ever-available supply of sanitizing wipes, and it is as though you have entered a family-friendly universe. This is a good thing, because for several months the hospital will be the only world that Aidan, Ashley, Conner and their families will know. Aidan, Ashley and Conner are all getting ready to undergo bone marrow transplants (BMTs) to treat their primary immune deficiencies. With luck, they will go from a life of chronic illness to full health, but it is a long and risky journey.

These are not your "normal" transplant patients. A quick Internet search for immune deficiency and BMT reveals articles on transplant in infants with severe combined immune disease (SCID). For kids with SCID, transplant is the only hope of survival, and it is usually completed before 1 year of age. While Aidan, Ashley and Conner all have severe immune deficiencies, none has SCID, and they are older than the typical primary immune deficient BMT patient. Aidan is 5 and both Ashley and Conner are 12.

It seems that only disease would have brought these families together. Conner's family lives in Indiana near the

University of Indiana, Ashley's family lives in Indiana near the Ohio border, and Aidan's family lives in Illinois. But, for the past several years they have gotten to know and support one another through an informal email network and through the word-of-mouth that connects families living with immune deficiency. The three families share a strong faith in both their doctors and in a Higher Power, and they believe the transplants will save their children's lives.

Bone marrow transplant may be used to treat deficiencies in the blood such as those caused by leukemia or aplastic anemia, but it can also be used to replace a damaged or failing immune system. Testing prior to BMT can help determine how well the donor's marrow will genetically match the patient's, and it can give some insight into the potential success of the transplant. The most successful transplants are between nonidentical siblings who have an identical tissue type. Tissue type is determined through HLA typing, a blood test that characterizes how a person's antigens tell the difference between normal body tissue and foreign tissue.¹ Aidan, who will receive banked umbilical cord blood cells from his little brother, Liam, is receiving that "perfect" match.

¹ www.webmd.com/a-to-z-guides/Tissue-Type-Test#hw40264.

To understand the immune system, you need to know how the body makes blood. Blood cells originate in the marrow of the bone, and bone marrow cells have the capability to turn into red blood cells, white blood cells or platelets.² Lymphocytes are white blood cells that play a critical role in the immune system. Specific types of lymphocytes, called B cells, make antibodies that neutralize molecules that would set off an immune response. Other lymphocytes, called T cells, actually activate destructive cells in the body to kill any dangerous cells that are infected, mutated or cancerous. Some immune deficiencies affect B cells and T cells (as do Conner's, Ashley's and Aidan's), while other deficiencies affect only B cells. After they receive their transplants, all three children should have bone marrow that functions normally, creating the healthy B and T cells that will enable them to fight infections.

BMT Outcomes

According to data from the Center for International Blood and Marrow Transplant Research, an international organization that tracks transplant outcomes, 75 percent of SCID patients who received an identical sibling transplant and 59 percent of SCID patients who received an unrelated donor transplant between 1995 and 2005 survived at least three years.³

A European report, looking at non-SCID immune deficiency transplant success rates from 1968 through 1999, found a 78 percent survival rate three years or more post transplant for perfect sibling matches. The three-year or more survival rate with unrelated donors ranged from 42 percent to 59 percent, depending on other characteristics of the match.⁴

Patients who do not have a sibling donor can search for a matched, unrelated donor on the National Marrow Donor Program (NMDP) Registry of volunteer donors. Since 1987, the NMDP has facilitated more than 25,000 transplants, and roughly 260 patients receive matches through the registry each month.⁵ From 1999 through 2004, the NMDP facilitated 245 unrelated donor transplants for patients with SCID. Other immune deficient diseases have been treated with unrelated transplants, but such instances are rare.

Because the science of BMT continues to advance, it helps to talk with the doctors who are actively performing BMT on a regular basis. Some of the most experienced doctors are Dr. Alexandra (Lisa) Filipovich and Dr. Jack Bleesing at Cincinnati Children's Hospital Medical Center. Aidan, Ashley and Conner are all undergoing transplants with this team.

Dr. Bleesing firmly believes that the safety of BMT is continuing to evolve. At Cincinnati Children's Hospital, children are carefully evaluated and treated to make sure they are as healthy as possible when they undergo transplant. Drs. Bleesing and Filipovich believe that BMT should be considered before their immune deficiency has caused so many illnesses that their entire system is compromised. Healthier patients make for better outcomes. Also, doctors have improved the safety of donor-to-patient matches, and have gained insight into infection prevention during the recovery process. According to Dr. Bleesing, success rates for unrelated matches at Cincinnati Children's Hospital continue to improve and continue to approximate those for matched sibling transplants (keeping in mind that this estimate lumps together a variety of immune deficiency disorders that are fundamentally different in nature).

Bone marrow transplant is a risky procedure because, before you give these children a new immune system, you must first eliminate any immune function that they have. Only when there is no host immune system will the grafted immune system take over. Prior to the transplant, each child will undergo a preparatory treatment consisting of immunosuppressive and chemotherapeutic drugs to destroy his or her immune system. During recovery, the child will be vulnerable to new infections and to re-activation of infections that he or she may have had prior to the transplant.

Preparing for BMT

The preparatory regimen before BMT is called conditioning, and the type and degree of conditioning is specifically designed for each type of immune system disorder. Some research has shown that BMT is more effective if the patient is not weakened by intense ➤

² <http://children.webmd.com/Allogeneic-stem-cell-transplant>.

³ Based on raw data on characteristics and outcome for patients with severe combined immune deficiency registered with the Center for International Blood and Marrow Transplant Research (CIBMTR) from 1995 to 2005. The data presented here are preliminary and were obtained from the CIBMTR. The analysis has not been reviewed or approved by the Advisory or Scientific Committee of the CIBMTR. The data may not be published without the approval of the Advisory Committees.

⁴ Antoine, C. et al. Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: report of the European experience 1968–99, *The Lancet* Volume 361, Issue 9357, 15 February 2003, Pages 553-560.

⁵ The National Marrow Donor Program www.marrow.org/ABOUT/History/index.html.

conditioning.⁶ Ashley is benefiting from this research and will undergo a reduced intensity conditioning regimen (RIC). It means she should feel better prior to the transplant and should bounce back sooner. But, it also means that some of her original immune system and other bone marrow-derived cells may remain after transplant. Aidan will also undergo RIC. In his case, the emphasis will be on immunosuppressive rather than on chemotherapeutic drugs, to ensure there is no possibility that his immune system will reject the new bone marrow cells. It will also reduce the chance that Aidan's original, defective immune system will overwhelm the healthy transplant.

Drs. Filipovich and Bleesing believe that RIC is not an option for some patients. For example, in Conner's case, it is likely that the medical team will use traditional conditioning, a method Dr. Bleesing believes is a better approach in some circumstances: "If we think that the immune system is more globally defective; if we think that we need to replace more than the B cell and T cell components early on after BMT...[or in] disorders where we are not sure how everything works (and has been affected by the genetic defect). ...It is important to remember that we have been doing these things for 30 years. We did not wait until we completely understood the disease to start transplanting because we learned that [intense conditioning

followed by BMT] could take care of our patients."

Because of the difficulty, risks and expense of BMT, it is never easy for a doctor to prescribe or for a family to choose. Everyone wants to look to logical science for a clear decision, but there is some art involved. An important part of the decision is choosing the most experienced medical team possible. Aidan, Ashley and Conner's families were referred to the team at Cincinnati Children's Hospital because of the doctors' skills and experience and their cutting-edge BMT research. Cincinnati Children's has one of the largest pediatric BMT programs in the nation and is recognized for expertise in treating unusual disorders. In the summer of 2005, the program performed its 1,000th BMT since the transplant program was established in 1981.⁷

In a perfect world, where the risks could be minimized, the benefits maximized and the costs contained, every person who needs curative therapy for an immune deficiency might receive a brand-new functional immune system through BMT. But with the current state of knowledge, doctors must determine whether BMT is feasible and whether the benefits outweigh the risks. In a simplified scheme, patients can be assigned to three categories: patients who should receive a BMT as soon as possible (for example, people with specific, known disorders such as SCID); patients for whom BMT would eliminate the need for lifelong symptomatic (non-curative) therapy and who continue to have significant health issues (for example, certain severe forms of common variable immune deficiency, CVID); and patients for whom BMT would not be feasible (for example, because their immune deficiency disorder is not posing a significant burden on their health or daily life issues). As BMT research evolves, the distinction between these categories may evolve as well.

Once a family has made the decision to forge ahead with BMT, the family members will need a lot of support. Aidan, Ashley and Conner's families have been in touch throughout the decision-making process, and will continue to support each other through the transplant process. Although the children will not be together during their initial months after transplant (BMT patients are kept in isolation), they will be able to spend virtual time together through email and web pages provided in the hospital, and their families will be able to meet face-to-face. Each

About the National Marrow Donor Program (NMDP)

The NMDP offers a wide range of services to help patients and their families every step of the way, from diagnosis through survivorship. The NMDP also recruits people to its donor registry. To become a volunteer marrow or blood cell donor, a person must be between the ages of 18 and 60, meet health guidelines and be committed to donating to any patient in need. It's an opportunity to save a life.

To learn more about patient services or becoming a donor, visit www.marrow.org or call 800-MARROW-2 (800-627-7692).

⁶ Rao, et al, Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen, *Blood*, 15 January 2005, Vol. 105, No. 2, pp. 879-885.

⁷ www.cincinnatichildrens.org.

family is also receiving tremendous support from their friends, families and religious communities who have been very helpful in raising funds for this expensive procedure.

Ultimately, the three families are able to remain optimistic in the face of great risk because successful transplants could give their children the chance to have normally

functioning immune systems.

Conner put it succinctly when he explained to his mother, "Even if I go to heaven, it is OK, because at least I have a chance."

BMT may just be the chance that results in a long and healthy life for all three children.

Conner

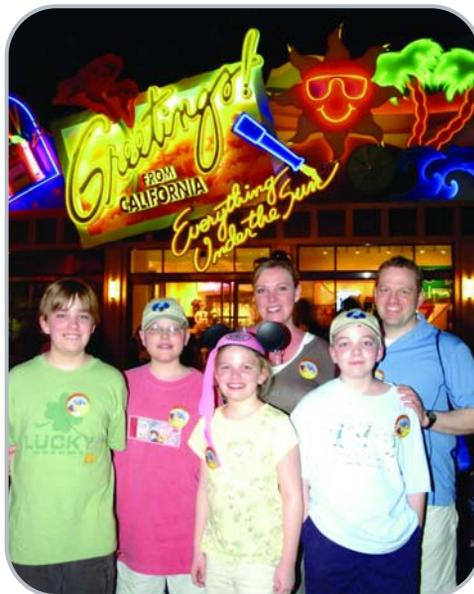
Conner is a triplet. He and his siblings were born almost two months early, and his repeated illnesses in infancy were attributed to his prematurity. He got sick a little more frequently than his brothers, and was always on and off antibiotics and breathing treatments, but it didn't seem unusual. When he was 9 years old, after having a cold, he suddenly became very sick and was hospitalized. He couldn't get enough oxygen, and the doctors never were able to discover why. Even after leaving the hospital, Conner was having significant trouble breathing. The hospital was a small community hospital in Lafayette, Ind., and the doctors were stumped.

A pulmonologist evaluated him, and immediately decided to measure his IgG levels, which were significantly low. A few months prior to his hospitalization, Conner had developed seizures and had gone on anti-seizure medication. When the family consulted a hematologist-oncologist to follow up on the low IgGs, he suggested that this was a transitory immune deficiency caused by the new medication. Conner went into semi-isolation to try to reduce his exposure to infection and build his immune system back up. Three months after he stopped the medication, Conner's IgG levels had still not risen. The family consulted with an immunologist, who advised that Conner's life would be in danger until he began IVIG therapy. CVID was a possible diagnosis.

The family then saw Dr. Melvin Berger, an immunologist at Cleveland Children's Hospital, who concurred with the CVID diagnosis. Dr. Berger mapped out a course of

treatment, including subcutaneous immune globulin therapy, but the family continued to search for more answers. When Conner was 10, the family decided to take him off treatment to see if there had been any improvement with his immune function. Within a few weeks, Conner developed bronchitis and then pancreatitis. His IgG levels had bottomed out again. Realizing that this was no transitory deficiency, they decided to consult Dr. Bleesing at Cincinnati's Children's Hospital. He found a defect in one pathway of Conner's complement system (a system that causes inflammatory response, eliminates pathogens and enhances the immune response⁸), and he also demonstrated that his natural killer cells and B cells weren't functioning normally.

While the family was trying to understand Conner's immune deficiency, his younger sister, Kelsey, became very ill with an unusual pneumonia. At that point, concerned about a genetic relationship, the family took all the kids to Cincinnati. When Dr. Bleesing tested the whole family, he discovered only slight depressions in IgG levels and questionable antibody responses, but all the kids had the defect in their complement system. So does Chris, Conner's dad. It is unclear if and how this deficiency affects people, or whether it is actually consistent with a clinical immunodeficiency disorder. Kelsey also has non-functional natural killer cells. Since she is doing well clinically, she has not yet started IVIG. The natural killer cell malfunction put Dr. Bleesing on the trail of some more specific immune deficiencies. Eventually, he found ➤



Conner (front row, right) with his family

⁸ www.emedicine.com/med/topic419.htm.

that Conner has a specific deficiency known as NEMO, a rare immunodeficiency that affects only boys. (No one knows why Kelsey is also having some symptoms.) This was a shock to the family since most other children with NEMO are much sicker than Conner. NEMO has been discovered only in the past decade, and it is believed to be fatal without treatment with bone marrow transplant. Even though Conner appears to have a less severe presentation, the doctors believed Conner might not be able to lead a full and normal life without a transplant. NEMO patients have been found to be vulnerable to damaging infections like tuberculosis. Development of a serious infection would greatly complicate BMT, so doctors at NIH urged the family to go through transplant while Conner is still healthy.

Conner has been looking for a cure since he first got sick and has been asking for BMT since he learned that he had an immune deficiency. He is willing to risk his life for a chance to have a normal life. He was thrilled with the news from NIH, and was really excited to talk with Dr. Filipovich. His family warned him about the chemotherapy conditioning and the risks in graphic detail, but Conner has never wavered, actively participating in his treatment decisions. He is already planning his DVD selection for his time of isolation in the BMT unit. His biggest concern is missing a year at school and his friends. Cincinnati is three hours from his hometown, but whether and when he will be able to have visitors depends on how he is doing.

It is helpful for Conner to go through this with other school-age kids so they can cheer each other along. Ashley is the same age as Conner. They met at the immunology department at Cincinnati Children's Hospital and have gotten together a few times since then. Conner is very open about transplant, but it is harder for Ashley to talk about it. Sharing it with him has made it easier for her to voice her fears. They plan to email and keep in touch by phone.

Ashley

Ashley was born full-term and healthy. But as an infant, she had chronic ear infections and had tubes placed when she was 6 months old. Her condition was then stable until she was a year old and she developed a cellulitis infection around her eye, landing her in the hospital. Right before she turned 2, she had a streptococcal and two blood infections. Her white blood cell and platelet counts were low, so the family went to Children's Hospital of Cincinnati, where they saw Dr. Karen Kalinyak, a hematologist. She asked for an immunology consult, and when Ashley was 3, she met Dr. Filipovich. Dr. Filipovich confirmed that

Ashley's immune system was compromised. Ashley's respiratory symptoms continued but responded well to antibiotics. When Ashley was 6, Dr. Filipovich told her family that she had CVID. Along with CVID, Ashley has severe lymphopenia—low levels of lymphocytes (white blood cells), which are important in regulating the immune system—caused by the T cells' inability to mature properly. Since she had already been hospitalized a few times with pneumonia, Ashley started IVIG.

As Ashley has grown older, she has done well, but she has had many side effects from the IVIG. When Ashley was 9, she developed debilitating headaches. At 10, she developed aseptic meningitis after an infusion. She missed five weeks of her treatments, and then switched to subcutaneous therapy, which helped alleviate the side effects. When frequent home infusions proved to be too long and painful, Ashley asked to switch back to office-based infusions. She immediately developed aseptic meningitis again. Now back on subcutaneous therapy, Ashley is doing really well, but her headaches have returned. The headaches, probably an inflammatory response to the infusions, are eased by regular steroid use. However, the amount of steroids Ashley needs to control her symptoms is not sustainable long-term.

Although Ashley is stable now, without a transplant soon, she will start having more health problems. Discussion about transplant started four years ago, when Dr. Filipovich first identified Ashley's immune deficiency, and she accepts the idea. A while ago, when Ashley asked if she would need infusions forever, her parents let her know that the infusions would continue unless Ashley received a new immune system via transplant. A few weeks after hearing it was time for the transplant, she was



Ashley with her parents and brothers

very concerned. But her strong spirit and spiritual faith are carrying her through. She does not let her disorder define her; it is only a small part of who she is.

Dr. Filipovich is optimistic that there will be a great outcome for Ashley. Shawna, Ashley's mother, says the doctors' biggest concerns are Ashley's social challenges, and the challenges that Ashley will face in adapting to the restrictive post-transplant environment. But Ashley has a matched donor from the national donor registry, so everyone is very positive about her long-term medical prognosis.

In the meantime, the family has developed rituals that help distract Ashley from her medical regimen. Every Friday night several friends come over to watch movies, eat takeout and keep Ashley company while she has her infusions. It takes a lot of the pressure off Ashley's parents, as she has so many wonderful cheerleaders.

Aidan

Aidan was a healthy infant until he developed a rare form of autoimmune anemia at 10 months. Although the family hoped this was an isolated diagnosis, Aidan soon lost platelet function and was diagnosed with Evans' syndrome (an autoimmune disease where the immune system attacks both red blood cells and platelets). When Aidan was a toddler, he developed Guillain-Barré syndrome, an acute neurological disorder that paralyzed him from the neck down. He immediately started treatment with IVIG.

In addition to the surprising number of autoimmune diseases that Aidan developed before he was 3, he also suffered an unusual number of infections. He saw an immunologist who diagnosed CVID and treated him with IVIG, even though his blood work was not typical of CVID. About a year ago, just before Aidan turned 5, the family consulted Dr. Gulbu Uzel, an immunologist at the National Institutes of Health, to learn if there was something amiss other than CVID. As soon as the family returned home from the appointment, Dr. Uzel called them and said, "I think he needs a bone marrow transplant." In reviewing Aidan's genetic tests, the doctor found that Aidan had a recombination activating gene (RAG) deficiency; she referred the family to Cincinnati Children's Hospital.

At Cincinnati Children's, Aidan is in good hands with Drs. Filipovich and Blessing. They are familiar with Aidan's autoimmune symptoms and his immune deficiency. Noting the RAG mutations, both doctors concur that Aidan needs a transplant. He has low levels of T cells, and his thymus does not output T cells as it should. Up until this point, Aidan has been very lucky that he has not suffered any of



Aidan (center) surrounded by his family

the more severe infections associated with a T cell defect. But, he has been developing new autoimmune conditions annually, and his T cell function continues to decline, leaving him increasingly vulnerable. So, the doctors want to transplant before his health spirals downward.

When Aidan's baby brother, Liam, was born, his bone marrow turned out to be a perfect genetic match, yet fortunately he did not have the same genetic defect. Liam's saved umbilical cord blood will provide the necessary cells for Aidan's transplant.

Aidan's mother, Amy, says family and friends have been a huge support. Aidan just wants to be a normal kid. He goes to school, plays with his brothers and cousins, and even participates in karate. He gets upset when kids tease him about some of his more obvious symptoms, like his vitiligo (a sun-sensitive skin autoimmune condition). To help, a teacher at his school presented a talk about respecting kids who are different and kids who have medical problems. Now Aidan is not teased so much, but he is scared. He knows he is going to feel "crummy" for a long time before he feels better. He understands he will be receiving blood from his baby brother to make him healthy, but he doesn't know the risks involved. His parents don't feel he is old enough at 6 to deal with that. But clearly, he is trying to comprehend it all. Aidan doesn't ask questions during his doctor appointments. He quietly listens and then fires questions at his parents on the ride home. His parents try to answer him as honestly as possible without distressing him even more.

Amy has high hopes the BMT will eliminate Aidan's autoimmune issues and that his B and T cells will return to normal. She hopes he'll end up with the normal immune system of a healthy child. ■